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PATHOGENESIS OF TYPE 2 DIABETES AND INSULIN RESISTANCE (M-E PATTI, SECTION EDITOR)

Update on Therapeutic Options in Lipodystrophy

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Abstract

Purpose of Review The purpose of this review is to summarize the therapeutic approach for lipodystrophy syndromes with conventional treatment options and metreleptin therapy in detail and to point out the current investigational treatments in development.

Recent Findings The observation of leptin deficiency in patients with lipodystrophy and the potential of leptin replacement to rescue metabolic abnormalities in animal models of lipodystrophy were followed by the first clinical study of leptin therapy in patients with severe lipodystrophy. This and several other long-term studies demonstrated important benefits of recombinant human leptin (metreleptin) to treat metabolic abnormalities of lipodystrophy. These studies ultimately led to the recent FDA approval of metreleptin for the treatment of generalized lipodystrophy and EMA approval for both generalized and partial lipodystrophy. Additional research efforts in progress focus on novel treatment options, predominantly for patients with partial lipodystrophy.

Summary Current treatment of generalized lipodystrophy includes metreleptin replacement as an adjunct to diet and standard treatment approach for metabolic consequences of lipodystrophy. Beyond metreleptin, a number of different compounds and treatment modalities are being studied for the treatment of partial lipodystrophy.

Keywords Generalized lipodystrophy · Investigational treatments · Leptin · Partial lipodystrophy

Introduction

Patients with lipodystrophy present with a highly challenging constellations of diabetes, insulin resistance, and lipid abnormalities [1, 2]. Although different genes are involved in lipodystrophy, and the patients with pathogenic variants in the same gene can show marked phenotypic heterogeneity, most patients share common metabolic consequences of severe insulin resistance which can progress to difficult-to-control diabetes and its complications, marked hypertriglyceridemia which can lead to episodes of acute pancreatitis, and severe hepatic steatosis [3, 4].

In an accompanying article in this issue, we reviewed various lipodystrophy diseases, prevalence, typical presentations, comorbidities, mortality, and pathophysiological mechanisms. Here, we review the standard treatment approach, how metreleptin therapy should be utilized, and current investigational approaches.

Standard Approach

The standard clinical treatment of lipodystrophy (summarized in Table 1) includes lifestyle modification, the use of oral and injectable diabetes medications and insulin (also includes concentrated formulations), lipid-lowering drugs, and other medications to treat complications of lipodystrophy.

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Table 1 A summary of standard treatment approach to lipodystrophy

Condition requiring treatment	Treatment agent	Efficacy (evidence base for efficacy)	References
Abnormal physical appearance	Cosmetic surgery	Fillers for fat loss with temporary efficacy on face (case reports, expert opinion) Liposuction and lipectomy: moderately effective in correcting hypertrophic depots, should be coupled with caloric restriction (expert opinion)	[5•, 6•]
Hyperphagia	Caloric restriction	May be effective if patients can sustain for long periods of time (anecdotal evidence, expert opinion)	[5•, 7–16]
	Appetite suppressants	Unknown	
	Bariatric surgery	Effective in improving metabolic complications (case series)	
Insulin resistance and/or diabetes	TZDs	Effective in lowering HbA1c in PL (open-label clinical study for troglitazone, case reports).	[5•, 17–21••, 22–28]
	Metformin	Limited efficacy in lowering HbA1c in GL and PL, commonly used (expert opinion)	
	DPP4 inhibitors	Limited efficacy in lowering HbA1c in GL and PL (expert opinion)	
	GLP-1 agonists	May be effective in lowering HbA1c in GL and PL, and other beneficial effects may be possible. Consideration is needed for pancreatitis risk (case series, expert opinion)	
	SGTL2 inhibitors	May be effective in lowering HbA1c, may help lower triglycerides and hepatic steatosis (case reports, expert opinion)	
	Insulin	Moderately effective in lowering HbA1c, large doses and concentrated forms may be needed (expert opinion)	
	SUs	Limited efficacy in lowering HbA1c (expert opinion)	
Hypertriglyceridemia	Statins	No systemic studies. Most patients are prescribed. High level of intolerance (expert opinion)	[5•, 29, 30]
	Fibrates	No systemic studies. Most patients are prescribed. High level of intolerance (expert opinion)	
	Fish oil	No systematic studies. Patients are prescribed	
	TZDs	May lower levels of triglycerides (open-label clinical study for troglitazone, case reports)	
	Therapeutic plasma exchange	Efficient in treating or preventing pancreatitis (case reports, expert opinion)	
PCOS	Metformin	No systematic studies, useful in helping with ovulation (expert opinion)	[5•, 17–21••, 22–24]
	TZDs	May help lower androgen levels (Open-label clinical study for troglitazone, case reports).	
Fatty liver disease	Cholic acid	Not effective (double-blind placebo-controlled study)	[32]

