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Lipodystrophies in non-insulin-dependent children: Treatment options and results from recombinant human leptin therapy

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ABSTRACT

Lipodystrophy is a general definition containing different pathologies which, except for those observed in insulin-treated subjects falling outside the scope of this paper, are characterized by total or partial lack of body fat, that, according to the amount of missing adipose tissue, are divided in generalized or partial lipodystrophy. These diseases are characterized by leptin deficiency, which often leads to metabolic derangement, causing insulin resistance, dyslipidemia, and increasing cardiovascular risk. In this narrative review, we presentend the clinical presentation of different types of lipodystrophies and metabolic unbalances related to disease in children and adolescents, focusing on the main treatment options and the novel results from recombinant human leptin (metreleptin) therapy. Milestones in the management of lipodystrophy include lifestyle modification as diet and physical activity, paired with hypoglycemic drugs, insulin, hypolipidemic drugs, and other drugs with the aim of treating lipodystrophy complications. Metreleptin has been recently approved for pediatric patients with general lipodystrophy (GL)> 2 years of age and for children with partial lipodystrophy (PL)> 12 years of age not controlled with conventional therapies. New therapeutic strategies are currently being investigated, especially for patients with PL forms, specifically, liver-targeted therapies. Further studies are needed to achieve the most specific and precise treatment possible.

1. Introduction

Lipodystrophy (LD) is a general definition containing an heterogeneous group of pathologies which, except for those observed in insulin-treated subjects falling outside the scope of this paper and briefly described below, are characterized by total or partial lack of body fat. According to the amount of missing adipose tissue, lipodystrophies are termed generalized lipodystrophy (GL) or partial lipodystrophy (PL) [1,2]. This condition can be genetically determined or acquired and according to this additional difference, lipodystrophies are further classified as congenital GL (CGL), familial PL (FPLD), acquired GL (AGL) and acquired PL (APL). These four subgroups account for the majorities of lipodystrophies seen in the clinical practice, but it's worth to mention also other conditions as lipodystrophy associated to auto-inflammatory or complex syndromes [2,3]. Lipodystrophies are also heterogeneous in clinical features and they are characterized by low leptin level and share common metabolic disorders, including marked insulin resistance (IR), with or without diabetes, hypertriglyceridemia, steatohepatitis and features of hyperandrogenism and ovarian polycystosis. The severity of the metabolic phenotype is proportional to the degree of adipose tissue loss [4].

In this narrative review, we presentend the clinical presentation of different types of lipodystrophies and metabolic unbalances related to disease in children and adolescents, focusing on the main treatment options and the novel results from recombinant human leptin (metreleptin) therapy.

2. Methods

We conducted a narrative review of the literature, presenting a non-

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systematic summation and analysis of available literature on the topic of lipodystrohy in children and adolescents and its medical treatment. A set of inclusion criteria were established to refine the aim of the narrative review: articles in English language; original scientific papers, clinical trials, meta-analyses and reviews published on a specific topic in the last twenty years, up to May 2022; case reports or series and letters were excluded. The authors assessed the abstracts of the available literature (n = 150) and reviewed the full texts of potentially relevant articles (n = 80) that were analyzed to provide a critical discussion. Additionally, the reference list of all articles was checked to identify relevant studies. The research terms adopted, alone and/or combined, were lipodystrophy, adolescents, children, pharmacological treatment, metreleptin, multidisciplinary treatment, multidisciplinary approach. The databases PubMed, Scopus, EMBASE and Web of Science were used from July to September 2022) for research purposes. The contributions were independently collected by V.R., V.C.M. and critically analyzed with V.C., V. F., C.M. The resulting draft was discussed by V.C. and critically revised by V.C., G.Z. The final version was then recirculated and approved by all.

3. Lipodystrophies

3.1. Prevalence

Lipodystrophies are rare and too often underestimated pathologies. The recently estimated worldwide from searches of large electronic medical record databases was 3.07 cases per million population (0.23 cases/million of GL and 2.84 cases/million of PL) [5]. Interestingly, a recent work by Gonzaga-Jauregui, through genetic analyses, estimated a genetic prevalence of disease of ~1 in 7.000 in the general population and a clinical prevalence of disease of 1 in 20.000 individuals, underlining the underdiagnosis of these pathologies [6]. This estimated prevalence by Gonzaga-Jauregui is in contrast with previous reported estimates from the literature, the main reason reported for this discrepancy is that the availability of both clinical and genetic data from a single large clinical care cohort (the DiscovEHR database) allowed the authors to characterize these disorders also by evaluating the fraction of individuals presenting with the expected associated comorbidities [6]. Moreover, consistently with previous reports [5], Gonzaga-Jauregui et al. observed a females-males ratio of 3:1. Interestingly, this has been reported to be a diagnostic bias due to the increased likelihood of detecting abnormal fat distribution in females versus males, mainly because of the more muscular appearance in the absence of subcutaneous fat [6].

Hereafter, we report the current classification of lipodystrophies, based on clinical presentation, which may change as our understanding of the disease improves.

3.2. Classification and clinical features

3.2.1. Genetic lipodystrophy syndromes

3.2.1.1. Congenital generalized lipodystrophy. CGL (Berardinelli-Seip syndrome) is an autosomal recessive disorder and it the most common lipodystrophy in infancy and early childhood. Specifically, a recently systematic review (evaluating 351 studies) stated that this condition accounts for around half of pediatric lipodystrophies, excluding HIV-related ones [3,5,7,8]. Its prevalence, estimated to be around 1:10 million, decreases in older children, close to puberty, while FPLD increases [2]. Affected patients lack adipose tissue and are phenotypically characterized by muscular overdevelopment of subcutaneous veins, which are generally already visible at birth [9]. Four major subtypes of CGL exists. These conditions have a different genetic etiologies, but share many similar phenotypical features, as shown in (Table 1)[2,10].

