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Review

Fatty liver in lipodystrophy: A review with a focus on therapeutic perspectives of adiponectin and/or leptin replacement

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ABSTRACT

Lipodystrophy is a group of clinically heterogeneous, inherited or acquired, disorders characterized by complete or partial absence of subcutaneous adipose tissue that may occur simultaneously with the pathological, ectopic, accumulation of fat in other regions of the body, including the liver. Fatty liver adds significantly to hepatic and extra-hepatic morbidity in patients with lipodystrophy. Lipodystrophy is strongly associated with severe insulin resistance and related comorbidities, such as hyperglycemia, hyperlipidemia and nonalcoholic fatty liver disease (NAFLD), but other hepatic diseases may co-exist in some types of lipodystrophy, including autoimmune hepatitis in acquired lipodystrophies, or viral hepatitis in human immunodeficiency virus (HIV)-associated lipodystrophy. The aim of this review is to summarize evidence linking lipodystrophy with hepatic disease and to provide a special focus on potential therapeutic perspectives of leptin replacement therapy and adiponectin upregulation in lipodystrophy.

Contents

Abbreviations: ACC, acetyl-CoA carboxylase; AdipoR, adiponectin receptor; AGL, acquired generalized lipodystrophy; AGPAT, 1-acyl-sn-glycerol-3-phosphate acyltransferase beta; Akt, protein kinase B; ALT, alanine aminotransferase; AMPK, 5′-adenosine monophosphate–activated protein kinase; aP, adipocyte-specific; APL, acquired partial lipodystrophy; AST, aspartate aminotransferase; BAT, brown adipose tissue; BMI, body mass index; BSCL, Berardinelli Berardinelli-Seip congenital lipodystrophy; C/EBP, CCAAT-enhancer-binding protein; CAV, caveolin; CIDEC, cell death-inducing DNA fragmentation factor-like effector C; CGL, congenital generalized lipodystrophy; ChREBP, carbohydrate-responsive element-binding protein; DGAT, diacylglycerol O-acyltransferase; F-IRKO, fat insulin receptor knock out; F-IR/IGFRKO, fat insulin receptor and IGF-1 receptor knock out; FAS, fatty acid synthase; FXR, farnesoid X receptor; FPLD, familial partial lipodystrophy; FSP, fat specific protein; GH, growth hormone; GHRH, GH releasing hormone; GLP, glucagon-like peptide; GPAT, glycerol-3-phosphate acyltransferase; HAART, highly active antiretroviral therapy; HALS, HIV-associated lipodystrophy syndrome; HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IGF, insulin-like growth factor; INSR, insulin receptor; IR, insulin resistance; IRS, insulin receptor substrate; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; LMNA, lamin A/C; MAD, mandibuloacral dysplasia-associated lipodystrophy; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NEFA, non-esterified fatty acids; PLIN, perilipin; PPAR, peroxisome proliferator-activated receptor; PTRF, polymerase I and transcript release factor; RCT, randomized controlled trial; RXR, retinoid X receptor; SCD, stearoyl-CoA desaturase; SGLT, sodium–glucose cotransporter; SPARMs, selective PPARγ modulators; SREBP, sterol regulatory element-binding protein; SS, simple steatosis; T2DM, type 2 diabetes mellitus; Treg, T-regulatory cells; TRL, triacylglycerol-rich lipoproteins; TZDs, thiazolidinediones; WAT, white adipose tissue; Wnt, wingless tail; ZMPSTE, zinc metalloprotease.

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1. Introduction

Lipodystrophy is a group of clinically heterogeneous, inherited or acquired disorders characterized by complete (generalized lipodystrophy) or partial (partial lipodystrophy) absence of subcutaneous fat (lipoatrophy) that may occur simultaneously with the pathological accumulation of adipose tissue (lipohypertrophy) in other regions of the body [1,2]. Congenital lipodystrophy is extremely rare, with approximately 1000 reported cases (familial or sporadic) [3,4]. Based on the assumption that only one fourth of the patients may be reported, the prevalence of congenital lipodystrophy may be estimated to be approximately less than one in a million [4]. On the other hand, acquired lipodystrophy is much more common; especially lipodystrophy associated with the human immunodeficiency virus (HIV) infection and the related highly active antiretroviral therapy (HAART) is currently the most prevalent form (HIV-associated lipodystrophy syndrome; HALS) [1]. Classification of the types of lipodystrophy is presented in Table 1 [5,6].

Lipodystrophy is characterized by ectopic fat accumulation, due to insufficient storage capacity of subcutaneous adipose tissue, and thus to severe insulin resistance (IR), often manifesting by acanthosis nigricans, type 2 diabetes mellitus (T2DM), hyperlipidemia and nonalcoholic fatty liver disease (NAFLD) [7]. NAFLD encompasses nonalcoholic simple steatosis (SS), in which the predominant histological characteristic is lipid accumulation in the hepatocytes, nonalcoholic steatohepatitis (NASH), characterized by the addition of hepatic inflammation, fibrosis, and NASH-related cirrhosis and hepatocellular carcinoma [8]. Apart from its hepatic morbidity, NAFLD has been also associated to extra-hepatic morbidity, including metabolic complications, chronic kidney disease, cardiovascular disease and malignancies, which all contribute to higher mortality, especially observed in NASH patients [9–11]. A distinct difference between NAFLD associated with common obesity and NAFLD of lipodystrophy are leptin levels, which are high in the former [12] and very low in the latter [13]. However, leptin levels may not be low in individuals with partial lipodystrophy, since there is a variable degree of fat accumulation in other parts of the body. Other adipokines, such as adiponectin, are similarly low in obesity-associated [14] and lipodystrophy-associated [13] NAFLD (Fig. 1). Therefore, leptin and/or adiponectin replacement may represent specific therapeutic target(s) for lipodystrophy-associated NAFLD. This may be feasible today, since recombinant human methionyl leptin (metreleptin) has been approved for the treatment of metabolic complications in patients with congenital generalized (CGL) or acquired generalized (AGL) lipodystrophy (non-HIV-associated) in the USA and both generalized and partial lipodystrophy in Japan [15] and Europe (https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta). Other leptin analogues are in various stages of development. Additionally, thiazolidinediones (TZDs) increase adiponectin levels and selective peroxisome proliferator-activated receptor (PPAR)γ modulators (SPARMs), as well as adiponectin receptor agonists are under development.

The aim of this review is to summarize evidence linking lipodystrophy with hepatic disease, and provide a special focus on potential therapeutic perspectives of leptin replacement therapy and adiponectin upregulation in lipodystrophy.

2. Literature search

We performed a computerized literature search in the PubMed electronic database, not limited by publication time or language. We used the query: "lipodystrophy AND (NAFLD OR NASH OR (fatty liver) OR (nonalcoholic fatty liver disease) OR (nonalcoholic steatohepatitis) OR (non-alcoholic fatty liver disease) OR (non-alcoholic steatohepatitis))", which provided 317 articles (last update January 6, 2019). The literature search was extended to the reference list of each selected article. Finally, automatic alerts (up to the submission of the study) were activated in PubMed ("My NCBI") to add relevant articles published after the initial search.

3. Liver metabolism complicated by lipodystrophy: the basics

Lipodystrophy may mechanistically occur due to errors during the development of pre-adipocytes from the pluripotent mesenchymal stem cells, or during the differentiation of pre-adipocytes to adipocytes and mature adipocytes, or due to early apoptosis or cell death of mature adipocytes [4,5,16] (Fig. 2). Different mutations during this process have been associated with distinct lipodystrophic syndromes (Table 1), although evidence is still far from established. For example, mutations in Berardinelli-Seip congenital lipodystrophy (*BSCL)-2* gene, coding for seipin, has been linked with CGL2, mutations in 1-acyl-sn-glycerol-3-phosphate acyltransferase beta (*AGPAT)2* gene with CGL1, and mutations in *PPARγ* gene with familial partial lipodystrophy (FPLD)3 (Table 1) [4,5]. Furthermore, mutations of lamin (*LMNA*), encoding for nuclear lamina proteins, and *ZMPSTE24*, required for posttranslational lamina processing, predispose to apoptosis of mature adipocytes and have been associated with familial partial lipodystrophy syndromes (mandibuloacral dysplasia) [5]. The lipodystrophic syndrome is expected to be more severe, when the respective mutation(s) affects the earlier stages of the development of pre-adipocytes and differentiation of adipocytes compared with later stages.

Patients with lipodystrophy lack adipocytes, so they cannot effectively store triglycerides. This limits the disposal of excess dietary triglycerides in the unaffected adipocytes, if any, and subsequently triglycerides are stored ectopically in non-adipose tissues, such as the

Table 1
Classification of human lipodystrophy.[a]

Type	Subtypes (gene mutation, if any)	Lipodystrophic pattern	Metabolic complications	Inheritance	Remarks
Congenital					
CGL (Berardinelli-Seip lipodystrophy)	CGL1 (*AGPAT2*) CGL2 (*BSCL2*) CGL3 (*CAV1*) CGL4 (*RTRF*)	Complete or near complete lipoatrophy.	Severe	Autosomal recessive	
FPLD	FPLD1 or Köbberling type (unknown) FPLD2 or Dunningan or Face-Sparing variety (*LMNA*) FPLD3 (*PPARγ*) FPLD4 (*PLIN1*) FPLD5 (*CIDEC*) FPLD6 (*LIPE*) MAD type A (*LMNA*) MAD type B (*ZMPSTE24*)	Lipoatrophy of the limbs. Adipose tissue of the trunk is less affected. Adipose tissue of the face is not affected. Lipohypertrophy of the neck may exist.	Moderate to severe	Autosomal recessive or autosomal dominant	
Acquired					
AGL (Lawrence syndrome)	AGL1 (−): panniculitis variety AGL2 (−): autoimmune disease variety AGL3 (−): idiopathic	Complete or near complete lipoatrophy. Lipoatrophy of the trunk is usually less severe than that of CGL.	Severe	NA	Association with autoimmune diseases (e.g., juvenile dermatomyositis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, Sjogren syndrome and panniculitis).
APL (Barraquer-Simons syndrome)		Lipoatrophy of the limbs. Lipoatrophy of the upper part of the body. Lipohypertrophy of the lower part of body may exist.	Mild to moderate	NA	Association with membranoproliferative glomerulonephritis type 2, infections and autoimmune diseases (e.g., dermatomyositis/ polymyositis, systemic lupus erythematosus)
HALS		Lipoatrophy of the limbs. Lipohypertrophy of the trunk and/or neck may exist.	Mild to moderate	NA	HALS is the most common form of acquired lipodystrophy. HALS is associated with HIV infection and HAART (especially HIV-1 protease inhibitors).