DPP4 dipeptidyl peptidase 4, *GL* generalized lipodystrophy, *GLP-1* glucagon-like peptide-1, *PCOS* polycystic ovary syndrome, *PL* partial lipodystrophy, *SGLT2* sodium/glucose cotransporter 2, *SU* sulfonylurea, *TZDs* thiazolidinediones

Diet and Exercise

Although the precise efficacy of diet and exercise for the treatment of diseases associated with lipodystrophy is not clear, a balanced macronutrient composition is generally recommended [5•, 7, 8]. Patients with severe hypertriglyceridemia are asked to follow a low-fat diet. Carbohydrate restriction can help control diabetes and help reduce hypertriglyceridemia. Patients are encouraged to consume dietary fiber and foods rich in omega-3 fatty acids [5•]. Alcohol consumption is not recommended because of the risk of hypertriglyceridemia, acute pancreatitis, and hepatic steatosis. Like all patients with dysglycemia, patients with lipodystrophy should be advised to avoid smoking to maintain a better cardiovascular health. Although most patients with lipodystrophy are advised to be physically active, patients with cardiac problems (such as CGL4 which is associated with exercise-induced ventricular arrhythmias and *LMNA* patients with cardiomyopathy) should avoid exercise [9, 10].

Treatment of Hyperlipidemia

High levels of lipids are usually treated with statins and fibrates [29, 30]. Fish oil, rich in omega-3 fatty acids, can be used to treat hypertriglyceridemia. Combination of fibrates with statins may be needed, but should be used with caution because of the risk for myopathy and hepatotoxicity. Therapeutic apheresis is an option in patients with extreme

hypertriglyceridemia unresponsive to other treatments or when they are at risk of acute pancreatitis despite treatment with lipid-lowering medications [5•].

Treatment of Diabetes

Patients with diabetes may benefit from metformin and thiazolidinediones (TZDs) [17–21••, 22]. Several studies suggested that TZDs may improve metabolic profile in patients with PL; however, apart from troglitazone (no longer available), evidence is limited for currently approved TZDs, but TZD continue to be used in most centers for patients with PL [19, 21••, 22–24]. However, the use in GL should be undertaken cautiously, as their efficacy has not been studied extensively [5•, 21••]. Given that patients have severe insulin resistance, most patients may need large doses and concentrated forms of insulin, such as U-500 regular insulin (five times more concentrated than standard U-100 insulin). While U500 is regular insulin, its pharmacokinetic profile is more similar to NPH [25], allowing patients to inject U-500 twice or three times daily. Other oral and injectable antidiabetics can be used in lipodystrophy [26–28], but their efficacy has not been studied [5•]. Sodium glucose transporter inhibitors [28] and GLP-1 receptor agonists [26, 27] may be particularly attractive agents to study in PL. While these agents are being used in clinical practice, no systematic evaluation of efficacy in this unique group of patients has been conducted. Of course, the risk of pancreatitis should be weighed in the decision to start incretin-based therapies.

Other

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 the chin, around the lower back of the neck between the shoulders, vulvar and other regions by liposuction or surgical excision. Lipoatrophic areas may also benefit from autologous adipose tissue transplantation, facial reconstruction, and implants [5•, 6].