Table 1
Features of the four subtypes of GCL [2,10].

CGL subtype	Involved gene	Phenotypes
CGL 1 [2,10]	AGPAT 2 (1 acylglycerol 3-phosphate acyltransferase β2)	• Total fat absence except for mechanical fat • Severe insulin resistance (IR) • Metabolic abnormalities • Cystic bone lesions
CGL 2 [2,10]	BSCL2 (Berardinelli-Seip congenital lipodystrophy 2)	• Near total absence of fat • Severe IR • Metabolic abnormalities • Mental retardation • Cardiomyopathy • Cystic bone lesions (rare)
CGL 3 [2,10]	CAV 1 (Cavin-1)	• Near total absence of fat execpt for bone marrow fat • Severe IR • Metabolic abnormalities • Bone metabolism dysfunctions: vitamin D- resistance, hypocalcemia, osteopenia • Delayed growth and short stature
CGL 4 [2,10]	PTRF (Polymerase and transcript release factor), LMNA (Lamin A/C), PPARG (Peroxisome proliferator-activated receptor gamma gene)	• Near total absence of fat execpt for bone marrow fat • Severe IR • Metabolic abnormalities • Gastrointestinal (GI) dysfunctions: pyloric stenosis, GI dysmotility • Muscular abnormalities: myopathy, percussion- induced muscle wounding • Bone abnormalities: scoliosis, atlanto-axial instability • Cardiac problems: arrhytmias, atrial fibrillation, prolonged QT, sudden death • Progeroid phenotype (specifically in the LMNA variant)

3.2.1.2. Familial partial lipodystrophy. FPLD is the most common subtype of lipodystrophy in adults [1,2,9]. Affected patients, especially females, in which phenotypic features are more evident, exhibit a typical fat tissue. Specifically, absence of fat tissue is mainly seen in the upper and lower extremities, while fat accumulation can be observed in certain areas (as the face, neck, perineal and intra-abdominal depots) [1–3, 11–13]. The typical facial fat accumulation, together with increased fat in the dorsocervical region and thin limbs, resemble a Cushingoid-phenotype.

Altough partial loss of fat may be apparent in early life, the pathological features tend to more pronounced over time and most patients start to lose adipose tissue after puberty [1]. This is the reason why only few patients have been reported in pediatric clinical practices [7]. These most frequent subtypes of FPLD and their specific phenotypical characteristics are reported in (Table 2)[2,10].

3.2.2. Acquired lipodystrophy syndromes

3.2.2.1. Acquired generalized lipodystrophy (Lawrence syndrome). AGL, being generalized, affect the whole body causing widespread fat loss. Affected patients, as in other types of lipodystrophies, show typical metabolic complications as IR, diabetes, hypertriglyceridemia and non-alcoholic steatohepatitis (NASH) [14–16].

Clinically AGL patients are very similar CGL ones, except for the fact that patients with AGL are born with normal fat tissue. Indeed, loss of fat tissue typically starts in late childhood or adolescence. The cause of the disease is still unknown, but it may be present together with other autoimmune diseases (as juvenile dermatomyositis, type 1 diabetes and

Table 2
Features of FPLD subtypes [1,2,9,10,13].

FPLD subtype	Involved gene	Phenotypes
FLDP 1 (Koberling type) [1,2,9,10]	Polygenic	• Absence of adipose tissue limited to extremities • Truncal obesity • "Ledge" between lipodystrophic and non-lipodystrophic areas • Severe IR • Metabolic abnormalities
FLDP 2 (Dunnigan type) [1,2,9,10]	LMNA	• Absence of adipose tissue mainly in the limbs with excess fat in the face and neck • Increased muscularity • Labial pseudohypertrophy • Severe IR • Metabolic abnormalities
FLDP 3 [1,2,9,10,13]	PPARG	• Mild absence of adipose tissue mainly in the limbs without excess fat in the face and neck • Hirsutism • Severe IR • Metabolic abnormalities
FLDP 4 [1,2,9,10]	PLIN1 (Perilipin 1)	• Absence of adipose tissue mainly in the limbs and femorogluteal depot • Severe IR • Metabolic abnormalities
FLDP 5 [1,2,9,10]	CIDEC (Cell death inducing DFFA like effector C)	• Partial lipodystrophy • Severe IR • Metabolic abnormalities • Diabetic ketoacidosis • Achantosis nigricans
FLDP 6 (Lipomatosis-associated syndromes) [1,2,9,10]	LIPE (Lipase E) MFN2 (Mitofusin 2)	• Late-onset partial adipose tissue loss in the lower limbs • Multiple lipomatosis (LIPE type) • Progressive myopathy (LIPE type) • Upper body adipose hyperplasia (lipomatosis without encapsulation) (MFN2 type) • Low leptin levels (MFN2 type)

autoimmune hepatitis). Moreover, AGL may be associated with and/or complement abnormalities [14–17].

3.2.2.2. Acquired partial lipodystrophy (Barraquer-Simons syndrome). APL is a condition characterized by partial fat loss from the face, neck, arms, chest and abdomen with preservation of adipose tissue in the lower limbs [2,18,19]. Its onset occurs in late childhood or adolescence and, interestingly, the male:female ratio is around 1:4. The fat loss is progressive, starting from the face, and proceeding to the upper extremities, thorax and abdomen, a cephalocaudal manner [2,18,19].

APL's etiology remains unknown, however, even in this case a link with autoimmune abnormalities can be observed [2,18,19].

3.2.2.3. Rare genetic lipodystrophy syndrome and progeroid disorders. LD may be also part of the clinical picture of many complex syndromes and progeroid disorders, as Hutchinson-Gilford progeria syndrome, atypical progeroid syndrome, MDP syndrome [20], JMP syndrome, CANDLE syndrome [21], SHORT syndrome, [22] Néstor-Guillermo progeria syndrome [23], Neonatal progeroid syndrome, Werner syndrome etc. [23,24]. Being these rare conditions, no further details are here reported, but the main characteristics are presented in Table 3.