Abbreviations: AGL, acquired generalized lipodystrophy; AGPAT2, 1-acyl-sn-glycerol-3-phosphate acyltransferase beta; AKT, protein kinase B; APL, acquired partial lipodystrophy; BSCL, BernadelliBerardinelli-Seip congenital lipodystrophy; CAV, caveolin; CIDEC, cell death-inducing DNA fragmentation factor-like effector C; CGL, congenital generalized lipodystrophy; HAART, highly active antiretroviral therapy; HALS, HIV-associated lipodystrophy syndrome; HIV, human immunodeficiency virus; LIPE, lipase E, hormone sensitive type; LMNA, lamin A/C; MAD, mandibuloacral dysplasia-associated lipodystrophy; NA, not applicable; PLIN, perilipin; PPAR, peroxisome proliferator-activated receptor; PTRF, polymerase I and transcript release factor; ZMPSTE, zinc metalloprotease.

[a] The classification largely follows the latest version of UpToDate [7].

liver and skeletal muscles [17]. Ectopic fat accumulation in insulin-targeted organs, including the liver, promotes IR and its complications, including NAFLD [8]. This sequence may explain the early stages of NAFLD (hepatic steatosis), but not the subsequent hepatic inflammation and fibrosis [18]. Therefore, lipodystrophy itself may possibly predispose to hepatic steatosis usually at a young age [19], the chronicity of which subsequently drives to hepatic inflammation and fibrosis. However, this remains to be definitely shown.

In common obesity, mature adipocytes exist, but their functional capacity to store triglycerides is eventually saturated. Therefore, when the adipose tissue storage capacity is exhausted, triglycerides are also ectopically deposited and accumulate outside the adipose tissue, including the liver and the skeletal muscle [18,20]. However, IR and ectopic fat accumulation are usually less severe in common obesity than in generalized lipodystrophy in which the adipose tissue storage capacity is non-existing by definition [21]. The main metabolic and phenotypic abnormalities in CGL vs. obesity are illustrated in Fig. 1.

4. Fatty liver in mouse models of lipodystrophy

The mouse models of lipodystrophy carry either the specific genetic mutations observed in the different types of human CGL and FPLD or are deficient in key molecules involved in adipose tissue development. Liver function has been evaluated in most of these models, leading to some general conclusions: 1) Mouse models of CGL1 and CGL2 (but not of CGL3 or CGL4) demonstrate similar metabolic abnormalities to those observed in humans [22–30]. Among them, only the *Agpat2*$^{-/-}$ mouse model (CGL1) develops hepatic steatosis and NASH, thus being closer to the human course of the disease [25]. 2) Mouse models targeting key molecules of fat development demonstrate a phenotype closer to human CGL than FPLD [31–34]. In several of these models, steatosis progressing to NASH, fibrosis and cirrhosis are observed. Therefore, they can serve as useful experimental tools for identifying mechanisms linking adipose tissue function with NAFLD. 3) Mouse models of FPLD have normal metabolic and liver function, thus they do not accurately represent the human phenotype and studies based on them may have limited translational potential [35–41]. 4) Leptin is the main treatment tested in several mouse models to-date and it leads to significant improvement of glucose, lipid and hepatic metabolism [42–46]. The key characteristics of mouse models of lipodystrophy are summarized in Table 2.

4.1. Liver in mouse models related to the human types of CGL

4.1.1. AGPAT2 (CGL1)

Knock out mice for AGPAT2 (*Agpat2*$^{-/-}$) develop severe lipodystrophy characterized by the complete absence of white adipose tissue (WAT) and brown adipose tissue (BAT) and generalized organomegaly [25]. They exhibit IR, hyperglycemia, hypertriglyceridemia and hypoleptinemia [25]. In the liver, they develop severe steatosis and NASH in the first 2–3 weeks accompanied with an approximately 2-fold increase in liver weight, 7-fold (male) and 2-fold (female) increase in hepatic triglycerides and 30–85% decrease in protein levels of hepatic insulin receptor (INSR), insulin receptor substrate (IRS)1 and IRS2. Histologically, except of the higher number of lipid droplets, they demonstrate an abnormal lobule architecture, focal ballooning, oncocytic transformation and higher number of eosinophilic bodies with sparse neutrophils in portal spaces, but no sign of fibrosis. It was suggested that the high hepatic pool of triglycerides related to

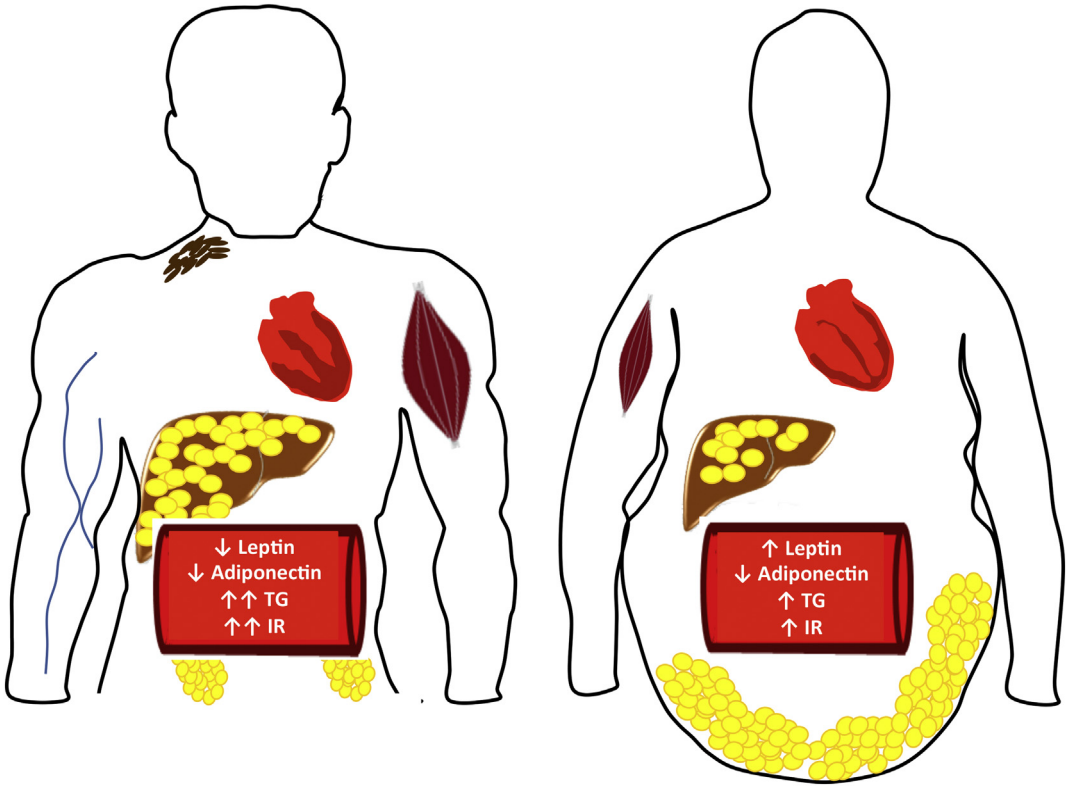

Fig. 1. Metabolic abnormalities in CGL vs. obesity. Individuals with CGL have a muscular appearance with prominent veins, acromegalic characteristics, hepatomegaly and occasional heart muscle hypertrophy. The complete lack of adipose tissue results in low leptin and adiponectin levels, high triglycerides and severe insulin resistance with acanthosis nigricans. They initially develop hepatic steatosis that progresses rapidly to NASH and liver fibrosis. In common obesity, muscle hypertrophy is not observed. Leptin levels are high corresponding to the higher fat mass. Adiponectin levels are low, but usually higher than those in CGL. Insulin resistance and triglycerides are high, but usually lower than those in CGL. Abbreviations: CGL, congenital generalized lipodystrophy; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; TG, triglycerides.

the steatosis may derive from diet (as chylomicron remnants), as well as from hepatic *de novo* lipogenesis. However, hepatic adenoviral expression of human AGPAT1 and AGPAT2 in *Agpat2*$^{-/-}$ mice did not improve steatosis [26,47]. In contrast, leptin replacement in *Agpat2*$^{-/-}$ mice ameliorated hepatic function, indicated by a robust decrease in hepatic triglycerides and glycogen [43]. This improvement is probably multifactorial and involves a decrease of hepatic *de novo* lipogenesis through the regulation of carbohydrate-responsive element-binding protein (ChREBP) transcriptional function, increase in thyroxine levels and reduction of IR [43]. Finally, 3T3-L1 preadipocytes with knockdown of *AGPAT2* treated with pioglitazone demonstrate an increase in the expression of adipocyte differentiation markers, such as CCAAT-enhancer-

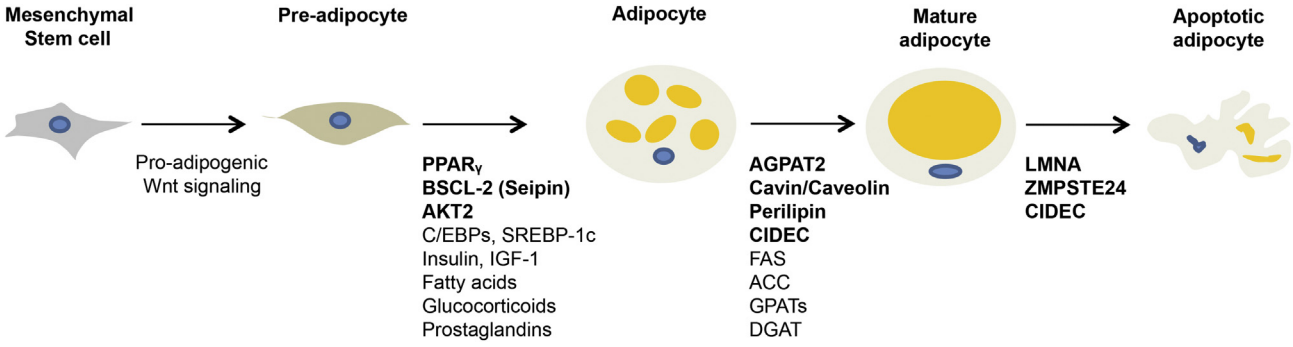

Fig. 2. Involvement of molecules related to lipodystrophic syndromes in the development, differentiation and apoptosis of adipocytes. Mesenchymal stem cells form preadipocytes by activation of Wnt signaling pathway. Preadipocytes differentiate to adipocytes after exposure to adipogenic factors, such as insulin, IGF-1, glucocorticoids, prostaglandins and activation of certain transcription factors (i.e., initially C/EBP β/δ followed by PPARγ and SREBP-1c). Additionally to PPARγ (related to FPLD3), seipin, encoded by *BSCL2* (related to CGL2) and Akt2 (non-distinct form of FPLD) are probably participating in the differentiation of preadipocytes to adipocytes. Next, adipocytes increase the size of their lipid droplets in response to energy excess by activation of lipogenic genes, such as AGPAT2 (related to CGL1), GPATs, DGAT1, resulting in biosynthesis of triglycerides and phospholipids. Cavin/Caveolin (related to CGL4 and CGL3) can also improve the ability of adipocytes to store larger lipid droplets by adjusting the dynamics of caveolae (small invaginations of plasma membrane). Similarly, perilipin-1 (related to FPLD4) regulates lipid storage and hydrolysis, while CIDEC (related to FPLD5) stimulates lipid droplet formation and may also promote adipocyte apoptosis. Lamin, encoded by LMNA (related to FPLD2 and MAD type A), is a filament protein that provides stability to adipocytes by supporting the nuclear envelope, while ZMPSTE24 (related to MAD type B) is a protein important for the maturation of lamin. Consequently, mutation in LMNA or ZMPSTE24 leads to premature adipocyte apoptosis. Abbreviations: ACC, acetyl-CoA carboxylase; AGPAT, 1-acyl-sn-glycerol-3-phosphate acyltransferase beta; Akt, protein kinase B; BSCL, Berardinelli Berardinelli-Seip congenital lipodystrophy; C/EBP, CCAAT-enhancer-binding protein; CIDEC, cell death-inducing DNA fragmentation factor-like effector C; CGL, congenital generalized lipodystrophy; DGAT, diacylglycerol O-acyltransferase; FAS, fatty acid synthase; FPLD, familial partial lipodystrophy; GPAT, glycerol-3-phosphate acyltransferase; IGF, insulin-like growth factor; LMNA, lamin A/C; MAD, mandibuloacral dysplasia-associated lipodystrophy; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; Wnt, wingless tail; ZMPSTE, zinc metalloprotease.