Leptin

The Road to Leptin Replacement in Patients with Lipodystrophy

In the late 1990s, the observation that some of the patients with lipodystrophy had low leptin levels allowed to hypothesize that leptin replacement would be a promising option for patients with lipodystrophy [31]. Moreover, the Brown and Goldstein lab demonstrated remarkable metabolic efficacy of leptin in mice with lipodystrophy [33]. This ultimately led our team (in a collaborative study between NIDDK and the UT Southwestern at Dallas) to initiate an open-label, prospective, phase II study in a small cohort of nine patients of severely affected with lipodystrophy. The study was designed as a two-center, open-label, proof-of concept study. Eight patients had GL and one patient had FPLD, and all patients had baseline serum leptin level of less than 4 ng/ml. The first patient received the first dose of leptin in July 2000. A significant decrease in HbA1c was observed (1.9%) in eight of the nine patients who had diabetes. The insulin tolerance test showed a significant improvement in whole-body sensitivity to insulin. Triglyceride levels decreased by 60% after 4 months of metreleptin treatment. Liver volume decreased by an average of 28%, and levels of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) declined. The daily caloric intake decreased in parallel with a decrease in the resting metabolic rate. All but one patient lost weight with an important fraction of the weight loss mostly attributed to the decrease in liver volume. When treatment was discontinued, fasting triglyceride and insulin levels began to increase within 48 h, which was corrected by the resumption of metreleptin therapy [31••].

Metreleptin is an analog of human leptin made through recombinant DNA technology with an added methionyl group. Longer-term longitudinal follow-up subsequently demonstrated the sustained efficacy of metreleptin therapy in cohorts of both adults and children [34–36]. The response to metreleptin replacement across many of these studies was characterized by a significant amelioration of the metabolic derangements driven by insulin resistance and a marked reduction in hepatic fat and histologic improvement in steatohepatitis [31••, 37]. Based on these studies, metreleptin was approved by the Food and Drug Administration (FDA) in 2014 for treatment of GL (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm387060.htm). Very recently, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for metreleptin for patients with GL > 2 years of age and for PL patients > 12 years of age not controlled on conventional therapies (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004218/WC500249804.pdf) followed by official approval in the European Union and the United Kingdom (UK) on July 31, 2018 (https://www.businesswire.com/news/home/20180731005522/en/Aegerion%E2%80%99s-Myalepta%C2%AE%E2%96%BC-Approved-Europe-Treatment-Patients-Ultra-Rare). Leptin replacement therapy is also approved in Japan as a therapy indicated specifically for the treatment of diabetes and/or hypertriglyceridemia in patients with congenital or acquired lipodystrophy (both generalized and partial) (http://www.shionogi.co.jp/en/company/news/2013/pmrltj0000000ufd-att/e_130325.pdf). On the other

hand, 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. Patients may access metreleptin through compassionate use programs and other regulatory mechanisms in certain other countries (Turkey, other countries in the Middle East, and Northern Africa, etc.).

The Effects of Metreleptin Treatment

The metabolic effects of metreleptin in GL can be observed in several weeks after the treatment. Hyperphagia improves shortly after the treatment with metreleptin [31••, 38–40]. Food-seeking behavior and related neural activity diminish, and satiety is restored [41–43]. The decrease in appetite can lead to weight loss but it usually stabilizes after several months [39]. Fasting glucose declines as result of improved peripheral glucose disposal and both hepatic glucose output and hepatic steatosis also improve [40, 44•]. Metreleptin also improves insulin secretion [45, 46]. HbA1c decreases by 2% within the first year of metreleptin treatment in GL [47•]. Within weeks after the initiation of metreleptin, triglycerides are reduced, with a near 60% reduction in triglycerides within the first year of treatment [47•]. Metreleptin causes slight decreases in total cholesterol and LDL cholesterol levels but does not alter HDL levels [48–50]. Metreleptin therapy resulted in less dramatic and heterogeneous improvements in patients with PL, although a subset of patients with PL may benefit from metreleptin [47•, 51–53].

Metreleptin improves hepatic steatosis, decreases liver volume, lowers liver enzymes, and does not cause any progression in hepatic fibrosis [40, 44•, 54, 55]. One year treatment with metreleptin resulted in an improved nonalcoholic steatohepatitis (NASH) score in adults [56•, 57], and a significant improvement in the nonalcoholic fatty liver disease (NAFLD) score in children [58]. Metreleptin was used with success in GL after liver transplantation to achieve rapid clearance of fat from the liver and normalization of histology [59].

