

# Congenital Lipodystrophies and Dyslipidemias

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**Abstract** Lipodystrophies are rare acquired and genetic disorders characterized by the selective loss of adipose tissue. One key metabolic feature of patients with congenital inherited lipodystrophy is hypertriglyceridemia. The precise mechanisms by which the lack of adipose tissue causes dyslipidemia remain largely unknown. In recent years, new insights have arisen from data obtained in vitro in adipocytes, yeast, drosophila, and very recently in several genetically modified mouse models of generalized lipodystrophy. A common metabolic pathway involving accelerated lipolysis and defective energy storage seems to contribute to the dyslipidemia associated with congenital generalized lipodystrophy syndromes, although the pathophysiological changes may vary with the nature of the mutation involved. Therapeutic management of dyslipidemia in patients with lipodystrophy is primarily based on specific approaches using recombinant

leptin therapy. Preclinical studies suggest a potential efficacy of thiazolidinediones that remains to be assessed in dedicated clinical trials.

**Keywords** Lipodystrophy · *BSCL2*/seipin · Caveolin 1 · Hypertriglyceridemia · Insulin resistance

## Introduction

Lipodystrophies regroup a heterogeneous group of syndromes in which the primary defect is a lack of adipose tissue that may be congenital or acquired in origin [1••, 2, 3] (summarized in Table 1). Lipodystrophy should be considered in patients manifesting the combination of insulin resistance (with or without overt diabetes), dyslipidemia (mainly hypertriglyceridemia), and liver steatosis [4]. Lipodystrophies are classified according to the origin of the disease (genetic or acquired) and the anatomical distribution of adipose tissue (generalized or partial). The severity of the metabolic phenotype is about proportional to the degree of adipose tissue loss, and therefore tends to be worse in generalized lipodystrophy. In this review, we will focus on the clinical characteristics, molecular mechanisms, and treatment of dyslipidemias related to congenital lipodystrophies, with special mention of Berardinelli–Seip congenital lipodystrophy (BSCL).

## Classification of Congenital Lipodystrophies and Clinical Characterization

### Congenital Generalized Lipodystrophies (BSCL)

BSCL is characterized by an almost complete lack of adipose tissue from birth or early infancy [1••, 2, 3, 5]. Metabolic complications generally appear progressively during

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**Table 1** Classification, clinical features, and molecular basis of inherited lipodystrophies

Gene/protein	Specific clinical features	Main role of the affected protein
Congenital generalized lipodystrophies <sup>a</sup>		
<i>AGPAT2</i> / <i>AGPAT2</i>	Bone lesions	Acylation of lysophosphatic acid to form phosphatidic acid in TG and phospholipid biosynthetic pathway
<i>BSCL2</i> /seipin	Extreme lack of body fat, mild mental retardation, cardiomyopathy	Required for lipid droplet formation and for adipogenesis
<i>CAVI</i> /caveolin 1	Short stature, vitamin D deficiency (single case)	Integral protein of caveolae which binds fatty acids and translocates them to lipid droplets
<i>PTRF</i> /cavin 1	Muscular dystrophy, pyloric stenosis	Integral protein of caveolae which regulates the expression of caveolin 1 and caveolin 3
<i>FOS</i> /c-FOS	Growth retardation, hypercholesterolemia (single case)	Transcription factor involved in adipocyte differentiation
Partial lipodystrophies <sup>b</sup>		
<i>LMNA</i> /lamin A/C	Dunnigan syndrome—preserved or excess facial and neck fat at puberty	Protein of the nuclear envelope
<i>PPARG</i> / <i>PPAR</i> $\gamma$	Preserved abdominal fat, hypertension	Transcription factor for adipocyte differentiation
<i>PLIN1</i> /perilipin 1	Small white adipocytes and increased fibrosis	Integral component of the adipocyte lipid droplet involved in lipid storage and lipolysis regulation
<i>CIDEA</i> / <i>CIDEA</i>	White adipocytes with multilocular lipid droplets (single case)	Regulation of lipid droplet size, thereby favoring lipid storage and inhibiting lipolysis
<i>AKT2</i> / <i>AKT2</i>	Single family	Serine/threonine kinase involved in insulin receptor signaling and adipocyte differentiation

*AGPAT2* 1-acylglycerol-3-phosphate-*O*-acyltransferase 2 (also known as lysophosphatidic acid acyltransferase  $\beta$ ), *AKT2* v-Akt murine thymoma viral oncogene homolog 2 (also known as protein kinase B), *CIDEA* cell-death-inducing DNA-fragmentation-factor-like effector C (also known as fat-specific protein FSP27 homolog), *PPAR* $\gamma$  peroxisome-proliferator-activated receptor  $\gamma$ , *TG* triglyceride

<sup>a</sup> Extended lack of adipose tissue, dyslipidemia, severe insulin resistance, fatty liver, pseudoacromegaly

<sup>b</sup> Loss of subcutaneous fat from the extremities, dyslipidemia, insulin resistance, fatty liver

childhood. Early insulin resistance (reflected by the presence of acanthosis nigricans) progresses to overt diabetes during the teenage years or later. Plasma leptin and adiponectin concentrations are reduced in correlation with the amount of residual fat [6], although in BSCL type 2, a surprisingly detectable adiponectin level has been reported [7].