Table 2
Mouse models of lipodystrophy.

Mouse model	Human equivalent		Adipose tissue	Leptin	IR	Triglycerides	Glucose	Liver	Treatment
	Mutation	Phenotype							
Agpat2$^{-/-}$ [25,26,43,47]	CGL1	CGL1	No WAT No BAT	LLL	↑↑↑	↑↑	↑↑	Hepatomegaly SS, NASH	Leptin: ↓ SS, ↓ triglycerides [43]
Seipin−/− [31,49,50]	CGL2	CGL2	↓↓ WAT ↓↓ BAT	↓↓↓	↑↑	↓	↔/↑	Hepatomegaly SS	Pioglitazone: ↓ IR and SS [50] n-3 PUFA: ↓ triglyceride synthesis [28]
Caveolin-1$^{-/-}$ [23,24]	CGL3	Mild lipodystrophy	↓↓ WAT ↑↑↑ BAT	↓↓	↔	↑↑	↔/↑	Normal, but ↑ gluconeogenesis	
PTRF$^{-/-}$ [51]	CGL4	CGL4	↓↓	↓↓	↑↑	↑↑	↑	NA	
LMNA$^{-/-}$ [32,36]	FPLD2	Normal	↓	NA	↔	↓	↓↓	Normal	
LMNA$^{-/-}$ fat-KO [53]		FPLD2	↓	NA	↑	NA	↑	Hepatomegaly, SS	
PPARγ P467L [29]	FPLD3	Normal	↔	NA	↔	↔	↔	NA	
Plin1$^{-/-}$ [40,41]	FPLD4	Mild LD	↓↓	↑/↓	↔/↑	↔/↑	↔/↑	Normal	
FSP27$^{-/-}$ [34]	FPLD5	Normal	↓↓ WAT ↔ BAT	↔	↔	↔	↓	No SS after HFD	
A-ZIP/F [45,56]		CGL	No WAT ↓↓↓ BAT	↓↓↓	↑↑	↑↑↑	↑↑↑	Hepatomegaly, SS	Leptin: ↓ triglycerides, ↓ glucose [45]
PPARγ$^{+/-}$ mice treated with a PPARγ/RXR inhibitor (HX531) [57]		CGL	No WAT	LLL	↑↑	↑↑	↑↑	SS	Adiponectin: ↓ IR, ↓ serum triglycerides, ↓ liver and ↓ muscle triglycerides Leptin: ↓ IR Adiponectin+Leptin: ↓↓ IR
aP2-SREBP-1c [30,42,46,58]		CGL	↓↓ WAT ↑↑↑ BAT	↓↓↓	↑↑	↑↑	↑↑↑	Hepatomegaly SS → NASH→ Fibrosis→Cirrhosis	Leptin: ↓ liver triglycerides, ↓ SS, ↓ IR and ↓ glucose [46]
F-IRKO F-IR/IGFRKO [59,60]		CGL	↓↓ WAT ↓↓ BAT	↓↓↓	↑↑	↑↑↑	↑↑	Hepatomegaly SS → NASH→ Fibrosis→Cirrhosis	Leptin: no SS, normal glucose, normal insulin

Abbreviations: ↓, decreased; ↑, increased; ↔, unaffected; AGPAT, 1-acyl-sn-glycerol-3-phosphate acyltransferase beta; AP, activator protein; BAT, brown adipose tissue; CGL, congenital generalized lipodystrophy; F-IRKO, fat insulin receptor knock out; F-IR/IGFRKO, fat insulin receptor and insulin growth factor receptor knock out; FSP, fat specific protein; HFD, high fat diet; IR, insulin resistance; LMNA, lamin A/C; NA, not available; NASH, nonalcoholic steatohepatitis; PLIN, perilipin; PPAR, peroxisome proliferator-activated receptor; PTRF, polymerase I and transcript release factor; RXR, retinoid X receptor; SREBP, sterol regulatory element-binding protein; SS, simple steatosis; WAT, white adipose tissue.

binding protein (C/EBP)α and PPARγ [48]. However, whether pioglitazone treatment or other treatment elevating adiponectin levels can rescue the lipodystrophic phenotype of these mice has not been investigated.

4.1.2. Seipin (CGL2)

seipin$^{-/-}$ mice (gene *BSCL2*) demonstrate a milder phenotype compared to *Agpat2*$^{-/-}$ mice, in contrast to what is observed in humans with these disorders. Seipin$^{-/-}$ mice have a severe loss of WAT with very low leptin and adiponectin levels, but normal weight [31,49]. Additionally, they have IR and hepatosplenomegaly [31,49,50]. In contrast to other lipodystrophic animal models, seipin$^{-/-}$ mice have low circulating triglycerides, probably due to increased hepatic uptake of triacylglycerol-rich lipoproteins (TRL) and non-esterified fatty acids (NEFA) [31,49,50]. Histologically, seipin$^{-/-}$ mice demonstrate a profound hepatic steatosis with increased triglyceride accumulation, but no sign of NASH [31]. Hepatic insulin signaling is impaired, as indicated by the reduction in the expression of IRS1, IRS2 and protein kinase B (AKT)2. The hepatic expression of certain lipogenic genes, such as the fatty acid synthase (FAS), PPAR-γ and stearoyl-CoA desaturase (SCD)1 is moderately increased. Treatment of seipin$^{-/-}$ mice with pioglitazone reduces IR and steatosis, probably by restoring the normal liver uptake of TRL [50]. Finally, a diet rich in n-3 polyunsaturated fatty acids prevents seipin$^{-/-}$ mice from steatosis by reducing triglyceride synthesis [28].

4.1.3. Caveolin-1 (CGL3) and Cavin (CGL4)

Caveolin (CAV)-1$^{-/-}$ mice demonstrate a mild phenotype. They are lean, have a significant reduction of adipose tissue, have low leptin and adiponectin levels, and are resistant to diet-induced weight gain [23]. Circulating glucose, insulin and cholesterol levels are normal, but triglyceride levels are increased [23,24]. In this model, there are no signs of hepatic steatosis or insulin signaling impairment and only a chronic increase in hepatic gluconeogenesis is observed. Thus, its phenotype is radically different from that observed in humans, which is of intermediate degree between CGL1 and CGL2.

Polymerase I and transcript release factor (*PTRF*) encodes cavin, a protein that shows similar tissue distribution and parallel change in its expression profile with caveolin-1 and caveolin-3. PTRF$^{-/-}$ mice have normal weight with increased lean mass and reduced fat mass (by approximately 40%) with low leptin and adiponectin levels. Additionally, they have IR, high triglycerides and free fatty acids [51]. The presence of steatosis or NASH has not been investigated in this mouse model. On the contrary, transgenic overexpression of *PTRF* leads to obesity and increased hepatic fat accumulation with increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [52].

4.2. Liver in mouse models related to human types of FPLD

To the best of our knowledge, there are mice models mimicking human FPLD2 – FPLD5, but not FPLD1 for which the specific mutation remains largely unknown.

4.2.1. LMNA (FPLD2)

Knock out mice for LMNA A/C (LMNA$^{-/-}$) or LMNA$^{+/-}$ do not demonstrate metabolic abnormalities [32,36], thus they do not mimic human FPLD2. In contrast, fat-specific expression of mutant lamin A or C leads to progressive partial lipodystrophy, which resembles the course of the disease observed in humans. In these mice, mild hepatomegaly (by approximately 35%) and steatosis are observed, without inflammation or fibrosis [53]. Notably, hepatocyte-specific deletion of lamin A and C leads to hepatic steatosis, but also to NASH and fibrosis after high-fat diet feeding in male mice [54].

4.2.2. PPARγ (FPLD3)

Several models knocking-out *PPARγ* do exist, including mice bearing the *P465L* mutation, which corresponds to the mutation observed in human FPDL3. Unexpectedly, mice carrying the *P465L* mutation have

normal amount of adipose tissue and are insulin sensitive [29,38]. On the other hand, leptin deficient *ob*/*ob* mice with the *P465L* mutation develop lipodystrophy; it is speculated that coexistence of the *P465L* mutation and the leptin-deficient state creates a mismatch between insufficient adipose tissue expandability and excessive energy availability, thus unmasking the deleterious effects of *PPARγ* mutations on carbohydrate metabolism and replicating the phenotype observed in humans with dominant-negative *PPARγ* mutations [44]. However, it remains unclear whether *ob*/*ob* mice with the *P465L* mutation develop steatosis and/or NASH [44].

4.2.3. PLIN1 (FPLD4)

Knock out mice for perilipin (Plin1$^{-/-}$) are lean, muscular, have approximately 30% less adipose tissue and small adipocytes; their leptin levels are higher than expected for the reduced adipose mass. They tend to be glucose intolerant and insulin resistant, especially after high-fat feeding. They have normal liver size and hepatic fat content [40,41]. In contrast, it was recently reported, that fat-specific Plin1$^{-/-}$ mice develop hepatomegaly and steatosis, due to changes in hepatic lipid metabolism and may serve as a model for the investigation of FPLD4 [33].

4.2.4. CIDEC (FPLD5)

Cell death inducing DNA fragmentation factor-like effector C (CIDEC) or fat specific protein (FSP)27 is a protein affecting the storage of fat in lipid droplets. FSP27$^{-/-}$ mice are protected from diet-induced obesity and IR [34]. Additionally, silencing of hepatic FSP27 prevents fasting and improves diet-induced steatosis [39]. These metabolic changes in FSP27-deficient mice are in contrast with the profound metabolic abnormalities (i.e. severe IR, T2DM, NAFLD) observed in humans with CIDEC-mutations.

4.2.5. Akt2

Akt2$^{-/-}$ mice display IR early in life and the males progress rapidly to diabetes due to β-cell loss. They have high triglyceride levels and mild hepatomegaly [35,37]. Selective deletion of both *Akt1* and *Akt2* in adipose tissue results in hepatomegaly and steatosis [55]. Mutations in *Akt2* as possible causes of lipodystrophy are also suspected in humans, but it is still not considered a molecularly distinct form of FPLD.