Although the primary function of leptin is the regulation of appetite through an interaction with specific leptin receptors located in the hypothalamus [60], metreleptin also improves insulin sensitivity independent of food intake [61•]. In a very recent study, Brown et al. [61•] showed that metreleptin increased peripheral and hepatic insulin sensitivity, decreased fasting glucose and triglycerides, and decreased liver fat content in patients with lipodystrophy whose food intake were held constant by controlled diet in an inpatient metabolic ward setting.

Metreleptin also improves proteinuria and hyperfiltration, both of which are commonly present in patients with lipodystrophy [40, 62]. Metreleptin normalizes gonadotropin secretion and improves fertility [40, 63•, 64, 65]. Androgen levels decrease after metreleptin in lipodystrophic women with PCOS [66]. Since leptin had important neuroendocrine and immunoregulatory functions in rodents with leptin deficiency, these aspects were studied in the earlier cohorts of patients [63•, 67], demonstrating a baseline subtle defect in T cell populations and in cytokine secretory capability, followed by recovery upon leptin replacement [67].

Although animal studies indicate that metreleptin is not teratogenic even at very high doses and placental transfer of metreleptin into the fetus was low, the effects of metreleptin during pregnancy, and on labor and delivery are not known in humans. Although there are no adequate and well-controlled studies of metreleptin in pregnant women and it is not approved in pregnancy (pregnancy category C), several pregnancies have occurred in patients with lipodystrophy while they were on metreleptin without any evidence for teratogenicity [68, 69]. It is also not known if metreleptin is present in human milk though endogenous leptin is known to be present in human milk (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125390s000lbl.pdf). Figure 1 summarizes the clinical effects of metreleptin in patients with lipodystrophy. Data on quality of life and mortality in response to metreleptin are beginning to emerge (unpublished results from a global collaboration).

The Clinical Use of Metreleptin in Patients with Lipodystrophy

Metreleptin is administered as a daily subcutaneous injection. Metreleptin can be administered once daily at any time of day regardless of meals (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125390s000lbl.pdf). Several studies show that leptin (0.04 to 0.08 mg/kg/day by subcutaneous injection) in patients with GL results in significant efficacy on appetite, resting energy expenditure, and metabolic parameters [37].

Currently, the recommended starting daily dose is 5 mg (1 ml) in females greater than 40 kg, 2.5 mg (0.5 ml) in males greater than 40 kg and 0.06 mg/kg (0.012 mL/kg) in males and females less than or equal to 40 kg. The dose can be adjusted 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). The maximum dose is a practical ceiling dictated by vial size rather than known toxicity. Metreleptin should be reconstituted with preservative-free sterile water for injection in pediatric patients, particularly in neonates and premature infants (not with bacteriostatic water which contains benzyl alcohol) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125390s000lbl.pdf) (https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm388903.pdf).

There is no lower or upper age limit for initiation of metreleptin in the US, although marketing authorization of metreleptin is in effect for patients with GL > 2 years of age and for patients with PL > 12 years in Europe. In the US, no

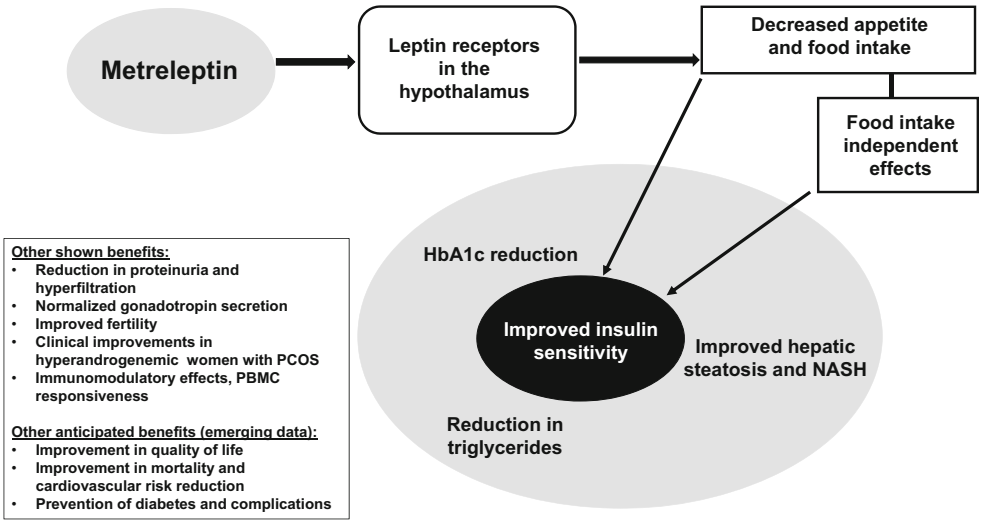

Fig. 1 The mechanism of action and clinical effects of metreleptin therapy in patients with lipodystrophy. PBMCs, peripheral blood mononuclear cells

