Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy

Abstract

Lipodystrophy syndromes are rare diseases that are often characterized by a general or partial absence of body fat. Fat tissues are also known as adipose tissues, and the lack of adipose tissues would lead to serious consequences and the development of a series of metabolic issues. These syndromes are genetically and clinically heterogeneous, with different phenotypes influenced by underlying molecular defects. They are all factors that determine the type of lipodystrophy a patient has. Due to the rarity of this disorder, not many studies have been done on it, which leads to people's lack of knowledge about this disease and increases the difficulty of treating it. In this article, we first consider the classification and clinical aspects of lipodystrophy syndromes, covering the onset and the differences in phenotypes of patients. Then, we discuss the molecular and cellular mechanisms of several types of lipodystrophies and the role they play in the development of adipose tissues. Next, we focus on other metabolic dysfunctions caused by lipodystrophy, such as insulin resistance, fatty liver, and hypertriglyceridemia. Lastly, we evaluate therapeutic strategies aimed at improving metabolic control and quality of life in affected patients. Future direction of study and potential therapies may be improved with a deeper and thorough understanding of the genetic and mechanistic basis of lipodystrophy.

Keywords: Lipodystrophy syndromes, adipose tissue, adipogenesis, gene mutations, metabolic dysfunctions

Introduction

Lipodystrophy syndromes (LD) are a heterogeneous group of rare disorders that often present as the lack of mature adipose tissue in specific or generalized areas. It leads to the inability to store body fat and excess nutrients (Fourman and Grinspoon 2022). Two main classes of lipodystrophy are Congenital Generalized Lipodystrophy (CGL) and Familial Partial Lipodystrophy (FPDL). Adipose tissues are formed through a process called adipogenesis, and it is crucial for the adipose tissue to function normally.

Adipogenesis is the process by which mesenchymal stem cells develop and differentiate into mature adipose tissues and ends with cell apoptosis. This also includes the triacylglycerol (TAG) fatty acid cycle. It is the process where the lipid droplets undergo lipolysis (the breakdown of lipid droplets) and lipogenesis (the synthesis of new lipid droplets)(Poulos et al. 2016). However, if a gene mutation or other factors affect the components that play a role in regulating this process, it would lead to serious, life-threatening consequences.

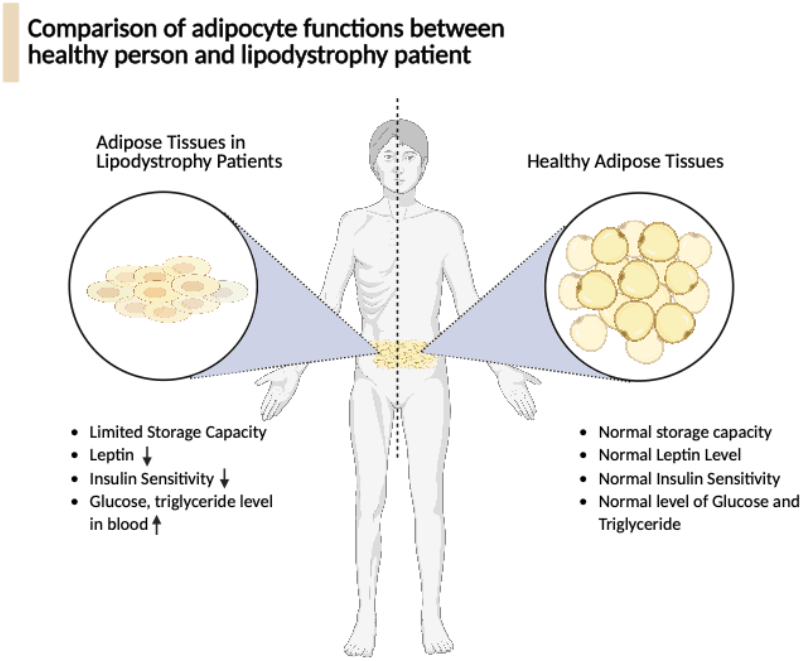
LD can be either congenital or acquired, and it is classified based on the location of lost adipose tissue, and further divided into subtypes according to the gene segment that is mutated (Akinci, Gular, and Oral 2024) (Table 1). CGL (also called

Berardinelli-Seip syndrome) is characterized by the total absence of adipocytes, both mechanical and metabolic fat tissues (Oswiecimska n.d.). CGLs are autosomal recessive, and the symptoms often start showing shortly after birth. It is further divided into CGL1, CGL2, CGL3, and CGL4, which link to four different gene mutations. FPLD presents as an abnormal distribution of adipose tissue, with fat loss around the limbs, torso, and hips. It can be autosomal recessive or dominant depending on the gene that is involved. Since the body is not able to store excess energy in those areas, other body parts, such as the face, neck, and internal organs like the liver, gain extra adipose tissue (Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic n.d.). Same as CGL, it is also divided into several subtypes, including FPLD1 (Kobberling-type lipodystrophy), FPLD2 (Dunnigan Variety lipodystrophy), FPLD3, FPLD4, FPLD5, and FPLD6. The product of all the genes associated with any kind of lipodystrophy plays an important role in phospholipid and triglyceride synthesis. Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome) have similar symptoms, respectively; however, they can be caused by autoimmune diseases, the side effects of antiretroviral therapy (ART) for HIV patients, and sometimes idiopathic (Misra and Garg 2003).

Not only will the lack of excess energy affect the body's normal functions, but other complications that arise with lipodystrophy also have a big effect on patients' lives. Some common metabolic abnormalities include leptin deficiency, insulin resistance, diabetes, hypertriglyceridemia, and fatty liver disease (figure 1). Currently, there are a lot of clinical trials in progress, trying to discover a new way to treat or cure lipodystrophy, especially targeting leptin deficiency. Metrelepin, for example, is a treatment created specifically for LD patients. It is a targeted treatment for leptin deficiency, which is a common metabolic issue associated with LD. (Araújo-Vilar e Santini 2019). However, patients still need to have a healthy diet and other medications for other metabolic issues. Currently, there is only one treatment that is directly for LD patients due to the rarity of this disease. According to studies, only about 3/million people around the world are affected by some type of lipodystrophy syndrome. While the prevalence of CGL is estimated to be 0.23/ million people, the prevalence of FPDL is around 2.84/million people (Chiquette et al. 2017). It is also estimated to shorten a patient's lifespan by 30 or more years. The main cause of death is shown to be liver diseases and infections caused by adipose tissue dysfunction, but also varies from type to type of lipodystrophy (Lima et al. 2018).

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
Generalized Lipodystrophy Syndrome					
Congenital Generalized Lipodystropy (Berardinelli-Seip syndrome)	CGL1	AGPAT2	Autosomal recessive	Near total absence of adipose tissue, generalized musularity, metabolic abnormalities. Starts showing symptoms shortly after birth.	Loss of metabolic fat, retains mechanical fat tissues
	CGL2	BSCL2	Autosomal recessive		Mild mental retardation
	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
Acquired Generalized Lipodystrophy (Lawrence Syndrome)	NA	NA	NA	Near total absence of adipose tissue, metabolic issues. Develops during childhoold/ puberty.	Could be caused by autoimmune diseases, panniculitus, idiopathic or immunotherapy
Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/adolescense.	Palpable "ledge" between normal and lipodistrophic
	FPLD2 (Dunnigan)	LMNA	Autosomal dominant		High risks of cardiovascular diseases
	FPLD3	PPARG	Autosomal dominant		Less severe and distal fat loss
	FPLD4	PLIN1	Autosomal dominant		Increased fibrosis of adipose tissue, small lipid droplets in adipocytes
	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

▲ (Table 1) Classification, clinical features, and molecular basis of lipodystrophies



▲ (Figure 1) Comparison of adipocytes functions between a healthy person and a lipodystrophy patient. The storage of an adipocytes is limited in lipodystrophy patients. Common metabolic abnormalities include leptin deficiency, insulin resistance and increase glucose level in blood streams. (Made by Biorender)

Clinical aspects of lipodystrophy syndromes

Since lipodystrophy is such a rare disease and not well known to the public, it is often misdiagnosed or undiagnosed by clinicians. It heavily relies on clinical history and physical examinations that reveal the composition of adipose tissues. Metabolic dysfunctions are also important markers when diagnosing lipodystrophy. Although patients with CGL show symptoms such as a lack of body fat shortly after birth, it is often left undiagnosed until their childhood or adulthood, when they start showing metabolic abnormalities. As for FPDL, it is even more commonly unrecognized due to patients only losing adipose tissue partially. It could be easily mixed up with other types of common metabolic diseases like obesity or severe diabetes mellitus. Presentations of AGL and APL are generally similar to CGL and FPDL, also including the metabolic issues that come with it(Lima et al. 2025).

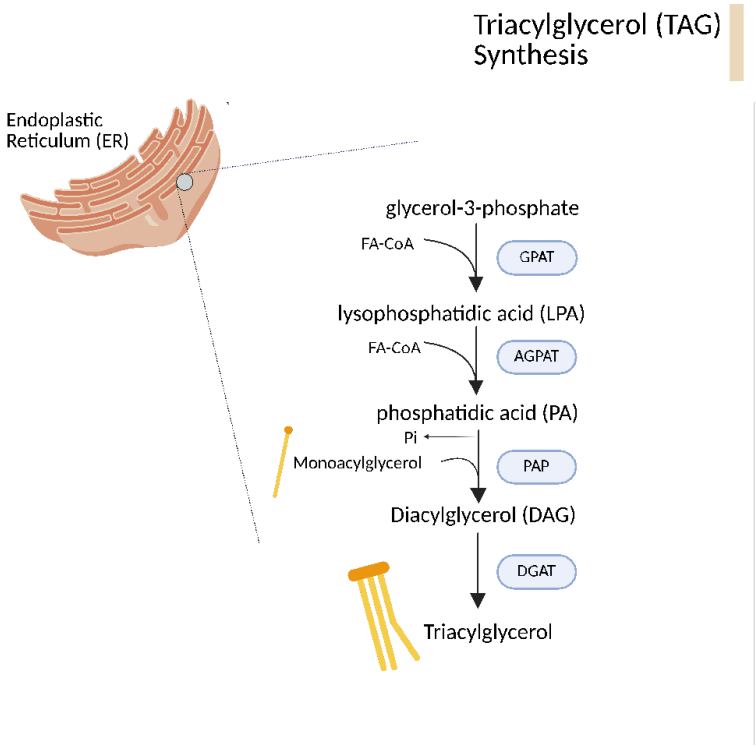
Some phenotypes that are associated with lipodystrophy are muscular appearance, prominent veins, and the lack of body fat. For CGL patients, the absence of metabolic adipose tissues is more common than mechanical tissues. Although patients still in some degrees lack functional mechanical fat tissues. Except for CGL2, in which patients generally do not acquire both kinds of fat tissues(Garg 2011). In contrast, FPDL is characterized by the abnormal distribution with a slight loss of adipose tissue, meaning that patients still acquire most of their functional fat tissues. In addition, as mentioned before, the onset of CGL is often shortly after birth, but for FPDLs, its onset is usually around puberty or adolescence. Next, we will be discussing some specific types of lipodystrophies in detail based on the step of adipogenesis affected and the mechanisms behind them.

Genetics behind lipodystrophy

Type 1 Congenital Generalized Lipodystrophy (CGL1)

Type 1 Congenital Generalized Lipodystrophy (CGL1) is caused by a mutation in the gene AGPAT2. AGPAT2 is the gene coding for a specific enzyme, 1-acylglycerol-3-phosphate O-acyltransferase 2, which catalyzes the acylation of lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1,2 diacylglycerol-3-phosphate)(Gale et al. 2006) (figure 2). It is an important precursor of the biosynthesis of triacylglycerol (TAG) and phospholipid synthesis from glycerol-3-phosphate. This step esterifies a second fatty acyl group at the sn-2 position of the glycerol backbone. Phosphatidic acid is further acylated by other enzymes, creating triacylglycerol and phospholipids. The AGPAT family consists of 11 isomers;

however, AGPAT2 is expressed at higher levels in adipose tissue than the other isomers. The presence of mechanical adipose tissue can be explained by the increased expression of the other isomers. However, studies have shown that the expression of AGPAT2 is required for the accumulation of triacylglycerol, especially in metabolic adipose tissues. Defects in AGPAT2 genes also impact insulin signaling, meaning that gluconeogenesis will be unrestricted, which leads to the development of hyperglycemia and diabetes(de Melo et al. 2025).



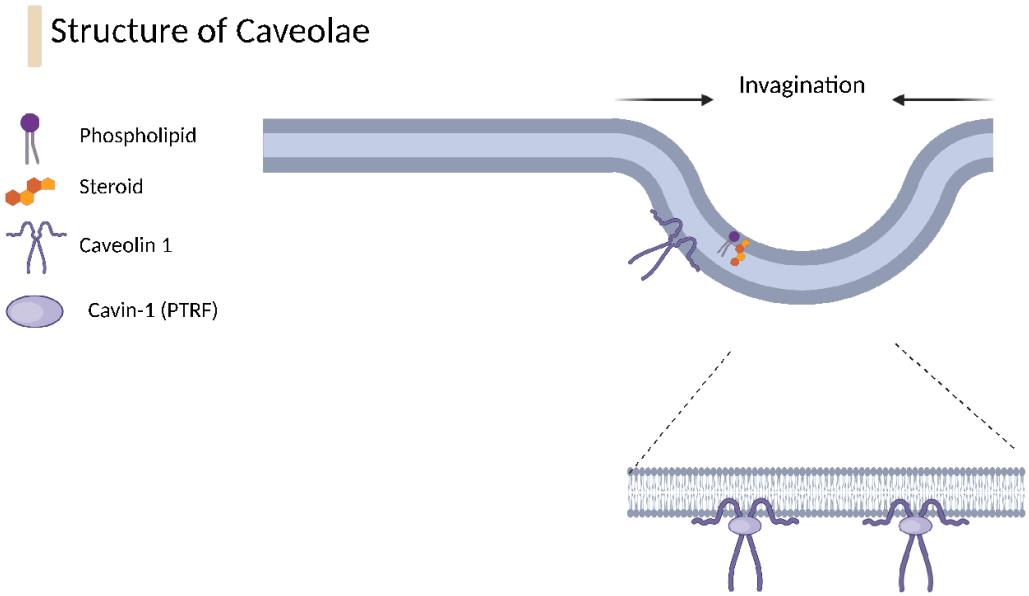
▲ (Figure 2) The process of Triacylglycerol synthesis. In the second step, where LPA is acylated to PA, AGPAT is the enzyme that catalyzes this reaction. Without it, the reactions after it will not occur properly, meaning that adipocytes can't develop properly. (Made by Biorender)

Type 4 Congenital Generalized Lipodystrophy (CGL4)

Type four Congenital Generalized Lipodystrophy (CGL4) is associated with the gene mutation in the PTRF gene (Polymerase I and Transcript Release Factor)(Salle-Teyssières et al. 2016). The PTRF gene encodes cavin-1, which is one of the essential proteins that is required for the biogenesis of caveolae. Caveolae are one of the most abundant invaginations in the cell membrane of lots of mammalian cells (Figure 3). Cavin-1 starts the whole process of the synthesis of caveolae by recruiting other proteins necessary, such as caveolins. Without it, cells won't be able to produce caveolae. Although it is abundant, its functions have only been understood in the past

few decades. It plays a role in signal transduction, endocytosis, and mechanotransduction (Stea and D'Alessio 2025). Cavin-1 binds with the caveolins to form Caveolae. There are three members in the caveolin family, caveolin 1,2 is expressed in a lot of cells, like smooth muscle cells, fibroblasts, and adipocytes. Caveolin 3 is expressed exclusively in cardiac and skeletal muscle. It is shown that the lack of PTRF-CAVIN doesn't affect the level of caveolin expressed (Rajab et al. 2010). However, it affects caveolin's ability to localize to the cell's surface, which makes the formation of caveolae impossible. Absence of caveolae causes the cell to not be able to develop properly, causing abnormalities and dysfunctions.

Some symptoms that are uniquely associated with this type of lipodystrophy are myopathy, which affects skeletal muscle structure, and distal metaphyseal deformation, causing bone stiffness and limited range of motion (Ardissone et al. 2013). Cardiac arrhythmias are also one of the symptoms caused by the lack of PTRF-CAVIN, and it could be life-threatening (Rajab et al. 2010). These symptoms can be explained by the location where caveolins 1,2and 3 are expressed.



(Figure 3) The structure of caveolae. Caveolae are clusters in the cell membrane. Cavin-1 and caveolin 1 bind together and form caveolae. (Made by Biorender)

Type 2 Familial Partial Lipodystrophy (FPDL2)

The gene LMNA, which encodes the protein called Lamins, is the gene that causes Type 2 Familial Partial Lipodystrophy (FPDL2). It is also the most common type of lipodystrophy syndrome (Corsa et al. 2021). In cells, Lamin A and Lamin C are expressed predominantly. The main functions of Lamin A/C are the regulation of nucleus shape, providing structural stability to the nuclear envelope and cytoskeleton

and also controlling gene regulation (Maung et al. 2026)·(Bagias et al. 2020). Specifically nuclear lamina and chromatin, and the interaction between them. One way that Lamin A can affect cell development is the interference with the cleavage step of post translational regulation of Lamin A. ZMPSTE24 plays an important role in this, and it is also considered to be one of the factors that causes lipodystrophy. This modification is crucial and ensures that Prelamin A (the precursor of Lamin A before the post translational regulation) will function normally. Not only will the lack of Lamin A affect cell functions, but the accumulation of Prelamin A could also be toxic to cells (Varlet, Helfer, and Badens 2020).

A high risk of cardiovascular diseases is also associated with FPDL2. Epicardial adipose tissue (EAT), which is fat tissue surrounding the myocardium and major coronary arteries(Talman et al. 2014), is a recently found biomarker that is related to FPDL2. It is found that FPDL2 patients have higher EAT volume than type two diabetes patients (Godoy-Matos et al. 2015). However, it is not related to other metabolic issues that are also presented in lipodystrophy (Lamothe et al. 2025). Other studies will also need to be done to have a clearer insight into this condition and the correlation between them.

Type 3 Familial Partial Lipodystrophy (FPDL3)

Type 3 Familial Partial Lipodystrophy (FPDL3) is caused by pathogenic variants of the PPARG gene. PPARG encodes for PPARγ (Peroxisome proliferator-activated receptor γ), known as the master regulator of adipocyte differentiation, maintenance, and functions(Broekema et al. 2019). PPARγ has three isomers, PPARγ1, PPARγ2, and PPARγ3. Among them, PPARγ2 is predominantly expressed in adipocytes. PPARγ acts as a ligand-activated transcription factor. It binds to its target gene as a heterodimer with PPAR-response elements (PPREs)(Madsen et al. 2022). After binding, PPARγ induces many targeted genes that are involved in the development of adipose tissues. The TAG cycle is also upregulated. Mutations in PPARG might cause excess differentiation and growth of adipocytes. Therefore, it leads to increased cellular stress and dysfunctions in adipocytes(Soares et al. 2024).

Compared to FPDL2, FPDL3 patients show less severe fat loss. One way to explain this is that more large adipocytes are preserved since mutations in PPARG could lead to excess cell growth. Fat accumulation in areas such as the face and neck are also not observed(Bagias et al. 2020). However, FPDL3 patients also show more severe metabolic symptoms, specifically hypertriglyceridemia, diabetes, and insulin resistance(Soares et al. 2024).

Acquired Generalized Lipodystrophy (AGL)

As we can see, a wide variety of gene mutations that affect different cellular functions could all lead to LD. However, gene mutations are not the only cause of

lipodystrophy. Other environmental factors can also trigger the onset of lipodystrophy. Acquired Generalized Lipodystrophy (AGL, also called Lawrence Syndrome) is another form of lipodystrophy, which has similar symptoms to CGL but is not caused by genetic mutations(Al-Jawad et al. 2025).