3.2.3. Other causes of acquired lipodystrophy

Among the others causes of acquired lipodystrophy it's worth to mention irradiation, cancer therapies and central nervous tissue (CNS) tumors. Specifically, lipodystrophy developments has been associated to whole body irradiation for bone marrow transplant [25–29] and cranial irradiation [30]. Also checkpoint inhibitors, used in cancer treatments, may lead to variable fat loss [31,32]. Altough uncommon conditions, it's important to assess eventual signs of fat loss and/or metabolic abnormalities in children subjected to aggressive cancer treatments. Being this condition also associated to hypothalamic tumors, in young children presenting with lipodystrophy, it is fundamental to evaluate also the possibility of CNS tumors, especially when history and clinical

Table 3
Features of different lipodystrophy-associated complex and progeroid syndromes [2,20–24].

Syndrome subtype	Involved gene	Phenotypes
Hutchinson-Gilford progeria syndrome [20]	LMNA	• Severe lipodystrophy, initially partially, it may progress to complete absence of fat tissue • Short stature, low body weight • Progeroid features
Atypical progeroid syndrome [20]	LMNA	• Severe fat loss • Muscular and cutaneous defects • Cardiac anomalies: cardiomyopathy and rhythm abnormalities • Progeroid features
MADA syndrome [20]	LMNA	• Partial loss of fat from the extremities with normal/excessive facial and neck fat deposits • Craniofacial and skeletal abnormalities • Cutaneous defects
MDP syndrome [20]	POLD1 (Polymerase delta 1, catalytic subunit)	• Progressive fat loss • Mandibular hypoplasia • Deafness • Progeroid features
JMP syndrome [21]	PSMB8 (Proteasome 20 S subunit beta 8)	• Panniculitis-induced lipodystrophy • Autoinflammatory syndrome • Skeletal and muscle problems: joint contractures, muscle atrophy • Anemia
CANDLE syndrome [21]	PSMB8	• Partial loss of fat from upper extremities and face • Autoinflammatory syndrome with recurrent fever • Chronic dermatitis
SHORT syndrome [22]	PIK3R1 (Phosphoinositide-3-Kinase Regulatory Subunit 1)	• Variable pattern of fat tissue absence • Short stature • Hyperextensibility • Teething delay
Néstor-Guillermo progeria syndrome [23]	BANF1 (BAF nuclear assembly factor 1)	• Variable pattern of fat tissue absence • Growth retardation • Skeletal and muscle problems: thin limbs, stiff joints • Progeroid features
Neonatal progeroid syndrome [23]	CAV1	• Generalized fat tissue absence • Progeroid features at birth
Werner syndrome [23]	WRN (Werner syndrome ATP-dependent helicase)	• Partial fat tissue loss, mainly in the lower limbs • Progeroid features
Others [2,20,21,23,24]	**Cockayne syndrome, Bloom syndrome, AREDYLD syndrome etc.**	• Generalized fat tissue absence, progeroid appearance + /- specific pathological features according to the syndrome: o Short stature o Mental retardation o Telangiectasia o Increased cancer risks etc.

evaluation do not fit for other types of LD [2,30]. In addition, lipodystrophy associated to insulin therapy in diabetic patients and HIV-related lipodystrophy has to be considered [33–37]. Among lipodystrophic lesions in patients on insulin therapy, lipohypertrophy (LH) due to inappropriate injection habits is the most common [33,38]. Buyruk et al., evaluating more than 200 diabetic patients treated with insulin therapy in Endocrinology Department between 2015 and 2018, reported LH in 61, 8% of subjects evaluated, lipoatrophy in 5.6% of the patients [38]. Importantly, a consequence of LH at injection site is a delayed insulin release and an increased risk of unpredictable hypoglycemia, that may deteriorate metabolic control and negatively affect adherence to treatment and quality of life [34]. The main studies concerning this topic are on adult patients, thus, definite conclusions about prevalence and relevance of this problem in children can't be drawn. For what concerns HIV, current antiretroviral therapy (ART) has been associated with body fat redistribution and metabolic abnormalities, both in adults and in children [35,37]. Recently, Tshamala et al. performed a cross-sectional study in Kinshasa (Democratic Republic of Congo) and recruited 80 HIV-infected children on ARV therapy, 80 non-infected children and 65 HIV-infected antiretroviral therapy-naïve children [36]. The authors reported a not statistically different frequency of lipoatrophy between HIV-infected children on ARV therapy (16.3%) and HIV-infected antiretroviral therapy-naïve children (21.5%); while a significantly higher rate of LH and hypercholesterolemia was noted in HIV-children on ARV compared to the controls ($p < 0.05$) [36]. These results confirmed previous researches in different countries [37,39,40]. Lipodystrophy in these patients may represent an increased risk for future complications, in particular cardiovascular problem, thus it is pertinent to underline the importance of multidisciplinary care for HIV-infected children and adolescents, in order to minimize the risk of the development of future metabolic complications [35,37,41].