specific degree of metabolic abnormality is required, as long as the diagnosis of GL can be substantiated. Special attention should be taken for elderly patients as they have greater likelihood of having impaired kidney, liver, and cardiac function, and may have other concomitant diseases and treatments. Moreover, few patients over age 65 were enrolled in clinical trials, so robust response and side effect profile data are not available. Thus, starting metreleptin at the low end of the dosing range would be a good strategy in elderly patients.

In the US, providers are required to complete a certification of Risk Evaluation and Mitigation Strategy (REMS) program to be able to prescribe metreleptin (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=314). Prescribers must be certified with the program by enrolling and completing training before prescribing metreleptin. In the US, there is a single distributor pharmacy as mandated by the REMS program. All prescriptions reach this pharmacy and the drug is distributed through the infrastructure of this pharmacy.

Adverse Events and Safety Issues with Metreleptin

Side effects are not rare but usually mild to moderate during metreleptin treatment [48]. Injection site reactions are the most common side effect. Hypoglycemia can develop during metreleptin because of improved insulin action and may be prevented by reducing or stopping antidiabetic medications including insulin. The dose and need of lipid-lowering should be reevaluated after metreleptin. Also, extra caution should be taken when withdrawing metreleptin as acute cessation of the therapy might trigger acute pancreatitis [48, 70]. Patients with lipodystrophy mostly benefit from metreleptin with regard to kidney and liver function; however, several cases, including AGL patients with distinct autoimmune conditions, showed worsening of renal and hepatic parameters during treatment [62, 71]. Therefore, kidney and liver function should be monitored during therapy. It should be also noted that no formal pharmacokinetic studies were conducted in patients with renal or hepatic impairment. Although renal clearance is thought to be the major route of metreleptin elimination without any breakdown into its metabolites, no formal metabolism studies have been conducted with metreleptin (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125390s000lbl.pdf). No effect of metreleptin therapy on bone mineral density and content and bone metabolism has been reported [54, 72, 73] .

Two important adverse events linked to metreleptin are neutralizing antibody and T cell lymphoma development. Although metreleptin antibodies were observed in a substantial number of patients with lipodystrophy treated with metreleptin, in vivo neutralizing antibodies to metreleptin have been reported in a small number of patients [74, 75]. Neutralizing antibodies may have the potential to influence the biological activity of both exogenous and endogenous leptin, and such neutralizing antibodies may be associated with worsening of metabolic control [69, 74]. In addition, two patients with neutralizing antibody formation were reported to develop severe infections around the time of detection of neutralizing antibody [74]. T cell lymphoma has been reported in three patients with AGL treated with metreleptin [76•], and we are aware of two others. Previous reports before the introduction of metreleptin described the development of lymphoma in patients with acquired lipodystrophy, which was attributed to autoimmunity and immunodeficiency [76•, 77]. It is currently thought that lymphoma development in acquired lipodystrophy is more likely to be associated with the natural history of the disease rather than being a treatment effect associated with metreleptin. There is also recent emerging data suggesting that papillary thyroid cancer may be observed more frequently in patients with insulin resistance than what is seen in the general population [78, 79]. Although several centers are observing a similar trend in patients with

lipodystrophy, its association with leptin therapy remains to be sorted out (unpublished observations).

Other Treatment Strategies for Lipodystrophy Syndromes

Bariatric Surgery and Other Forms of Caloric Restriction

The imbalance between the intake of calories and capacity to store excess energy indicated the need for reduced caloric intake to maintain metabolic balance in lipodystrophy. Bariatric surgery has been one the most effective treatments for patients with obesity, type 2 diabetes and hyperlipidemia, independent of weight loss [11, 12]. These findings led to an early investigation of Roux-en-Y gastric bypass (RYGB) in patients with FPLD, which resulted in both significant weight loss and metabolic improvement [13–15]. RYGB led to the discontinuation of insulin treatment in a series of three patients with FPLD1 [13]. RYGB was also performed in several patients with FPLD2, which was associated with substantial metabolic improvements and significant weight loss [15, 16]. However, no long-term effects of metabolic surgery have been reported yet and no systematic studies comparing the effects of caloric reduction versus bariatric surgery have been undertaken.