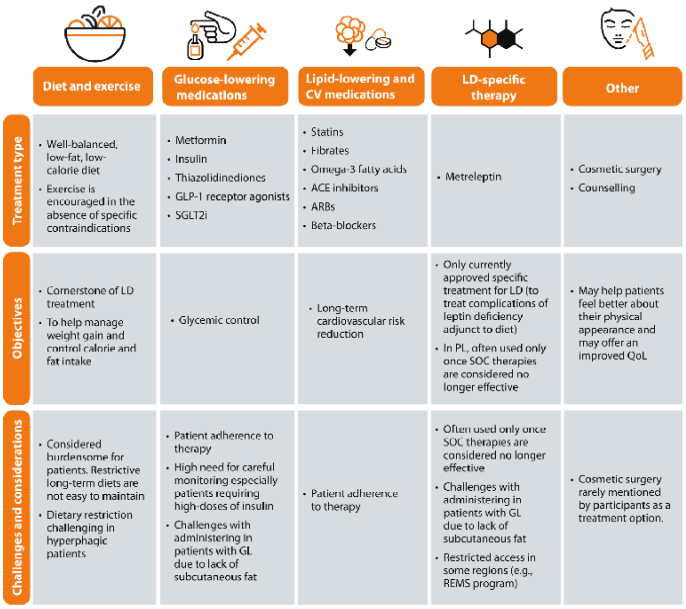
Adverse effects of highly active antiretroviral therapy (HAART) in patients with HIV are one of the factors that lead to AGL. The mechanism by which antiretroviral drugs play a role in the development of lipodystrophy is not understood completely. Proteins such as thymidine analog nucleoside reverse transcriptase inhibitors (NRTI), which are used in HAART, are shown to disrupt adipose tissue functions(Guzman and Vijayan 2025). It decreases the expression of adiponectin, which regulates the oxidation of glucose and fatty acids. NRTI also induces mitochondrial toxicity, which also plays a role in the development of AGL.

Another possible cause of AGL is autoimmune disease. Specifically, perilipin 1 (PLIN1) autoantibodies are found in AGL patients (Corvillo et al. 2022). Anti-perilipin is also found in patients with panniculitis associated AGL. Perilipin is found only in adipose tissue and forms a layer that coats lipid droplets. It leads to an increase in lipolysis activities, which decreases the fat storage in the body(Corvillo et al. 2018).

Treatments

Metreleptin

Currently, there isn't a definite treatment for lipodystrophy, but some treatments for specific metabolic abnormalities are being invented (Araújo-Vilar and Santini 2019). For example, Metreleptin (Recombinant methionyl human leptin) is a drug invented specifically for lipodystrophy. It targets leptin deficiency in patients. Leptin is a hormone that regulates energy metabolism. It is secreted by adipose tissue, and it regulates a person's appetite and food intake (Tsoukas, Farr, and Mantzoros 2015). Since lipodystrophy patients lack functional adipose tissue, leptin secretion also decreases. This causes patients to show extreme hyperphagia, which means the excessive intake of food. This worsens insulin resistance and creates excess fat that must be stored in internal organs or muscles. Metreleptin's main purpose is to mimic the naturally occurring leptin hormone, and it must be administered at least once daily (Rodriguez, Mastronardi, and Paz-Filho 2015). Metreleptin is found to be more efficient in Generalized lipodystrophy patients due to the low levels of leptin that are produced(Gilio, Foss-Freitas, and Oral 2025). However, the risk of using Metreleptin for special groups of people, such as pregnant women are not certain. Other common drugs, such as insulin or metformin, can also help patients control their symptoms; however, they are not a cure for LD. Cosmetic surgery is also an option for patients to minimize the psychological discomfort and to have a better quality of life (Table 2).



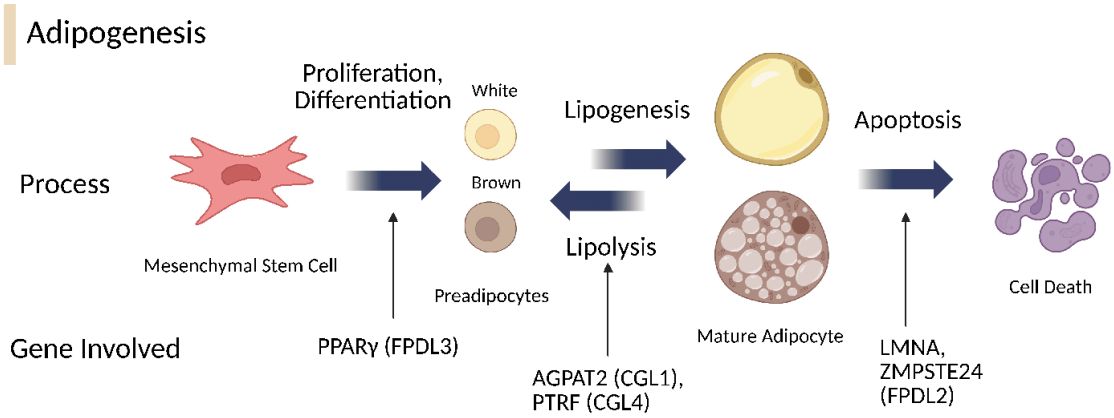
	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.

(Table 2) Possible medications to control metabolic issues that arises with lipodystrophy. Including the objectives, possible challenges and other considerations Reproduced from (Patni et al. 2024) under the terms of the CC BY license

Change in Daily Routine

Although Metreleptin can generally help with metabolic dysfunctions, lifestyle modification also plays a significant role in managing lipodystrophy. A low-fat diet is recommended for patients. Carbohydrate intake is also restricted to control diabetes. Physical exercises are also encouraged. However, patients with cardiovascular issues should avoid doing too much exercise to prevent the development of other serious complications (Akinci et al. 2024).

Conclusion and the Future



(Figure 4) Steps of adipogenesis. Starting from mesenchymal stem cells, after proliferation and differentiation, it develops into preadipocytes. Then, through lipogenesis, preadipocytes grow into mature adipocytes. When a person is fasting, adipocytes go through lipolysis to produce energy by breaking down triglycerides into glycerol and free fatty acid. The last step is apoptosis, which ultimately leads to cell death. (Made by Biorender)

Among the four types of lipodystrophies discussed above, they demonstrate how any stage of adipogenesis can cause LD. In this review, we discussed CGL1, CGL4, FPDL2, and FPDL3 just as examples of how different gene mutations that regulate different steps of adipogenesis all lead to similar consequences (Figure 4). In addition, we showed that acquired causes can also lead to adipocyte dysfunctions, which lead to AGL. Genes that are associated with lipodystrophy have a large variety, which play roles in various processes. They all lead to the lack or abnormal distribution of mature adipocytes, which is the most common phenotype of lipodystrophy. The amount of lost adipocytes differs, as well as the location for CGL and FPDL patients. Metabolic abnormalities also play an important role in the characterization of lipodystrophy. Insulin resistance, leptin deficiency, and fatty liver disease are all common metabolic issues that result from a lack of mature adipocytes. Currently, treatments can only target certain symptoms and are not able to cure them. Although treatments that are approved for lipodystrophy still only have limited effects, a change in the patient's daily routine would also help in controlling this disease.

In the future, gene editing could be applied to the treatment of this disease. Preclinical trials have been conducted on mouse models with CGL2, which has a gene mutation at the BSCL2 gene. Seipin knockout (SKO) mice, which generally show similar metabolic symptoms to CGL2 patients, were generated, and were injected with adeno-associated virus (AAV) vectors (Sommer et al. 2022). AVV targets adipocytes,

which act as a target in gene therapy for lipodystrophy. The results of the trials show that gene therapy effectively restores adipose tissue development and function (Tiwari et al. 2024). However, there is still a lot that needs to be done to start using gene therapy for lipodystrophy in humans.

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Thank you for submitting your manuscript, entitled *"Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy."* The topic is timely and clinically relevant, and your review covers important genetic and mechanistic aspects of lipodystrophy syndromes.

Before the manuscript can proceed to peer review, **we ask that you revise the paper to include a dedicated Methods section appropriate for a review article**. Specifically, please describe:

- The databases searched (e.g., PubMed, Scopus, Web of Science, etc.)
- The time frame covered by the search
- Keywords and Boolean search criteria used
- Inclusion and exclusion criteria
- Whether any language or study-category restrictions were applied
- The general approach to study selection and synthesis

Providing this information will necessarily strengthen transparency and methodological rigor.

In addition, we encourage you to address the editorial comments below to improve clarity, structure, and scholarly precision before external review:

- Again, the manuscript currently lacks a methods/search strategy section. As this is a narrative review, it should at the bare minimum state the search strategy, selection criteria, and how evidence was prioritized.
- Several references could be dated in the future or are otherwise very recent (e.g., 2025 and 2026). Please confirm that these are all published or in press, that DOIs are accurate, and that no placeholder or non-verifiable sources are included.
- The organization and flow are a bit unclear and repetitive. I would introduce a clearer structural outline (e.g., genetics -> pathophysiology -> clinical features -> treatment -> future directions), shorten some of your paragraphs on genetics to not distract as much from the main points, and reduce repetition in your introduction vs. conclusion. You should not have to repeat yourself over and over again to make the point clear. Integration > repetition.
- If the figures were made by the author in BioRender, please make this clear, and if not made by the author, they should be properly sourced.
- Some language could be made more precise.
    - Avoid statements such as "only one treatment" without qualification (what do you mean? what is this treatment?)
    - Replace informal or awkward phrasing with precise language (e.g., "a lot of clinical trials." How many? Do you mean trials or treatments? Do you really need to use this phrasing when you introduce the treatments later on?)
    - Some minor grammatical issues (e.g., adipogenesis "ends with apoptosis." What do you mean? This does not sound correct as-is)

Moreover, **the review remains largely descriptive.** I would, for instance, highlight more unresolved issues in the field, compare mechanistic differences across CGL vs. FPLD, and provide some more critical commentary on translational barriers for gene therapy.

We look forward to receiving your revised manuscript, and again, we believe that the core of your manuscript shows promise.

Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy

Abstract

Lipodystrophy syndromes are rare diseases that are often characterized by a general or partial absence of body fat. Fat tissues are also known as adipose tissues, and the lack of adipose tissues would lead to serious consequences and the development of a series of metabolic issues. These syndromes are genetically and clinically heterogeneous, with different phenotypes influenced by underlying molecular defects. They are all factors that determine the type of lipodystrophy a patient has. Due to the rarity of this disorder, not many studies have been done on it, which leads to people's lack of knowledge about this disease and increases the difficulty of treating it. In this article, we first consider the classification and clinical aspects of lipodystrophy syndromes, covering the onset and the differences in phenotypes of patients. Then, we discuss the molecular and cellular mechanisms of several types of lipodystrophies and the role they play in the development of adipose tissues. Next, we focus on other metabolic dysfunctions caused by lipodystrophy, such as insulin resistance, fatty liver, and hypertriglyceridemia. Lastly, we evaluate therapeutic strategies aimed at improving metabolic control and quality of life in affected patients. Future direction of study and potential therapies may be improved with a deeper and thorough understanding of the genetic and mechanistic basis of lipodystrophy.

Keywords: Lipodystrophy syndromes, adipose tissue, adipogenesis, gene mutations, metabolic dysfunctions

1. *Introduction*

Lipodystrophy syndromes (LD) are a heterogeneous group of rare disorders characterized by the partial or complete loss of mature adipose tissue in localized or generalized areas. This results in the inability to store body fat and excess nutrients (Fourman and Grinspoon 2022). Two main classes of lipodystrophy are Congenital Generalized Lipodystrophy (CGL) and Familial Partial Lipodystrophy (FPLD). Adipose tissues are formed through a process called adipogenesis, and it is crucial for the adipose tissue to function normally.

Adipogenesis is the process by which mesenchymal stem cells differentiate into mature adipose tissue. This process also includes the triacylglycerol (TAG) fatty acid cycle, which regulates lipid storage and mobilization in adipocytes. It is the process where the lipid droplets undergo lipolysis (the breakdown of lipid droplets) and lipogenesis (the synthesis of new lipid droplets)(Poulos et al. 2016). However, if a gene mutation or other factors affect the components that play a role in regulating adipogenesis, it would lead to serious, life-threatening consequences.

LD can be either congenital or acquired, and it is classified based on the location of lost adipose tissue, and further divided into subtypes according to the gene segment that

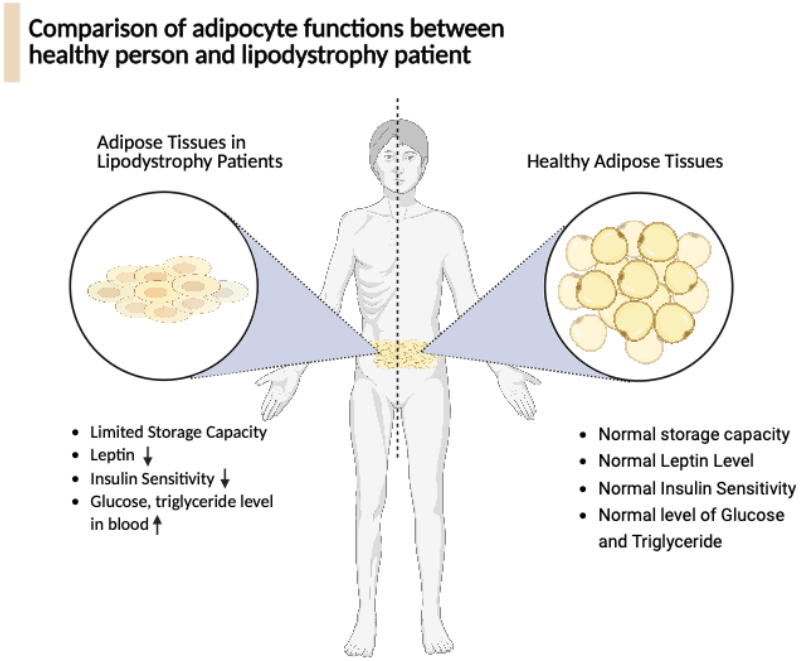
is mutated (Akinci, Gular, and Oral 2024) (Table 1). CGL (also called Berardinelli-Seip syndrome) is characterized by the near-complete absence of adipocytes, both mechanical and metabolic fat tissues (Oswiecimska n.d.). CGLs are autosomal recessive, and the symptoms often start showing shortly after birth. It is further divided into CGL1, CGL2, CGL3, and CGL4, which link to four different gene mutations. FPLD presents as an abnormal distribution of adipose tissue, with fat loss around the limbs, torso, and hips. It can be autosomal recessive or dominant depending on the gene that is involved. Since the body is not able to store excess energy in those areas, other body parts, such as the face, neck, and internal organs like the liver, gain extra adipose tissue (Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic n.d.). Same as CGL, it is also divided into several subtypes, including FPLD1 (Kobberling-type lipodystrophy), FPLD2 (Dunnigan Variety lipodystrophy), FPLD3, FPLD4, FPLD5, and FPLD6. Proteins or enzymes that are encoded by the genes associated with any kind of lipodystrophy all play important roles in the development of adipocyte. Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome) have similar symptoms, respectively; however, they can be caused by autoimmune diseases, the side effects of antiretroviral therapy (ART) for HIV patients, and sometimes idiopathic (Misra and Garg 2003).

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
Generalized Lipodystrophy Syndrome					
Congenital Generalized Lipodystropy (Berardinelli-Seip syndrome)	CGL1	AGPAT2	Autosomal recessive	Near total absence of adipose tissue, generalized musularity, metabolic abnormalities. Starts showing symptoms shortly after birth.	Loss of metabolic fat, retains mechanical fat tissues
	CGL2	BSCL2	Autosomal recessive		Mild mental retardation
	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
Acquired Generalized Lipodystrophy (Lawrence Syndrome)	NA	NA	NA	Near total absence of adipose tissue, metabolic issues. Develops during childhoold/ puberty.	Could be caused by autoimmune diseases, panniculitus, idiopathic or immunotherapy
Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/adolescense.	Palpable "ledge" between normal and lipodistrophic
	FPLD2 (Dunnigan)	LMNA	Autosomal dominant		High risks of cardiovascular diseases
	FPLD3	PPARG	Autosomal dominant		Less severe and distal fat loss
	FPLD4	PLIN1	Autosomal dominant		Increased fibrosis of adipose tissue, small lipid droplets in adipocytes
	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

▲ Table 1: Classification, clinical features, and molecular basis of lipodystrophies (Made with Google Sheet)

Not only will the lack of excess energy affect the body's normal functions, but other complications that arise with lipodystrophy also have a big effect on patients' lives. Some common metabolic abnormalities include leptin deficiency, insulin resistance, diabetes, hypertriglyceridemia, and fatty liver disease (figure 1). Currently, around 200 clinical trials are in progress, trying to discover a new way to treat or cure lipodystrophy, especially targeting leptin deficiency. Metreleptin, for example, is a treatment created specifically for LD patients. It is a targeted treatment for leptin deficiency, which is a common metabolic issue associated with LD. (Araújo-Vilar e Santini 2019). It currently the only FDA-approved treatment for LD patients. Due to the rarity of this disease, limited research has been done, making Metreleptin the primary choice for LD patients (Ajluni et al. 2016). Patients will still need to have a healthy diet and other medications for other metabolic issues. According to studies, only about 3/million people around the world are affected by some type of lipodystrophy syndrome. While the prevalence of CGL is estimated to be 0.23/ million people, the prevalence of FPLD is around 2.84/million people (Chiquette et al. 2017). It is also estimated to shorten a patient's lifespan by 30 or more years. The main cause of death is shown to be liver diseases and infections caused by adipose tissue dysfunction, but also varies from type to type of lipodystrophy (Lima et al. 2018).

This literature review aims to highlight the molecular mechanisms of lipodystrophy, focusing on the genetic causes, differences between types of lipodystrophies, and other metabolic conditions caused by adipose tissue abnormalities. In addition, the treatment developed and other possibilities for a cure.



⚠ Figure 1: Comparison of adipocytes functions between a healthy person and a lipodystrophy patient. The storage of an adipocytes is limited in lipodystrophy patients. Common metabolic abnormalities include leptin deficiency, insulin resistance and increase glucose level in blood streams. (Made with BioRender)

2. Method

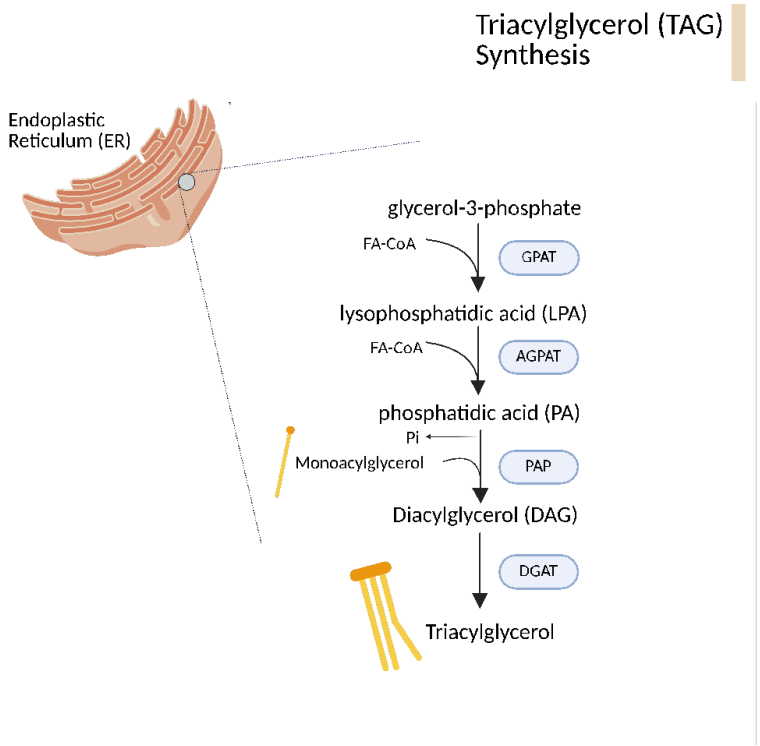
A literature search was conducted using PubMed and Google Scholar databases. The search included following keywords: “lipodystrophy genetics”, “adipocyte differentiation”, “AGPAT2”, “PTRF Cavin-1”, “LMNA mutation”, “PPARγ mutation”, “lipodystrophy metabolic abnormalities”. Articles published between 2000 and 2026 were included. Only publications in English language were considered. Studies were included if they were peer-reviewed primary research articles or comprehensive reviews focusing on genetic, molecular, or metabolic mechanisms of lipodystrophy syndromes. Case studies with relevant insights and information were also included. Non peer reviewed sources, articles published before 2000, case reports with only quantitative data and without further analysis were excluded. Titles and abstracts were first screened for relevance. Full article was reviewed if they met the inclusion criteria.