4.3. Liver in mouse models of lipodystrophy reflecting major adipocyte functions

There are several models of lipodystrophy created based on targeting important adipose tissue functions, and consequently, presenting a phenotype close to human CGL.

In A-ZIP/F mice, a dominant-negative protein (A-ZIP/F), which prevents the DNA from the binding of B-Zipper transcription factors of both C/EBP and Jun families, is expressed in adipocytes. This results in a complete loss of WAT and in a massive reduction of BAT [56]. These mice display profound IR, diabetes, dyslipidemia, hypoleptinemia and hyperphagia. The liver is enlarged by approximately 2-fold and contains lipid droplets of various sizes that accumulate in centrolobular pattern, having both micro- and macrovesicular steatosis. Hepatic triglycerides are increased by approximately 3- to 5-fold, but inflammation, fibrosis or cirrhosis are not different in these mice. Steatosis is partially related to the increase of at least three rate-limiting enzymes involved in the lipogenesis (FAS, acetyl-CoA carboxylase and ATP-citrate lyase) [56]. Leptin replacement in these mice normalizes hepatic triglycerides by activating the hepatic 5′-adenosine monophosphate–activated protein kinase (AMPK) through the sympathetic nervous system (α-adrenergic receptors) [45].

PPARγ$^{+/-}$ mice treated with a PPARγ/retinoid X receptor (RXR) inhibitor (HX531) demonstrate a complete loss of visible WAT after 4 weeks, probably due to a reduction in the expression of molecules that regulate triglyceride accumulation in WAT [57]. These mice are hyperglycemic, hyperinsulinemic, hypoleptinemic and have no detectable circulating adiponectin. They have high serum triglyceride levels and increased triglyceride accumulation in the skeletal muscle and the liver. Treatment with either adiponectin or leptin improves insulin sensitivity, which is completely restored only after combined adiponectin and leptin treatment. Finally, treatment with adiponectin reduces serum (~50% reduction), liver (~30%) and muscle (~75%) triglycerides [57].

Since overexpression of the nuclear form of sterol regulatory element-binding protein (SREBP)-1c in cultured 3T3-L1 preadipocytes promotes adipocyte differentiation, transgenic mice overexpressing SREBP-1c in adipose tissue under the control of the adipocyte-specific (aP2) enhancer/promoter have been developed, named aP2-SREBP-1c [30]. These mice demonstrate a severe loss of WAT with a profound increase in BAT. They have IR, diabetes, high triglyceride levels, but normal AST and ALT. At eight days of life, aP2-SREBP-1c mice have profound steatosis with swollen hepatocytes and a 14-fold increase in hepatic triglycerides. At 40 days, steatosis, hepatocellular swelling and hepatic triglycerides are still increased, but are diminished compared with those of eight days [30]. Leptin administration improves IR and diabetes, reduces hepatic triglycerides and reverses steatosis [46]. These effects are probably achieved through central nervous system [42]. Interestingly, older mice (after 20 week) demonstrate not only steatosis but also NASH with fibrosis (lobular inflammation, ballooning, pericellular fibrosis and focal necrosis). However, whether leptin administration can reverse NASH at these mice has not been tested yet [58].

Fat insulin receptor knock out (F-IRKO) and fat insulin receptor and insulin-like growth factor (IGF)-1 receptor knock out (F-IR/IGFRKO) mice are characterized by adipose-specific deletion of INSR or combined deletion of INSR and IGF-1 receptor, respectively [59]. These mice demonstrate the typical metabolic abnormalities observed in CGL (IR, hyperglycemia, dyslipidemia). They additionally demonstrate a progressive hepatic disease, starting from severe steatosis at 12 weeks progressing to NASH with fibrosis and dysplastic nodules at 52 weeks. Thus, they can mimic the course of hepatic disease observed in human lipodystrophy. Likewise, by inactivating INSR and IGF-1 receptor in mature adipocytes with a tamoxifen-inducible system, a similar phenotype is observed [60]. Interestingly, leptin treatment can fully restore the metabolic abnormalities, including steatosis in these mice [60].

5. Fatty liver in clinical studies of lipodystrophy: associations and implications

The lipodystrophic patients have severe systemic and hepatic IR, as shown by the distinctly decreased insulin-mediated suppression of glucose production during the hyperinsulinemic clamp (40%) compared with the control subjects (92%) [61]. The extent of fat loss is associated with the severity of IR and the related metabolic abnormalities: patients with severe lipodystrophy have severe IR, severe hyperlipidemia and advanced hepatic disease [7]. Hepatomegaly is commonly observed in patients with lipodystrophy. In a systematic review, the rates of hepatomegaly were 84%, 80%, 54% and 29% in CGL, AGL, FPLD and acquired partial lipodystrophy (APL), respectively [62], being generally higher in generalized than partial syndromes, with the lower rates in APL, in which hepatomegaly is milder or absent [63,64]. Mild to severe elevation of liver function tests (LFTs) are frequently observed [63,65], but LFTs may also be normal, especially in partial syndromes [66–68]. As in non-lipodystrophic NAFLD, LFTs cannot establish the severity of NAFLD. In acquired syndromes (AGL and APL), the possible coexistence of autoimmune chronic hepatitis and the chronic use of corticosteroids [64,65] may further complicate the hepatic manifestation of the disease, since both are closely associated with fatty liver, but the specific contribution of the metabolic (NAFLD), autoimmune (autoimmune hepatitis) and pharmacologic (corticosteroids) components is difficult to estimate.

The full spectrum of NAFLD (SS, NASH, NASH-related cirrhosis and hepatocellular carcinoma) has been described in lipodystrophy. The median age at diagnosis of hepatic steatosis in a cohort with CGL was 12 years, but it may be diagnosed as early as 6 months [19]. Severe hepatic steatosis was initially described in magnetic resonance spectroscopy (MRS) studies [61,69]. Later, NAFLD was confirmed in studies with liver biopsies. In one of the largest histologically confirmed cohorts ($n = 50$), 90% of lipodystrophic patients had NAFLD, with 82% having NASH (borderline 20% and definite 62%) [70]. Notably, ballooning, being the hallmark of NASH, was evident in 74% of patients, four patients (8%) had advanced cirrhosis and other four (8%) had autoimmune hepatitis [70]. Similarly high rates of NASH (85–95%) were reported in other histologically confirmed studies [6,71], including those with partial lipodystrophy [72]. These are the highest rates of NASH being recorded in a subpopulation, which is additionally characterized by low weight and body mass index (BMI). Therefore, it seems rational that the most recent guidelines suggest that the diagnosis of NASH in a lean individual should raise the suspicion of lipodystrophy [15]. High rates of cirrhosis have been also recorded even in pediatric populations rendering the hepatic component of lipodystrophy even more alarming. More specifically, three of 53 lipodystrophic patients (6%) had cirrhosis in a pediatric cohort [6]. Notably, although more data are needed, it seems that severe recurrence of NAFLD is observed the first few months after orthotopic liver transplantation [73]. Moreover, sporadic cases of hepatocellular carcinoma have been reported, mainly in patients with prolonged hepatic disease [65]. Notably, one third of deaths in CGL have been attributed to liver diseases (complications of liver cirrhosis or hepatic failure), which results to a mean loss of approximately 40 years of life (mean age of death 24 years) [74].

The severity of NAFLD may depend not only on the type of lipodystrophy, being more severe in generalized lipodystrophy, but also on the specific mutation within the same type. For example, earlier hepatic involvement (median age at diagnosis 3.5 vs. 16.0 years, respectively), higher LFTs, and more severe NAFLD have been described in CGL2 compared with CGL1 patients [19], which is generally in line with more severe metabolic abnormalities observed in CGL2, as mentioned above. Likewise, in patients with FPLD, the degree of steatosis was less severe in the patients with *PPARG* mutations than those with *LMNA* mutations [75].

Patients with HALS have approximately 2.5-fold more hepatic fat, 2-fold more intra-abdominal fat and 2-fold less subcutaneous fat than non-HIV controls [76,77]. However, hepatic fat content is similar in HIV patients without NAFLD and non-HIV controls [77]. The prevalence of NAFLD in HIV patients varies between 40% and 75% [78–80], largely depending on the diagnostic technique. It is higher than the general population (25–30%) [81], but lower than generalized lipodystrophy. Longer nucleoside reverse-transcriptase inhibitor exposure is positively associated with hepatic disease in HIV [78]. However, the prevalence of NAFLD was higher (65–85%) in the early years of HIV infection, possibly because of malnutrition, concomitant infections and higher hepatotoxicity of older HAART regimens [82]. NASH was reported in approximately 40–70 and cirrhosis in 5–20% of HIV patients [79,80,83]. These rates are somehow lower than those reported in generalized and acquired lipodystrophy, but much higher than those observed in the general population (3–5%) [84].

An issue that further complicates hepatic disease in HIV patients is the co-infection with hepatitis C virus (HCV) and/or hepatitis B virus (HBV), which are usual. LFTs seem to be higher in HIV/HCV co-infection than HIV mono-infection [85]. Hepatic steatosis and fibrosis were evident in 56% and 91%, respectively, of patients with HIV/HCV co-infection [86], although no definitive conclusion could be drawn for the higher rates of fibrosis than steatosis in this study. Importantly, high rates of cirrhosis were observed in HIV patients co-infected with viral hepatitis (8%). Cirrhosis rates were higher in HIV/HCV (19%) than HIV/HBV (6%) patients, but even higher when multiple hepatitis infections co-existed: 42% in HIV/HCV/HBV and 67% in HIV/HCV/HBV/hepatitis D virus [87], implying that both the type of viruses and multiple viral co-infections affect the disease severity. Compared with HCV mono-infection, patients with HIV/HCV co-infection had approximately 1.5-fold higher odds ratio for fibrosis and 3-fold higher odds ratio for advanced fibrosis; lower CD+ count (indicative of more severe immunodeficiency) was associated with higher fibrosis rates [88,89]. Progression of fibrosis seems to be common in patients with HIV/HCV co-infection; in studies with paired liver biopsies, fibrosis progressed in 35–45% within 2.5–4.5 years [90-93]. Fibrosis also progresses more rapidly in HIV/HCV than HCV patients [93]. Given that fibrosis is the main histological prognostic factor for advanced hepatic disease [94], HIV/HCV co-infection should be considered as a high risk factor of advanced hepatic disease. Importantly, the hepatic impact of HIV/hepatitis co-infection specifically in patients with lipodystrophy remains to be shown.

A summary of the main factors contributing to the fatty liver of lipodystrophy is presented in Fig. 3.