Insulin-Like Growth Factor-1

Insulin-like growth factor-1 (IGF-1) has highly similar sequence homology to insulin. IGF-1, at supraphysiological doses, can lower blood glucose similar to insulin [80]. The use of IGF-1 has been shown to be effective in maintaining glycemic control in two patients with CGL [81–83]. However, long-term potential unfavorable effects of IGF-I, such as hypertrophy of lymphoid tissue, water retention with soft tissue swelling, increased intracranial pressure, and potential mitogenic effects have restricted its clinical use for lipodystrophy [84–86].

Cholic Acid

A randomized, double-blind, placebo-controlled, crossover study evaluated cholic acid, an endogenous ligand for the farnesoid X receptor (FXR), for the treatment of hepatic steatosis in patients with lipodystrophy. The drug was well tolerated but did not reduce hepatic triglyceride content or levels of ALT, AST, and gamma-glutamyl transpeptidase (GGT) [32].

Investigational Treatments in Lipodystrophy

After the successful introduction of metreleptin for the treatment of GL, most of the current research efforts have been focused on patients with PL. Studies suggest that some patients with PL may also benefit from metreleptin; however, the response is less clear for this heterogeneous group of patients [47•, 51–53]. Retrospective evaluation of the databases from the long-term metreleptin studies suggest that patients with partial lipodystrophy who have moderately to severely low leptin and significant baseline metabolic abnormalities are more likely to benefit from metreleptin [47•, 51]. Current efforts are aimed at understanding subtypes of partial lipodystrophy, which may be associated with response to therapy. Given that most patients with partial lipodystrophy either have no access to metreleptin treatment or do not respond to metreleptin, novel therapies are currently being investigated. Disease heterogeneity and lack of precise diagnostic criteria are major obstacles to novel therapeutic development in partial lipodystrophy.

Liver-Specific Treatment Strategies Under Development for FPLD

Genomic studies in patients with lipid abnormalities have uncovered multiple circulating factors originating from the liver that may play a key role in the regulation of lipid metabolism, steatosis, and insulin sensitivity. A number of therapeutic agents have been developed to manipulate these liver-specific secreted proteins (Fig. 2).

Volanesorsen

Volanesorsen is a second-generation antisense oligonucleotide drug targeted to human apoC-III. As a component of triglyceride-rich lipoproteins and a potent inhibitor of lipoprotein lipase, ApoC-III is a major regulator of plasma triglyceride levels (Fig. 2) [87]. The FDA granted orphan drug designation to volanesorsen for the treatment of patients with familial chylomicronemia syndrome (https://www.prnewswire.com/news-releases/akcea-therapeutics-receives-orphan-drug-designation-from-the-us-fda-for-volanesorsen-isis-apociii-rx-for-the-treatment-of-familial-chylomicronemia-syndrome-300108774.html). Volanesorsen was reported to be associated with a mean triglyceride reduction of over 70% from baseline in the phase 3 clinical trials [88, 89]. The BROADEN study recruited patients with partial lipodystrophy and hyperglyceridemia. The effect and safety profile of volanesorsen in this patient population are expected to be reported in the second quarter of 2019 (ClinicalTrials.gov Identifier: NCT02527343), and an open-label extension study is ongoing (ClinicalTrials.gov Identifier: NCT02639286).

Evinacumab and Antisense Oligonucleotides Targeting ANGPTL3

Angiopoietin-like 3 (ANGPTL3) increases plasma levels of triglycerides, LDL cholesterol, and high-density lipoprotein

(HDL) cholesterol [90]. Evinacumab, a human ANGPTL3-blocking antibody, has been shown to lower cholesterol and triglyceride levels (Fig. 2) [91, 92]. The FDA granted breakthrough therapy designation status to evinacumab for the treatment of hypercholesterolemia in patients with homozygous familial hypercholesterolemia (https://www.prnewswire.com/news-releases/regeneron-announces-evinacumab-has-received-fda-breakthrough-therapy-designation-for-homozygous-familial-hypercholesterolemia-hofh-300435044.html). A new FPLD clinical study using antisense oligonucleotides against ANGPTL3 to treat hyperlipidemia is in progress (ClinicalTrials.gov Identifier: NCT03514420).