Discussion

3. Genetics and Pathophysiology

3.1 Type 1 Congenital Generalized Lipodystrophy (CGL1)

Type 1 Congenital Generalized Lipodystrophy (CGL1) is caused by a mutation in the gene AGPAT2. AGPAT2 is the gene coding for a specific enzyme, 1-acylglycerol-3-phosphate O-acyltransferase 2, which catalyzes the acylation of lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1,2 diacylglycerol-3-phosphate)(Gale et al. 2006) (figure 2). It is an important precursor of the biosynthesis of triacylglycerol (TAG) and phospholipid synthesis from glycerol-3-phosphate. This step esterifies a second fatty acyl group at the sn-2 position of the glycerol backbone. Phosphatidic acid is further acylated by other enzymes, creating triacylglycerol and phospholipids. The AGPAT family consists of 11 isomers; however, AGPAT2 is expressed at higher levels in adipose tissue than the other isomers. The presence of mechanical adipose tissue can be explained by the increased expression of the other isomers. However, studies have shown that the expression of AGPAT2 is required for the accumulation of triacylglycerol, especially in metabolic adipose tissues. Defects in AGPAT2 genes also impact insulin signaling, meaning that gluconeogenesis will be unrestricted, which leads to the development of hyperglycemia and diabetes(de Melo et al. 2025).



▲ Figure 2: The process of Triacylglycerol synthesis. In the second step, where LPA is acylated to PA, AGPAT is the enzyme that catalyzes this reaction. Without it, the reactions after it will not occur properly, meaning that adipocytes can't develop properly. (Made with BioRender)

3.2 Type 4 Congenital Generalized Lipodystrophy (CGL4)

Type four Congenital Generalized Lipodystrophy (CGL4) is associated with the gene mutation in the PTRF gene (Polymerase I and Transcript Release Factor)(Salle-Teyssières et al. 2016). The PTRF gene encodes cavin-1, which is one of the essential proteins that is required for the biogenesis of caveolae. Caveolae are one of the most abundant invaginations in the cell membrane of lots of mammalian cells (Figure 3). Cavin-1 starts the whole process of the synthesis of caveolae by recruiting other proteins necessary, such as caveolins. Without it, cells won't be able to produce caveolae. Although it is abundant, its functions have only been understood in the past few decades. It plays a role in signal transduction, endocytosis, and mechanotransduction (Stea and D'Alessio 2025). Cavin-1 binds with the caveolins to form Caveolae. There are three members in the caveolin family, caveolin 1,2 is expressed in a lot of cells, like smooth muscle cells, fibroblasts, and adipocytes. Caveolin 3 is expressed exclusively in cardiac and skeletal muscle. It is shown that the lack of PTRF-CAVIN doesn't affect the level of caveolin expressed (Rajab et al. 2010). However, it affects caveolin's ability to localize to the cell's surface, which makes the formation of caveolae impossible. Absence of caveolae causes the cell to not be able to develop properly, causing abnormalities and dysfunctions.

Some symptoms that are uniquely associated with this type of lipodystrophy are myopathy, which affects skeletal muscle structure, and distal metaphyseal deformation, causing bone stiffness and limited range of motion (Ardissone et al. 2013). Cardiac arrhythmias are also one of the symptoms caused by the lack of PTRF-CAVIN, and it could be life-threatening (Rajab et al. 2010). These symptoms can be explained by the location where caveolins 1,2and 3 are expressed.

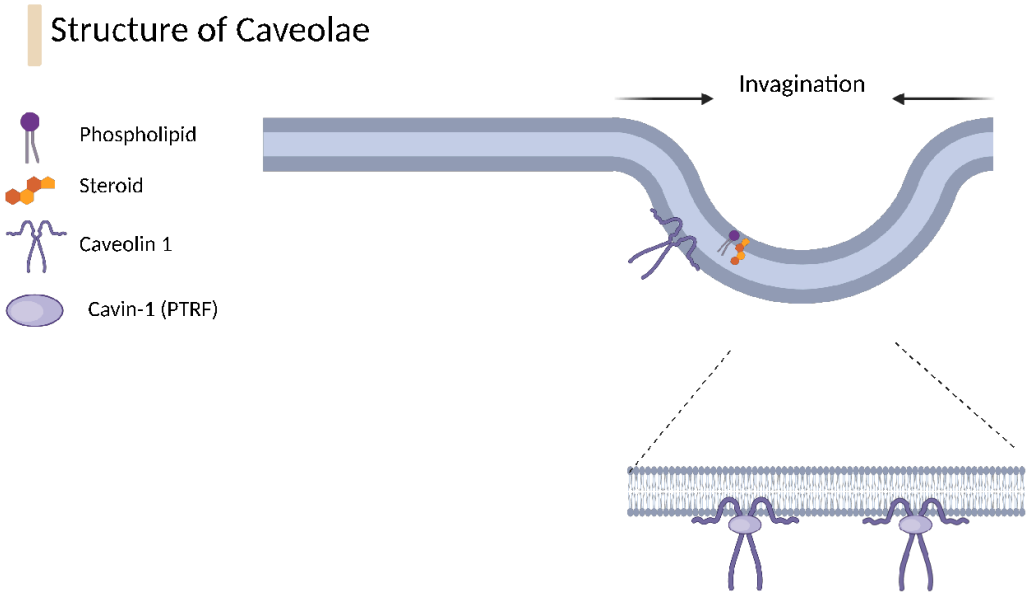


 Figure 3: The structure of caveolae. Caveolae are clusters in the cell membrane. Cavin-1 and caveolin 1 bind together and form caveolae. (Made with Biorender)

3.3 Type 2 Familial Partial Lipodystrophy (FPLD2)

The gene LMNA, which encodes the protein called Lamins, is the gene that causes Type 2 Familial Partial Lipodystrophy (FPLD2). It is also the most common type of lipodystrophy syndrome (Corsa et al. 2021). In cells, Lamin A and Lamin C are expressed predominantly. The main functions of Lamin A/C are the regulation of nucleus shape, providing structural stability to the nuclear envelope and cytoskeleton and also controlling gene regulation (Maung et al. 2026)·(Bagias et al. 2020). Specifically nuclear lamina and chromatin, and the interaction between them. One way that Lamin A can affect cell development is the interference with the cleavage step of post translational regulation of Lamin A. ZMPSTE24 plays an important role in this, and it is also considered to be one of the factors that causes lipodystrophy. This modification is crucial and ensures that Prelamin A (the precursor of Lamin A before the post translational regulation) will function normally. Not only will the lack of Lamin A affect cell functions, but the accumulation of Prelamin A could also be toxic to cells (Varlet, Helfer, and Badens 2020), which could affect the cell's ability to develop properly.

A high risk of cardiovascular diseases is also associated with FPLD2. It is found that FPLD2 patients have higher Epicardial adipose tissue (EAT) volume than type two diabetes patients (Talman et al. 2014) (Godoy-Matos et al. 2015). However, it is not related to other metabolic issues that are also presented in lipodystrophy (Lamothe et al. 2025). Other studies will also need to be done to have a clearer insight into this condition and the correlation between them.

3.4 Type 3 Familial Partial Lipodystrophy (FPLD3)

Type 3 Familial Partial Lipodystrophy (FPLD3) is caused by pathogenic variants of the PPARG gene. PPARG encodes for PPARγ (Peroxisome proliferator-activated receptor γ), known as the master regulator of adipocyte differentiation, maintenance, and functions(Broekema et al. 2019). PPARγ has three isoforms, PPARγ1, PPARγ2, and PPARγ3. Among them, PPARγ2 is predominantly expressed in adipocytes. PPARγ acts as a ligand-activated transcription factor. It binds to its target gene as a heterodimer with PPAR-response elements (PPREs)(Madsen et al. 2022). After binding, PPARγ induces many targeted genes that are involved in the development of adipose tissues. The TAG cycle is also upregulated. Mutations in PPARG might cause excess differentiation and growth of adipocytes. Therefore, it leads to increased cellular stress and dysfunctions in adipocytes(Soares et al. 2024).

Compared to FPLD2, FPLD3 patients show less severe fat loss. One way to explain this is that more large adipocytes are preserved since mutations in PPARG could lead to excess cell growth. Fat accumulation in areas such as the face and neck are also not

observed (Bagias et al. 2020). However, FPLD3 patients also show more severe metabolic symptoms, specifically hypertriglyceridemia, diabetes, and insulin resistance(Soares et al. 2024).

3.5 Acquired Generalized Lipodystrophy (AGL)

As we can see, a wide variety of gene mutations that affect different cellular functions could all lead to LD. However, gene mutations are not the only cause of lipodystrophy. Other environmental factors can also trigger the onset of lipodystrophy. Acquired Generalized Lipodystrophy (AGL, also called Lawrence Syndrome) is another form of lipodystrophy, which has similar symptoms to CGL but is not caused by genetic mutations(Al-Jawad et al. 2025).

Adverse effects of highly active antiretroviral therapy (HAART) in patients with HIV are one of the factors that lead to AGL. The mechanism by which antiretroviral drugs play a role in the development of lipodystrophy is not understood completely. Proteins such as thymidine analog nucleoside reverse transcriptase inhibitors (NRTI), which are used in HAART, are shown to disrupt adipose tissue functions(Guzman and Vijayan 2025). It decreases the expression of adiponectin, which regulates the oxidation of glucose and fatty acids. NRTI also induces mitochondrial toxicity, which also plays a role in the development of AGL.

Another possible cause of AGL is autoimmune disease. Specifically, perilipin 1 (PLIN1) autoantibodies are found in AGL patients (Corvillo et al. 2022). Anti-perilipin is also found in patients with panniculitis associated AGL. Perilipin is found only in adipose tissue and forms a layer that coats lipid droplets. It leads to an increase in lipolysis activities, which decreases the fat storage in the body(Corvillo et al. 2018).

4. Diagnosis and Clinical Features

Since lipodystrophy is such a rare disease and not well known to the public, it is often misdiagnosed or undiagnosed by clinicians. It heavily relies on clinical history and physical examinations that reveal the composition of adipose tissues. Metabolic dysfunctions are also important markers when diagnosing lipodystrophy. Although patients with CGL show symptoms such as a lack of body fat shortly after birth, it is often left undiagnosed until their childhood or adulthood, when they start showing metabolic abnormalities. As for FPLD, it is even more commonly unrecognized due to patients only losing adipose tissue partially. It could be easily mixed up with other types of common metabolic diseases like obesity or severe diabetes mellitus. Presentations of AGL and APL are generally similar to CGL and FPLD, also including the metabolic issues that come with it (Lima et al. 2025).

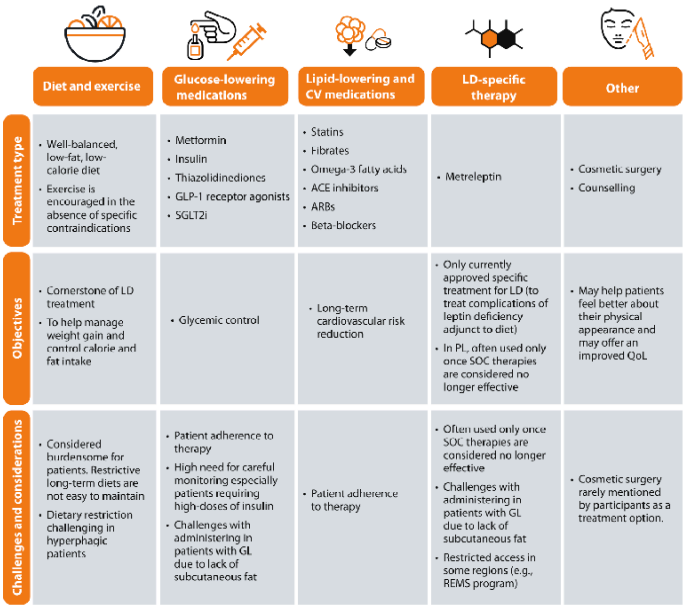
Some phenotypes that are associated with lipodystrophy are muscular appearance, prominent veins, and the lack of body fat. For CGL patients, the absence of metabolic adipose tissues is more common than mechanical tissues. Metabolic adipose tissues are in

charge or energy storage and hormone secretion, while the mechanical tissues, also known as subcutaneous fat tissue, are found under the skin and internal organs to provide protection and support. Although patients still in some degrees lack functional mechanical fat tissues. Except for CGL2, in which patients generally do not acquire both kinds of fat tissues (Garg 2011). In contrast, FPLD is characterized by the abnormal distribution with a slight loss of adipose tissue, meaning that patients still acquire most of their functional fat tissues. In addition, as mentioned before, the onset of CGL is often shortly after birth, but for FPLDs, its onset is usually around puberty or adolescence. In general, CGL patients lack the ability to build up mature adipose tissues, while FPLD patients can't store or regulate adipose tissue properly. Next, we will be discussing some potential treatments for lipodystrophy and the mechanisms behind them.

5. Treatments

5.1 Metreleptin

Currently, there isn't a definite treatment for lipodystrophy, but some treatments for specific metabolic abnormalities are being invented (Araújo-Vilar and Santini 2019). For example, Metreleptin (Recombinant methionyl human leptin) is a drug invented specifically for lipodystrophy. It targets leptin deficiency in patients. Leptin is a hormone that regulates energy metabolism. It is secreted by adipose tissue, and it regulates a person's appetite and food intake (Tsoukas, Farr, and Mantzoros 2015). Since lipodystrophy patients lack functional adipose tissue, leptin secretion also decreases. This causes patients to show extreme hyperphagia, which means the excessive intake of food. This worsens insulin resistance and creates excess fat that must be stored in internal organs or muscles. Metreleptin's main purpose is to mimic the naturally occurring leptin hormone, and it must be administered at least once daily (Rodriguez, Mastronardi, and Paz-Filho 2015). Metreleptin is found to be more efficient in Generalized lipodystrophy patients due to the low levels of leptin that are produced(Gilio, Foss-Freitas, and Oral 2025). However, the risk of using Metreleptin for special groups of people, such as pregnant women are not certain. Other common drugs, such as insulin or metformin, can also help patients control their symptoms; however, they are not a cure for LD. Cosmetic surgery is also an option for patients to minimize the psychological discomfort and to have a better quality of life (Table 2).



	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.

⚠ Table 2: Possible medications to control metabolic issues that arises with lipodystrophy. Including the objectives, possible challenges and other considerations (Reproduced from (Patni et al. 2024) under the terms of the CC BY license)

5.2 Change in Daily Routine

Although Metreleptin can generally help with metabolic dysfunctions, lifestyle modification also plays a significant role in managing lipodystrophy. A low-fat diet is recommended for patients. Carbohydrate intake is also restricted to control diabetes. Physical exercises are also encouraged. However, patients with cardiovascular issues should avoid doing too much exercise to prevent the development of other serious complications (Akinci et al. 2024).

5.3 Limitations and Possibility of Gene Editing

Although Metreleptin is an effective way for LD patients to manage metabolic complications, it is not able to cure it. In the future, gene editing could be applied to the treatment of this disease. Preclinical trials have been conducted on mouse models with CGL2, which has a gene mutation at the BSCL2 gene. Seipin knockout (SKO) mice, which generally show similar metabolic symptoms to CGL2 patients, were generated, and were injected with adeno-associated virus (AAV) vectors (Sommer et al. 2022). AVV targets adipocytes, which act as a target in gene therapy for lipodystrophy. The results of the trials show that gene therapy effectively restores adipose tissue development and function (Tiwari et al. 2024). However, even though AVV is commonly used in clinical trials, it hasn't been used to directly target adipose tissue. Novel AVV serotypes that targets adipose tissue or alternative promoter are critical for the development of an improved gene therapy strategy for LD patients. Therefore, there isn't enough evidence currently to

suggest that the results from mouse models can be translated to humans. Continued research on LD and advances in gene therapy are necessary to develop a more effective therapeutic strategy for this rare disorder.

6. *Conclusion and the Future*

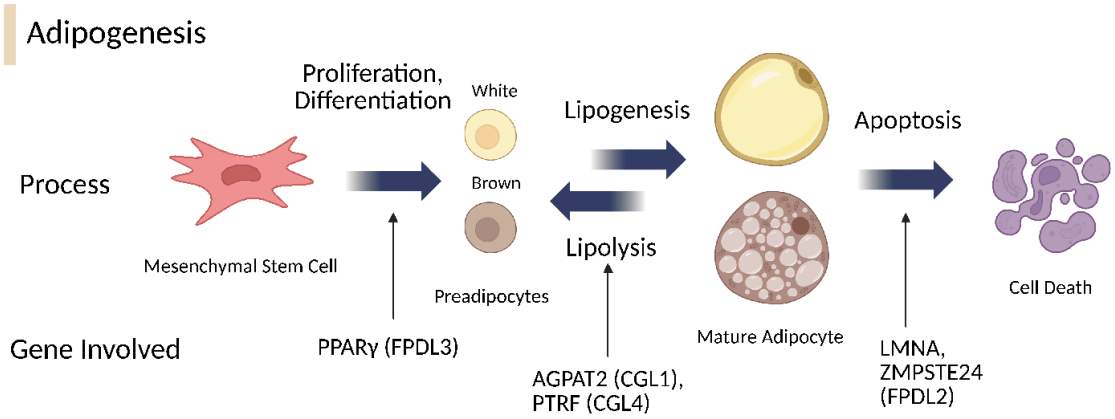


Figure 4: Steps of adipogenesis. Starting from mesenchymal stem cells, after proliferation and differentiation, it develops into preadipocytes. Then, through lipogenesis, preadipocytes grow into mature adipocytes. When a person is fasting, adipocytes go through lipolysis to produce energy by breaking down triglycerides into glycerol and free fatty acid. The last step is apoptosis, which ultimately leads to cell death. (Made with BioRender)

Although genes involved in lipodystrophy syndromes affect various cellular processes, such as lipid synthesis, signal transduction, and nuclear structure, they all lead to a common outcome -impaired adipocyte development and function. The examples discussed in this review, including CGL1, CGL4, FPLD2, and FPLD3, demonstrate how different stages of adipogenesis and gene mutations that are involved in adipogenesis all lead to similar consequences (Figure 4). In addition to genetic causes, acquired factors can also contribute to adipocyte dysfunctions, as seen in AGL.

LD highlights the essential role of adipose tissue as an endocrine and metabolic organ. It not only stores energy but also maintains metabolic homeostasis and regulates hormones. The absence of adipocytes, as shown in this review, could cause life-threatening disorders. Understanding this condition not only helps people recognize the role of adipose tissue in metabolism but also helps raise awareness of rare diseases. For conditions like lipodystrophy, many patients remain undiagnosed throughout their lives. Not only is conducting research with so few samples challenging, but scientists may

be less willing to dedicate time to studying rare diseases compared to diseases that affect a larger population. Increased awareness and improved diagnostic tools not only help identify individuals affected by this disease earlier but also give them a chance to manage their condition in a more effective way.

Since the discovery of lipodystrophy syndromes around the mid-20th century, lots of progress has been made to get a better understanding of lipodystrophy. From the phenotypes to the metabolic abnormalities and the underlying genetic causes, research have been done to seek for ways to reduce patient's pain and suffering. Having a deep understanding of lipodystrophy will be crucial to the development of a more effective and targeted therapeutic strategy.

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Revision Letter

17 Mar, 2026

Dear Editors,

I am writing for the resubmission of the manuscript “Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy”. First, thank you very much for your comments and suggestions, as well as the time and effort you devoted to reviewing my manuscript. The feedback had helped me improve the quality and clarity of the paper. Below, I address the changes made in the manuscript.

Comment: Again, the manuscript currently lacks a methods/search strategy section. As this is a narrative review, it should at the bare minimum state the search strategy, selection criteria, and how evidence was prioritized.
Response: A new paragraph after the introduction is added, addressing the points mentioned.

Comment: Several references could be dated in the future or are otherwise very recent (e.g., 2025 and 2026). Please confirm that these are all published or in press, that DOIs are accurate, and that no placeholder or non-verifiable sources are included.
Response: References included in the paper from 2025 and 2026 have been double-checked, and they are all published. DOIs cited are accurate, and they are all verifiable sources.