BSCL is a rare heterogeneous recessively inherited disorder. Positional cloning strategies have led to the identification of two major loci: *BSCL1* on chromosome band 9q34 [8] encoding acylglycerol-3-phosphate-*O*-acyltransferase 2 (*AGPAT2*) [9] and *BSCL2* on chromosome band 11q13 encoding seipin [10], which are involved in most cases [11]. In a few cases, other BSCL-causative genes have been identified: *CAVI* (*BSCL3*) encoding caveolin 1 has been reported in single patient [12] and *PTRF* (*BSCL4*) encoding polymerase I and transcript release factor also known as cavin 1 [13, 14] has been reported in about 20 patients. Recently, a mutation in the *FOS* (encoding the transcription factor c-Fos) promoter has been identified in a single patient, in whom the phenotype and the mode of inheritance are not well characterized [15]. It is likely that additional loci exist, as some patients with BSCL do not harbor mutations in any of the known genes.

## Partial Lipodystrophies

Partial lipodystrophies are characterized by loss of fat affecting the limbs, with variable truncal involvement and normal or excess fat on the face and neck [1••, 2–4]. The onset of lipodystrophy usually occurs during childhood or puberty or later. Metabolic features range from asymptomatic impaired glucose tolerance with mild dyslipidemia to severe insulin resistance, diabetes, and dyslipidemia, depending on the extent of fat tissue loss. Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease are common complications.

The familial partial lipodystrophy (FPL) syndromes are usually transmitted according to an autosomal dominant mode of inheritance [16]. A positional cloning strategy led to the identification of the first locus for the Dunnigan variety of FPL, i.e., *LMNA*, on chromosome locus 1q21-22 [17–19]. *LMNA* encodes type A lamins, which are integral components of nuclear lamina. The candidate gene approach has led to the identification of four other FPL-causative genes: *PPARG*, encoding peroxisome-proliferator-activated receptor (*PPAR*)  $\gamma$  [20, 21], a key transcription factor involved in adipocyte differentiation; *AKT2*, encoding v-AKT murine thymoma oncogene homolog 2 [22], involved in insulin signaling; and *CIDEA*, encoding cell-death-inducing DNA fragmentation

factor  $\alpha$  like C [23], and *PLIN*, encoding perilipin 1 [24], both involved in lipid droplet (LD) maintenance (Table 1).

#### Clinical Characteristics of Dyslipidemia in Inherited Lipodystrophies

Hypertriglyceridemia is a common feature of BSCL, although it is variable among individuals within the same family and also within the same individual over time depending on age, food, and environmental factors such as physical activity [5, 25]. Such hypertriglyceridemia results from the accumulation of both chylomicrons and very low density lipoproteins (VLDL), and may lead to eruptive xanthomas and acute pancreatitis. Plasma levels of phospholipids and total cholesterol are usually within the normal range or are slightly elevated, whereas high-density lipoprotein (HDL) levels are decreased. However, increased plasma total cholesterol levels have sometimes been reported [12, 15]. Free fatty acids (FFA) levels are variable, normal, or slightly elevated. Hepatomegaly is a constant feature of BSCL [1•, 2, 3, 5, 25]. Accumulation of liver triglycerides (TGs) leads to hepatic steatosis and to increased VLDL synthesis, which contributes, to hypertriglyceridemia [26].

In vivo mechanistic studies are few in number and are confined mostly to individual case studies (with unknown genetic origin). For instance, in a 25-year-old patient with BSCL, the ability of insulin to inhibit lipolysis was markedly blunted [27]. In six patients with BSCL, the postprandial lipid metabolism evaluated using labeled TG-rich lipoprotein (TRL) emulsion revealed that both lipoprotein lipase (LPL)-mediated lipolysis and removal of TRL remnant were impaired and delayed [28]. The data on LPL activity are quite variable since in some reports LPL activity was reported to be normal [29, 30], whereas it was markedly reduced in other cases [31]. In striking contrast, plasma TG lipolysis appeared increased and uncontrolled in patients carrying the PPAR $\gamma$  P467L mutation [32]. Although P467L mutation causes partial lipodystrophy, these findings brought important insights into the pathological mechanisms of lipodystrophies. Postprandial FFA concentrations were increased in these patients and paralleled the peak of TG concentrations in the postprandial state. However, this rise in FFA concentrations was not linked to increased lipolysis, but rather to the inability of the tissue to internalize and store the <sup>13</sup>C-palmitic acid coming from labeled TRL. Similar studies with BSCL patients of various genotypes will be necessary to establish if this is also the case in these patients. Nonetheless, a strong body of evidence suggests that adipose tissue failure strongly impairs the postprandial TG metabolism, owing to defective TG uptake. Indeed, lipodystrophy is associated with the inability to store excess of energy, since BSCL patients fed a high-fat diet over a period of time display increased plasma TG and FFA levels [29, 30]. When seven patients with different types of