3.3. Recognition and diagnosis of lipodystrophy

Recognition of a (LD) shoud be based on clinical and family history and a complete physical examination that may reveal a specific body composition and metabolic state [8,42]. Because of their rarity and heterogeneity, these disorders may frequently be unrecognized or misdiagnosed. Recently, Araùjo-Vilar et al. proposed a stepwise approach for diagnosis of the different subtypes of rare lipodystrophy syndromes, based on literature and their own experience [42]. The first diagnostic step is determination of whether the patient has lipodystrophy. This may be easier in case of GL, because of its pervasive features, but it may be more difficult in PL, where the presentation can be more subtle. Thus, facing a patients whit lipodystrophy features LD should be suspected when either congenital deficiency of subcutaneous adipose tissue or progressive loss of adipose tissue are reported, especially if associated with other diseases (for instance autoimmune diseases or somatic abnormalities) or if fat loss in limbs occurs with fat accumulation in other body regions [3,42]. Additional features helping diagnostic process may be failure to thrive, prominent muscles and veins, acanthosis nigricans or cushingoid appearance [3,9]. Unfortunately there are no diagnostic criteria for LD based on body measurements or imaging but skinfold measurements, dual-energy X-ray absorptiometry and magnetic resonance, can assist with diagnosis [3,42]. The second step proposed in the diagnostic pathway is the evaluation of the extent of lipodystrophy [42]. Indeed, once the diagnosis of lipodystrophy is established, clinicians should define whether the disorder is generalized or partial [42]. The third step then expect clinicians to define whether the condition (GL or PL) is genetically determined or acquired and according to this additional difference, classify the pasthology as CGL/AGL or FPLD/APL, as previously described. Once diagnosis is established, physician shoud also be aware of the possible complications of the condition, specifically of the metabolic dysfunctions related [3,42]. Further details on diagnostic process are behind the scope of our review, but bearing in mind this relative simple stepwise process may be extremely useful when facing this heterogeneous group of pathologies.

3.4. Metabolic dysfunctions

Common denominator of all forms of lipodystrophy is IR, which in turn induces the development of a metabolic derangement [3,13,17,43–45]. Usually, complications' onset is before adulthood and tends to be more severe and have an earlier onset in CL [2]. Indeed, disease severity primarily depends on the degree of adipose tissue loss, type of lipodystrophy, age, and sex, however it can be diverse even among subjects with the same pathogenic genetic variant [2,12,46–48].

Healthy adipose tissue is central in maintaining normal metabolic homeostasis. Under physiological conditions, it performs numerous roles, including excess calorie storage, buffering postprandial circulating lipid fluxes, synthesizing and secreting hormones and adipokines, such as leptin and adiponectin, which are crucial in regulating critical processes, such as food intake and insulin sensitivity [49,50]. In lipodystrophy, secondary to adipokine deficiency, there are excessive postprandial levels of circulating triglycerides and non-esterified fatty acids, which, unable to be stored in adipose tissue, are deposited in ectopic sites [1,13,14], such as the liver, skeletal muscles, and pancreas, causing local damage of these organs and metabolic sequelae [51,52]. Insulin resistance is probably secondary to the lipotoxicity of this mechanism and is proportional to the extent of the alteration in adipose tissue [13,45]. Indeed, leptin is crucial in modulating energy homeostasis, neuroendocrine and immune functions, and glucose, lipid and bone metabolism [52–54], Table 4.

In patients with lipodystrophy, adipose tissue fails in performing these aforementioned roles, due to genetic or acquired defects in adipocyte differentiation, survival, and/or function [55]. Overall, metabolic derangement severity in lipodystrophy is proportional to the amount of fat mass loss [45,56].

Although the underlying molecular pathogenetic mechanism involves different genes and patients with pathogenic variants of the same gene sometimes exhibit phenotypic heterogeneity, most patients share common metabolic consequences, such as severe IR that can progress to difficult-to-control diabetes and its complications, severe hypertriglyceridemia potentially leading to episodes of acute pancreatitis, nonalcoholic fatty liver disease and severe hepatic steatosis [9,16,43]; besides, women are prone to suffer from polycystic ovary syndrome (PCOS) [2].

Among individuals with CGL, an early-onset complication is hyperphagia, secondary to severe leptin deficiency and typically characterized by increased appetite and food intake, extreme food-seeking and food-anxiety behavior, especially during growth and developmental years [57,58]. The hallmarks of this condition are accelerated linear growth, advanced bone age, and signs indicative of acromegaly, specifically enlargement of hands, feet, and jaw [16]. Besides that, patients with CGL1 often present with cystic bone lesions as well [43,59–61].

Table 4
Role of leptin on different organs and systems [51–54].

Organ or system	Effect of leptin
CNS – Hypothalamus	• Control of food intake, energy expenditure, and, therefore, body weight
Adipose tissue	• Regulation of adipocyte glucose metabolism
Pancreas	• Insulin and glucagon secretion • β-cells protection from lipotoxicity
Liver	• Lipid and glucose metabolism • Regulation of insulin sensitivity • Anti-inflammatory actions
Muscle	• Lipid and glucose metabolism • Regulation of insulin sensitivity • Stimulation of skeletal muscle growth
Kidney	• Regulation of glomerular filtration • Normalization of glucose levels • Reduction of lipid accumulation

Hyperinsulinemia and severe IR result from dysmetabolic complications due to partial or near-total deficiency of adipose tissue and leptin [43]. Patients with lipodystrophy have some of the classic clinical markers of IR, such as acanthosis nigricans, which is typically characterized by hyperkeratosis, sometimes with hyperpigmentation, typically most evident in body flexures and is most frequently seen after puberty [8,13,16,43,63]. A high serum insulin level stimulates keratinocytes and fibroblasts to grow and proliferate more powerfully, which underlies the process of AN formation [13,64]. An early complication of hyperinsulinemia and severe IR is diabetes mellitus [58], which is found in approximately 45% of GL patients [43,57,59] and is typically a hard-to-control diabetes; in fact, patients may often require high doses of insulin (>100 units/day) [43]. However, metabolic complications of diabetes, such as diabetic ketoacidosis, are rare and, when they occur, are assumed to result from severe hyperinsulinemia and lack of adipose tissue [9,43]. Another likely consequence of poorly controlled diabetes observed in patients with GL is increased susceptibility to infections [58]. However, the increased susceptibility to infections observed in patients with lipodystrophy could also be a consequence of reduced leptin levels [58]. Dyslipidemia, which severity reflects the degree of body fat reduction, is characterized by marked hypertriglyceridemia and reduced HDL cholesterol levels [13,65]. Significant hypertriglyceridemia probably depends on increased synthesis of VLDL by the fatty liver and reduced clearance of TG-rich lipoproteins [13,65]. Marked hypertriglyceridemia is thought to be the first lipid indicator of ongoing lipodystrophy [13,66], and TG values > 500 mg/dL unresponsive to medical therapy should raise suspicion of lipodystrophy. Hypertriglyceridemia, which typically develops in pediatric age, can result in recurrent episodes of acute pancreatitis and the development of eruptive xanthones, which occur, most often, after puberty [16].