Other Agents Working on Hepatic Lipid Metabolism

Gemcabene

Gemcabene is a monocalcium salt of a dialkyl ether dicarboxylic acid, which enhances the clearance of very low-density lipoprotein cholesterol via the reduction of hepatic apolipoprotein C-III mRNA, blocks the overall production of hepatic triglyceride and cholesterol synthesis, and increases HDL cholesterol (Fig. 2) [93]. Gemcabene also has anti-inflammatory properties [94]. In clinical studies, gemcabene has shown to lower triglycerides by 20–50%, depending on dose and severity of hypertriglyceridemia, increase HDL cholesterol, reduce LDL cholesterol by 17–21% when added to a statin, and to reduce hsCRP levels up to 50% [95, 96]. Gemcabene may have utility in hypertriglyceridemia of FLPD and ultimately in the prevention or treatment of NASH in these patients. The Gemcabene FPLD clinical study is ongoing (ClinicalTrials.gov Identifier: NCT03508687).

Obeticholic Acid

Obeticholic acid is a selective farnesoid X receptor agonist, which may offer therapeutic possibilities for hepatic steatosis (Fig. 2); a clinical study is ongoing (ClinicalTrials.gov Identifier: NCT02430077).

Agents Under Investigation for Other Forms of PL

Setmelanotide

Setmelanotide, a melanocortin-4 receptor agonist, has been used in a single patient with partial lipodystrophy associated with leptin deficiency who had refractory hypertriglyceridemia leading to recurrent bouts of pancreatitis (ClinicalTrials.gov Identifier: NCT03262610). This study is not yet reported.

Baricitinib

Baricitinib is an inhibitor of Janus kinases 1 and 2 (JAK1/2) [97]. A compassionate use treatment protocol is available for treatment of several rare autoinflammatory syndromes