Comment: The organization and flow are a bit unclear and repetitive. I would introduce a clearer structural outline (e.g., genetics, pathophysiology, clinical features, treatment, future directions), shorten some of your paragraphs on genetics to not distract as much from the main points, and reduce repetition in your introduction vs. conclusion. You should not have to repeat yourself over and over again to make the point clear. Integration > repetition.
Response: I have made some changes to the overall order of sections. Also, I have added some other information in the conclusion to reduce repetition. Some information in the genetic section is deleted to avoid too much distraction.

Comment: If the figures were made by the author in BioRender, please make this clear, and if not made by the author, they should be properly sourced.
Response: The source is added after each figure/table description in parentheses. All figures were made with Biorender, table one was made with Google Sheet, and table two was adapted from Patni et al. 2024.

Comment: Some language could be made more precise.
○ Avoid statements such as “only one treatment” without qualification (what do you mean? what is this treatment?)
○ Replace informal or awkward phrasing with precise language (e.g., “a lot of clinical trials.” How many? Do you mean trials or treatments? Do you really need to use this phrasing when you introduce the treatments later on?)
○ Some minor grammatical issues (e.g., adipogenesis “ends with apoptosis.” What do you mean? This does not sound correct as-is)
Response: I have made slight changes in response to the suggestions. I highlighted the parts in the manuscript that have been changed. Specifically, I used more precise wordings and deleted or changed parts that might be confusing.

EDITOR COMMENTS AND RECOMMENDATION:

The reviewers commend the author for the depth and breadth of research presented in this manuscript. Both reviewers suggest modifications to the text, specifically more formal, precise language as well as additional elaboration or clarity in the sections detailed below. Special attention should be paid to the "major points" 1-3 from Reviewer 1. In addition to the general feedback provided, Reviewer 2 has also given point by point edits that may be considered for general readability and clarity. Given the reviewer feedback, the editor's recommendation is to accept the manuscript following major revisions.

REVIEWER 1:

Brief Summary

This manuscript provides a narrative review of the genetic, molecular, and clinical aspects of lipodystrophy syndromes, focusing primarily on Congenital Generalized Lipodystrophy (CGL), Familial Partial Lipodystrophy (FPLD), and acquired forms. It explores the metabolic complications arising from these conditions, such as insulin resistance and fatty liver, and evaluates current therapeutic approaches, including metreleptin and potential AAV-mediated gene therapies.

General Impression

The authors have synthesized a broad range of literature to highlight the critical role of adipose tissue as an endocrine and metabolic organ through the lens of rare lipodystrophic disorders. The inclusion of future perspectives, such as gene editing targeting the *BSCL2* gene in mouse models, adds a valuable forward-looking dimension to the manuscript. However, the current draft contains several significant molecular inaccuracies, omits key genetic subtypes in the pathophysiology section, and lacks transparency in its methodological reporting. These issues must be rigorously addressed before the manuscript can be considered suitable for publication.

Major Comments

1. Mechanistic Inaccuracy in FPLD3 Pathophysiology: The authors state that mutations in the *PPARG* gene "might cause excess differentiation and growth of adipocytes," leading to cellular stress. This contradicts established molecular biology. Pathogenic variants in *PPARG* associated with FPLD3 are typically loss-of-function or dominant-negative mutations that fundamentally *impair* adipogenesis. This fundamental error should be corrected to accurately reflect the disease's molecular basis.
2. Omission of CGL2 (BSCL2) in Section 3: While the authors appropriately discuss *BSCL2* (seipin) in the context of preclinical gene therapy models, they entirely omit CGL2 from the main "Genetics and Pathophysiology" section, focusing only on CGL1 and CGL4. Given that *BSCL2* mutations cause the most severe and globally prevalent form of CGL, a dedicated subsection explaining seipin's role in lipid droplet biogenesis is mandatory.
3. Conflation of FPLD2 and ZMPSTE24 Pathology: In Section 3.3, the authors state that *ZMPSTE24* "is also considered to be one of the factors that causes lipodystrophy" in the context of FPLD2. The authors should clarify this distinction: classic FPLD2 is caused by heterozygous missense mutations in the *LMNA* gene itself. Mutations in *ZMPSTE24* (which impair prelamin A processing) cause distinct, more severe syndromic forms of lipodystrophy (e.g., Mandibuloacral Dysplasia). Blurring the lines between these genetic etiologies creates confusion both clinically and molecularly.

4. Incomplete Methodology Results: The authors include a "Method" section outlining their literature search strategy, keywords, and inclusion/exclusion criteria. However, they fail to report the actual results of this search. There is no mention of how many articles were initially retrieved, screened, or ultimately included. To ensure scientific rigour and reproducibility, the authors should provide these numbers.
5. Superficial Explanation of Lipotoxicity: While the manuscript notes that lipodystrophy leads to metabolic dysfunctions such as insulin resistance and fatty liver, it fails to provide a detailed molecular explanation of lipotoxicity. The paper needs to clearly explain how the inability to store triglycerides in adipocytes leads to ectopic lipid deposition in the liver and skeletal muscle, which directly interferes with insulin receptor signalling pathways.
6. Clarification of Metreleptin Indications: The manuscript presents metreleptin as the "primary choice for LD patients", but later notes it is "more efficient in Generalised lipodystrophy patients". The authors should explicitly clarify current clinical guidelines. Metreleptin is strictly indicated and FDA-approved for generalised lipodystrophy; its use in partial lipodystrophy is highly restricted and heavily scrutinised due to varying efficacy and risk profiles.
7. Omission of APL in Pathophysiology: The introduction introduces Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome). However, APL is entirely ignored in the subsequent "Genetics and Pathophysiology" section, which only covers AGL. APL should be discussed to provide a comprehensive overview of acquired forms.

Minor Comments

1. Overuse of Acronyms in Single Paragraphs: The authors correctly define acronyms such as HAART and NRTI upon their first use. However, since these terms appear only twice and within the same paragraph, introducing the acronyms is unnecessary and clutters the text. It is standard practice to write out the full terms if they are not used frequently throughout the remainder of the manuscript.
2. Scientific Phrasing and Grammar: Several sentences lack scientific precision or contain grammatical errors. For instance, the phrases "The storage of adipocytes is limited" and "Except for CGL2, in which patients generally do not acquire both kinds of fat tissues" require language editing for clarity and grammatical correctness.
3. Unsubstantiated Claims: The authors state that "around 200 clinical trials are in progress, trying to discover a new way to treat or cure lipodystrophy, especially targeting leptin deficiency". This specific claim requires a reference or a citation from a clinical trial registry to verify the figure.
4. Figure Formatting: References to figures within the text should be capitalised for consistency with academic formatting (e.g., change "(figure 1)" and "(figure 2)" to "(Figure 1)" and "(Figure 2)").

Conclusion/Recommendation

Major Revisions. The manuscript addresses a clinically significant and under-researched topic. However, to meet publication standards, the authors should address critical inaccuracies in *PPARG* biology, include comprehensive sections on CGL2 and APL pathophysiology, clearly separate *LMNA* from *ZMPSTE24* pathologies, and transparently report their methodological search results.

REVIEWER 2:

Content: This is a well-researched paper with a strong and thoughtful focus on the molecular and genetic basis of lipodystrophy. The sections on AGPAT2, LMNA, and PPARG are particularly well done and demonstrate a solid understanding of how specific gene mutations affect adipocyte biology. One of the strengths of the paper is its ability to move beyond listing conditions and instead explain underlying mechanisms. In several sections, especially in the genetic discussions, you clearly connect molecular changes to metabolic consequences, which adds real depth to the review. At the same time, there are a few areas where scientific wording could be refined further, particularly in the acquired lipodystrophy section and in some treatment descriptions, to ensure full accuracy and precision.

Grammar and Style: The writing is generally clear and understandable, and the overall flow of ideas is logical. The main issue here is consistency in tone. Some sections are written in a strong academic voice, while others shift into more conversational phrasing. Maintaining a consistent scientific tone throughout will strengthen the professionalism of the manuscript. There are also a few recurring grammar issues, including sentence structure, verb agreement, and phrasing, which can be addressed with a careful final pass.

Scientific Framing: The manuscript shows a good grasp of the literature and includes appropriate gene targets and pathways. A notable strength is the inclusion of both genetic and acquired forms of lipodystrophy, which gives the paper a more complete scope. The paper would become even stronger by more consistently linking molecular mechanisms to clinical presentation. In the strongest sections, this connection is clear and effective, and applying that same level of explanation across all sections would improve overall coherence.

Organization: The overall structure is logical and appropriate for a review article, moving from classification to mechanisms, then to diagnosis and treatment. This organization works well and helps guide the reader through complex material. Some paragraphs, particularly in the introduction and diagnosis sections, are quite dense and would benefit from being divided into smaller sections. The Methods section is functional but could be more clearly organized to match the level of detail seen in the rest of the paper.

Scholarly Tone: The paper demonstrates strong content knowledge and clear effort in engaging with the material. The tone is effective in many sections, particularly in the mechanistic discussions. To elevate the manuscript further, it would help to maintain that same level of academic tone throughout and avoid occasional conversational phrasing. This adjustment would better align the writing with the strength of the scientific content.

Final Assessment: Overall, this is a strong and well-developed review with clear strengths in its mechanistic explanations and topic selection. The paper shows good engagement with the literature and a solid understanding of adipocyte biology. With revisions focused on tone consistency, sentence clarity,

and refinement of scientific phrasing, the manuscript would reach a high level of quality and effectiveness.

Hello Dr. Grive,

I've attached the reviewed manuscript. I went through it for content, grammar, structure, and overall clarity, and added detailed edits to improve it and make it clinically sound. I also included a separate document with more detailed, overall feedback in case that's helpful. Please let me know if you have any questions or if you'd like me to take another pass at anything.

Title page and abstract

· Page 1, Title ("Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy"): The title is clear and appropriate for the paper's scope. You may want to consider whether "disease progression" is the most precise phrase here, since the paper is centered more on mechanisms, classification, and treatment than on longitudinal progression. A term such as "pathophysiology" may better match the content.

· Page 1, Abstract, opening sentence ("Lipodystrophy syndromes are rare diseases that are often characterized…"): The opening sentence introduces lipodystrophy well, but the wording is somewhat repetitive. "Rare diseases that are often characterized" could be made more concise.

· Page 1, Abstract, sentence beginning "Fat tissues are also known as adipose tissues…": This reads more like a general definition than part of a scientific abstract. You may want to replace this with a sentence emphasizing the metabolic role of adipose tissue instead.

· Page 1, Abstract, sentence containing "a series of metabolic issues": This is broad. It would be stronger if it named a few specific complications, such as insulin resistance, hepatic steatosis, or hypertriglyceridemia.

· Page 1, Abstract, sentence beginning "They are all factors that determine…": This is a bit unclear. It would help to specify whether you mean the clinical phenotype, the molecular defect, or the pattern of adipose loss.

· Page 1, Abstract, sentence beginning "Due to the rarity of this disorder…": This would read better as "these disorders," since you are discussing lipodystrophy syndromes rather than a single disease entity. The sentence also becomes somewhat repetitive with "this disease" later in the same thought.

· Page 1, Abstract, sentence beginning "In this article, we first consider…": This feels more narrative than review style. It may read more professionally if you state the review's scope directly rather than walking the reader through it step by step.

· Page 1, Abstract, final sentence beginning "Future direction of study…": This needs a small grammatical correction. The sentence would also benefit from a more precise phrasing of how genetic understanding may inform future therapies.

· Page 1, Abstract, overall: The abstract does a good job covering the paper's main sections, but it could become stronger by making the connection between gene mutations and metabolic outcomes more

explicit. Right now, the abstract introduces the topics clearly, but it does not fully show the mechanistic thread that becomes important later in the paper.

Introduction and Background

· Page 1–2, Introduction, Paragraph 1, sentence containing "inability to store body fat and excess nutrients": The introduction establishes the topic clearly, though this phrase could be made more precise. Since one of the key consequences is ectopic lipid storage, naming that directly may strengthen the scientific framing.

· Page 2, Introduction, Paragraph 1, sentence beginning "Adipose tissues are formed through a process called adipogenesis…": The explanation of adipogenesis is useful, but some of this material reads more like a textbook definition than an introduction to a review article. You may want to move more quickly from defining adipogenesis to explaining why it is relevant to lipodystrophy.

· Page 2, Introduction, Paragraph 1, sentence beginning "This process also includes the triacylglycerol (TAG) fatty acid cycle…": The TAG cycle discussion is informative, but the sentence is fairly dense and contains several concepts at once. It may help to simplify the structure so the role of lipid storage and mobilization stands out more clearly.

· Page 2, Introduction, Paragraph 1, sentence beginning "It is the process where the lipid droplets…": This is slightly unclear, as the referent for "It" is not immediately obvious. Clarifying the subject of the sentence may improve readability.

· Page 2, Introduction, Paragraph 1, sentence beginning "However, if a gene mutation…": The statement about gene mutations affecting adipogenesis is conceptually strong. It may be worth stating more explicitly that these disruptions impair adipocyte differentiation, lipid droplet formation, or adipose maintenance, depending on the gene involved.

· Page 2, Introduction, Paragraph 2, paragraph beginning "LD can be either congenital or acquired…": This classification paragraph contains important material, but it is doing a great deal at once. It may be easier for the reader if you divide it into one paragraph on congenital versus acquired forms and a second paragraph on subtype distinctions within CGL and FPLD.

· Page 2, Introduction, Paragraph 2, sentence beginning "CGL (also called Berardinelli-Seip syndrome)…": This sentence is clear, although it may help to define "mechanical and metabolic fat tissues" more carefully. Some readers may not immediately know how you are distinguishing these categories.

· Page 2, Introduction, Paragraph 2, sentence beginning "CGLs are autosomal recessive…": This is understandable, but the phrasing could be made more formal.

· Page 2, Introduction, Paragraph 2, sentence beginning "Same as CGL…": This sounds conversational. A more formal transition would improve continuity.

· Page 2, Introduction, Paragraph 2, sentence beginning "Since the body is not able to store excess energy…": The FPLD description is one of the stronger parts of the introduction because it links adipose

redistribution to metabolic consequences. This would become even stronger if you clarified that the apparent “gain” of fat in other regions often reflects abnormal redistribution rather than normal adipose expansion.

· Page 2, Introduction, Paragraph 2, sentence beginning “Proteins or enzymes that are encoded…”: This is a bit heavy structurally. The main point is good, but the sentence could be made clearer by emphasizing function first.

· Page 2, Introduction, Paragraph 2, phrase “and sometimes idiopathic”: The acquired forms are introduced clearly, although this phrase could be smoothed slightly to fit the tone of the rest of the paragraph.

· Page 3, Introduction, Paragraph 3, paragraph beginning “Not only will the lack of excess energy…”: This paragraph introduces metabolic complications well. The figure reference is useful, and the transition into treatment is natural, though the opening sentence itself is somewhat broad and could be made more concise.

· Page 3, Introduction, Paragraph 3, sentence containing “It currently the only FDA-approved treatment”: The metreleptin discussion is appropriate here, but there is a small grammar issue in this sentence.

· Page 3, Introduction, Paragraph 3, prevalence sentences containing “3/million,” “0.23/ million,” and “2.84/million”: The prevalence numbers are helpful. You may want to make sure units are presented consistently, for example “per million” rather than “/million.”

· Page 3, Introduction, Paragraph 3, sentence beginning “It is also estimated to shorten a patient’s lifespan…”: This is important and strengthens the clinical significance of the review.

· Page 3, Introduction, final sentence beginning “In addition, the treatment developed…”: This could be made slightly more polished. It feels incomplete in structure and would be a good place to state clearly that the review will examine both current therapies and emerging directions.

Methodology

· Page 3, Section title (“2. Method”): Consider changing “Method” to “Methods” to align with standard scientific formatting.

· Page 3, Methods paragraph, sentence beginning “The search included following keywords…”: The literature search description is straightforward, though it would read more smoothly if this were changed to “included the following keywords.”

· Page 3, Methods paragraph, keyword list: The keyword list is useful and appropriately targeted to the paper’s focus.

· Page 3, Methods paragraph, sentence beginning “Only publications in English language were considered”: This would read more naturally as “Only English-language publications were considered.”

· Page 3, Methods paragraph, sentence containing “comprehensive reviews”: The inclusion criteria are generally clear, though this phrase might benefit from a little more specificity if you want to distinguish narrative reviews from systematic reviews.

· Page 3, Methods paragraph, sentence beginning “Case studies with relevant insights…”: This is understandable, though the basis for relevance could be clarified slightly.

· Page 3, Methods paragraph, sentence beginning “Non peer reviewed sources…”: “Non peer reviewed” should be hyphenated. Also, the phrase “case reports with only quantitative data and without further analysis” is a little difficult to interpret. You may want to clarify the reasoning behind that exclusion.

· Page 3, Methods paragraph, final sentence beginning “Full article was reviewed…”: This should be plural.

· Page 3, Methods, overall: This section is functional, but it may become clearer if organized under brief subheadings such as Search Strategy, Inclusion Criteria, and Exclusion Criteria.

Discussion – Section 1: Genetics and Pathophysiology

· Page 4, CGL1, opening paragraph beginning “Type 1 Congenital Generalized Lipodystrophy…”: The AGPAT2 section contains strong mechanistic content. The explanation is scientifically valuable, but the sentence structure is quite dense. Breaking some of the longer sentences may make the biochemical pathway easier to follow.

· Page 4, CGL1, sentence beginning “AGPAT2 is the gene coding for…”: This would be more standard scientifically as a direct statement that the gene encodes the enzyme.

· Page 4, CGL1, sentence beginning “It is an important precursor…”: The explanation of phosphatidic acid synthesis is detailed, which is good for the review’s depth. You may want to make the link to adipocyte dysfunction slightly more explicit at the end of the paragraph so that the reader sees why this biochemical step matters clinically.

· Page 4, CGL1, sentence beginning “The AGPAT family consists of 11 isomers…”: This is useful, though a little hard to follow because several ideas are packed together.

· Page 4, CGL1, sentence beginning “The presence of mechanical adipose tissue…”: The contrast between AGPAT2 and other isomers is interesting and relevant. This may be one place where an extra citation or a more explicit mechanistic link would strengthen the section further.

· Page 4, CGL1, sentence beginning “Defects in AGPAT2 genes also impact insulin signaling…”: This point is important. It may be helpful to clarify whether this effect is direct or secondary to impaired adipocyte function, since the sentence currently reads somewhat definitive.

· Page 4, CGL4, opening sentence beginning “Type four Congenital Generalized Lipodystrophy…”: The opening sentence is clear. The subsection would benefit from more consistent capitalization and formatting in the disease name.

· Page 4, CGL4, sentence beginning “Caveolae are one of the most abundant invaginations…”: The explanation of caveolae is strong, though “lots of mammalian cells” reads conversationally. A more formal phrasing would strengthen tone.

· Page 4, CGL4, sentence beginning “Cavin-1 starts the whole process…”: This phrasing feels informal. A more academic wording would match the rest of the review.

· Page 4, CGL4, sentence containing “caveolin 1,2”: The discussion of caveolin isoforms is useful, but the formatting should be standardized.

· Page 4–5, CGL4, sentence beginning “Absence of caveolae causes the cell…”: The sentence describing cellular consequences would benefit from slightly more precision. Instead of “not be able to develop properly,” you may want to emphasize membrane organization, signal transduction, or adipocyte stability.

· Page 5, CGL4, paragraph beginning “Some symptoms that are uniquely associated…”: The clinical phenotype discussion is useful and helps connect molecular defects to patient presentation.

· Page 5, CGL4, final sentence beginning “These symptoms can be explained…”: This could be made more explicit in showing how tissue-specific expression relates to muscle and cardiac findings.

· Page 5, FPLD2, opening sentence beginning “The gene LMNA…”: The LMNA subsection is scientifically important, and the topic choice is strong. The first sentence is somewhat heavy structurally and may benefit from division into two shorter sentences.

· Page 5, FPLD2, sentence beginning “Specifically…”: This appears incomplete and may need revision into a full sentence.