The presence of metabolic dyslipidemia (hypertriglyceridemia and low HDL-C), resulting from ectopic adipose tissue accumulation, can lead to nonalcoholic fatty liver disease (NAFLD), which includes simple nonalcoholic steatosis, which can progress to nonalcoholic steatohepatitis (NASH), then to NASH-related fibrosis and cirrhosis [13,67]. Liver disease and hepatomegaly, which also occur in younger individuals, typically more severe in patients with CGL2 [16,59]. Adipose tissue and leptin deficiency also lead to consequences on the renal and cardiovascular levels: specifically, in patients with GL, from the nephrological point of view, proteinuria may occur, which may progress to renal failure, and later on, cardiovascular disease may develop [58]; in patients with FPLD2, on the other hand, a picture of cardiomyopathy may occur [8,43]. Leptin depletion and severe IR can impair reproductive function in female and male patients. PCOS, hyperandrogenism, and menstrual irregularity are quite common in adolescent girls with lipodystrophy [43]. In addition, specific forms of lipodystrophy such as seipin deficiency, observed in Berardinelli-Seip congenital lipodystrophy type 2 (BSCL2), can lead to specific reproductive dysfunction especially in men. In fact, Jiang et al. [62] demonstrated how seipin derived from testicular tissue, but not from adipose tissue, is critical for male fertility by regulating testicular phospholipid homeostasis [58,62]. Thus, adipocyte-specific seipin loss causes progressive lipodystrophy without any impact on fertility, whereas seipin loss in gamete cells causes complete male infertility and teratozoospermia [58,62].

Overall, these metabolic abnormalities associated with IR and hepatic steatosis are also observed in young people with FPLD [45], although more modest than in patients with CGL [43]. In contrast, in FPLD, metabolic complications are rare and prevail in adulthood [19,43].

4. Treatment options

Treatment options regarding lipodystrophy management include both those aimed at treating its complications and those used for specific metabolic problems. Therapies targeted to treat metabolic complications are distinguished according to whether they rely on the use of leptin or not and according to whether the lipodystrophy is general or partial [58], Fig. 1.

4.1. Non-leptin-based therapies

Milestones in the management of lipodystrophy include lifestyle modification, specifically diet and physical activity, oral and injectable hypoglycemic drugs, insulin, hypolipidemic drugs, and other drugs with the aim of treating lipodystrophy complications [43]: this is considered to be the standard clinical treatment of lipodystrophy [43].

The effectiveness of lifestyle modification in treating complications associated with lipodystrophy has not been clearly defined, however, adopting a well-balanced diet, exercise and avoiding recreational substances is still recommended [3,8,43,57,58]. In particular, carbohydrates, preferably whole grain, should be consumed judiciously to ensure better control of IR and diabetes; patients with severe hypertriglyceridemia should follow a low-fat diet; finally, patients are encouraged to consume dietary fiber and foods rich in omega-3 fatty acids [3]. Nevertheless, implementing dietary changes towards hypoglycemic and hypolipidemic goals is often difficult due to hyperphagia secondary to leptin deficiency [58]. Skilled dietitians can be consulted to devise an appropriate diet. Patients with lipodystrophy are lacking fat stores, thus their goal weight is expected to be dissimilar to that of ordinary patients. In particular, patients with GL commonly have protein-calorie malnutrition, but force-feeding would only worsen their metabolic status [58]. In contrast, target weight for patients with partial lipodystrophy is that for which the remaining adipose deposits can manage without leading to any ectopic accumulation [58]. Therefore, a valid standard in patients with any form of lipodystrophy is to consider as a target a lower BMI than the general healthy population [58]. It was recently reported that metabolic burden of patients with FPLD, who have asymmetrically distributed and/or reduced fat deposits, is similar to that of obese patients whose BMI is at least 8–10 points higher [68].

Among recreational substances, drinking alcoholic beverages is discouraged because of the increased risk of hypertriglyceridemia, acute pancreatitis, and hepatic steatosis; also, cigarette smoking should be avoided by patients with lipodystrophy to maintain better cardiovascular health, especially on the grounds that they are patients with dysglycemia [43]. Physical activity is recommended for the vast majority of patients with lipodystrophy; however, it should not be forgotten that patients with heart disease (such as those with CGL4, associated with exercise-induced ventricular arrhythmias, and LMNA patients with cardiomyopathy) should avoid exercise [43,59,69].

Furthermore, additional therapies are aimed at treatment of specific comorbidities, notably dyslipidemia, IR and diabetes, nonalcoholic fatty liver disease (NAFLD) and eventually cosmetic treatment and pain management.

Management of dyslipidemia and specifically hypertriglyceridemia relies on employing statins and fibrates [43]. Fish oil, rich in omega-3 fatty acids, has the potential to be used for treating hypertriglyceridemia [43]. Also, it may sometimes be necessary to combine fibrates and statins, but it should be used cautiously because of the risk of myopathy and hepatotoxicity. As a further option, where patients are non-responders to standard treatments, therapeutic apheresis is available, which can also be used when these patients are at risk of acute pancreatitis despite treatment with hypolipidemic drugs [3,43].