6. Therapeutic perspectives of fatty liver in lipodystrophy

Currently, metreleptin, or in the future leptin analogues or leptin receptor agonists, are rational choice(s) for the treatment of lipodystrophy, representing a partial replacement treatment, when endogenous leptin levels are lower than normal. Other medications, especially those that would increase adiponectin levels in a condition characterized by low adiponectin, have also been used or tested in clinical trials. Other classes of medications, acting through other pathways or acting downstream of leptin and/or adiponectin, are currently in trials and may be used for the treatment of lipodystrophy. The hepatic effects of these medications are hereby presented. The proposed management of lipodystrophy with potential beneficial hepatic effect is presented in Fig. 4.

6.1. Metreleptin

Despite the disappointing results of trials on recombinant leptin in common obesity and related disorders [3], metreleptin is valuable for patients with leptin deficiency, including those with lipodystrophy [95]. Although leptin replacement seems to ameliorate metabolic and non-metabolic derangements, and quality of life of lipodystrophic patients, data comes mainly from uncontrolled studies, and therefore randomized controlled trials (RCTs) are required. This is mainly due to the lack of a concerted effort by pharma to design multicenter RCTs and/or crossover RCTs that would be able to eliminate problems related to the rarity of disease. Progress in this area requires establishment and collaboration of multicenter registries to achieve sufficient numbers for double-blind, placebo controlled RCTs of adequate sample size [1]. Main characteristics of most relevant studies are the observational design, the relatively small sample size, the lack of control group and the high dropouts rates, which are summarized in Table 3, focusing on the hepatic effects of metreleptin.

As expected, metreleptin treatment increased circulating leptin levels in all studies. However, it should be emphasized that measuring leptin levels provides a non-specific indication for the diagnosis and follow-up of patients with lipodystrophy. After metreleptin treatment, the interference of anti-leptin antibodies with leptin assays renders the interpretation of leptin measurements difficult. There is also lack of standardized leptin assays among laboratories and thus absence of widely applicable cut-off diagnostic criteria, which further complicates the interpretation of leptin measurements [1]. It should be underlined that, despite ameliorating the metabolic derangements of lipodystrophy, metreleptin does not cause regeneration of adipose tissue [96].

Specifically for the liver, metreleptin decreased AST and ALT levels, hepatic volume and hepatic fat in most studies (Table 3). Mean NAFLD activity score (NAS) improved in cohorts with paired liver biopsies after metreleptin treatment [6,70]. However, improvement occurred

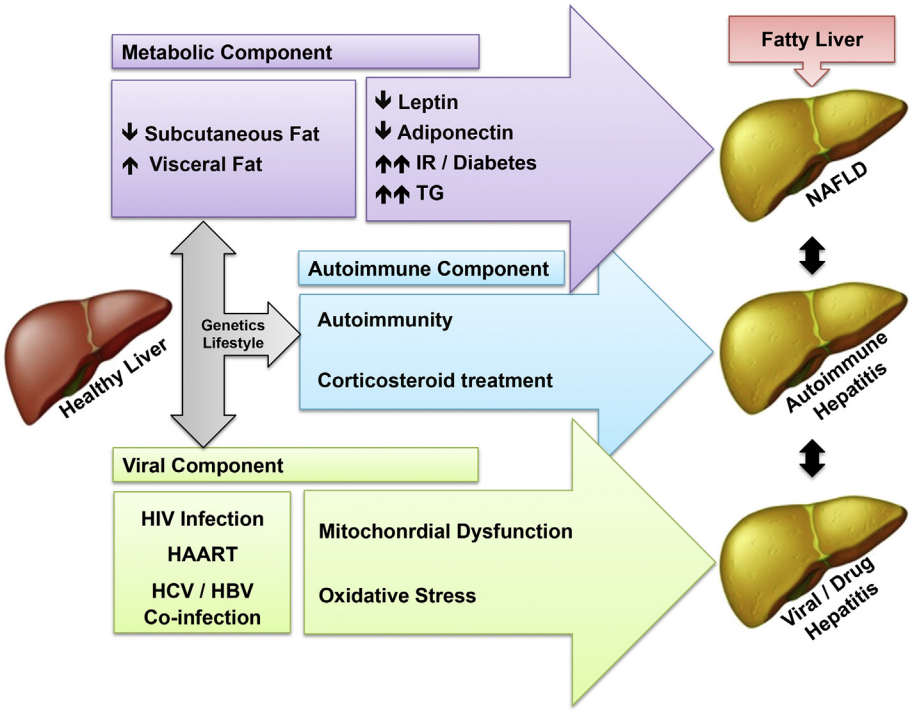

Fig. 3. A summary of the main factors contributing to the fatty liver of lipodystrophy. For the needs of presentation the factors have been divided into metabolic, autoimmune and viral components, although both overlap, and cross-talk exist among them. Regarding the metabolic component, which is commonly observed in both congenital and acquired lipodystrophies, the initial condition is subcutaneous lipoatrophy together with increase in visceral fat, which lead to low leptin and adiponectin levels and severe IR, associated with, diabetes and high TG levels. This sequence leads to NAFLD. Regarding the autoimmune component, which is more often present in acquired lipodystrophies, autoimmune mechanisms themselves contribute to autoimmune hepatitis, but also the chronic corticosteroid treatment may further result to drug-induced fatty liver. Regarding the viral component, which is more common in HALS, HIV infection itself, but also HAART mainly through mitochondrial dysfunction and increased oxidative stress lead to viral and/or drug-induced fatty liver. Co-infection with HCV and HBV, commonly observed in HIV-patients, further contribute to fatty liver. Genetics factors and lifestyle contribute to all components. Abbreviations: HAART, highly active antiretroviral therapy; HALS, HIV-associated lipodystrophy syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; TG, triglycerides.

in approximately 65–75% of patients, whereas NAS remained unchanged or even worsened in some patients [6,70]. Concomitant autoimmune hepatitis may be hypothesized as a possible cause of no improvement or worsening [6,97], thus possibly relating more with the disease itself rather than metreleptin treatment, but the numbers of cases are too limited to reach safe conclusions. Regarding specific hepatic lesions, ballooning was improved in both cohorts [6,70] and steatosis in one of them [70]. On the other hand, lobular and portal inflammation, and fibrosis remained largely unchanged after metreleptin treatment (Table 3). The effect of metreleptin on hepatic components seems to be less prominent in FPLD patients, similar to its effect on glucose and triglyceride levels [68,71,98].

Regarding liver cirrhosis, in one of the above cohorts [70], one patient had stable liver function and thrombocytopenia, and another had stable hepato-pulmonary syndrome during 6.5 and 3.5 years on metreleptin, respectively. A third patient with esophageal varices, splenomegaly, thrombocytopenia and prior episodes of hepatic encephalopathy, experienced an additional episode of hepatic encephalopathy during 2 years on metreleptin. A fourth patient died of hepatic failure after 1.5 years of metreleptin treatment [70]. In the above pediatric cohort, three patients with cirrhosis prior to metreleptin treatment died of complications of cirrhosis after four, six, and 12 years of metreleptin treatment [6]. However, the cases are very limited to support an adverse effect of metreleptin in advanced NASH and NASH-related cirrhosis; in this regard, they may simply represent the natural history of NASH-related cirrhosis, but it remains to be shown. Regarding liver transplantation, there is only one case with early recurrence of NASH, in whom metreleptin improved steatosis and resolved NASH within 6 months [73].

A parallel decrease in IR, glycated hemoglobin (HbA1c), triglyceride levels and insulin requirements were reported in most studies [70,71,99–106]. In a meta-analysis, metreleptin was shown to decrease glucose, HbA1c, triglycerides and total cholesterol, but not insulin, high- (HDL-C) and low-density lipoprotein cholesterol (LDL-C) [107]. Hepatic fat and IR are specifically improved after metreleptin treatment, as reflected by increased insulin suppression of glucose production during the hyperinsulinemic clamp [61,106]. Importantly, the effect of metreleptin on hepatic IR and fat are independent from its effect on food intake [106].

Discontinuation of leptin results in rapid deterioration of metabolic abnormalities, including LFTs, which, however, improve again, if metreleptin restarts [96]. Metreleptin discontinuation may unmask the worsening of metabolic abnormalities that occur due to the natural history of the disease [96].

Metreleptin was also administered in patients with HALS in two proof-of-concept RCTs. Although metreleptin had a beneficial metabolic effect in both of these studies, it tended to, but did not significantly decrease hepatic volume and lipid content [108] or LFTs [109]. However, studies of larger samples and longer duration are required in HALS.

Metreleptin was generally well tolerated with usually mild and transient side effects, including injection site events (erythema, urticarial), decreased appetite, weight loss, fatigue, nausea, vomiting, flushing, urinary tract infections and myalgia [6,68,99,101,105,110,111]. Hypoglycemia has been also reported [6,68,99,105,111], but it usually occurs due to inappropriate adjustment of concomitant anti-diabetic treatment, mainly insulin. Sporadic cases of peripheral T-cell lymphoma have been described [6,105], but it is unknown whether they are related to metreleptin or the natural course of the disease.

Other reported side effects, e.g., alopecia [99], myopathy [71], autoimmune hepatitis [70], worsening of pre-existing proteinuria [97], may not be related to metreleptin, since autoimmune diseases may coexist, most commonly with AGL and APL [15,97]. Notably, metreleptin did not appear to alter the clinical course of autoimmune diseases nor