· Page 5, FPLD2, sentence beginning “One way that Lamin A can affect cell development…”: The ZMPSTE24 discussion is relevant. This would be even stronger if you briefly clarified whether you are describing laminopathy-related processing defects more broadly or specifically FPLD2-associated mechanisms.

· Page 5, FPLD2, sentence beginning “Not only will the lack of Lamin A…”: The point about prelamin A accumulation is well made and adds mechanistic depth.

· Page 5, FPLD2, paragraph beginning “A high risk of cardiovascular diseases…”: This paragraph is interesting, though the transition from nuclear structure to epicardial adipose tissue is fairly abrupt. One bridging sentence may help.

· Page 5, FPLD2, final sentence beginning “Other studies will also need to be done…”: This reads somewhat informal. The idea is good, but the phrasing could be more academic.

· Page 5–6, FPLD3, opening sentence beginning “Type 3 Familial Partial Lipodystrophy…”: The PPARG subsection is relevant and well chosen. There is a small phrasing issue with “encodes for.”

· Page 6, FPLD3, sentence beginning “PPARγ has three isoforms…”: The mechanism is clearly described and fits well within the paper. Some small reductions in repetition may help readability.

· Page 6, FPLD3, sentence beginning “After binding, PPARγ induces many targeted genes…”: “induces many targeted genes” might be expressed more precisely, since this is really about transcriptional regulation of downstream targets.

· Page 6, FPLD3, sentence beginning “Mutations in PPARG might cause excess differentiation…”: This appears to be an oversimplification. Many pathogenic PPARG variants impair adipocyte function rather than simply increasing growth, so this phrasing may be misleading and should be reconsidered for accuracy.

· Page 6, FPLD3, paragraph beginning “Compared to FPLD2…”: The comparison with FPLD2 is useful and adds real value to the review. This is a strong section because it moves beyond listing mechanisms and begins comparing phenotypes.

· Page 6, FPLD3, final sentence beginning “However, FPLD3 patients also show…”: This is good, though it may help to clarify why a milder loss of adipose tissue can still be associated with more severe metabolic disease.

· Page 6, AGL, opening sentence beginning “As we can see…”: The opening sentence introduces acquired disease appropriately, but “As we can see” sounds conversational and could be removed.

· Page 6, AGL, paragraph beginning “Adverse effects of highly active antiretroviral therapy…”: The HAART discussion is interesting and clinically relevant. Some of the sentence structure is slightly long, but the content is strong.

· Page 7, AGL, sentence beginning “Proteins such as thymidine analog nucleoside reverse transcriptase inhibitors…”: This is not accurate. NRTIs are pharmacologic agents, not proteins, and this distinction is important for maintaining scientific accuracy. This sentence should be revised to reflect the correct classification and mechanism.

· Page 7, AGL, sentence beginning “It decreases the expression of adiponectin…”: The adiponectin and mitochondrial toxicity points are relevant and help ground the section mechanistically.

· Page 7, AGL, paragraph beginning “Another possible cause of AGL…”: The autoimmune mechanism is a good addition. The perilipin discussion is especially useful because it broadens the review beyond purely genetic forms.

· Page 7, AGL, sentence beginning “It leads to an increase in lipolysis activities…”: This is conceptually good, though it may help to clarify whether you mean uncontrolled lipolysis due to loss of lipid droplet protection.

Diagnosis and Clinical Features

· Page 7–8, Diagnosis, Paragraph 1 beginning “Since lipodystrophy is such a rare disease…”: This paragraph includes important diagnostic material, but it is quite long and would benefit from being divided into smaller units.

· Page 7, Diagnosis, opening phrase “not well known to the public”: This point about underrecognition is important and clinically relevant, though this phrasing may be less useful than a more clinician-focused one.

· Page 7–8, Diagnosis, sentence beginning “Although patients with CGL show symptoms…”: The contrast between CGL and FPLD diagnosis is helpful.

· Page 8, Diagnosis, sentence beginning “It could be easily mixed up with…”: “mixed up with” would benefit from more formal wording.

· Page 8, Diagnosis, paragraph beginning “Some phenotypes that are associated…”: The phenotype paragraph is detailed and generally useful. There is a small typo in “in charge or energy storage.”

· Page 8, Diagnosis, sentence beginning “Metabolic adipose tissues are in charge…”: The explanation of metabolic versus mechanical adipose tissue is useful, but the wording could be made more precise.

· Page 8, Diagnosis, sentence beginning “Although patients still in some degrees lack…”: This is difficult to follow and appears structurally incomplete. This portion may benefit from being rewritten for clarity.

· Page 8, Diagnosis, final sentence beginning “Next, we will be discussing…”: The transition into treatment is smooth and works well, though this phrasing reads somewhat narrative for a review article.

Treatments

· Page 8, Treatments, opening sentence beginning “Currently, there isn’t a definite treatment…”: This sounds somewhat informal. The idea is correct, though the phrasing could be slightly more formal.

· Page 8–9, Metreleptin subsection overall: The metreleptin discussion is one of the strongest applied sections of the paper. It explains the rationale for therapy clearly and appropriately ties it to leptin deficiency.

· Page 9, Metreleptin subsection, sentence beginning “Leptin is a hormone…”: This explanation is useful, though some of this material repeats ideas already implied in the section. You may be able to reduce repetition.

· Page 9, Metreleptin subsection, sentence beginning “This causes patients to show extreme hyperphagia…”: The connection between hypoleptinemia, hyperphagia, and ectopic fat storage is well stated and clinically meaningful.

· Page 9, Metreleptin subsection, sentence beginning “Metreleptin’s main purpose is to mimic…”: This is fine, though it may be worth noting whether the treatment’s benefit is metabolic, symptomatic, or both.

· Page 9, Metreleptin subsection, sentence beginning “Metreleptin is found to be more efficient…”: This might be adjusted slightly to reflect clinical response rather than efficiency.

· Page 9, Metreleptin subsection, sentence beginning “However, the risk of using Metreleptin…”: This contains a subject-verb agreement issue and could be clarified to improve readability.

· Page 9, Metreleptin subsection, final sentence beginning “Other common drugs…”: The closing sentence on adjunctive therapies and cosmetic surgery is appropriate. This gives the treatment section a more complete and realistic scope.

· Page 9, Lifestyle subsection title (“Change in Daily Routine”): This feels somewhat informal as a heading. A more standard heading may fit better with the rest of the paper.

· Page 9, Lifestyle subsection, paragraph beginning “Although Metreleptin can generally help…”: This section is brief but useful. It might be strengthened by explaining why a low-fat or carbohydrate-restricted diet is recommended in metabolic terms, rather than only listing the recommendations.

· Page 9, Lifestyle subsection, sentence containing “doing too much exercise”: This is understandable but may be rephrased more formally.

· Page 9–10, Gene Editing subsection, opening paragraph: This section is forward-looking and adds value to the paper. The discussion of gene therapy is a strong choice for the final treatment subsection.

· Page 10, Gene Editing subsection, sentence beginning “The results of the trials show…”: The mouse model example is useful and helps ground the idea in actual preclinical work.

· Page 10, Gene Editing subsection, sentences containing “AVV”: The acronym “AVV” appears to be used in place of “AAV” (adeno-associated virus). This should be corrected consistently throughout the section. In addition, phrases such as “AVV targets adipocytes” read somewhat absolute and may benefit from more precise wording.

· Page 10, Gene Editing subsection, sentence beginning “Therefore, there isn’t enough evidence…”: The translational caution here is important and scientifically appropriate. This section benefits from the fact that it does not overstate clinical readiness.

· Page 10, Gene Editing subsection, final sentence beginning “Continued research on LD…”: This conclusion is good and appropriately cautious.

Conclusion and Future Directions

· Page 10–11, Conclusion, opening sentence beginning “Although genes involved in lipodystrophy syndromes…”: This contains the paper’s central idea and is conceptually strong, but it is fairly long. Breaking it into two sentences may improve readability.

· Page 11, Conclusion, phrase “common outcome -impaired adipocyte development and function”: This contains a spacing and punctuation issue. It should be corrected for clarity and consistency with standard formatting.

· Page 11, Conclusion, paragraph beginning “LD highlights the essential role…”: This paragraph does a good job emphasizing adipose tissue as an endocrine and metabolic organ. That is one of the manuscript’s central strengths.

· Page 11, Conclusion, sentence beginning “For conditions like lipodystrophy…”: The discussion of awareness and diagnostic delay is relevant and provides a meaningful clinical takeaway.

· Page 11, Conclusion, sentence beginning “Since the discovery of lipodystrophy syndromes…”: “lots of progress has been made” reads somewhat informal.

· Page 11, Conclusion, sentence containing “research have been done”: This is a grammar issue.

· Page 11, Conclusion, final sentence beginning “Having a deep understanding…”: The final sentence is appropriate, though it may be strengthened by tying future therapy more directly to the specific mechanisms discussed earlier.

Figures and Tables

· Table 1 / Page 2: The table is useful and supports the classification section well. Make sure the labeling and formatting remain consistent with the journal’s style.

· Figure 1 / Page 3: The comparison figure is a helpful visual aid. The caption contains multiple grammatical issues, including “The storage of an adipocytes is limited” and “increase glucose level in blood streams.” These should be revised for clarity and correctness.

· Figure 2 / Page 4: The figure is relevant and supports the CGL1 discussion appropriately.

· Figure 3 / Page 5: The caveolae figure is helpful, though the caption could be a bit more precise scientifically. Also, “Biorender” should be standardized to “BioRender.”

· Table 2 / Page 9: This table adds practical value to the treatment section. Make sure the reproduced source and licensing note are formatted exactly as required by the target venue.

· Figure 4 / Page 10: This is one of the stronger figures in the manuscript because it helps unify the review conceptually. The caption is informative and supports the final conclusion well.

Molecular Basis of Lipodystrophy: Gene Mutations, Pathophysiology, and Therapy

Abstract

Lipodystrophy syndromes are a group of rare diseases characterized by a general or partial absence of body fat, caused by the inability to properly store and utilize adipose tissue. The lack of adipose tissue would lead to serious consequences and the development of a series of metabolic issues, including insulin resistance, leptin deficiency, and hypertriglyceridemia. Lipodystrophy syndromes are genetically and clinically heterogeneous, with different phenotypes influenced by underlying molecular defects. Both fat distribution and the molecular defect play a role in determining the type of lipodystrophy a patient has. Due to the rarity of these disorders, not many studies have been conducted on them. This results in the public's lack of awareness, increasing the difficulty of diagnosing and treating these conditions. This article examines the classification and clinical aspects of lipodystrophy syndromes, covering the onset and the differences in phenotypes of patients. It further discusses the molecular and cellular mechanisms of several types of lipodystrophies and the role they play in the development of adipose tissues. In addition, this review addresses other metabolic dysfunctions caused by lipodystrophy, such as insulin resistance, fatty liver, and hypertriglyceridemia. Lastly, we evaluate therapeutic strategies aimed at improving metabolic control and quality of life in affected patients. Future research and potential therapy may be improved with a deeper and more thorough understanding of the genetic and mechanistic basis of lipodystrophy, as it is critical for identifying key mechanisms and developing a more targeted treatment.

Keywords: Lipodystrophy syndromes, adipose tissue, adipogenesis, gene mutations, metabolic dysfunctions

1. *Introduction*

Lipodystrophy syndromes (LD) are a heterogeneous group of rare disorders characterized by the partial or complete loss of mature adipose tissue in localized or generalized areas. This results in the inability to store body fat, ectopic lipid storage, and excess nutrients (Fourman and Grinspoon 2022). Two main classes of lipodystrophy are Congenital Generalized Lipodystrophy (CGL) and Familial Partial Lipodystrophy (FPLD).

For adipose tissues to function normally, adipogenesis is crucial for the differentiation of the precursor cells. Adipogenesis starts with mesenchymal stem cells differentiating into mature adipose tissue. During adipogenesis, lipid storage and mobilization is regulated by the triacylglycerol (TAG) fatty acid cycle. Lipid droplets undergo lipolysis (the breakdown of lipid droplets) and lipogenesis (the synthesis of new lipid droplets)(Poulos et al. 2016). However, if a gene mutation or other factors affect the components involved in the regulation of adipogenesis, this would lead to impaired adipocyte differentiation, lipid droplet formation, and adipocyte functions.

LD can be either congenital or acquired. Congenital Lipodystrophy is classified based on the location of lost adipose tissue, and further divided into subtypes according to the gene segment that is mutated (Akinci, Gular, and Oral 2024) (Table 1). Meanwhile, acquired lipodystrophy is caused by external factors or side effects of other treatments.

CGL (also called Berardinelli-Seip syndrome) is characterized by the near-complete absence of adipocytes (Oswiecimska n.d.). CGLs are inherited in an autosomal recessive manner, with symptoms typically presenting shortly after birth. It is further divided into CGL1, CGL2, CGL3, and CGL4, which link to four different gene mutations. FPLD presents as an abnormal distribution of adipose tissue, with fat loss around the limbs, torso, and hips. It can be autosomal recessive or dominant depending on the gene involved. Since the body is not able to store excess energy in those areas, other body parts, such as the face, neck, and internal organs like the liver, gain extra adipose tissue (Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic n.d.). This results in the abnormal distribution of adipose tissues. As with CGL, FPLD is further divided into several subtypes, including FPLD1 (Kobberling-type lipodystrophy), FPLD2 (Dunnigan Variety lipodystrophy), FPLD3, FPLD4, FPLD5, and FPLD6. The development of adipocytes is tightly regulated by various proteins and enzymes. The genes that encode these proteins or enzymes are often the genes associated with lipodystrophy.

As for Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome), they have similar symptoms as CGL and FPDL. However, they are caused by autoimmune diseases, side effects of antiretroviral therapy (ART) for HIV patients, or even idiopathic reasons (Misra and Garg 2003).

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
Generalized Lipodystrophy Syndrome					
Congenital Generalized Lipodystropy (Berardinelli-Seip syndrome)	CGL1	AGPAT2	Autosomal recessive	Near total absence of adipose tissue, generalized musularity, metabolic abnormalities. Starts showing symptoms shortly after birth.	Loss of metabolic fat, retains mechanical fat tissues
	CGL2	BSCL2	Autosomal recessive		Mild mental retardation
	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
Acquired Generalized Lipodystrophy (Lawrence Syndrome)	NA	NA	NA	Near total absence of adipose tissue, metabolic issues. Develops during childhoold/ puberty.	Could be caused by autoimmune diseases, panniculitus, idiopathic or immunotherapy
Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/ adolescense.	Palpable "ledge" between normal and lipodistrophic areas
	FPLD2 (Dunnigan)	LMNA	Autosomal dominant		High risks of cardiovascular diseases
	FPLD3	PPARG	Autosomal dominant		Less severe and distal fat loss
	FPLD4	PLIN1	Autosomal dominant		Increased fibrosis of adipose tissue, small lipid droplets in adipocytes
	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN- associated, immunotherapy or idiopathic

▲ Table 1: Classification, clinical features, and molecular basis of lipodystrophies (Made with Google Sheet)

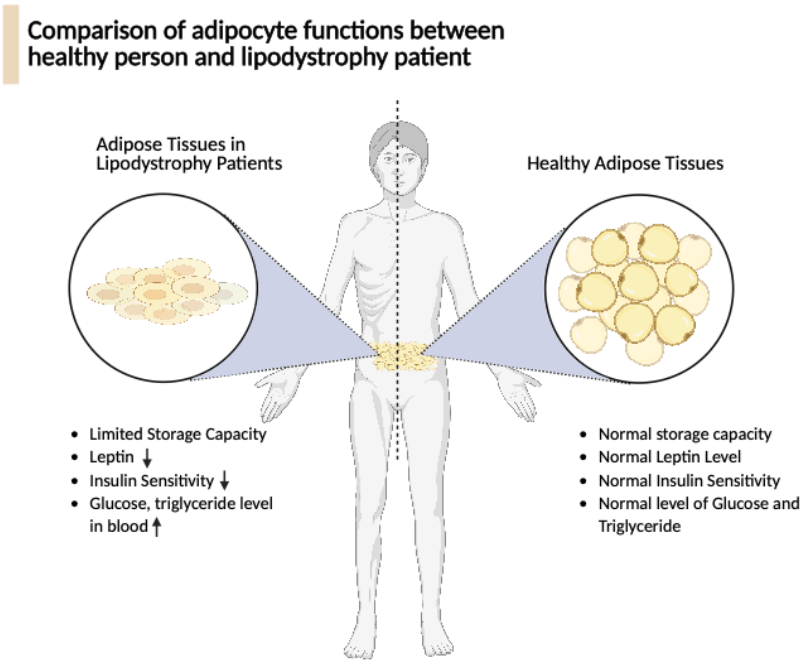
Not only will the lack of excess body fat affect the body's normal functions, but complications associated with lipodystrophy also have a significant effect on patients' lives. Some common metabolic abnormalities include leptin deficiency, insulin resistance, diabetes, hypertriglyceridemia, and fatty liver disease (Figure 1). Currently, around 200 clinical trials are underway to discover a new way to treat or cure lipodystrophy, with a particular focus on leptin deficiency (*Search ClinicalTrials.Gov For*, n.d.).

Metreleptin, for example, is a treatment created specifically for acquired or congenital generalized lipodystrophy patients. It is a targeted treatment for leptin deficiency, which is a common metabolic issue associated with LD (Araújo-Vilar & Santini, 2019). It is currently the only FDA- approved treatment for generalized lipodystrophy patients. However, conventional treatment, such as special diets, is still optimized before metreleptin (Meehan et al., 2016). Due to the rarity of this disease, limited research has been done, making Metreleptin the primary choice for CGL and AGL patients (Ajluni et al., 2016). As for FPLD patients, the use of Metreleptin is highly restricted. Therefore, they will need to maintain an appropriate diet and require other medications for the metabolic complications.

According to studies, only about 3 per million people around the world are affected by some type of lipodystrophy syndrome. While the prevalence of CGL is estimated to be

0.23 per million people, the prevalence of FPLD is around 2.84 per million people (Chiquette et al. 2017). It is also estimated to shorten a patient's lifespan by 30 or more years. The main cause of death is shown to be liver diseases and infections caused by adipose tissue dysfunction, but also varies from type to type of lipodystrophy (Lima et al. 2018).

This literature review aims to highlight the molecular mechanisms underlying lipodystrophy, with a focus on the genetic causes, differences between types of lipodystrophies, and other metabolic conditions caused by adipose tissue abnormalities, as well as the treatment developed and future directions of study, and the possibilities for fundamental treatments.



▲ Figure 1: Comparison of adipocyte functions between a healthy person and a lipodystrophy patient. Adipocyte storage is decreased in lipodystrophy patients. Common metabolic abnormalities include leptin deficiency, insulin resistance, and elevated blood glucose levels in the bloodstream. (Made with BioRender)

2. Methods

Search Strategy

A literature search was conducted using PubMed and Google Scholar databases. The search included the following keywords: “lipodystrophy genetics”, “adipocyte differentiation”, “AGPAT2”, “PTRF Cavin-1”, “LMNA mutation”, “PPARγ mutation”, “lipodystrophy metabolic abnormalities”. Titles and abstracts were first screened for

relevance. Full articles were reviewed to see if they met the inclusion criteria. 97 articles were initially screened, and 54 papers were ultimately referenced in this review.

Inclusion/Exclusion Criteria

Articles published between 2000 and 2026 were included. Only English language publications were considered. Studies were included if they were peer-reviewed primary research articles or comprehensive reviews, including both narrative reviews and systematic reviews, that focused on the genetic, molecular, or metabolic mechanisms underlying lipodystrophy syndromes. Case studies were included if they provided relevant insights, such as pathological or mutation analyses or clinical findings. Non-peer-reviewed sources and articles published before 2000 are excluded. Case reports that only report descriptive quantitative data, without the discussion of mechanistic interpretation, are also excluded, as clinical data are not the focus of this review.