IR, hyperglycemia and diabetes can be treated, depending on the severity of the scenario with different categories of drugs. In particular, metformin and from thiazolidinediones (TZDs) are effective [43,70,71]: in fact, several studies have suggested that TZDs can successfully enhance metabolic profile in PL patients. However, except for troglitazone (no longer commercially available), evidence is limited for currently approved TZDs, yet they are still used in most centers for patients with PL [43,70–72]. Nevertheless, their use in GL should be undertaken with caution, as their efficacy has not been studied extensively [3,43].

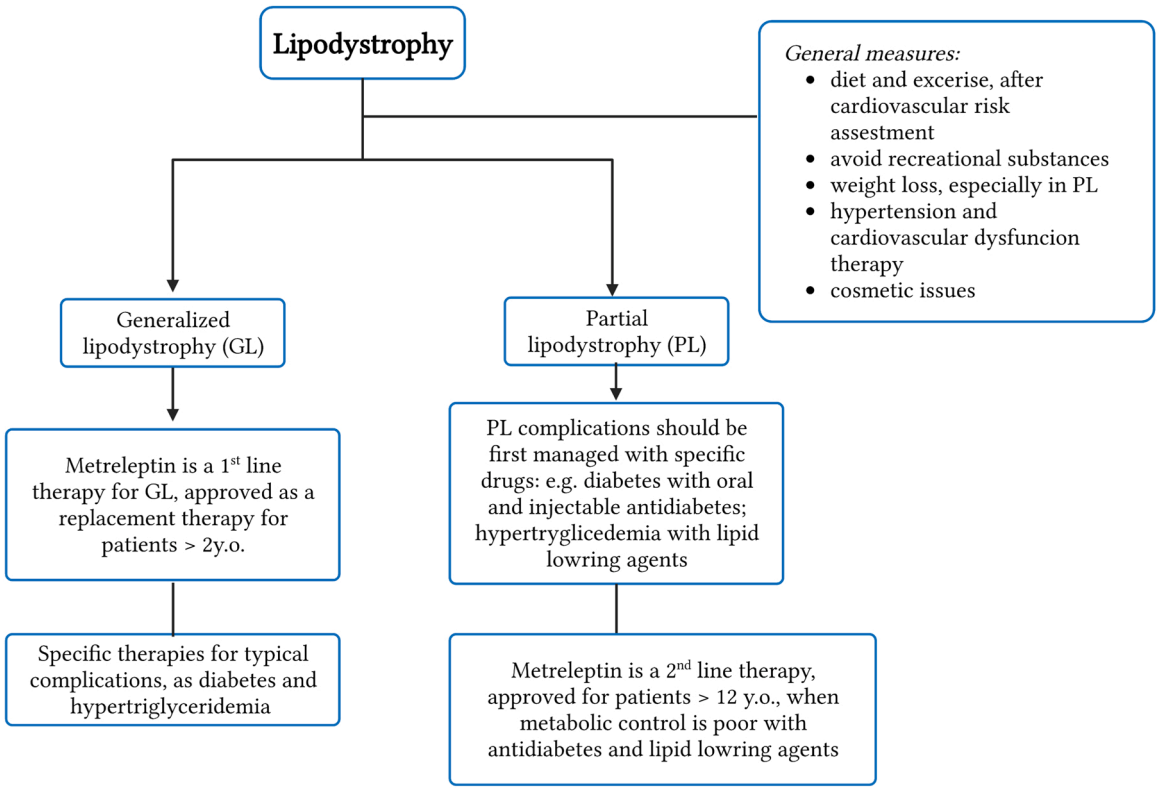

Fig. 1. Flow-chart for the treatment of pediatric patients with lipodystrophy [58]. a.

Furthermore, since diabetic patients with lipodystrophy have severe IR, most of them may need high doses and concentrated forms of insulin, such as regular insulin U-500 (five times more concentrated than standard insulin U-100) [73]. Other oral and injectable antidiabetics can be employed in lipodystrophy [74,75], but their therapeutic efficacy has not been studied [3]. Glucose sodium transporter inhibitors and GLP-1 receptor agonists might be particularly worthwhile options to investigate in PL [43,74,75]. Although these agents are used in clinical practice, a systematic evaluation of efficacy in this unique group of patients has not been conducted. Clearly, the risk of pancreatitis must be evaluated in the decision to initiate an incretin therapy.

As for treatment of lipodystrophy-related hepatopathy, a number of studies are ongoing [43]; for example, one randomized, double-blind, placebo-controlled study evaluated cholic acid, an endogenous ligand for the farnesoid X receptor (FXR). The treatment target was hepatic steatosis in patients with lipodystrophy; the drug was well tolerated but did not reduce hepatic triglyceride content or ALT, AST, and gamma-glutamyl-transpeptidase (GGT) levels [76].

Finally, patients with lipodystrophy may consider undergoing cosmetic surgery, which is especially helpful psychologically and can often provide a better quality of life. Undesirable localized fat surplus can be removed from the chin, the lower neck between the shoulders, the vulvar area, and other regions by liposuction or surgical excision. Lipoatrophic areas can also benefit from autologous adipose tissue transplantation, facial reconstruction, and implants [1,3].

As found by Strickland et al. [77], in patients with lipodystrophy developing diabetes as a complication, IR is significantly more pronounced than in diabetics without lipodystrophy, as well as hypertriglyceridemia, hepatic steatosis, which, in turn, is associated with increased hepatic transaminases. Based specifically on these clinical features, careful evaluation and aggressive therapy should be undertaken in patients with lipodystrophy for the choice and doses of antidiabetic drugs, as well as for marked hypertriglyceridemia and steatohepatitis; nevertheless, these specific treatments have recently been introduced to pediatric age groups [2]. In particular, promising results have been observed with leptin replacement therapy in patients with different types of lipodystrophy [78].