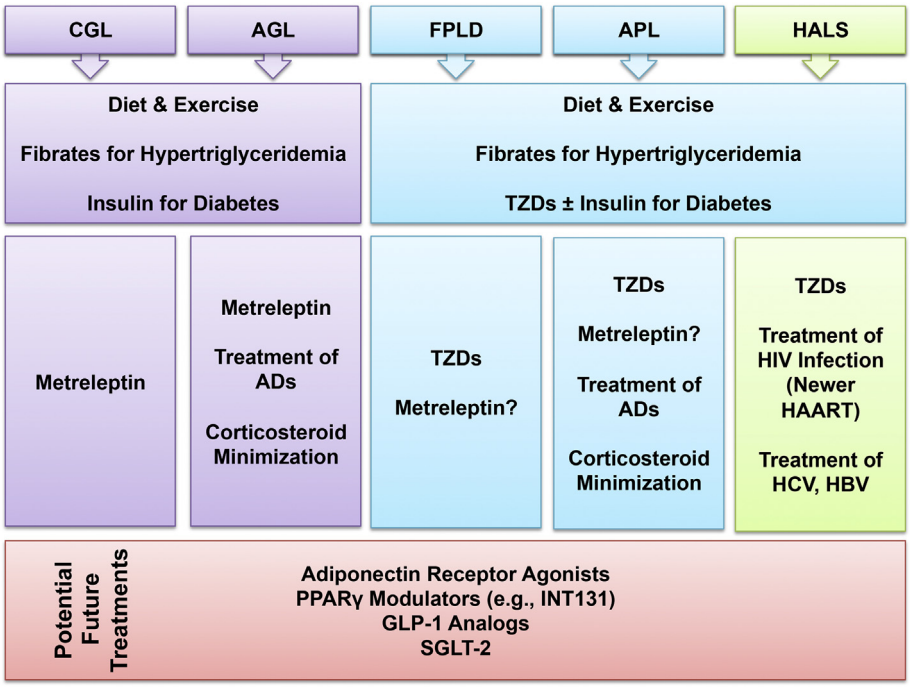

Fig. 4. Proposed management of lipodystrophy with potential beneficial hepatic effect. Diet and exercise is regarded as the standard care for all types of lipodystrophy. Fibrates should be used, if needed, for the management of hypertriglyceridemia in all types of lipodystrophy. Insulin should be used for the management of diabetes, if needed, in CGL and AGL, whereas TZDs may be initially used in partial lipodystrophy, including HAALS. Metreleptin seems to be beneficial for the treatment of steatosis and early NASH in patients with CGL and AGL, as well as in those with FPLD and APL. Existing data for metreleptin in HALS are not sufficient to propose for or against its use. Given the limited data, metreleptin use is not proposed for lipodystrophic patients with NASH and advanced fibrosis or cirrhosis (fibrosis stage 3–4), until novel data clarify the efficacy and safety of its use in these patients. In patients with partial lipodystrophy, including HALS, TZDs may exert beneficial effects on the liver, via upregulating adiponectin. In patients with acquired lipodystrophy, ADs, including autoimmune hepatitis, should be managed; the avoidance or minimization of corticosteroid would be beneficial for the liver. In patients with HALS, HIV infection should be managed preferably with newer HAART, considered to be less hepatotoxic. Furthermore, co-existing HCV and/or HBV infection should be managed. In the future, recombinant adiponectin may be used as a replacement treatment, possibly in all types of lipodystrophy, whereas, selective PPARγ modulators (e.g., INT131) may be also investigated. Abbreviations: ADs, autoimmune diseases; AGL, acquired generalized lipodystrophy; APL, acquired partial lipodystrophy; CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; GLP, glucagon-like peptide; HAART, highly active antiretroviral therapy; HALS, HIV-associated lipodystrophy syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PPAR, peroxisome proliferator-activated receptor; SGLT, sodium-glucose cotransporter; TZDs, thiazolidinediones.

clinical efficacy of immunosuppressive treatments [100]. The development of binding antibodies to metreleptin has been reported in two of seven patients in one study [69], one of three patients in another [100] and two of 53 in a third one [6]. In a pediatric cohort, binding antibodies increased in all patients at 28 months, but more dramatically in patients with negative response to treatment [112]. Antibodies are not an issue in most protein therapeutics to the extent they are not usually neutralizing; neutralizing antibodies have been rarely reported with the current metreleptin formulation; neutralizing antibodies have been associated with reduced metreleptin efficacy, but not consistently with adverse clinical consequences [113]. Newer leptin analogues, currently in development, are not expected to have these side effects.

6.2. Adiponectin

Apart from leptin, adiponectin administration seems to be an appealing strategy for a more integrated management of lipodystrophy, including a potentially beneficial hepatic effect. Adiponectin is considered to exert hepatic anti-steatotic, anti-inflammatory, anti-fibrotic and anti-apoptotic effects in cell lines and animal models [114]. In non-lipodystrophic individuals, lower levels of adiponectin in patients with SS than controls, and even lower in those with NASH were shown in a meta-analysis [14]. However, producing functionally active recombinant adiponectin is demanding, since it needs extensive post-translational modifications and appropriate multimerization [115]. Adiponectin analogues could be an alternative option. For example, osmotin, a plant antifungal protein, has been proposed as an adiponectin analogue [116], which has recently shown beneficial hepatic effects in *ob*/*ob* and *db*/*db* mice by activating adiponectin receptors (AdipoR1/R2) and their downstream pathways [117]. This finding warrants investigation of osmotin or other adiponectin analogues in lipodystrophy.

Except for recombinant adiponectin and adiponectin analogues, upregulation of endogenous adiponectin seems a rational approach in lipodystrophy. Towards this goal, TZDs have been tested, whereas the use of SPARMs is emerging and promising. However, the use of these medications theoretically requires a remaining functional adipose tissue (i.e., FPLD, APL, HAALS), whereas recombinant adiponectin or its analogues might be useful even in the total absence of adipose tissue (i.e., CGL, AGL).

6.2.1. Thiazolidinediones

TZDs are a family of compounds binding to PPARγ and thus causing redistribution of adipose tissue to subcutaneous compartment and activating several downstream molecules, including elevating adiponectin, thereby improving IR. In non-lipodystrophic patients with NAFLD, pioglitazone showed favorable effects, including improvement in steatosis and inflammation and has been proposed for the management of NAFLD [118]. The studies reporting the hepatic effects of TZDs in patients with lipodystrophy are summarized in Table 4. Troglitazone was the first TZD used in patients with lipodystrophy. It decreased the hepatic volume, in parallel with its beneficial effect on HbA1c and triglycerides, but was discontinued in 10% of lipodystrophic patients due to ALT increase, possibly due to drug hypersensitivity [119]. Troglitazone, officially introduced for T2DM treatment, was withdrawn due to relatively rare, but severe, hepatic failure [120].

Both rosiglitazone [121,122] and pioglitazone [123] decreased LFTs and hepatic fat and this has also been shown in HALS [76,77,122],

Table 3
The effect of metreleptin on hepatic components in clinical studies with lipodystrophic patients.

Reference[a]	Study design	Type of lipodystrophy	Metreleptin dose	Patients/controls (n; females; age [years])	Duration	Baseline/repeat liver biopsy	Hepatic effect	Remarks
[101][c]	Prospective case series, open label	CGL, FPLD or AGL	0.015–0.08 mg/kg/d	9; 9; 15–42/ NA	4 mo	No/No	1) Decrease in AST and ALT levels. 2) Decrease in hepatic volume (MRI).	
[61]	Prospective case series, controlled, open label; Group 1: CGL vs. Group 2: Control (baseline only)	CGL	0.015–0.08 mg/kg/d	3; 3; 26 ± 5/ 6; 6; 26 ± 5	3–8 mo	No/No	1) Decrease in hepatic and systemic IR. 2) Decrease in hepatic lipid content.	
[69]	Prospective case series	CGL or AGL	0.015–0.08 mg/kg/d	3; 2; 15–33/ NA	8–10 mo	No/No	Decrease in hepatic lipid content (MRS).	
[163][c]	Prospective cohort, open label	CGL, FPLD or AGL	0.015–0.08 mg/kg/d	14; 11; 12–67/ NA	1 y	No/No	Decrease in hepatic volume (MRI).	Data available for 8 patients at 12 mo.
[164][b]	Prospective cohort, open label	GGL, FPLD or AGL	0.015–0.06 mg/kg/d	10; 8; 17–67/ NA	4 mo – 1.5 y	Yes/Yes	1) Decrease in AST and ALT levels. 2) Decrease in hepatic volume and liver fat content (MRI). 3) Decrease in NASH rates. 4) Improvement in steatosis and ballooning. 5) No effect on parenchymal inflammation and fibrosis.	
[108]	RCT, double-blind, crossover, placebo controlled Group 1: metreleptin vs. Group 2: placebo	HALS	0.04 mg/kg/d	Group 1: 7; 0; 45.8 ± 2.0/ Group 2: 7; 0; 45.8 ± 2.0	2 mo	No/No	No effect on hepatic volume and lipid content (CT)	
[110][d]	Prospective case series, open label	CGL	0.015–0.06 mg/kg/d	7; 1; 2–14/ NA	4 mo	No/No	1) Decrease in AST and ALT levels. 2) Decrease in hepatic volume (CT).	
[103]	Prospective case series, open label	CGL or AGL	0.02–0.08 mg/kg/d	7; 5; 11–29/ NA	3 y	No/No	1) Decrease in AST and ALT levels. 2) Improvement in liver-to-spleen ratio (CT) 3) Decrease in liver fat content (MRI; 1 patient).	
[98]	Prospective case series, open label	FPLD	0.08 mg/kg/d	6; 6; 33–64/ NA	1 y	No/No	Modest, non-significant decrease in hepatic volume (MRI).	
[104]	Case report	FPLD	0.08–0.12 mg/kg/d	1; 1; 36/ NA	1.5 y	No/No	Decrease in hepatic volume (MRI).	
[97]	Prospective case series, open label	AGL	0.08 mg/kg/d	2; 1; 13 & 14/ NA	1 y	Yes/Yes	1) Decrease in AST and ALT levels in patient #1, but increase in patient #2. 2) Decrease in hepatic volume (MRI). 3) Resolution of steatosis, but stable inflammation (patient #1). 4) Worsening of inflammation (patient #2).	1) Both T1DM patients. 2) Worsening of pre-existing proteinuria (patient #2). 3) Patient #2 had been also on pioglitazone for 10 mo.
[112][d]	Prospective case series, open label	CGL	0.06–0.12 mg/kg/d	8; 2; 5–16/ NA	2.3 y	No/No	1) Decrease in hepatic volume (CT; 5 patients). 2) Decrease in steatosis (CT; 5 patients)	
[99]	Prospective cohort, open label	CGL, FPLD, AGL or APL	2.8 ± 0.4 mg/d (males) and 5.6 ± 0.3 mg/d (females)	55; 44; 7–68/ NA	2.5 y (<6 mo – 9 y)	No/No	Decrease in AST and ALT levels at 4 mo and sustained throughout 3 y.	13 patients withdrew from the study.
[109]	RCT, double-blind, placebo controlled Group 1: metreleptin +	HALS	Metreleptin; 0.04 mg/kg/d + Pioglitazone; 30 mg/d vs. Pioglitazone; 30 mg/d	Group 1: 5; 0; 43–57/ Group 2: 4; 0; 43–57	3 mo	No/No	Non-significant decrease in AST and ALT levels in Group 1 and non-significant increase in AST and ALT levels in group 2.	