Discussion

3. Genetics and Pathophysiology

3.1 Type one Congenital Generalized Lipodystrophy (CGL1)

Type one Congenital Generalized Lipodystrophy (CGL1) is caused by a mutation in the gene AGPAT2. AGPAT2 is the gene that encodes the enzyme 1-acylglycerol-3-phosphate O-acyltransferase 2. It catalyzes the acylation of lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1,2 diacylglycerol-3-phosphate)(Gale et al. 2006) (Figure 2). It is an important precursor for the biosynthesis of triacylglycerol (TAG) and phospholipids from glycerol-3-phosphate. This step esterifies a second fatty acyl group at the sn-2 position of the glycerol backbone. Phosphatidic acid is further acylated by other enzymes, creating triacylglycerol and phospholipids. Impaired formation of phosphatidic acid results in the absence of triacylglycerol production, thereby disrupting the normal adipose tissue development.

The AGPAT family consists of 11 isomers. Among the isomers, AGPAT2 is expressed at higher levels in adipose tissue than the other isomers. The presence of mechanical adipose tissue can be explained by the increased expression of the other isomers (Broekema et al., 2018). However, studies have shown that the expression of AGPAT2 is required for the accumulation of triacylglycerol, especially in metabolic adipose tissues. Defects in the AGPAT2 gene also impact insulin signaling, which is a direct effect of impaired adipocyte dysfunction (Santoro et al., 2021). This also causes gluconeogenesis to be unrestricted, which leads to the development of hyperglycemia and diabetes(de Melo et al. 2025).

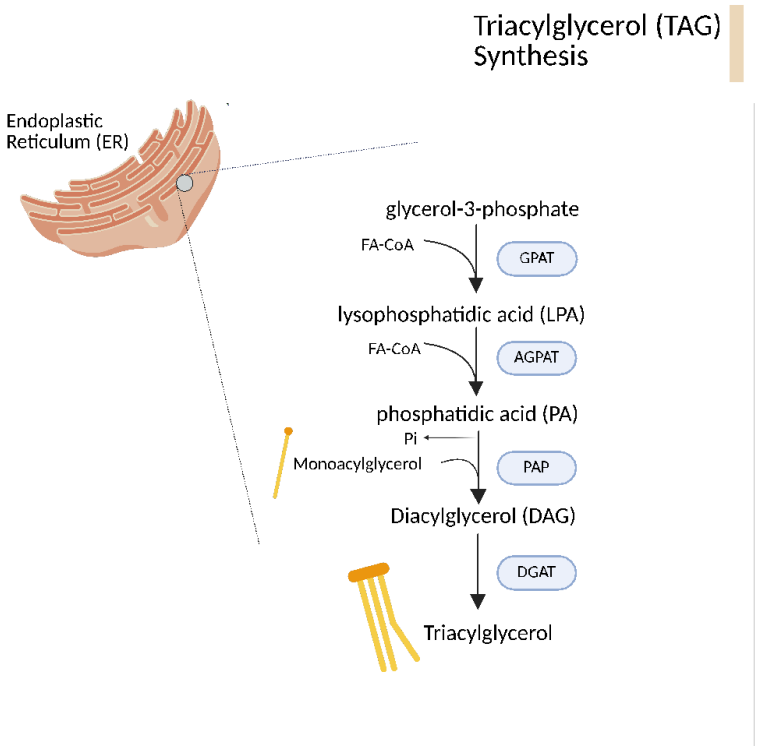


Figure 2: The process of Triacylglycerol synthesis. In the second step, where LPA is acylated to PA, AGPAT is the enzyme that catalyzes this reaction. Without it, the reactions after it will not occur properly, meaning that adipocytes can't develop properly. (Made with BioRender)

3.2 *Type 2 Congenital Generalized Lipodystrophy (CGL2)*

Type 2 Congenital Generalized Lipodystrophy (CGL2) is caused by pathogenic variants of the BSCL2 gene. It encodes the protein seipin, which is found in the endoplasmic reticulum (ER) (Akinci et al., 2024), Seipin plays an important role in the regulation of lipid droplet biogenesis. It interacts with proteins involved in TAG synthesis to facilitate adipogenesis. For instance, it binds with AGPAT2 to regulate PA metabolism. Seipin deficiency could lead to abnormal accumulation of PA. This increases the surface tension of the ER and decreases its line tension, disrupting the unidirectional lipid droplet budding. It causes the accumulation of newly synthesized neutral lipids in the ER, leading to severe ER stress and potentially being toxic to the cells (Li et al., 2022).

CGL2 is the most common type of congenital lipodystrophy. But mutations in the BSCL2 also lead to the most severe symptoms. Patients are born without any fat, including mechanical and metabolic adipose tissues. They also have an earlier onset of diabetes mellitus than other types of lipodystrophies. Other than adipocytes, seipin is also expressed in the brain and testis. This leads to mild mental disability, developmental language disorders, and an impaired reproductive system.

3.2 Type four Congenital Generalized Lipodystrophy (CGL4)

Type four Congenital Generalized Lipodystrophy (CGL4) is associated with the gene mutation in the PTRF gene (Polymerase I and Transcript Release Factor)(Salle-Teyssières et al. 2016). The PTRF gene encodes cavin-1, which is one of the essential proteins that is required for the biogenesis of caveolae. Caveolae are the most abundant invaginations of the plasma membrane across a wide range of mammalian cells (Figure 3). Cavin-1 plays a critical role in the initiation of caveolae synthesis through recruiting other structural proteins, such as caveolins. Without it, cells won't be able to produce caveolae. Although it is abundant, its functions have only been understood in the past few decades. It plays a role in signal transduction, endocytosis, and mechanotransduction (Stea and D'Alessio 2025). Cavin-1 binds with the caveolins to form Caveolae. There are three members in the caveolin family: caveolin-1, caveolin-2, and caveolin-3. They are expressed in a variety of cells, like smooth muscle cells, fibroblasts, and adipocytes. Caveolin 3 is expressed exclusively in cardiac and skeletal muscle. It is shown that the lack of PTRF-CAVIN doesn't affect the level of caveolin expressed (Rajab et al. 2010). However, it affects caveolin's ability to localize to the cell's surface, which makes the formation of caveolae impossible. The absence of caveolae causes abnormalities and dysfunctions, including impaired signal transduction and a lack of mechanoprotection. Without the extra membranes acting as a buffer against the force of mechanical stretching, cardiac cells are at a greater risk of rupturing (Grivas et al., 2020).

Clinical features uniquely associated with CGL4 include myopathy, which affects skeletal muscle structure, and distal metaphyseal deformation, causing bone stiffness and limited range of motion (Ardissone et al. 2013). Cardiac arrhythmias are also one of the symptoms caused by the lack of PTRF-CAVIN, and they could be life-threatening, showing the serious consequences of cavin-1 deficiency (Rajab et al. 2010). These symptoms can be explained by the location where caveolins 1, 2, and 3 are expressed.

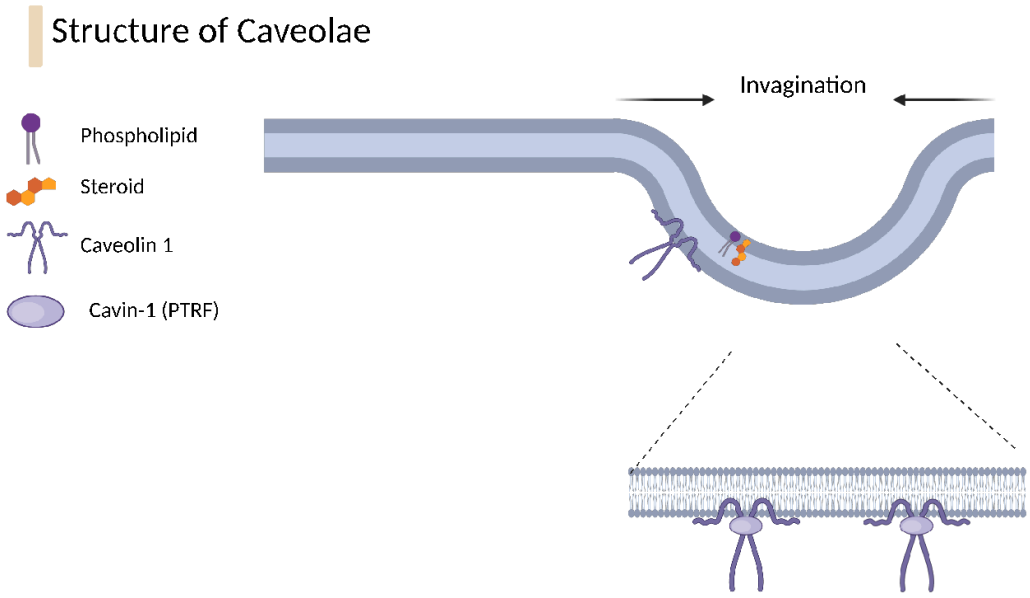


Figure 3: Structure and formation of caveolae. Caveolae are invaginations of the plasma membrane. Cavin-1 first binds with the plasma membrane, initiating caveolae synthesis. Caveolin 1 binds with cavin-1, which stabilizes its structure and forms caveolae. (Made with BioRender)

3.3 Type two Familial Partial Lipodystrophy (FPLD2)

The gene LMNA encodes the protein called Lamins. It is the gene that is associated with Type two Familial Partial Lipodystrophy (FPLD2). FPLD2 is the most common type of lipodystrophy syndrome (Corsa et al. 2021). In cells, Lamin A and Lamin C are expressed predominantly. The main functions of Lamin A/C are the regulation of nucleus shape, providing structural stability to the nuclear envelope and cytoskeleton, and also controlling gene regulation (Maung et al. 2026)'(Bagias et al. 2020). They are important intermediate filament proteins forming the nuclear lamina. They also play a role in organizing chromatin. Mutations in Lamin A/C can lead to premature aging syndrome (Hutchinson-Gilford Progeria Syndrome). The mutated LMNA gene produces a mutant product called progerin. As progerin accumulates in the nucleus, it destabilizes DNA, triggers premature senescence, and alters the shape of the nucleus (Gonzalo et al., 2017).

The interference with the cleavage step of post-translational regulation of Lamin A could also affect the patient. ZMPSTE24 plays an important role in this step, and it is also considered to be one of the factors that causes lipodystrophy. However, mutations in ZMPSTE24 cause another distinct form of lipodystrophy (mandibuloacral dysplasia), showing different symptoms and increased severity. Nevertheless, modification is crucial and ensures that Prelamin A (the precursor of Lamin A before post-translational regulation) functions normally. Not only will the lack of Lamin A affect cell functions, but

the accumulation of Prelamin A could also be toxic to cells (Varlet, Helfer, and Badens 2020), which could affect the cell's ability to develop properly.

These cellular abnormalities contribute to broader systemic symptoms. This includes a higher risk of cardiovascular diseases. It is found that FPLD2 patients have higher Epicardial adipose tissue (EAT) volume than type two diabetes patients (Talman et al. 2014) (Godoy-Matos et al. 2015). However, it is not related to other metabolic issues that are also presented in lipodystrophy (Lamothe et al. 2025). Additional studies will need to be conducted to gain a clearer insight into this condition and its correlation.

3.4 Type three Familial Partial Lipodystrophy (FPLD3)

Type three Familial Partial Lipodystrophy (FPLD3) is caused by pathogenic variants of the PPARG gene. PPARG encodes PPARγ (Peroxisome proliferator-activated receptor γ), a member of a superfamily of nuclear receptors. PPARγ is known as the master regulator of adipocyte differentiation, maintenance, and functions(Broekema et al. 2019). It has three isoforms: PPARγ1, PPARγ2, and PPARγ3. Among them, PPARγ2 is predominantly expressed in adipocytes. PPARγ acts as a ligand-activated transcription factor. It binds to its target gene as a heterodimer with PPAR-response elements (PPREs)(Madsen et al. 2022). After binding, PPARγ regulates the transcription of downstream target genes that are involved in the development of adipose tissues. Including the TAG cycle, which is upregulated by PPARγ for the development of adipocytes. Loss-of-function or dominant-negative mutations in pathogenic variants of PPARG cause excess differentiation and growth in adipocytes, fundamentally impairing adipogenesis. Therefore, leading to increased cellular stress and dysfunctions in adipocytes(Soares et al. 2024).

Compared to FPLD2, FPLD3 patients show less severe fat loss. One way to explain this is that more large adipocytes are preserved since mutations in PPARG could lead to excess cell growth. Fat accumulation in areas such as the face and neck is also not observed (Bagias et al. 2020). However, FPLD3 patients also show more severe metabolic symptoms, specifically hypertriglyceridemia, diabetes, and insulin resistance. One possible explanation is that although patients still preserve large adipocytes, they only have a few small, insulin-sensitive adipocytes (Soares et al. 2024).

3.5 Acquired Lipodystrophy

A wide range of gene mutations that affect different cellular functions could all lead to LD. However, gene mutations are not the only cause of lipodystrophy. Other environmental factors can also trigger the onset of lipodystrophy. Acquired Generalized Lipodystrophy (AGL) and Acquired Partial Lipodystrophy (APL) are forms of lipodystrophy that are not caused by genetic mutations(Al-Jawad et al. 2025). Despite having different mechanisms, they have similar symptoms to congenital lipodystrophy.

Acquired lipodystrophy is characterized by the gradual loss of fat tissue starting from childhood or adolescence. AGL patients show a generalized loss of adipose tissue, while APL patients show loss of adipose tissue from the upper body. This includes the face, neck, upper extremities, and upper trunk. They also share similar causes, including autoimmune diseases, panniculitis-associated causes, and idiopathic causes. However, while about 25% of AGL cases are associated with panniculitis, it is rare in APL patients (Hussain & Garg, 2016).

Adverse effects of highly active antiretroviral therapy in patients with HIV are among the factors that lead to acquired lipodystrophy. The mechanism by which antiretroviral drugs play a role in the development of lipodystrophy is not fully understood. One possibility is the use of thymidine analog nucleoside reverse transcriptase inhibitors in highly active antiretroviral therapies. They have been shown to disrupt adipose tissue functions (Guzman and Vijayan 2025). It decreases the expression of adiponectin, which regulates the oxidation of glucose and fatty acids. Nucleoside reverse transcriptase inhibitor also induces mitochondrial toxicity, which also plays a role in the development of acquired lipodystrophy. Lipodystrophy in HIV-infected patients is characterized by the loss of subcutaneous fat at the extremities and face.

Autoimmune diseases are also a significant cause of acquired lipodystrophy. In particular, perilipin 1 autoantibodies are found in AGL patients (Corvillo et al. 2022). Anti-perilipin is also found in patients with panniculitis-associated AGL. Perilipin is found only in adipose tissue and forms a layer that coats lipid droplets. Under normal conditions, perilipin forms a barrier between lipase and the surface of lipid droplets. However, when the autoantibodies are present, it disrupts the normal function of perilipin. It leads to an increase in lipolysis activities, which contributes to the gradual loss of adipose tissue in AGL patients (Corvillo et al. 2018).

In APL patients, the presence of C3 nephritic factor (C3NeF) is commonly associated. It acts as an autoantibody against the body's own complement system, particularly complement component C3. When C3NeF binds with C3 convertase, it stabilizes C3 convertase and prevents its natural decay. Since the function of C3 convertase is to cleave C3 into its active fragment, prolonged activation leads to a low level of C3 (*Nephritic Factor - an Overview | ScienceDirect Topics*, n.d.). As the breakdown of C3 continues, it activates the terminal pathway. It ultimately leads to the lysis of adipocytes, which explains the fat loss. However, the factor that limits fat loss to the upper body remains unclear (Corvillo & López-Trascasa, 2018).

4. *Diagnosis and Clinical Features*

Since lipodystrophy is so rare, it is often misdiagnosed or left undiagnosed by clinicians. It heavily relies on clinical history and physical examinations that reveal the composition of adipose tissues. Metabolic dysfunctions are also important markers when diagnosing lipodystrophy. Although patients with CGL show symptoms such as a lack of

body fat shortly after birth, it is often left undiagnosed until their childhood or adulthood, when they start showing metabolic abnormalities. As for FPLD, it is even more commonly unrecognized due to patients only losing adipose tissue partially. It could be easily misdiagnosed as other types of common metabolic diseases, like obesity or severe diabetes mellitus. Presentations of AGL and APL are generally similar to CGL and FPLD, also including the metabolic issues that come with it (Lima et al. 2025).

Lipotoxicity is a direct consequence of adipose tissue dysfunction. Since adipose tissues aren't able to store as many lipid droplets as are produced, excess lipid droplets circulate in the bloodstream as free fatty acids. As the level of circulating free fatty acids elevates, it becomes toxic for non-adipose tissues, resulting in increased oxidative stress (Engin, 2017; Sies, 2020). Since the liver is the major organ that maintains the body's homeostasis, excess fatty acid accumulates at the liver, leading to fatty liver (Kikuchi & Takamura, 2017; Liu et al., 2010). This imbalance of fatty acids in the liver interferes with the insulin signaling pathways. In addition, the body stores excess fat in skeletal muscles, as it is the organ responsible for most of the energy uptake (Merz & Thurmond, 2020). Without skeletal muscles, glucose isn't consumed properly, which also disrupts the insulin signaling pathways.

Some phenotypes associated with lipodystrophy include a muscular appearance, prominent veins, and a lack of body fat. Two main types of fat tissue serve different functions in the body: metabolic and mechanical adipose tissue. Metabolic adipose tissue is responsible for energy storage and hormone secretion, while mechanical tissue, also known as subcutaneous fat, is found under the skin and internal organs to provide protection and support. For CGL patients, the loss of metabolic adipose tissues is more severe than the loss of mechanical tissues. Yet patients still, to some degree, lack functional mechanical fat tissues. Only CGL2 patients do not acquire both mechanical and metabolic adipose tissues (Garg 2011).

In contrast, FPLD is characterized by the abnormal distribution with a slight loss of adipose tissue, meaning that patients still acquire most of their functional fat tissues. In addition, as mentioned before, the onset of CGL is often shortly after birth, but for FPLDs, its onset is usually around puberty or adolescence. In general, CGL patients lack the ability to build up mature adipose tissue, while FPLD patients can't store or regulate adipose tissue properly. The following section will address potential treatments and their underlying mechanisms.

5. Treatments

5.1 Metreleptin

Currently, there isn't a definitive cure for lipodystrophy, but some treatments targeting specific metabolic abnormalities have been developed (Araújo-Vilar and Santini 2019). For example, Metreleptin (Recombinant methionyl human leptin) is a drug invented specifically for lipodystrophy. It targets leptin deficiency in patients. Leptin is

secreted by adipose tissue, and it regulates a person's appetite and food intake (Tsoukas, Farr, and Mantzoros 2015). Since lipodystrophy patients lack functional adipose tissue, leptin secretion also decreases. This causes patients to show extreme hyperphagia, which means the excessive intake of food. This worsens insulin resistance and creates excess fat that must be stored in internal organs or muscles. Metreleptin's main purpose is to mimic the naturally occurring leptin hormone, and it must be administered at least once daily (Rodriguez, Mastronardi, and Paz-Filho 2015). It helps reduce patients' appetite and decreases the intake of calories, which contributes to the accumulation of lipid droplets. The use of metreleptin in FPLD patients is not approved by the FDA since it does not work as efficiently in FPLD patients as in CGL patients(Gilio, Foss-Freitas, and Oral 2025). Individual cases of FPLD could be evaluated for whether the requirements for the metreleptin treatment are met. However, the risk of using Metreleptin for special groups of people with generalized lipodystrophy, such as pregnant women, is not certain. Other common drugs, such as insulin or metformin, can also help patients control their symptoms; however, they are not a cure for LD. Cosmetic surgery is also an option for patients to minimize the psychological discomfort and to have a better quality of life (Table 2).

	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.

⚠ Table 2: Possible medications to control metabolic issues that arise with lipodystrophy. Including the objectives, possible challenges, and other considerations (Reproduced from (Patni et al., 2024) under the terms of the CC BY license)

5.2 Lifestyle Modification

Although Metreleptin can generally help with metabolic dysfunctions, lifestyle modification also plays a significant role in managing lipodystrophy. A low-fat diet is

recommended for patients. Carbohydrate intake is also restricted to control diabetes. Since the body cannot store excess energy properly, it would be beneficial for patients to reduce the intake of food that will be metabolized into excess fat or energy. Physical exercises are also encouraged. However, patients with cardiovascular issues should avoid excessive exercise to prevent further complications (Akinci et al. 2024).