lipodystrophies were fed 30 % excess energy as fat, there was an increase in energy expenditure as a result of an increase in fat oxidation [33].

#### Mouse Models as Tools to Decipher the Molecular Mechanisms Involved in Dyslipidemia Related to Lipodystrophies

As human studies are difficult to conduct, the development of mouse models has provided key tools to improve our understanding of the molecular mechanisms involved in the origin of lipodystrophy and also important models to study the metabolic BSCL phenotypes (reviewed in [34]).

Inability to expand adipose tissue results in metabolic complications. The first proof of this concept in a mouse model arose from transgenic mice that express diphtheria toxin A under the adipose-tissue-specific AP2 promoter, resulting in a massive loss of adipose tissue. The inability to store TG in the adipose tissue resulted in a twofold increase in plasma TG levels and liver weight. No significant changes in cholesterol levels was reported. Even if this was not per se a model of lipodystrophy, this was the first publication that stated that in mice, limitation of the expansion of adipose tissue results in hypertriglyceridemia and liver steatosis [35].

#### Transcription Factors of Adipogenesis and Lipogenesis

Five years later, the two first mouse models of general lipodystrophy were generated. The overexpression of the nuclear mature form of the transcription factor SREBP1c under the AP2 promoter results in an alteration of the expression of key adipogenic factors, such as PPAR $\gamma$  and CCAAT/enhancer-binding protein  $\alpha$  (C/EBP $\alpha$ ), and results in a severe lipodystrophic phenotype, similar to human BSCL [36]. Insulin resistance and diabetes in these mice were associated with liver steatosis and hypertriglyceridemia. Notably, the plasma total cholesterol level was also increased in this model.

On the other hand, A-ZIP/F mice specifically express in adipose tissue, under the AP2 promoter, a dominant negative protein that binds to C/EBP $\alpha$ , a key transcription factor involved in adipogenesis [37]. A-ZIP/F mice are severely lipodystrophic and display a threefold increase in plasma TG levels and liver steatosis, suggesting that the lack of C/EBP $\alpha$  activity in the adipocyte was largely the cause of the lipodystrophic phenotype. Indeed, the lack of C/EBP $\alpha$  expression in adipose tissue was sufficient to induce a massive loss of white adipose tissue (WAT), a fatty liver, and a severe hypertriglyceridemia [38]. WAT transplantation in A-ZIP/F mice improves glucose and insulin levels but has a modest effect on TG levels. Leptin levels were improved by WAT transplantation in a dose-dependent manner, and the highest

plasma leptin concentration coincided with the strongest effect on TG levels [39]. Consistently, leptin treatment of AP2-nSREBP1c mice reversed insulin resistance [40], and hepatic overexpression of leptin in an A-ZIP/F background corrects hypertriglyceridemia [41]. These data suggest that leptin levels play a key role in TG homeostasis in lipodystrophic mouse models.

PPAR $\gamma$  is the master regulator of adipogenesis, and embryonic stem cells lacking PPAR $\gamma$  cannot undergo adipogenesis [42]. Global PPAR $\gamma$  deletion is lethal [42, 43]. Adipose-tissue-specific deletion of PPAR $\gamma$  under the AP2 promoter results in mild and progressive lipodystrophy without a change in plasma TG levels [44]. In contrast, using the adiponectin promoter, Wang et al. [45•] demonstrated that the ablation of PPAR $\gamma$  in adipocytes leads to a severe and almost complete lipodystrophic phenotype. The mice were strongly hypoleptinemic, hypoadiponectinemic, and insulin-resistant, with a massive liver steatosis and a fivefold increase in plasma TG levels. In conclusion, genetic impairment of adipogenesis compromises adipose tissue development and homeostasis, resulting in severe lipodystrophy associated with massive liver steatosis and hypertriglyceridemia. Together, these findings reinforce the central role of adipose tissue in TG homeostasis.