(continued on next page)

Table 3 (*continued*)

Reference[a]	Study design	Type of lipodystrophy	Metreleptin dose	Patients/controls (n; females; age [years])	Duration	Baseline/repeat liver biopsy	Hepatic effect	Remarks
	pioglitazone vs. Group 2: pioglitazone							
[96]	Case report	AGL	0.06 mg/kg/d	1; 1; 10/ NA	2.5 y (intermittent)	Yes/Yes	1) Decrease in AST and ALT levels after restarting metreleptin. 2) Histology (NASH) unchanged (at 2 y).	She received metreleptin for 2y, then she discontinued for 9 mo and restarted for at least 1 y.
[111]	Prospective, parallel group, open label; Group 1: severe hypoleptinemia vs. Group 2: moderate hypoleptinemia	FPLD	0.08 mg/kg/d	Group 1: 14; 14; 40.8 ± 13.1/ Group 2: 10; 10; 36.3 ± 16.6	6 mo	No/No	1) Decrease in AST levels in group 1, but not group 2. 2) ALT unchanged in both groups. 3) Similar decrease in hepatic lipid content in both groups (MRS)	
[73]	Case report	AGL	0.08 mg/kg/d	1; 1; 41/ NA	6 mo	Yes/Yes	1) Decrease in hepatic lipid content (MRS). 2) Resolution of NASH in the liver transplant.	Recurrence of NASH early after orthoptic liver transplantation.
[70][b]	Prospective cohort, open label	CGL, FPLD, AGL or APL	0.06–0.24 mg/kg/d	50; 42; 26 ± 2/ NA	4–68 mo	Yes/Yes (n = 27; 54%)	1) Decrease in AST and ALT levels. 2) Decrease in NASH rates. 3) Improvement in steatosis, ballooning and NAS. 4) No effect on lobular and portal inflammation, and fibrosis.	27 patients were included in the analysis.
[71]	Retrospective case series, open label	CGL or FPLD	0.05–0.24 mg/kg/d	9; 5; 2–43/ NA	9 mo – 5 y	No/No	Decrease in AST, ALT and GGT levels in <6 mo.	
[100]	Prospective case series, open label	AGL	0.02–0.04 mg/kg/d	3; 2; 9–16/ NA	3–6 y	No/No	1) Decrease in AST, ALT and GGT levels at 6 mo. 2) Improvement in hepatomegaly (physical examination).	All patients had concomitant autoimmune diseases.
[68]	Prospective cohort, open label	FPLD or APL	0.02–0.08 mg/kg/d	23; 22; 63–67/ NA	3 mo – 1 y	No/No	AST and ALT unchanged.	AST, ALT data available for 6 patients at 12 mo.
[102]	Prospective case series, open label	CGL or AGL	0.06–0.13 mg/kg/d	3; 2; 10–19/ NA	3 mo – 3 y	No/No	Decrease in AST and ALT levels.	
[6]	Prospective cohort, open label	CGL, FPLD or AGL	0.02–0.19 mg/kg/d	53; 41; 0.5–18/ NA	14 mo – 14.2 y	Yes (17; 32%)/ Yes (17; 32%)	1) Decrease in AST and ALT levels. 2) Improvement in ballooning and NAS. 3) No effect on steatosis, lobular and portal inflammation, and fibrosis.	
[105]	Prospective cohort, open label	CGL or AGL	0.03–0.21 mg/kg/d	66; 51; 1–68/ NA	63 ± 46 mo	No/No	1) Decrease in ALT levels. 2) Decrease in hepatic volume (MRI).	
[106]	Non-randomized, cross-over	CGL, FPLD or AGL	10 mg/d	23; 17; 14–70/ NA	14d and 6 mo	No/No	1) Increase in insulin sensitivity and decrease in hepatic fat after treatment initiation independently from its effect on food intake. 2) Decrease in insulin sensitivity after treatment discontinuation.	

Studies with nine or less patients were conventionally considered as case series, whereas those with 10 or more patients as cohort studies.
Abbreviations: AGL, acquired generalized lipodystrophy; APL, acquired partial lipodystrophy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGL, congenital generalized lipodystrophy; CT, computed tomography; d, day(s); FPLD, familial partial lipodystrophy; GGT, gamma-glutamyltransferase; HALS, HIV-associated lipodystrophy syndrome; HIV, human immunodeficiency virus; IR, insulin resistance; mo, months; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; RCT, randomized controlled trial; T1DM, diabetes mellitus type 1; y, years.
[a] References are presented in publication time order.
[b] The Safar Zadeh et al. study includes partial data of 10 patients previously described by Javor et al. study.
[c] The Moran et al. study possibly includes partial data of patients previously described by Oral et al. study.
[d] The Beltrand et al. (2007) study includes the 4-mo data of 7 of 8 patients described by Beltrand et al. (2010) study.

although no effect of rosiglitazone on LFTs was reported in one study with HALS [124] (Table 4). This effect was similar to that shown in NASH patients without lipodystrophy [125–127].

Despite an increase in subcutaneous fat reported in one study after rosiglitazone treatment in HALS [128] and in two cases with FPLD [121], both pioglitazone and rosiglitazone do not generally seem to

Table 4
The effect of insulin sensitizers (metformin and thiazolidinediones) on hepatic components in clinical studies with lipodystrophic patients.

Reference[a]	Study design	Type of lipodystrophy	Medication; dose	Patients/controls (n; females; age [years])	Duration	Baseline/repeat liver biopsy	Hepatic effect	Remarks
Metformin								
[138]	RCT, double-blind, placebo controlled Group 1: metformin vs. Group 2: placebo	HALS	Metformin; 1000 mg/d	Group 1: 14; 3; 44.1 ± 2.1/ Group 2: 12; 3; 45.6 ± 1.9	3 mo	No/No	No effect on AST levels.	
Thiazolidinediones								
[119]	Prospective cohort, open label	CGL, FPLD, AGL or APL	Troglitazone; 200–600 mg/d	20; 18; 6–65/ NA	6 mo	No/No	Decrease in hepatic volume (MRI).	1) Two patient discontinued treatment because of increase in ALT levels. 2) No effect on leptin levels.
[77] [76,122]	RCT, double-blind, placebo controlled Group 1: rosiglitazone vs. Group 2: placebo	HALS	Rosiglitazone; 8 mg/d	Group 1: 15; 3; 44 ± 3/ Group 2: 15; 2; 42 ± 2	6 mo	No/No	1) Decrease in ALT levels. 2) Decrease in liver fat (MRS).	
[123]	Case report	HALS	Pioglitazone; 30 mg/d	1; 1; 50/ NA	NA	No/No	Decrease in steatosis (CT)	
[132]	Case report	FPLD	Pioglitazone; 15–30 mg/d	1; 1; 25/ NA	1.5 y	No/No	1) Decrease in AST and ALT levels. 2) Improvement of steatosis (US)	
[124]	RCT, double-blind, placebo controlled Group 1: rosiglitazone vs. Group 2: placebo	HALS	Rosiglitazone; 8 mg/d	Group 1: 23; 2; 46.7 ± 2.1/ Group 2: 17; 1; 45.4 ± 2.1	6 mo	No/No	1) No effect on AST, ALT and GGT levels. 2) No effect on hepatic IR. 3) No effect on hepatic insulin clearance.	
[165]	Prospective case series, open label	FPLD	Rosiglitazone; 8 mg/d	5; 4; 19–50/ NA	1 y	No/No	Decrease in AST and ALT levels.	
[121]	Prospective case series, open label	FPLD	Rosiglitazone; 8 mg/d	2; NA; 14 & 16/ NA	1.8 y	No/No	Decrease in liver fat content (MRI).	
[166]	Case report	AGL	Pioglitazone; 15 mg/d	1; 0; 19/ NA	1.5 y	No/Yes (after treatment)	1) Slight decrease in AST and ALT levels. 2) Slight improvement in steatosis (transient elastography).	The patient received metreleptin (0.02 mg/kg/d) after pioglitazone, but was not compliant to treatment.
Head-to-head comparisons								
[128]	Randomized, 2 active arms, open label, no placebo Group 1: metformin vs. Group 2: rosiglitazone	HALS	Metformin; 1000 mg/d vs. Rosiglitazone; 8 mg/d	Group 1: 18; 3; 48 ± 2/ Group 2: 19; 3; 47 ± 2	6 mo	No/No	Similar decrease in AST and ALT levels in both groups.	

Studies with nine or less patients were conventionally considered as case series, whereas those with 10 or more patients as cohort studies.
Abbreviations: AGL, acquired generalized lipodystrophy; APL, acquired partial lipodystrophy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGL, congenital generalized lipodystrophy; CT, computed tomography; d, day(s); FPLD, familial partial lipodystrophy; GGT, gamma-glutamyltransferase; HALS, HIV-associated lipodystrophy syndrome; HIV, human immunodeficiency virus; mo, months; IR, insulin resistance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, not applicable; RCT, randomized controlled trial; US, ultrasound; y, years.
[a] References are presented primarily in pharmaceutical category order and secondarily in publication time order.

affect body weight, subcutaneous and visceral fat in lipodystrophic patients, including HALS [76,77]. Even long-term (up to eight years) treatment with rosiglitazone and pioglitazone in two patients with FPLD did not restore adipose tissue in lipodystrophic areas [129]. To compare with, in T2DM patients, rosiglitazone increases fat mass by 3–4 kg in 12 weeks [130,131]. Likewise, TZDs increase body weight and fat in NASH patients without lipodystrophy [127]. It seems that TZDs affect subcutaneous and total body fat in non-lipodystrophic individuals, whereas they have limited or null effect in lipodystrophic ones, in whom adipose tissue does not exist or is dysfunctional. This may be the reason why TZDs were evaluated to the most in patients with partial lipodystrophy and HALS, in whom a residual adipose tissue function exists. On the other hand, the near total absence of fat in patients with generalized lipodystrophy renders the effect of TZDs rather questionable (Table 4).

A parallel decrease in glucose and insulin levels and/or HbA1c and IR has been reported after rosiglitazone [76,121,122,124,128] and pioglitazone [132]. As expected, insulin requirements decrease during TZD treatment and rise upon their discontinuation [97]. TZDs also increased adiponectin, but not leptin levels, which is reported mainly in patients with HALS [76,77,122,124,133]. Importantly, adiponectin change was inversely associated with ALT and hepatic fat change [122], which

implies that the effect of TZDs is mediated, at least partly, through adiponectin, similar to non-lipodystrophic NASH patients [120].

The effect of rosiglitazone and pioglitazone on triglyceride levels seems to differ in lipodystrophy, similarly to non-lipodystrophic NASH patients [125–127]. More specifically, pioglitazone improves triglycerides [123,132], whereas rosiglitazone increases them [77,122,128]. Furthermore, rosiglitazone increased total cholesterol [77,122] and LDL-C [124] in HALS and increased remnant-like particle cholesterol [128]. These effects of rosiglitazone on lipid profile may adversely affect cardiovascular risk in lipodystrophy, a population with a high cardiovascular risk.

Both pioglitazone and rosiglitazone were reportedly well tolerated in lipodystrophy. No serious events have been reported, including bladder cancer or osteoporotic fractures.

6.2.2. Selective PPARγ modulators

Currently, the use of rosiglitazone has been restricted in practice, because of an alleged increase in myocardial infarction risk shown in non-lipodystrophic patients [134], and pioglitazone use has been suspended in some European countries because of a possibly slight increase in bladder cancer risk after long-term use in T2DM patients [135]. In light of these considerations, SPARMs have been developed, including INT131. INT131 is a potent non-thiazolidinedione SPARM designed to exhibit a biological profile of strong efficacy, but minimal side effects compared to PPAR-γ full agonists [120]. Phase I studies in non-lipodystrophic individuals have shown that adiponectin increases in response to INT131 in both a dose and a time dependent manner. In phase 2 trials, INT131 was well tolerated, improved glycemic profile and increased adiponectin in T2DM patients in a dose-dependent manner, similarly to maximum dose of pioglitazone (45 mg/d) [136]. Importantly, less adverse effects, including edema, fluid retention and weight gain were observed compared with rosiglitazone or pioglitazone [120]. Based on these observations, INT131 and other SPARMs that may follow seem to be promising candidates for clinical trials in patients with partial lipodystrophy and HALS, with the potential to improve both glucose metabolism and NAFLD.