4.2. Leptin therapy

Since patients with lipodystrophy had low serum leptin levels the hypothesis of its pharmacological use has been hypothesized since the 1990 s [79]. Akinci et al. [1] carried out an early study on a small cohort of nine total patients, including eight with GL and one with FPLD, all of whom had a serum leptin level at baseline of less than 4 ng/mL [43]. Replacement therapy relies on using metreleptin, a human leptin analog realized through recombinant DNA technology by adding a methionyl group [43]. Thus, a transgenic mouse model expressing a truncated version of the nuclear protein SREBP-1c (for sterol-regulatory-element-binding protein-1c) under the control of the adipose-specific enhancer aP2 was the first model on which the use of leptin was tested. It has been shown by Shimomura et al. [80] in a mouse model mimicking the characteristics of CGL that continuous systemic infusion of low doses of recombinant leptin is able to modulate insulin resistance caused by leptin deficiency. Thereafter, in July 2000 this replacement drug was first administered to people. Overall, several studies evaluated its efficacy [1,3,43,79] showing significant improvement in multiple metabolic parameters, Fig. 2.

Specifically, Akinci et al. [1] showed an improvement in IR, with a concomitant marked reduction in HbA1c value in patients with diabetes mellitus (- 1.9% from baseline); dyslipidemia, particularly hypertriglyceridemia, was generally reduced (−60% in 4 months of treatment); concerning hepatopathy, an average 28% reduction in liver volume was observed, with a decrease also in the value of liver enzymes (alanine aminotransferase ALT and aspartate aminotransferase AST) [1,19,43]. Hyperphagia also improved with a reduction in daily caloric intake, and concomitant weight loss (observed in eight out of nine patients). In addition, on withdrawal of treatment, within 48 h, fasting

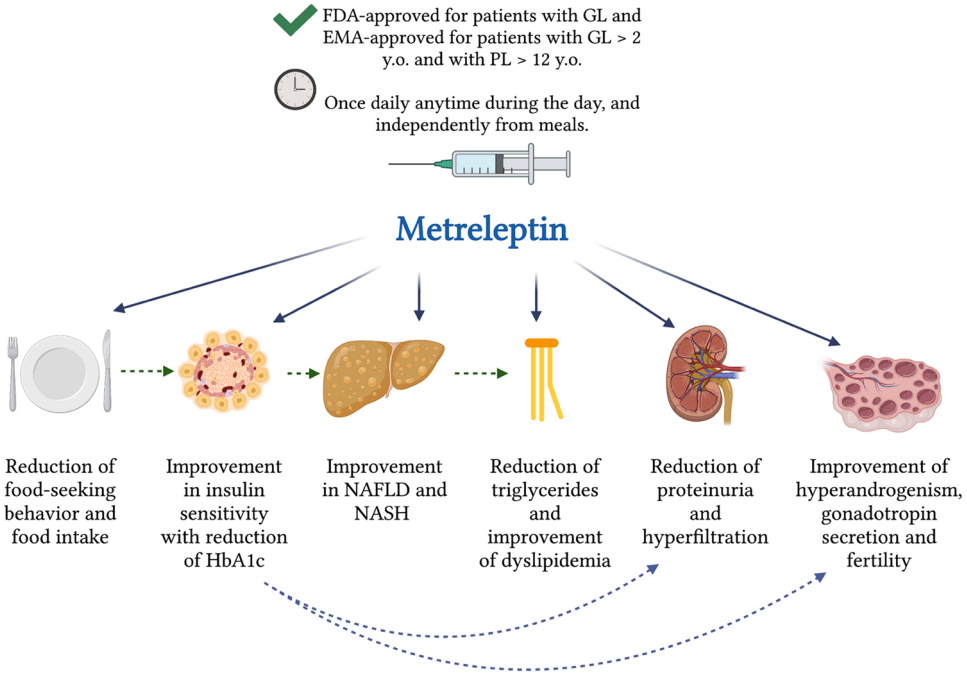

Fig. 2. Benefits of the treatment with Metreleptin [1,3,43,79].

triglyceride and insulin levels began to increase, subsequently correcting again upon reintroduction of metreleptin therapy [81]. This first study was followed by several others, which performed a long-term longitudinal follow-up, demonstrating the durable efficacy and safety of metreleptin therapy in cohorts of adults and children [42,43,82,83], confirming significant improvement in metabolic imbalances, by a marked reduction in hepatic fat and histological improvement in steatohepatitis [43,79].

In 2014, the Food and Drug Administration (FDA) approved metreleptin for the treatment of GL [84], and more recently, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) [78] granted marketing approval for metreleptin for patients with GL > 2 years of age and for patients with PL > 12 years of age not controlled with conventional therapies [43]. Furthermore, in Japan, the therapeutic use of leptin is specifically indicated in patients with congenital or acquired lipodystrophy (either generalized or partial to treat diabetes and/or hypertriglyceridemia [43]. In contrast, metreleptin is not approved for use in human immunodeficiency virus (HIV)-related lipodystrophy or in patients with metabolic diseases, such as obesity, diabetes, and hypertriglyceridemia [43,79].

Even from the first weeks after treatment with metreleptin begins, metabolic parameters in lipodystrophic patients improve [43,79,82]. Generally, patients with GL benefit most, however, PL patients also achieve improvements, but the response for this heterogeneous group of patients is less conclusive [85–87]. Nevertheless, since patients with PL are very heterogeneous, the majority of whom do not have access to or do not respond to metreleptin treatment, new therapies are being investigated.

By rebalancing the appetite-satiety circuit, food-seeking behavior and hyperphagia are reduced [79,88] and consequently weight loss is also observed [43,89]. Notably, although leptin's main target for appetite regulation is leptin-specific receptors located at the hypothalamic level [90], Brown et al. [91] showed that it also improves peripheral and hepatic insulin sensitivity [43,91].