#### Caveolae

Caveolae are specialized invaginations of the plasma membrane that are found in numerous cell types and that are particularly abundant in adipocytes. In 2001, Razani et al. [46] highlighted that caveolin-1-deficient mice were resistant to a high-fat diet and displayed fat loss and adipocyte abnormalities with ageing. Caveolin 1 is one of the key component of caveolae [47]. Following up this publication, several groups intended to understand why caveolin 1 deficiency leads to lipodystrophy with ageing. Despite unchanged messenger RNA levels, the protein levels of the insulin receptor are dramatically reduced in *Cav1*<sup>-/-</sup> mice fat pads, altering therefore insulin signaling and sensitivity in this tissue [48]. In addition, caveolin 1 localizes to LDs in adipocytes [49] and its translocation to the LD can be rapidly induced by cholesterol incubation in 3 T3-L1 adipocyte cell lines [50]. Caveolin 1 deficiency strongly affects phospholipid composition and the morphology of LDs isolated from primary adipocytes [51]. Finally, caveolin 1 deficiency constitutively activates the autophagic process [52] and increases the susceptibility to cell death [53]. *Cav1*<sup>-/-</sup> mice are hypertriglyceridemic in the fasting and postprandial states and display strong delay in postprandial TG clearance [46]. LPL activity is not affected, and the origin of this hypertriglyceridemia is mainly attributed to the inability of caveolin-1-deficient adipocytes to store lipids properly in the LDs. Since caveolin 1 is a cholesterol-binding protein, the consequences of its deletion on plasma

cholesterol metabolism have been studied. Caveolin 1 deficiency has no impact on cholesterol levels on a wild-type background, but does lead to an increase in low density lipoprotein (LDL) cholesterol levels on an *ApoE*<sup>-/-</sup> background [54]. Intriguingly, this rise in LDL cholesterol levels was associated with a decrease in the area of atherosclerotic lesions, as CD36 expression is strongly decreased in caveolin-1-deficient macrophages. It remains unclear, however, whether lipodystrophy per se is involved in the hypercholesterolemia reported in these mice as the adipose tissue phenotype was not reported.

#### Lipid Synthesis

The ability to store lipids as TG is a key function of adipocytes. Impairment in TG synthesis compromises adipose tissue function and is involved in the development of lipodystrophy. AGPAT2, which is mutated in BSCL type 1 allows, the transformation of lysophosphatidic acid (LPA) to phosphatidic acid, a key step in TG synthesis. *Agpat2*<sup>-/-</sup> mice lack both brown adipose tissue and WAT, and are hypertriglyceridemic, hyperinsulinemic, hyperglycemic, and severely hypoleptinemic [55]. On the basis of the severity of liver steatosis, the study authors analyzed the expression of the genes involved in hepatic lipid metabolism and found that despite AGPAT2 deficiency, lipogenesis and TG synthesis were increased in the liver of *Agpat2*<sup>-/-</sup> mice. Molecular analysis revealed that the monoacylglycerol transferase 1 expression level was increased 54-fold, suggesting that the induction of the alternative monoacyl glycerol pathway might explain in part the massive liver TG accumulation in *Agpat2*<sup>-/-</sup> mice. However, liver adenoviral overexpression of acylglycerol-3-phosphate-*O*-acyltransferase 1 (AGPAT1) and AGPAT2 in *Agpat2*<sup>-/-</sup> mice failed to improve liver steatosis, suggesting that lipodystrophy and insulin resistance are critical for the liver phenotype of these animals [56•]. Indeed, cellular studies have shown that AGPAT2 (but not AGPAT1) knockdown [57] in 3T3L1 cells strongly impairs adipogenesis [58]. AGPAT2 deficiency alters lipid synthesis and leads to an accumulation of lysophosphatidic acid. Treatment with the PPAR $\gamma$  agonist rosiglitazone partially restored the adipogenesis [57].

Lipin 1, another key enzyme in the TG synthesis pathway, is also involved in generalized lipodystrophy in mice [59]. Spontaneous loss-of-function mutations in the gene encoding lipin 1 have been identified in the fatty liver dystrophic (Fld) mouse model, which is characterized by TG accumulation and a massive liver steatosis in the presuckling period [60]. These lipid abnormalities were associated with a strong decrease in adipose tissue LPL activity. At that time, the gene involved in the Fld phenotype was unknown. More than 10 years later, Reue et al. [59] showed that adult Fld mice have normal TG levels, only a modest liver mass increase (20%), but a massive adipose tissue loss (80%) associated with glucose intolerance.