5.3 Limitations and Possibility of Gene Editing

Although Metreleptin is an effective way for LD patients to manage metabolic complications, it is not able to cure them. In the future, gene editing could be applied to treating this disease. Preclinical trials have been conducted on mouse models with CGL2, which has a gene mutation at the BSCL2 gene. Seipin knockout (SKO) mice, which generally show similar metabolic symptoms to CGL2 patients, were generated and injected with adeno-associated virus (AAV) vectors (Sommer et al. 2022). AAV can be engineered to transduce adipocytes, enabling targeted gene therapy for lipodystrophy. The results of the trials show that gene therapy effectively restores adipose tissue development and function (Tiwari et al. 2024). However, even though AAV is commonly used in clinical trials, it hasn't been used to directly target adipose tissue. Novel AAV serotypes that target adipose tissue or an alternative promoter are critical for the development of an improved gene therapy strategy for LD patients. Therefore, there isn't enough evidence currently to suggest that the results from mouse models can be translated to humans. Continued research on LD and advances in gene therapy are necessary to develop a more effective therapeutic strategy for this rare disorder.

6. Conclusion and the Future

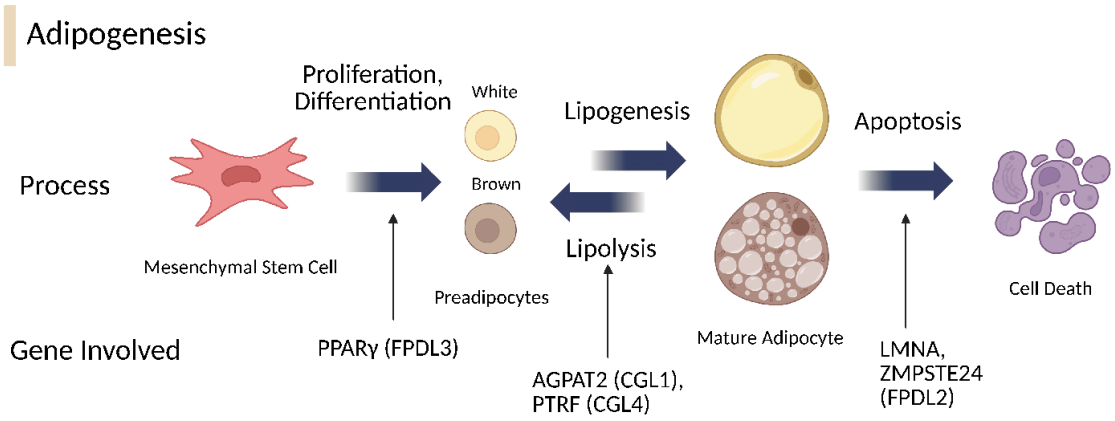


Figure 4: Steps of adipogenesis. Starting from mesenchymal stem cells, after proliferation and differentiation, it develops into preadipocytes. Then, through lipogenesis,

preadipocytes grow into mature adipocytes. When a person is fasting, adipocytes go through lipolysis to produce energy by breaking down triglycerides into glycerol and free fatty acids. The last step is apoptosis, which ultimately leads to cell death. (Made with BioRender)

Genes involved in lipodystrophy syndromes affect various cellular processes, such as lipid synthesis, signal transduction, and nuclear structure. They all lead to a common outcome: impaired adipocyte development and function. The examples discussed in this review, including CGL1, CGL4, FPLD2, and FPLD3, demonstrate how different stages of adipogenesis and gene mutations that are involved in adipogenesis all lead to similar consequences (Figure 4). In addition to genetic causes, acquired factors can also contribute to adipocyte dysfunctions, as seen in AGL.

LD highlights the essential role of adipose tissue as an endocrine and metabolic organ. It not only stores energy but also maintains metabolic homeostasis and regulates hormones. The absence of adipocytes, as shown in this review, could cause life-threatening disorders. Understanding this condition not only helps people recognize the role of adipose tissue in metabolism but also helps raise awareness of rare diseases. For conditions like lipodystrophy, many patients remain undiagnosed throughout their lives. Not only is conducting research with so few samples challenging, but scientists may be less willing to dedicate time to studying rare diseases compared to diseases that affect a larger population. Increased awareness and improved diagnostic tools not only help identify individuals affected by this disease earlier but also give them a chance to manage their condition in a more effective way.

Since the discovery of lipodystrophy syndromes in the mid-20th century, significant progress has been made in understanding lipodystrophy. From phenotypes and metabolic abnormalities to underlying genetic causes, research has been conducted to find ways to reduce patients' pain and suffering. Having a deep understanding of lipodystrophy, such as the mechanisms of various genes and their relationship with adipogenesis, will be crucial to the development of a more effective and targeted therapeutic strategy.

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Molecular Basis of Lipodystrophy: Gene Mutations, ~~Disease Progression,~~Pathophysiology, and Therapy

Abstract

Lipodystrophy syndromes are a group of ~~are~~ rare diseases ~~that are often~~ characterized by a general or partial absence of body fat~~.~~, caused by the inability to properly store and utilize ~~Fat tissues are also known as~~ adipose tissues~~.~~; ~~and the~~The lack of adipose tissue~~s~~ would lead to serious consequences and the development of a series of metabolic issues, including insulin resistance, leptin deficiency, and hypertriglyceridemia. Lipodystrophy~~These~~ syndromes are genetically and clinically heterogeneous, with different phenotypes influenced by underlying molecular defects. Both fat distribution and the molecular defect play a role in ~~They are all factors that~~ determine~~e~~ing the type of lipodystrophy a patient has. Due to the rarity of these~~is~~ disorders, not many studies have been conducted~~done~~ on ~~it~~them. This~~, which~~ results~~leads to~~in the public's~~people's~~ lack of ~~knowledge~~awareness, increasing the difficulty of diagnosing and treating these conditions~~about this disease and increases the difficulty of treating it~~. T~~ In t~~his article ~~article, we first~~ examine~~consider~~s the classification and clinical aspects of lipodystrophy syndromes, covering the onset and the differences in phenotypes of patients. ~~Then, we~~ It further discusses the molecular and cellular mechanisms of several types of lipodystrophies and the role they play in the development of adipose tissues. In addition~~Next~~, this review addresses ~~we focus on~~ other metabolic dysfunctions caused by lipodystrophy, such as insulin resistance, fatty liver, and hypertriglyceridemia. Lastly, we evaluate therapeutic strategies aimed at improving metabolic control and quality of life in affected patients. Future ~~direction of~~ research~~study~~ and potential therapy~~ies~~ may be improved with a deeper and more thorough understanding of the genetic and mechanistic basis of lipodystrophy, as it is critical for identifying key mechanisms and developing a more targeted treatment.

Keywords: Lipodystrophy syndromes, adipose tissue, adipogenesis, gene mutations, metabolic dysfunctions

1. *Introduction*

Lipodystrophy syndromes (LD) are a heterogeneous group of rare disorders characterized by the partial or complete loss of mature adipose tissue in localized or generalized areas. This results in the inability to store body fat, ectopic lipid storage, ~~-~~and excess nutrients (Fourman and Grinspoon 2022). Two main classes of lipodystrophy are Congenital Generalized Lipodystrophy (CGL) and Familial Partial Lipodystrophy (FPLD). ~~Adipose tissues are formed through a process called adipogenesis, and it is crucial for the adipose tissue to function normally.~~

For adipose tissues to function normally, adipogenesis is crucial for the differentiation of the precursor cells. Adipogenesis starts with ~~Adipogenesis is the~~

process by which mesenchymal stem cells differentiatinge into mature adipose tissue. DuringThis adipogenesisprocess, lipid storage and mobilization is regulated by also includes the triacylglycerol (TAG) fatty acid cycle.; which regulates lipid storage and mobilization in adipocytes. It is the processL where the lipid droplets undergo lipolysis (the breakdown of lipid droplets) and lipogenesis (the synthesis of new lipid droplets)(Poulos et al. 2016). However, if a gene mutation or other factors affect the components that play a roleinvolved in the regulation ofregulating adipogenesis, thisit would lead to impaired adipocyte differentiation, lipid droplet formation, and adipocyte functions.to serious, life-threatening consequences.

LD can be either congenital or acquired. Congenital Lipodystrophy, and it is classified based on the location of lost adipose tissue, and further divided into subtypes according to the gene segment that is mutated (Akinci, Gular, and Oral 2024) (Table 1). Meanwhile, acquired lipodystrophy is caused by external factors or side effects of other treatments.

CGL (also called Berardinelli-Seip syndrome) is characterized by the near-complete absence of adipocytes, both mechanical and metabolic fat tissues (Oswiecimska n.d.). CGLs are inherited in an autosomal recessive manner, and thewith symptoms typicallyoften presenting start showing shortly after birth. It is further divided into CGL1, CGL2, CGL3, and CGL4, which link to four different gene mutations. FPLD presents as an abnormal distribution of adipose tissue, with fat loss around the limbs, torso, and hips. It can be autosomal recessive or dominant depending on the genee that is involved. Since the body is not able to store excess energy in those areas, other body parts, such as the face, neck, and internal organs like the liver, gain extra adipose tissue (Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic n.d.). This results in the abnormal distribution of adipose tissues. As with Same as CGL, FPLDit is furtheralso divided into several subtypes, including FPLD1 (Kobberling-type lipodystrophy), FPLD2 (Dunnigan Variety lipodystrophy), FPLD3, FPLD4, FPLD5, and FPLD6. The development of adipocytes is tightly regulated by various proteins and enzymes. The genes that encode these proteins or enzymes are often the genes associated with lipodystrophy.Proteins or enzymes that are encoded by the genes associated with any kind of lipodystrophy all play important roles in the development of adipocyte.

As for Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome), they have similar symptoms as CGL and FPDL. However, they are caused by autoimmune diseases, side effects of antiretroviral therapy (ART) for HIV patients, or even idiopathic reasons (Misra and Garg 2003).Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome) have similar symptoms, respectively; however, they can be caused by autoimmune diseases, the side

~~effects of antiretroviral therapy (ART) for HIV patients, and sometimes idiopathic (Misra and Garg 2003).~~ ¶

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
Generalized Lipodystrophy Syndrome					
Congenital Generalized Lipodystropy (Berardinelli-Seip syndrome)	CGL1	AGPAT2	Autosomal recessive	Near total absence of adipose tissue, generalized musularity, metabolic abnormalities. Starts showing symptoms shortly after birth.	Loss of metabolic fat, retains mechanical fat tissues
	CGL2	BSCL2	Autosomal recessive		Mild mental retardation
	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
Acquired Generalized Lipodystrophy (Lawrence Syndrome)	NA	NA	NA	Near total absence of adipose tissue, metabolic issues. Develops during childhoold/ puberty.	Could be caused by autoimmune diseases, panniculitus, idiopathic or immunotherapy
Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/ adolescense.	Palpable "ledge" between normal and lipodistrophic areas
	FPLD2 (Dunnigan)	LMNA	Autosomal dominant		High risks of cardiovascular diseases
	FPLD3	PPARG	Autosomal dominant		Less severe and distal fat loss
	FPLD4	PLIN1	Autosomal dominant		Increased fibrosis of adipose tissue, small lipid droplets in adipocytes
	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

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	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
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Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/adolescense.	Palpable "ledge" between normal and lipodistrophic
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	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

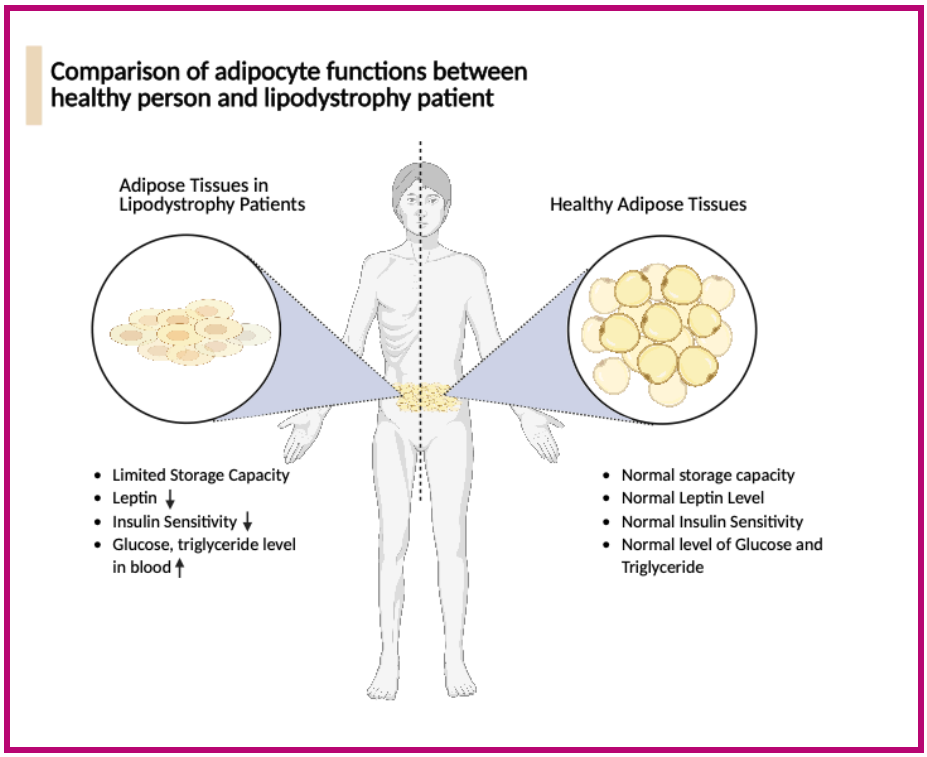
▲ Table 1: Classification, clinical features, and molecular basis of lipodystrophies (Made with Google Sheet)

Not only will the lack of excess ~~energy~~body fat ~~affect~~affect the body's normal functions, but ~~other~~ complications ~~t~~associated~~hat arise~~ with lipodystrophy also have a significant~~big~~ effect on patients' lives. Some common metabolic abnormalities include leptin deficiency, insulin resistance, diabetes, hypertriglyceridemia, and fatty liver disease (F~~f~~igure 1). Currently, around 200 clinical trials are ~~in progress, trying~~underway to discover a new way to treat or cure lipodystrophy, with a particular focus on ~~especially targeting~~ leptin deficiency (*Search ClinicalTrials.Gov For*, n.d.)~~ncy~~.

Metreleptin, for example, is a treatment created specifically for acquired or congenital generalized lipodystrophy ~~LD~~ patients. It is a targeted treatment for leptin deficiency, which is a common metabolic issue associated with LD~~D~~ (Araújo-Vilar & Santini, 2019)~~. (Araújo-Vilar e Santini 2019)~~. It is currently the only FDA- approved treatment for generalized lipodystrophy ~~LD~~ patients.~~.~~ However, conventional treatment, such as special diets, is still optimized before metreleptin (Meehan et al., 2016). Due to the rarity of this disease, limited research has been done, making Metreleptin the primary choice for CGL and AGL patients ~~LD patients~~ (Ajluni et al., 2016). As for FPLD patients, the use of Metreleptin is highly restricted. Therefore, they will need to maintain ~~Patients will still need to have~~ an appropriate ~~healthy~~diet and require other medications for the ~~other~~ metabolic complications~~issues~~.

According to studies, only about 3 per ~~/~~million people around the world are affected by some type of lipodystrophy syndrome. While the prevalence of CGL is estimated to be 0.23 per ~~/~~million people, the prevalence of FPLD is around 2.84 per ~~/~~million people (Chiquette et al. 2017). It is also estimated to shorten a patient's lifespan by 30 or more years. The main cause of death is shown to be liver diseases and infections caused by adipose tissue dysfunction, but also varies from type to type of lipodystrophy (Lima et al. 2018).

This literature review aims to highlight the molecular mechanisms underlying~~of~~ lipodystrophy, ~~focusing~~ with a focus on the genetic causes, differences between types of lipodystrophies, and other metabolic conditions caused by adipose tissue abnormalities, as well as ~~. In addition,~~ the treatment developed and future directions of study, and the ~~other~~ possibilities for ~~a~~ fundamental treatments.~~cure~~.



Comparison of adipocyte functions between healthy person and lipodystrophy patient
Adipose Tissues in Lipodystrophy Patients
Healthy Adipose Tissues
Limited Storage Capacity
Leptin ↓
Insulin Sensitivity ↓
Glucose, triglyceride level in blood ↑
Normal storage capacity
Normal Leptin Level
Normal Insulin Sensitivity
Normal level of Glucose and Triglyceride

▲ Figure 1: Comparison of adipocyte functions between a healthy person and a lipodystrophy patient. Adipocyte storage ~~The storage of adipocytes~~ is ~~is limited~~decreased in lipodystrophy patients. Common metabolic abnormalities include leptin deficiency, insulin resistance, and elevated blood~~increased~~ glucose levels in the bloodstream. (Made with BioRender)

2. Methods

Search Strategy

A literature search was conducted using PubMed and Google Scholar databases. The search included the following keywords: “lipodystrophy genetics”, “adipocyte differentiation”, “AGPAT2”, “PTRF Cavin-1”, “LMNA mutation”, “PPARγ mutation”, “lipodystrophy metabolic abnormalities”. Titles and abstracts were first screened for relevance. Full articles were reviewed to see if they met the inclusion criteria. 97 articles were initially screened, and 54 papers were ultimately referenced in this review.

Inclusion/Exclusion Criteria

Articles published between 2000 and 2026 were included. Only ~~publications in the~~ English language publications were considered. Studies were included if they were peer-reviewed primary research articles or comprehensive reviews, including both narrative reviews and systematic reviews, that focused ~~focusing~~ on the genetic, molecular, or metabolic mechanisms underlying ~~of~~ lipodystrophy syndromes. Case studies were included if they provide~~with~~d relevant insights ~~and information~~, such as pathological or mutation analyses, or clinical findings ~~were also included~~. Non~~-peer~~-peer-reviewed sources and ~~,~~articles published before 2000 are excluded.~~;~~ Ccase reports that only report~~with~~ descriptive ~~only~~ quantitative data~~-~~, without the discussion of mechanistic interpretation, are also excluded, as clinical data are not the focus of this review.~~and without further analysis were excluded. Titles and abstracts were first screened for relevance. Full article was reviewed if they met the inclusion criteria.~~

Discussion

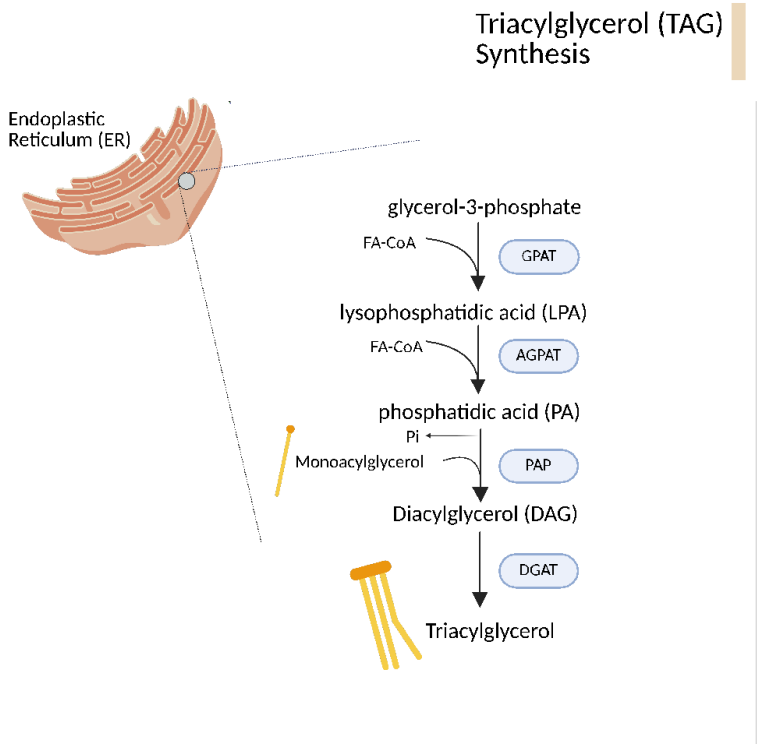
3. Genetics and Pathophysiology

3.1 Type one ~~1~~ Congenital Generalized Lipodystrophy (CGL1)

Type one~~1~~ Congenital Generalized Lipodystrophy (CGL1) is caused by a mutation in the gene AGPAT2. AGPAT2 is the gene that ~~coding for~~ encodes the ~~a specific~~ enzyme ~~,~~ 1-acylglycerol-3-phosphate O-acyltransferase 2. It~~, which~~ catalyzes the acylation of lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1,2 diacylglycerol-3-phosphate)(Gale et al. 2006) (F~~f~~igure 2). It is an important precursor for~~of~~ the biosynthesis of triacylglycerol (TAG) and phospholipid~~s synthesis~~ from glycerol-3-phosphate. This step esterifies a second fatty acyl group at the sn-2 position of the glycerol backbone. Phosphatidic acid is further acylated by other enzymes, creating triacylglycerol and phospholipids. Impaired formation of phosphatidic acid results in the absence of triacylglycerol production, thereby disrupting the normal adipose tissue development.