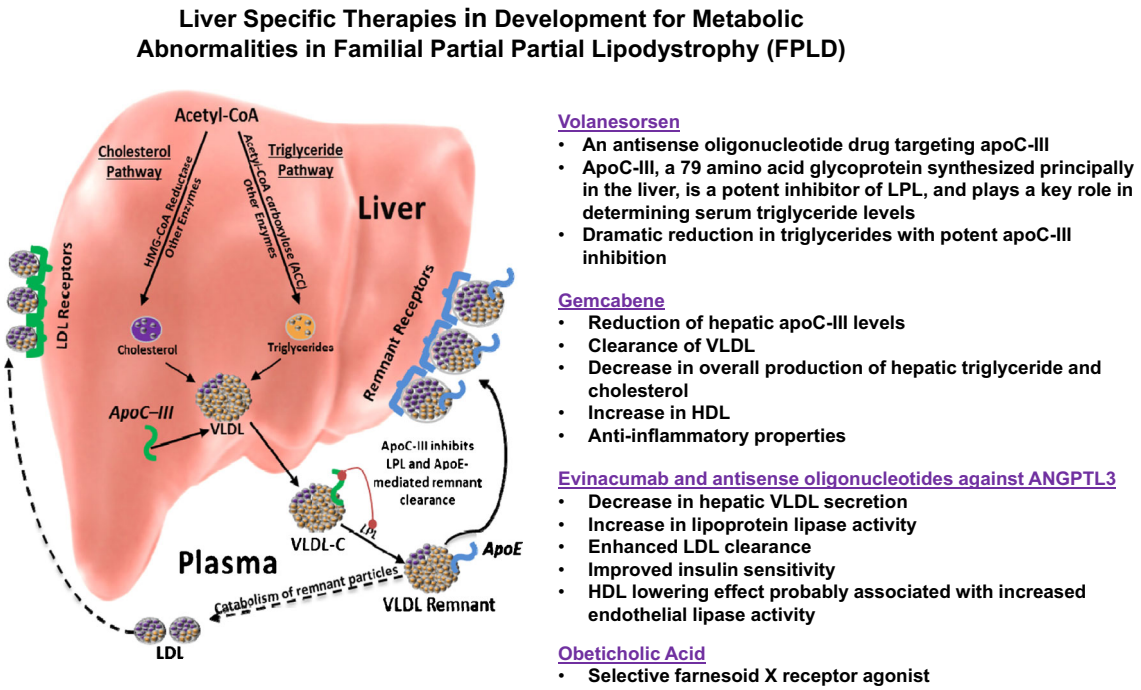

Fig. 2 The proposed mechanism of action of three different liver-focused treatment classes currently under investigation in patients with familial partial lipodystrophy. ApoE, apolipoprotein E; ANGPTL3, angiopoietin-like 3; ApoC-III, Apolipoprotein C-III; HDL, high-density lipoprotein, HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein

associated with lipodystrophy, such as CANDLE syndrome (ClinicalTrials.gov Identifier: NCT01724580) [98]. The first set of results from this trial indicate a positive effect, with improvement in both clinical manifestations and inflammatory and IFN biomarkers in patients with CANDLE, and other monogenic interferonopathies [98].

What Is on the Horizon?

In addition to the therapies already mentioned and under investigation, there may be potential for other endocrine and liver-specific therapies. A very recent study reported that a controlled-release mitochondrial protonophore, a liver-targeted mitochondrial uncoupling agent, reversed hypertriglyceridemia, nonalcoholic steatohepatitis, and diabetes in lipodystrophic mice [99].

An important area deserving special attention is the communication between the bone marrow and adipose tissue. There are circulating mesenchymal stem cells (MSC) that originate either from the bone marrow or other sources. There appears to be a tight-linked communication between the nutritional status and the MSC pool. We are now learning that rapid weight loss or weight gain can signal back to this pool to determine if there is a need to make new stem cells or reduce the pool [100–102]. Accurate mapping of the players for this communication may identify novel therapeutic targets for lipodystrophy syndromes. In addition, the status of the MSCs and the adipogenic potential as well as the alterations due to the specific gene defects leading to lipodystrophy syndromes are not well studied.

Ultimately, the advances in CRISPR/Cas technology may lead to definitive cure of rare metabolic diseases and lipodystrophy syndromes may represent the "low hanging fruit" as this technology becomes clinically applicable.

Conclusions

The treatment of metabolic abnormalities associated with lipodystrophy is challenging. Adequate metabolic control cannot be achieved in most patients through the combination of standard treatments. Metreleptin, a recombinant methionylated analog of human leptin, is an approved therapy for patients with GL in the US and for both generalized and partial forms of the diseases in Europe. Most patients with GL benefit from leptin replacement and there may be subsets of patients within the PL spectrum who may also benefit from therapy. As we understand the central and peripheral pathways governing glucose and lipid metabolism in humans and uncover novel mechanisms leading to lipodystrophy syndromes, we will likely continue to find new lessons of nature hiding within the patients presenting with selective fat loss.

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Compliance with Ethical Standards

Conflict of Interest Baris Akinci has attended Scientific Advisory Board Meetings organized by Aegerion Pharmaceuticals, and has received honoraria as a speaker from AstraZeneca, Lilly, MSD, Novartis, Novo Nordisk, Boehringer-Ingelheim, Servier, and Sanofi-Aventis.

Rasimcan Meral declares that he has no conflict of interest.

Elif Arioglu Oral reports the following conflicts: grant support: Aegerion Pharmaceuticals, Ionis Pharmaceuticals, Akcea Therapeutics, Gemphire Therapeutics (current), GI Dynamics, AstraZeneca (past 2 years). Consultant or advisor: AstraZeneca and BMS (Past), Thera Therapeutics, Regeneron, Aegerion (current). Drug support: Aegerion Pharmaceuticals, Akcea Therapeutics, Rhythm Pharmaceuticals. Other support: Boehringer-Ingelheim (past 2 years) and Aegerion Pharmaceuticals (current). She also has two patents: one patent is currently with Aegerion for the use of metreleptin for the treatment of lipodystrophy syndromes (issued and licensed, but she has not received any royalties, they go to the NIH), and the second patent is for the use of metreleptin for the treatment of NASH.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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