The adipose tissue of these mice displayed a strong morphological default with abnormal LDs. Lipin 1 exerts a phosphatidate phosphatase type 1 activity, which catalyzes the transformation of PA to diacylglycerol, also a key step in TG biosynthesis [61]. Lipin 1 deficiency strongly prevents differentiation of 3T3-L1 cells and mouse embryonic fibroblasts into adipocytes [62]. In mice, lipin 1 loss of function restricted to the mature adipocyte strongly affects TG synthesis, leads to PA accumulation, and induces lipodystrophy [63•]. Lipin 1 deficiency severely compromises adipogenesis through impairment in TG synthesis and storage in adipocytes, leading to a severe lipodystrophic phenotype. However, unlike the other lipodystrophic models, lipin 1 deficiency is not associated with hypertriglyceridemia in adult mice, in total deficient mice [59] or in adipocyte-specific deficient mice [63•]. Indeed, hypertriglyceridemia is transient and resolves after weaning, whereas lipodystrophy, in contrast, starts to be visible [59]. Lipin 1 overexpression in liver decreases VLDL secretion, whereas its deficiency increases it [64, 65]. However, liver TG synthesis is not affected in Fld mice [64], but lipin 1 has been found in the nucleus, where it amplifies the PPAR  $\gamma$  coactivator 1  $\alpha$ /PPAR $\alpha$  induction of the expression of genes involved in  $\beta$ -oxidation [66]. Further work is needed to understand why the effect of lipin 1 on VLDL secretion does not alter plasma TG levels in the basal condition.

#### *Bscl2*-Deficient Mouse Models: The Paradoxical Hypotriglyceridemia

*BSCL2* was identified in 2001 as the first gene implicated in BSCCL in humans. However, its function was unknown at that time [10]. Studies from yeast and human cells suggested that seipin is involved in LD morphology [67–70]. On the other hand, seipin deficiency strongly impairs adipogenesis [71, 72] and increases the basal rate of lipolysis, preventing, therefore, adipocyte TG accumulation [73, 74]. Seipin-deficient mice display a severe lipodystrophy associated with insulin resistance and massive liver steatosis [73–76]. Mature adipocyte AP2-driven seipin deficiency alters adipocyte function and LD morphology, and progressively leads to lipodystrophy [77]. The insights from mouse models suggest that seipin is required not only for normal adipocyte differentiation but also for the maintenance of mature adipocyte function. However, the exact function of seipin remains largely unknown. Seipin deficiency is associated with PA accumulation in yeast [78], and seipin has been shown to interact with lipin [79]. These results suggest that seipin could be involved in TG synthesis, but the exact physiological relevance of seipin/lipin interaction has not yet been established.

One striking observation, regarding the human observations, is that all three available seipin-deficient mouse models are hypotriglyceridemic in the fasting state [73–75], whereas

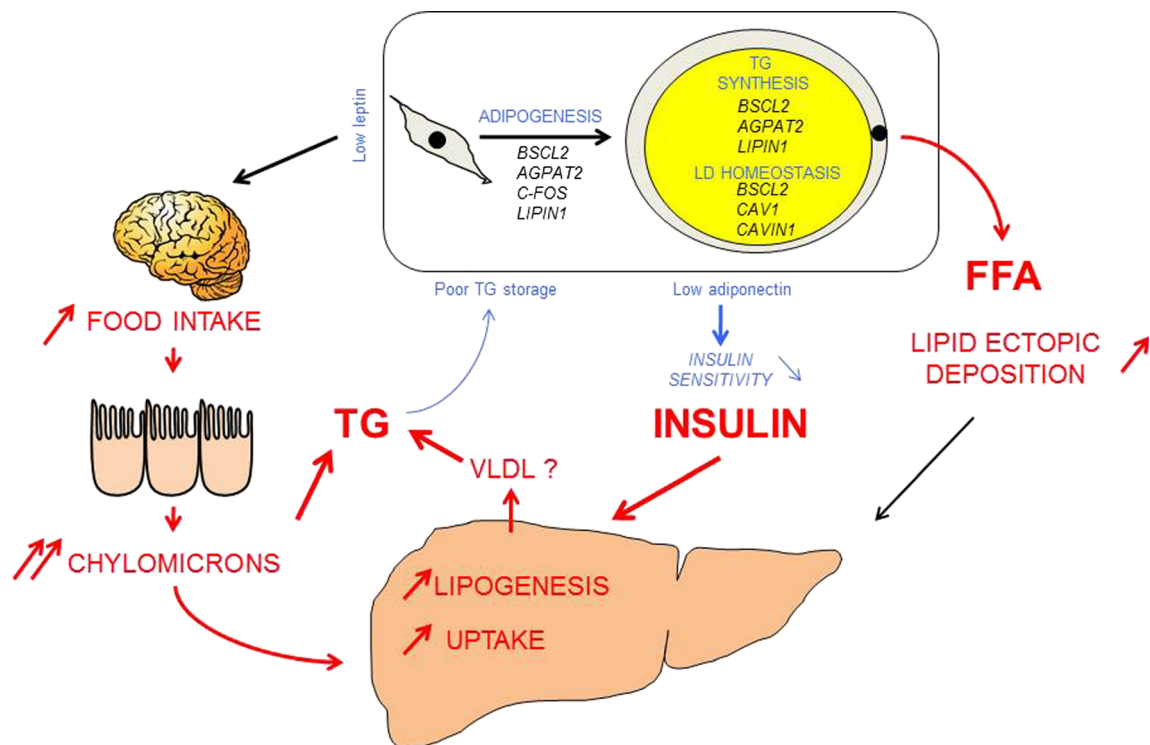
one of the three models is also hypotriglyceridemic in the fed state [74]. We have shown that the reduced plasma TG levels could be partly due to accelerated VLDL clearance and increased TG uptake by the liver [74]. This finding raises the question of a potential liver function of seipin, in addition to its key role in adipocytes. However, thiazolidinedione (TZD) treatment improves insulin sensitivity, reduces liver steatosis, increases energy expenditure, and normalizes VLDL clearance by increasing WAT mass and adipokine (adiponectin and leptin) secretion. Nonetheless, if lipodystrophy is the key mechanism involved in the metabolic complications associated with seipin deficiency, it is quite difficult to understand why seipin-deficient mice do not display hypertriglyceridemia. It is interesting to note that the only other lipodystrophic mouse model without hypertriglyceridemia is the Fld mouse, given the fact that lipin 1 and seipin have been shown to interact.