In IR and diabetes mellitus, metreleptin improves peripheral glucose disposal, so fasting blood glucose value is reduced as well as hepatic gluconeogenesis degree [79,91,92]; studies claim that within one year of treatment HbA1c decreases by 2% in GL patients [85]. In addition, metreleptin also improves insulin secretion [43,81].

Metreleptin also acts on dyslipidemia and hypertriglyceridemia; in fact, within a few weeks of treatment initiation, triglycerides decrease, eventually reducing by about 60% within the first year [85,93]; it is also effective, albeit to a lesser extent, on total cholesterol and LDL cholesterol levels, but not HDL [79,81,82].

This replacement therapy also acts on hepatopathy: in both children and adults it improves both hepatic steatosis and the degree of nonalcoholic steatohepatitis (NASH), reduces liver volume, lowers liver enzymes, and causes no progression of liver fibrosis [81,85–87,92,94].

Kidney also benefits from this treatment: patients with lipodystrophy generally have proteinuria and hyperfiltration, which are lowered with metreleptin use [43,95].

Metreleptin normalizes gonadotropin secretion, improving fertility [96,97]; in women with lipodystrophy and PCOS, metreleptin administration regularizes androgen hormone secretion [98].

Its use in pregnancy to date has been investigated only in animal studies, and these have indicated that, even at very high doses, it is not teratogenic because feto-placental passage is minimal [43]; however, the effects of metreleptin during pregnancy and on labor and delivery are not known in humans. This drug is not yet approved in pregnancy; however, several pregnancies have been carried to term in patients with lipodystrophy on metreleptin therapy with no evidence of teratogenicity [99,100].

Metreleptin can be administered once daily anytime during the day, and independently from meals. Recommended initial dosage is 5 mg/day (1 mL) in females weighing > 40 kg, 2.5 mg/day (0.5 mL) in males weighing > 40 kg, and 0.06 mg/kg/day (0.012 mL/kg/day) in males and females weighing ≤ 40 kg; The dose can be modified by 1.25–2.5 mg/day (or 0.02 mg/kg) with a maximum dose of 10 mg/day (or 0.13 mg/kg/day) [43,78,84]. There is no lower or upper age limit for the initiation of metreleptin administration in the United States, although in Europe there is marketing authorization for metreleptin for patients with GL > 2 years of age and for patients with PL > 12 years of age [78,84]. Particular attention should be paid to elderly patients, who are more likely to have renal, hepatic, and cardiac comorbidities and receive concomitant treatments. In addition, few patients aged > 65 years have been enrolled in clinical trials, so few reliable data on

response and side effect profile are available [43]. Therefore, starting metreleptin at the low end of the dosing interval would be a good strategy in elderly patients [43].

Generally, side effects are mild to moderate [79]: injection site reactions are the most common side effect, then comes hypoglycemia, which is related to improved insulin action and preventable by reduction or discontinuation of antidiabetic drugs, including insulin. As metreleptin administration has pleiotropic consequences, including lowering dyslipidemia, dose and need for specific dyslipidemia medications should be reevaluated during this therapy, monitoring serum cholesterol and triglycerides and both avoiding to leave this condition untreated, otherwise it may progressively worsen, and even to overtreat it. In addition, special caution should be taken when discontinuing metreleptin, as acute discontinuation of therapy could trigger acute pancreatitis [43,101].

It is good to monitor renal and hepatic function during treatment because, although they usually benefit from this treatment, it has happened that patients with AGL with distinct autoimmune conditions had worsening renal and hepatic parameters during treatment [93,95].

Rare but noteworthy are two other important adverse events: neutralizing antibody formation and the development of T-cell lymphoma. Although metreleptin antibodies have been observed over time in a substantial number of patients with lipodystrophy treated with metreleptin, in vivo neutralizing antibodies against metreleptin have been reported in a small number of patients [102,103]. These can potentially affect the biological activity of exogenous and endogenous leptin, causing worsening of metabolic control [100,102]. T-cell lymphoma was reported in three patients with AGL treated with metreleptin [104,105]: some authors attributed the origin of the lymphoma to autoimmunity and immunodeficiency, others associated it with the natural history of the disease [43,104,105].

4.3. Other therapeutic strategies

After the successful introduction of metreleptin for the treatment of GL, current research is now focusing on patients with PL. Indeed, although metreleptin therapy was shown to be beneficial in patients with GL, the same results have not been shown in PL patients [2]. Thus, new therapeutic strategies are currently being investigated. Specifically, liver-targeted therapies, agents acting on hepatic metabolism and other medications are under development for patients with PL forms [2,106].

5. Conclusions

Milestones in the management of lipodystrophy unrelated to inappropriate insulin injection habits include lifestyle modification as diet and physical activity, paired with hypoglycemic drugs, insulin, hypolipidemic drugs, and other drugs with the aim of treating lipodystrophy complications. Each patient benefits from these general measures. Patients with GL (>2 years) should be treated with metreleptin, as replacement therapy in order to correct metabolic alterations. If this first strategy fails, specific drugs such as insulin or statins can be added. On the other hand, PL patients (>12 years) are at first treated with specific drugs, and, if metabolic control is poor, metreleptin is added as second-line therapy to address metabolic complications. Therefore, treatment of lipodystrophies must be multidisciplinary and management approach must include its various complications. New therapeutic strategies are currently being investigated, especially for patients with PL forms. Specifically, liver-targeted therapies are under development for patients with PL forms. There is still much to be learned about management, support and therapy optimization of patients with lipodystrophy. Thus, further studies are needed to achieve the most specific and precise treatment possible.

CRediT authorship contribution statement

V.C., V.C.M., V.R.: Conceptualization. **V.C., V.C.M., V.R., V.F., C. M., G.Z.**: Methodology. **V.C.M., V.R.**: Investigation. **V.C., V.C.M., V. R., V.F., C.M.**: Writing – original draft. **V.C., V.F., C.M., G.Z.**: Writing – review & editing. **V.C., G.Z.**: Supervision. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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