6.3. Other medications

Among the oral antidiabetic medications, metformin has been used more frequently in lipodystrophy [15], due to its low cost and long-term availability. Most data for metformin are derived from studies in HALS. Together with a favorable effect on glucose and lipid metabolism [128,137,138], metformin decreased LFTs in some [128], but not all studies (Table 4). It should be underlined that metformin decreased subcutaneous and/or visceral fat [128,137,138]; the decrease in fat mass results in a general IR decrease, which is favorable in non-lipodystrophic T2DM patients, but not in those with lipodystrophy. Therefore, metformin is discouraged in patients with lipodystrophy.

Other medications have also been used in lipodystrophy with, however, minimal or null hepatic effect. Among anti-diabetic drugs, sulfonylureas showed limited efficacy [65]. Glucagon-like peptide (GLP)-1 analogues, including exenatide and liraglutide, showed a beneficial effect on IR in some lipodystrophic patients [139,140], but whether their hepatic effect resembles that of non-lipodystrophic NAFLD patients [141], remains to be shown. Furthermore, ipragliflozin, a sodium–glucose cotransporter (SGLT)-2 inhibitor, showed beneficial effect on steatosis in a patient with CGL [142], as shown in non-lipodystrophic NAFLD.

Growth hormone (GH) deficiency has been associated with both lipodystrophy and NAFLD. HAART in HIV patients alters GH secretion and about one-third of patients have biochemical GH deficiency [143]. Therefore, medications acting on GH axis, including recombinant GH, GH releasing hormone (GHRH) and IGF-1, have been tested for the treatment of HALS [144]. A meta-analysis showed that both recombinant GH and tesamorelin, a GHRH analogue, reduced visceral adipose mass, but only recombinant GH reduced subcutaneous adipose mass [144]. Thus, tesamorelin may be more promising and safer than treatment with recombinant GH for lipodystrophy [143], since the reduction in subcutaneous fat is not desirable in patients with lipodystrophy. The combination of rosiglitazone and recombinant GH may be preferable than GH monotherapy for HALS, since the TZD may abrogate the increase in IR induced by the recombinant GH [145].

Uridine supplementation has been launched as an approach against HAART-associated mitochondrial toxicity. Its beneficial effect on hepatic mitochondrial function was shown in thymidine-analogue treated HIV patients [146]. However, uridine did not affect hepatic fat content and ALT levels in HALS, despite increasing in subcutaneous and/or abdominal adipose mass [147,148].

Cholic acid, a farnesoid X receptor (FXR) agonist, a promising target for the treatment of NASH [141], has been evaluated in a 1-year, double-blind, placebo controlled RCT in patients with FPLD and AGL [149]. Although well tolerated, cholic acid did not affect hepatic triglyceride content or LFTs [149].

Although hypolipidemic medications, including statins, fibrates, ezetimibe, niacin and omega-3 were or are still in use for lipodystrophy [15], and some of them have been proved beneficial for NAFLD in non-lipodystrophic patients [10,141,150], data on their hepatic effects in

Table 5
Clinical trials for the treatment of lipodystrophy in "recruiting" or "active status" with primary or secondary hepatic outcomes.

Medication	Disease	Class/mechanism of action	Hepatic outcomes	Status	Sponsor	Primary completion date
ISIS 304801 (Volanesorsen)	FPLD	ASOs for reduction of apoC-III	Hepatic steatosis (MRI)	Phase 2/3	IONIS Pharmaceuticals	09/30/2018
ISIS 304801	Partial lipodystrophy	ASOs for reduction of apoC-III	Hepatic steatosis (MRI)	Phase 2	NIDDK	12/31/2018
ISIS 703802	FPLD	Reduction of ANGPTL3	Hepatic steatosis (MRI)	Phase 2	Akcea Therapeutics	04/30/2019
Gemcabene	FPLD	Small molecule reducing LDL-C and TGs by inhibiting hepatic TG and cholesterol synthesis, and by increasing VLDL-C clearance	Hepatic fat content (MRI-PDFF) Hepatic fibrosis (magnetic elastography)	Phase 1 Phase 2	University of Michigan	03/01/2020
Obeticholic acid	FPLD	Selective FXR agonist	Hepatic TG (MRS)	Phase 2	UT Southwestern Medical Center	09/2018
Aramchol	HALS	FABACs	Hepatic steatosis (MRI) Serum ALT and AST levels	Phase 2	University of California	09/30/2018
Tesamorelin	HALS	Synthetic GHRH	Hepatic lipid content (MRI)	Phase 4	Columbia University	04/30/2021

Abbreviations: ALT, alanine aminotransferase; ANGPTL, angiopoietin-like; AST, aspartate aminotransferase; apo, apolipoprotein; ASOs, anti-sense oligonucleotides; FABACs, fatty-acid/bile-acid conjugates; FPLD, familial partial lipodystrophy; FXR, farnesoid X receptor; GHRH, growth-hormone-releasing hormone; HALS, HIV-associated lipodystrophy syndrome; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; MRI-PDFF, MRI-proton density fat fraction; MRS, magnetic resonance spectroscopy; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

lipodystrophy are limited. "Heart positive" was an RCT designed to evaluate the effect of niacin, fenofibrate or both medications in HALS [151], but the results of this study have not been reported, possibly due to niacin withdrawal from the market.

Ongoing clinical trials in lipodystrophic patients with primary or secondary hepatic outcomes are summarized in Table 5. There are also many other drugs under investigation for NAFLD in non-lipodystrophic patients, including obeticholic acid and tropifexor (FXR agonists), cenicriviroc (chemokine receptors 2/5 inhibitor), elafibranor (PPARα/δ ligand), saroglitazar (PPARα and PPAR γ agonist), IVA337 (pan-PPARγ agonist), emricasan (caspase inhibitor), selonsertib (apoptosis signaling kinase-1 inhibitor), MGL-3196 (thyroid hormone receptor-β agonist), aramchol (SCD1 inhibitor), BMS 130-045 (pegylated fibroblast growth factor-21) [152]. However, the translation of results of these RCTs in non-lipodystrophic NAFLD patients should be cautiously interpreted, and not be used without trials evaluating their efficacy and safety specifically in lipodystrophic NAFLD patients.

7. Closing remarks and perspectives

Although metreleptin seems to have beneficial effect on fatty liver of lipodystrophy, it should be emphasized that replacing leptin does not result in full replacement of all missing adipokines in lipodystrophy. A more rational approach would be the replacement of more adipokines, since most are lacking [153]. In this regard, clinical trials with metreleptin combined with recombinant adiponectin or medications upregulating adiponectin may be important [115,120]. Medications upregulating adiponectin may be currently preferable due to the complex post-translational modifications that adiponectin requires to be functional. To-date, the main medications upregulating adiponectin are PPARγ modulators, including TZDs and the more selective ones like INT131 [120], but their investigation probably requires partly functional adipose tissue, so there are not promising candidates for CGL and AGL.

Another issue requiring careful benefit-risk assessment is the effect of metreleptin on hepatic inflammation and fibrosis. We previously hypothesized that leptin may adversely affect hepatic fibrosis in NAFLD patients, acting as a pro-inflammatory and fibrogenic factor, as shown in experimental studies [154,155]. Indeed, leptin affects thymic homeostasis, by promoting Th1-cell immune responses and contributing to Th1/Th2 balance [156]. Hypoleptinemia and aleptinemia leads to impaired Th1 response and induction of the T-regulatory cells (Treg), thus reducing the immunocompetence and increasing the susceptibility to infections [157]. On the other hand, hyperleptinemia and leptin resistance results in an expansion of Th1 cells and low proportion and proliferation of Treg cells, thus increasing secretion of proinflammatory cytokines that sustain and enhance the development of immunoinflammatory responses [3]. However, there is a distinct difference between NAFLD of lipodystrophy and common NAFLD: leptin levels are low or very low in the former, whereas normal or high in the latter [158]. Therefore, metreleptin administration leads to its restoration in lipodystrophy, but supraphysiologic levels in common NAFLD. Based on this speculation, metreleptin treatment in lipodystrophy may have a preventive role on inflammation and fibrosis, since it ameliorates hepatic volume and steatosis, which are prerequisites for the subsequent inflammation and fibrosis. On the other hand, metreleptin administration in common NAFLD associate with normal or high BMI is not expected to essentially improve steatosis, since obesity is a leptin resistant state, and may act as a pro-inflammatory and fibrogenic factor, because it is not a true replacement treatment. However, even in lipodystrophy, when advanced fibrosis or NASH-related cirrhosis has been established, metreleptin may also act as a pro-inflammatory and fibrogenic factor, implying that it may possibly be administered in early stages of NAFLD, when significant inflammation and fibrosis are not present. Considering the above, large RCTs of sufficient duration are needed to study efficacy and safety of metreleptin in lipodystrophic patients with SS and early NASH [3].

It should be noted that leptin receptor agonists and/or leptin analogues (protein therapeutics) are expected to be devoid of the main problem plaguing metreleptin i.e., the possible development of neutralizing anti-leptin antibodies. In this regard, a leptin analogue (7i) was shown to exert beneficial effect on hepatic steatosis in a mouse model of diet-induced obesity [159]. The introduction of novel leptin analogues preserving the anti-steatotic, but lacking the proinflammatory and fibrogenic leptin action would be of paramount importance for the treatment of NAFLD in lipodystrophy [154].

Transplantation of adipose tissue has been also proposed as an alternative treatment of metabolic abnormalities in lipodystrophy. Preadipocytes isolation and culture have been proposed to be followed by adipocyte repopulation and transplantation [160]. Although intriguing in concept, this has not been largely investigated, so the metabolic effects of adipose tissue transplantation remain essentially unknown in lipodystrophy. Autologous fat transfer together with dermal fillers has been tested mainly for esthetically restoring facial lipoatrophy in HIV patients, providing encouraging results [161]. It should be also taken under consideration that there are reported cases, in whom hematopoietic stem cell transplantation to treat leukemia or neuroblastoma resulted in abnormal patterns of adipose tissue distribution, mimicking APL, later in life [162], thus representing an emerging type of lipodystrophy, which may provide useful information on the genetic and pathophysiologic processes of lipodystrophy.

It should be highlighted that the lack of RCTs in the treatment of lipodystrophy does not make recommendations straight forward and/or the evaluation of the comparative efficacy and/or the risk-benefit of any treatment fully proven. The lack of comparative evaluation among different pharmacologic agents (e.g., metreleptin, TZDs, metformin, GLP-1 analogues) renders empiric the choice of the best agent and could be only decided on a person-by-person basis. Last but not least, these facts make the evaluation of cost-effectiveness of each pharmacologic approach unknown at this point in time [1].

In conclusion, advances in adipose tissue physiology and in the genetics of lipodystrophy have radically improved our understanding of this heterogeneous disease and metreleptin treatment has provided beneficial metabolic effects, including reducing hepatic volume and steatosis. More clinical trials are needed, with less heterogeneous populations, focusing mainly on the effect of leptin on early hepatic inflammation and fibrosis as well as the potential effect of combination treatments. A global registry of patients with lipodystrophy may facilitate the establishment of clinical trials in the future [1].

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Author contributions

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