This large body of work suggests that, in general, all the genes involved play a key role in adipocyte differentiation of function, and that their deficiency leads to lipodystrophy. Most of the work that intended to show an effect of liver deletion of these genes failed to recapitulate the same phenotype. However, liver steatosis is a common feature, and the increase of lipogenesis, due to the selective hepatic insulin resistance, and the increased FFA uptake also contribute to this phenotype. Interestingly, two key parameters have not been systematically studied in these different models: VLDL production and postprandial TG clearance. When assessed, the postprandial TG clearance is delayed, which is consistent with the human kinetic studies (Fig. 1).

#### Therapeutic Management of Dyslipidemias in Lipodystrophies

The main objectives in patients with lipodystrophies are to reduce hypertriglyceridemia and the cardiovascular risk. An additional aim in this population is to address NAFLD and nonalcoholic steatohepatitis (NASH), the latter being life-threatening owing to the risk of liver cirrhosis and hepatocellular carcinoma.

Apart from studies of recombinant leptin therapy, there are only very few prospective controlled studies in patients with inherited lipodystrophies, owing to the rarity of the disease. Therefore, the analysis of both efficacy and safety of available therapeutics is based on case series or expert opinion [80, 81, 102]. In some cases, we refer to studies conducted in patients with HIV-associated lipodystrophy to extrapolate some results in congenital lipodystrophies.



**Fig. 1** All the genes involved in Berardinelli–Seip congenital lipodystrophy are key for adipocyte differentiation or function. The lack of mature and functional adipocytes will basically generate three main defaults: (1) accelerated lipolysis; (2) poor lipid uptake; (3) low adipokine secretion. The inability of adipose tissue to store the dietary lipids will lead to an increased in plasma triglyceride (TG) levels, especially in the

postprandial state, and an increased TG-rich lipoprotein uptake in the liver, contributing to ectopic lipid deposition. In addition, the hyperinsulinemia combined with the selective hepatic insulin resistance leads to increased de novo lipogenesis. The level of very low density lipoprotein (VLDL) secretion and its contribution to hypertriglyceridemia remain unclear. FFA free fatty acid, LD lipid droplet

### Lifestyle Modifications

Restriction of total fat intake to between 20 and 30 % of total dietary energy is often sufficient to maintain normal serum TG concentrations [80]. The importance of this nutritional intervention is sustained by the results obtained in *Agnat2<sup>-/-</sup>* deficient mice, in which a fat-free diet for 2 weeks markedly decreased plasma and hepatic TG levels by 50–60 % [55]. In addition, high consumption of carbohydrate (especially fructose) should also be avoided. The beneficial effect of a Mediterranean diet, enriched in *n*-3 polyunsaturated fatty acids (PUFAs), on metabolic parameters has been demonstrated in HIV-positive patients with highly active antiretroviral therapy (HAART)-induced metabolic syndrome [82]. Additional studies are warranted to determine whether this Mediterranean diet is equally effective in patients with inherited lipodystrophies. Finally, there are no solid data available concerning the metabolic effect of regular physical activity in patients with lipodystrophy.

### *n*-3 Polyunsaturated Fatty Acids

Despite the lack of controlled trials, the use of *n*-3 PUFAs, eicosapentaenoic acid and docosahexaenoic acids, is

recommended since they can reduce plasma TG levels by up to 50 %. Recently, *n*-3 PUFAs have failed to demonstrate cardiovascular protection in a large randomized trial conducted in patients with type 2 diabetes mellitus (T2DM) or prediabetes [83].

### Fibrates

Fibrates, which act as PPAR $\alpha$  agonists, could be also used as hypotriglyceridemic drugs, although robust efficacy trials are lacking in the context of lipodystrophy [80]. Moreover, fenofibrates did not reduce the incidence of cardiovascular events in large recent randomized trials performed in patients with T2DM [84, 85].

### Statins

In contrast to what observed has been observed with fibrates, statins have clearly demonstrated a consistent reduction in the incidence of cardiovascular events in several randomized trials [86]. Thus, statins should be recommended in patients with lipodystrophy, especially in those with diabetes and/or atherosclerosis. However, some pilot studies conducted in HIV patients with HAART suggest that statins are less effective in

patients with lipodystrophy [87, 88]. It is unclear whether such resistance also operates in inherited lipodystrophies.

#### Insulin Sensitizers: Metformin and Thiazolidinediones

Since insulin resistance is one of the key feature of lipodystrophies, insulin sensitizers appear to be a logical option for the treatment of metabolic disorders.

Metformin is rather an inhibitor of hepatic gluconeogenesis than a true insulin sensitizer [89]. Metformin has been used in acquired (HAART) and congenital partial lipodystrophies. A recent meta-analysis of trials conducted in patients with HAART suggests that metformin significantly reduces both fasting insulin and plasma TG levels compared with placebo, with no effect on LDL cholesterol and HDL cholesterol. Moreover, metformin was superior to rosiglitazone in reducing lipid levels [90]. A mechanistic study of the effect of metformin (2 g/day) and rosiglitazone (8 mg/day) on postprandial lipemia has been performed in patients with HIV-associated lipodystrophy [91]. In this 6-month prospective, randomized, open study, metformin was superior to rosiglitazone for the reduction in body weight as well as in subcutaneous and abdominal fat. Metformin reduced fasting TG levels, but had no effect on the postprandial plasma TG profile. In contrast, rosiglitazone increased fasting plasma TG levels, but simultaneously decreased postprandial TG excursion, resulting in an area under the curve unchanged from the baseline. However, rosiglitazone also significantly increased the levels of remnant-like particles enriched in cholesterol, a phenomenon that might increase atherosclerosis risk [91]. No data are available for pioglitazone.

The discovery of the TZD class of antidiabetic drugs as high-affinity PPAR $\gamma$  ligands was a major breakthrough in the pharmacology of PPAR $\gamma$ . TZDs (also termed glitazones) are potent insulin sensitizers that efficiently and sustainably improve glycemic control in patients with T2DM [92]. By contrast to metformin, TZDs improve whole-body insulin sensitivity during hyperinsulinemic–euglycemic clamp studies in patients with T2DM [93, 94], reflecting an increase in peripheral glucose disposal. Although both metformin and TZDs decrease hepatic glucose production, only TZDs decrease liver fat content [93, 95]. The partitioning of lipids to WAT (i.e., “lipid steal” hypothesis) following TZD treatment likely accounts for the indirect improvement in skeletal muscle insulin sensitivity and the reduction in liver steatosis, similar to what is seen in animal models. In addition, serum adiponectin concentrations are increased by TZD treatment, but not by metformin treatment, and this increase in adiponectin levels correlates with a reduction in liver fat content [93]. However, their use has been challenged in clinical practice because of side effects which include weight gain, fluid retention precipitating cardiac failure, and bone fractures [92].

Several data sustain the efficacy of TZDs in inherited lipodystrophies. The first demonstration of the beneficial effect of TZDs came from an open-label prospective study with troglitazone in patients with various lipodystrophy syndromes [96]. After 6 months of treatment, troglitazone reduced hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>), fasting plasma TG, and FFA levels, and increased the amount of subcutaneous fat, but did not increase the amount of visceral fat [96]. The hepatotoxicity observed with troglitazone was probably related to a direct toxicity of the molecule (which was withdrawn from the market shortly afterward), rather than a TZD class effect. Indeed, these seminal findings were confirmed in many individual cases reporting a decrease of fasting TG and plasma FFA levels, as well as liver enzyme levels, with either rosiglitazone treatment [97] or pioglitazone treatment [98, 99] in patients with FPL. In most of these cases, TZD was used in combination with metformin. Recently, an MRI study demonstrated that changes in adipose tissue distribution coincided with biochemical improvement in two FPL patients treated with rosiglitazone (8 mg/day). Notably, rosiglitazone induced a significant decrease (more than 50 %) in the amount of liver fat [100]. Together with the improvement of liver histological features in patients with NASH treated with pioglitazone [101], these data suggest that TZDs are the drugs of choice to treat liver damage in patients with lipodystrophy. Simha et al. [102] suggested that prolonged TZD treatment was unable to promote fat deposition in lipodystrophic regions in FPL patients, and that the increase in body weight was due to fat accumulation in nonlipodystrophic regions (i.e., truncal fat).

Compared with FPL treatment, there are only very few reports of TZD treatment in BSCL [96, 103]. As mentioned already, our data in *Bscl2*<sup>-/-</sup> mice suggest a beneficial effect of TZDs in BSCL [74]. A case report sustains this hypothesis since the addition of rosiglitazone treatment (8 mg/day) to treatment with metformin (850 mg twice daily) and sulfonylurea (glibenclamide) in a 19-year-old male with BSCL type 2 led to a reduction of HbA<sub>1C</sub> (-1.3 %) and fasting insulin levels and a normalization of plasma TG levels (from 4.3 to 1.7 mmol/l). Moreover, the levels of liver enzymes (alanine aminotransferase and  $\gamma$ -glutamyl transpeptidase) were also reduced. These metabolic effects occurred independently of changes in fat mass [103].

To precisely assess the efficacy and safety of TZDs in patients with inherited lipodystrophies, some randomized controlled trials are warranted. In the light of its beneficial effects on cardiovascular events [104], linked to a better plasma lipid profile than rosiglitazone [105], as well as its positive action on NASH [101], pioglitazone should be chosen first.

#### Recombinant Leptin Replacement Therapy

Marked improvements in metabolic parameters were observed with leptin replacement therapy in patients with

generalized lipodystrophies. Recently, the long-term (i.e., 3 years) effects of metreleptin (an analogue of human leptin) on dyslipidemia were reported in 55 patients with lipodystrophy (36 BSCL patients and 19 partial lipodystrophy patients) [106]. Notably, the mean percentage of TG reduction was 36.7 % after 4 months of treatment and 35.4 % at 3 years. The reduction was even more drastic in patients with elevated plasma TG levels at the baseline (200 mg/dl or higher), with a 51.2 % decrease at 3 years. In addition, metreleptin also reduced total cholesterol and LDL levels (-105.8 % and -64.3 % at 3 years, respectively), whereas there was no effect on HDL levels. Leptin recombinant therapy also exerts some beneficial action on glucose homeostasis, with a reduction of the levels of HbA<sub>1C</sub> and liver enzymes (suggesting a beneficial effect on NAFLD). In some patients, a resistance to leptin replacement therapy has been observed, linked to the development of antibodies against recombinant leptin [107]. In a 28-month trial conducted in eight children with BSCL, a negative or a partial effect of leptin therapy on hypertriglyceridemia, liver steatosis, and insulin resistance was observed in five patients, despite a significant increase in leptin dosage. This lack of efficacy was related to neutralizing leptin antibodies.

## Conclusion

Adipose tissue failure leads to numerous metabolic complications. The commonest lipid disorder trait associated with lipodystrophy is hypertriglyceridemia. Uncontrolled lipolysis and the inability of adipocytes to store dietary lipids will promote TG and FFA accumulation in plasma. Increased lipid liver uptake combined with increased lipogenesis contributes to liver steatosis. Animal models are unique tools to dissect the molecular mechanism involved in plasma TG regulation in the context of lipodystrophy. Notably, the respective dietary lipogenesis versus de novo liver lipogenesis has not been established yet.

Interestingly, most of the mechanistic studies suggest that the adipocyte function of the different genes involved, rather than their liver function, is at the molecular basis of the lipid disorder associated with lipodystrophy. However, the unexpected hypotriglyceridemic phenotype of *Bscl2*<sup>-/-</sup> mice as well as the normal TG levels of adult Fld mice suggest that, at least in mice, the adipose failures which result from different causes do not have similar consequences for circulating TG.

The use of animal models is also a unique opportunity to identify new targets and to test new therapeutic approaches. As tested in mice 15 years ago, leptin therapy in humans has beneficial effects but remains a very heavy severe treatment, with the risk of developing antibodies. Case reports and animals studies suggest that pioglitazone might be beneficial

to improve both lipodystrophy and the associated metabolic complications in BSCL. Clinical studies with kinetic lipid assessment will be needed to establish if TZDs are appropriate in the clinical management of lipodystrophy.

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## Compliance with Ethics Guidelines

**Conflict of Interest** Xavier Prieur, Cedric Le May, Jocelyne Magré, and Bertrand Cariou declare that they have no conflict of interest.

**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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- Of importance
- Of major importance

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