The AGPAT family consists of 11 isomers.~~;~~ Among the isomers, ~~however,~~ AGPAT2 is expressed at higher levels in adipose tissue than the other isomers. The presence of

mechanical adipose tissue can be explained by the increased expression of the other isomers (Broekema et al., 2018). However, studies have shown that the expression of AGPAT2 is required for the accumulation of triacylglycerol, especially in metabolic adipose tissues. Defects in the AGPAT2 genes also impact insulin signaling, which is a direct effect of impaired adipocyte dysfunction (Santoro et al., 2021). ~~meaning~~ This also causes~~that~~ gluconeogenesis ~~will~~to be unrestricted, which leads to the development of hyperglycemia and diabetes(de Melo et al. 2025).



▲ Figure 2: The process of Triacylglycerol synthesis. In the second step, where LPA is acylated to PA, AGPAT is the enzyme that catalyzes this reaction. Without it, the reactions after it will not occur properly, meaning that adipocytes can't develop properly. (Made with BioRender)

3.2 *Type 2 Congenital Generalized Lipodystrophy (CGL2)*

Type 2 Congenital Generalized Lipodystrophy (CGL2) is caused by pathogenic variants of the BSCL2 gene. It encodes the protein seipin, which is found in the endoplasmic reticulum (ER) (Akinci et al., 2024), Seipin plays an important role in the regulation of lipid droplet biogenesis. It interacts with proteins involved in TAG synthesis to facilitate adipogenesis. For instance, it binds with AGPAT2 to regulate PA metabolism. Seipin deficiency could lead to abnormal accumulation of PA. This increases the surface tension of the ER and decreases its line tension, disrupting the unidirectional lipid droplet

budding. It causes the accumulation of newly synthesized neutral lipids in the ER, leading to severe ER stress and potentially being toxic to the cells (Li et al., 2022).

CGL2 is the most common type of congenital lipodystrophy. But mutations in the BSCL2 also lead to the most severe symptoms. Patients are born without any fat, including mechanical and metabolic adipose tissues. They also have an earlier onset of diabetes mellitus than other types of lipodystrophies. Other than adipocytes, seipin is also expressed in the brain and testis. This leads to mild mental disability, developmental language disorders, and an impaired reproductive system.

3.2 Type four Congenital Generalized Lipodystrophy (CGL4)

Type four Congenital Generalized Lipodystrophy (CGL4) is associated with the gene mutation in the PTRF gene (Polymerase I and Transcript Release Factor)(Salle-Teyssières et al. 2016). The PTRF gene encodes cavin-1, which is one of the essential proteins that is required for the biogenesis of caveolae. Caveolae are the most abundant invaginations of the plasma membrane across a wide range of mammalian cells (Figure 3). Cavin-1 plays a critical role in the initiation of caveolae by recruiting other structural proteins, such as caveolins. Without it, cells won't be able to produce caveolae. Although it is abundant, its functions have only been understood in the past few decades. It plays a role in signal transduction, endocytosis, and mechanotransduction (Stea and D'Alessio 2025). Cavin-1 binds with the caveolins to form Caveolae. There are three members in the caveolin family: caveolin-1, caveolin-2, and caveolin-3. They are expressed in a variety of cells, like smooth muscle cells, fibroblasts, and adipocytes. Caveolin 3 is expressed exclusively in cardiac and skeletal muscle. It is shown that the lack of PTRF-CAVIN doesn't affect the level of caveolin expressed (Rajab et al. 2010). However, it affects caveolin's ability to localize to the cell's surface, which makes the formation of caveolae impossible. The absence of caveolae causes abnormalities and dysfunctions, including impaired signal transduction and a lack of mechanoprotection. Without the extra membranes acting as a buffer against the force of mechanical stretching, cardiac cells are at a greater risk of rupturing (Grivas et al., 2020).

Clinical features uniquely associated with CGL4 are myopathy, which affects skeletal muscle structure, and distal metaphyseal deformation, causing bone stiffness and limited range of motion (Ardissone et al. 2013). Cardiac arrhythmias are also one of the symptoms caused by the lack of PTRF-CAVIN, and they could be life-threatening, showing the serious consequences of cavin-1 deficiency (Rajab et al. 2010). These symptoms can be explained by the location where caveolins 1, 2, and 3 are expressed.

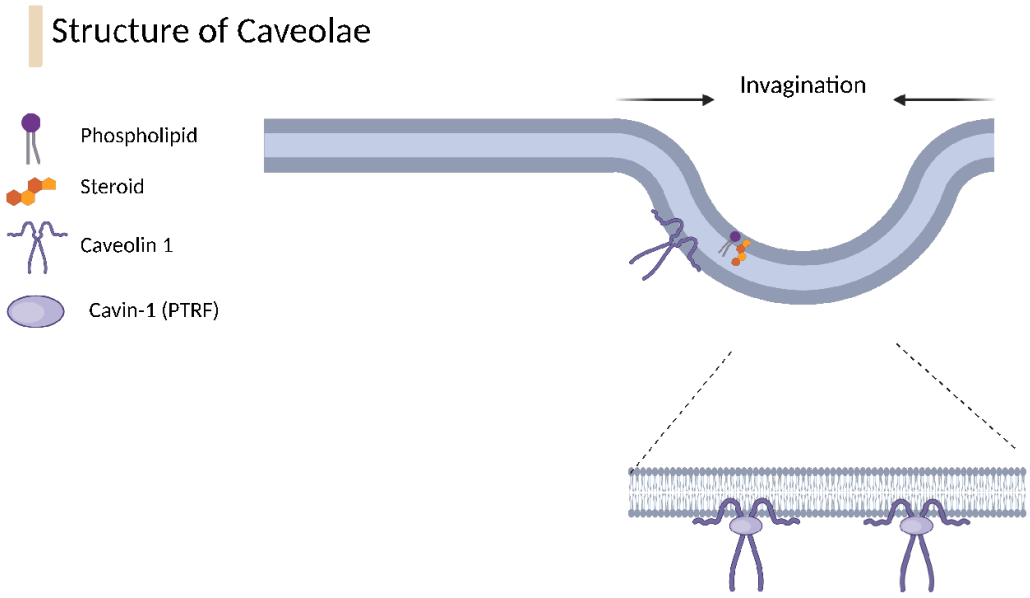


Figure 3: ~~The~~ structure and formation of caveolae. Caveolae are invaginations~~clusters~~ of~~in~~ the ~~cell~~ plasma membrane. Cavin-1 first binds with the plasma membrane, initiating caveolae synthesis. C~~and~~ caveolin 1 binds with cavin-1, which stabilizes its structure ~~together~~ and forms caveolae. (Made with BioRrender)

3.3 Type ~~two~~2 Familial Partial Lipodystrophy (FPLD2)

The gene LMNA~~, which~~ encodes the protein called Lamins.~~,~~ It is the gene that ~~causes~~ is associated with Type ~~two~~2 Familial Partial Lipodystrophy (FPLD2). ~~It~~ FPLD2 is ~~is also~~ the most common type of lipodystrophy syndrome (Corsa et al. 2021). In cells, Lamin A and Lamin C are expressed predominantly. The main functions of Lamin A/C are the regulation of nucleus shape, providing structural stability to the nuclear envelope and cytoskeleton, and also controlling gene regulation (Maung et al. 2026)(Bagias et al. 2020). They are important intermediate filament proteins forming the nuclear lamina. They also play a role in ~~Specifically,~~ organizing~~the nuclear lamina and~~ chromatin~~, and the interaction between them~~. Mutations in Lamin A/C can lead to premature aging syndrome (Hutchinson-Gilford Progeria Syndrome). The mutated LMNA gene produces a mutant product called progerin. As progerin accumulates in the nucleus, it destabilizes DNA, triggers premature senescence, and alters the shape of the nucleus (Gonzalo et al., 2017).

~~One way that Lamin A can affect cell development is t~~The interference with the cleavage step of post-translational regulation of Lamin A could also affect the patient. ZMPSTE24 plays an important role in this step, and it is also considered to be one of the factors that causes lipodystrophy. However, mutations in ZMPSTE24 cause another distinct form of lipodystrophy (mandibuloacral dysplasia), showing different symptoms and increased severity. ~~This m~~Nevertheless, modification is crucial and ensures that Prelamin A (the precursor of Lamin A before ~~the~~ post-translational regulation) ~~will~~

~~function~~functions normally. Not only will the lack of Lamin A affect cell functions, but the accumulation of Prelamin A could also be toxic to cells (Varlet, Helfer, and Badens 2020), which could affect the cell's ability to develop properly.

These cellular abnormalities contribute to broader systemic symptoms. This includes a~~A~~ higher risk of cardiovascular diseases ~~is also associated with FPLD2~~. It is found that FPLD2 patients have higher Epicardial adipose tissue (EAT) volume than type two diabetes patients (Talman et al. 2014) (Godoy-Matos et al. 2015). However, it is not related to other metabolic issues that are also presented in lipodystrophy (Lamothe et al. 2025). ~~Other~~ Additional studies will ~~also~~ need to be conducted~~done~~ to gain a~~have a~~ clearer insight into this condition and ~~the~~its correlation ~~between them~~.

3.4 Type three~~3~~ Familial Partial Lipodystrophy (FPLD3)

Type three~~3~~ Familial Partial Lipodystrophy (FPLD3) is caused by pathogenic variants of the PPARG gene. PPARG encodes ~~for~~ PPARγ (Peroxisome proliferator-activated receptor γ), a member of a superfamily of nuclear receptors. PPARγ is known as the master regulator of adipocyte differentiation, maintenance, and functions(Broekema et al. 2019). It ~~PPARγ~~ has three isoforms: ~~,~~PPARγ1, PPARγ2, and PPARγ3. Among them, PPARγ2 is predominantly expressed in adipocytes. PPARγ acts as a ligand-activated transcription factor. It binds to its target gene as a heterodimer with PPAR-response elements (PPREs)(Madsen et al. 2022). After binding, PPARγ regulates the transcription of downstream target genes ~~induces many targeted genes~~ that are involved in the development of adipose tissues. Including t~~T~~he TAG cycle, which is ~~also~~ upregulated by PPARγ for the development of adipocytes. Loss-of-function or dominant-negative m~~M~~utations in pathogenic variants of PPARG ~~might~~ cause excess differentiation and growth in~~of~~ adipocytes, fundamentally impairing adipogenesis. Therefore, leading ~~it leads~~ to increased cellular stress and dysfunctions in adipocytes(Soares et al. 2024).

Compared to FPLD2, FPLD3 patients show less severe fat loss. One way to explain this is that more large adipocytes are preserved since mutations in PPARG could lead to excess cell growth. Fat accumulation in areas such as the face and neck ~~are~~is also not observed (Bagias et al. 2020). However, FPLD3 patients also show more severe metabolic symptoms, specifically hypertriglyceridemia, diabetes, and insulin resistance. One possible explanation is that although patients still preserve large adipocytes, they only have a few small, insulin-sensitive adipocytes (Soares et al. 2024).

3.5 Acquired ~~Generalized~~ Lipodystrophy ~~(AGL)~~

A ~~s we can see,~~ a wide ~~variety~~ range of gene mutations that affect different cellular functions could all lead to LD. However, gene mutations are not the only cause of lipodystrophy. Other environmental factors can also trigger the onset of lipodystrophy. Acquired Generalized Lipodystrophy (AGL~~, also called Lawrence Syndrome~~) and Acquired Partial Lipodystrophy (APL) are forms ~~is another form~~ of lipodystrophy~~, which has similar~~

~~symptoms to CGL but is~~that are not caused by genetic mutations(Al-Jawad et al. 2025). Despite having different mechanisms, they have similar symptoms to congenital lipodystrophy.

¶

Acquired lipodystrophy is characterized by the gradual loss of fat tissue starting from childhood or adolescence. AGL patients show a generalized loss of adipose tissue, while APL patients show loss of adipose tissue from the upper body. This includes the face, neck, upper extremities, and upper trunk. They also share similar causes, including autoimmune diseases, panniculitis-associated causes, and idiopathic causes. However, while about 25% of AGL cases are associated with panniculitis, it is rare in APL patients (Hussain & Garg, 2016).

~~———~~Adverse effects of highly active antiretroviral therapy ~~(HAART)~~ in patients with HIV are among~~one of~~ the factors that lead to acquired lipodystrophy~~AGL~~. The mechanism by which antiretroviral drugs play a role in the development of lipodystrophy is not fully understoo~~od completely~~. One possibility is ~~Proteins such as~~ the use of t~~t~~hymidine analog nucleoside reverse transcriptase inhibitors ~~(NRTI), which are used~~ in highly active antiretroviral therapies~~HAART~~. They~~;~~ ~~are~~have been shown to disrupt adipose tissue functions (Guzman and Vijayan 2025). It decreases the expression of adiponectin, which regulates the oxidation of glucose and fatty acids. Nucleoside reverse transcriptase inhibitor ~~NRTI~~ also induces mitochondrial toxicity, which also plays a role in the development of ~~AGL~~acquired lipodystrophy. Lipodystrophy in HIV-infected patients is characterized by the loss of subcutaneous fat at the extremities and face.¶

~~Another possible cause of AGL is~~ A~~a~~utoimmune disease~~s~~ are also a significant cause of acquired lipodystrophy~~.~~: ~~Specifically~~In particular, perilipin 1 ~~(PLIN1)~~ autoantibodies are found in AGL ~~AGL~~ patients (Corvillo et al. 2022). Anti-perilipin is also found in patients with ~~panniculitis associated~~panniculitis-associated AGL ~~AGL~~. Perilipin is found only in adipose tissue and forms a layer that coats lipid droplets. Under normal conditions, perilipin forms a barrier between lipase and the surface of lipid droplets. However, when the autoantibodies are present, it disrupts the normal function of perilipin. It leads to an increase in lipolysis activities, which ~~decreases~~ contributes to the gradual loss of adipose tissue in ~~the fat storage in t~~AGL patients ~~he body~~(Corvillo et al. 2018).

In APL patients, the presence of C3 nephritic factor (C3NeF) is commonly associated. It acts as an autoantibody against the body's own complement system, particularly complement component C3. When C3NeF binds with C3 convertase, it stabilizes C3 convertase and prevents its natural decay. Since the function of C3 convertase is to cleave C3 into its active fragment, prolonged activation leads to a low level of C3 (*Nephritic Factor - an Overview | ScienceDirect Topics*, n.d.). As the breakdown of C3 continues, it activates the terminal pathway. It ultimately leads to the lysis of adipocytes,

which explains the fat loss. However, the factor that limits fat loss to the upper body remains unclear (Corvillo & López-Trascasa, 2018).

¶

4. Diagnosis and Clinical Features

Since lipodystrophy is s~~uch a~~ rare ~~disease and not well known to the public~~, it is often misdiagnosed or left undiagnosed by clinicians. It heavily relies on clinical history and physical examinations that reveal the composition of adipose tissues. Metabolic dysfunctions are also important markers when diagnosing lipodystrophy. Although patients with CGL show symptoms such as a lack of body fat shortly after birth, it is often left undiagnosed until their childhood or adulthood, when they start showing metabolic abnormalities. As for FPLD, it is even more commonly unrecognized due to patients only losing adipose tissue partially. It could ~~be easily mixed up with~~be easily misdiagnosed as other types of common metabolic diseases, like obesity or severe diabetes mellitus. Presentations of AGL and APL are generally similar to CGL and FPLD, also including the metabolic issues that come with it (Lima et al. 2025).

Lipotoxicity is a direct consequence of adipose tissue dysfunction. Since adipose tissues aren't able to store as many lipid droplets as are produced, excess lipid droplets circulate in the bloodstream as free fatty acids. As the level of circulating free fatty acids elevates, it becomes toxic for non-adipose tissues, resulting in increased oxidative stress (Engin, 2017; Sies, 2020). Since the liver is the major organ that maintains the body's homeostasis, excess fatty acid accumulates at the liver, leading to fatty liver (Kikuchi & Takamura, 2017; Liu et al., 2010). This imbalance of fatty acids in the liver interferes with the insulin signaling pathways. In addition, the body stores excess fat in skeletal muscles, as it is the organ responsible for most of the energy uptake (Merz & Thurmond, 2020). Without skeletal muscles, glucose isn't consumed properly, which also disrupts the insulin signaling pathways.

Some phenotypes ~~that are~~ associated with lipodystrophy ~~are~~ include a muscular appearance, prominent veins, and ~~the~~ a lack of body fat. Two main types of fat tissue serve different functions in the body: metabolic and mechanical adipose tissue. Metabolic adipose tissue is responsible for energy storage and hormone secretion, while mechanical tissue, also known as subcutaneous fat, is found under the skin and internal organs to provide protection and support. For CGL patients, the ~~absence~~ loss of metabolic adipose tissues is more severe~~common~~ than the loss of mechanical tissues. Yet~~. Although~~ patients still, to ~~in~~ some degree,~~s~~ lack functional mechanical fat tissues. ~~Metabolic adipose tissues are in charge or energy storage and hormone secretion, while the mechanical tissues, also known as subcutaneous fat tissue, are found under the skin and internal organs to provide protection and support. Although patients still in some degrees lack functional mechanical fat tissues.~~ Only CGL2 patients ~~Except for CGL2, in which patients generally~~ do

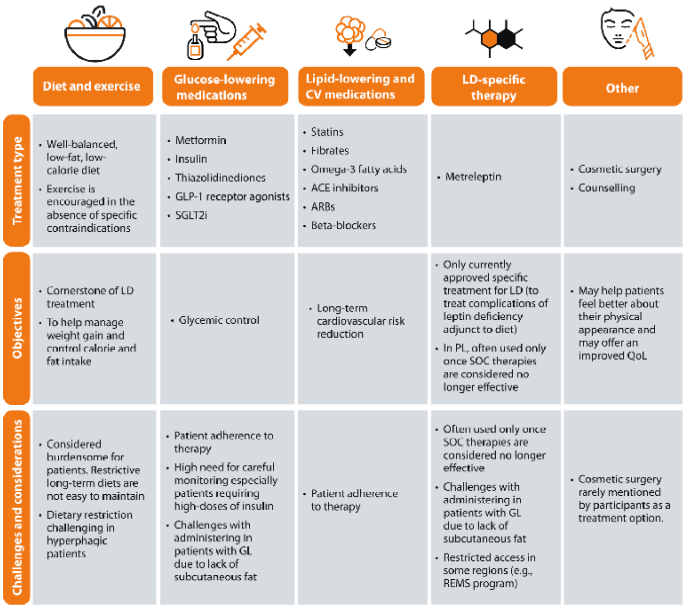
not acquire both mechanical and metabolic adipose tissues~~kinds of fat tissues~~ (Garg 2011).

In contrast, FPLD is ~~characterized~~characterized by the abnormal distribution with a slight loss of adipose tissue, meaning that patients still acquire most of their functional fat tissues. In addition, as mentioned before, the onset of CGL is often shortly after birth, but for FPLDs, its onset is usually around puberty or adolescence. In general, CGL patients lack the ability to build up mature adipose tissue~~s~~, while FPLD patients can't store or regulate adipose tissue properly. ~~Next, we~~ The following section will address potential treatments and their underlying mechanisms. ~~will be discussing some potential treatments for lipodystrophy and the mechanisms behind them.~~

5. Treatments

5.1 Metreleptin

Currently, there isn't a definitive~~e treatmen~~cure~~t~~ for lipodystrophy, but some treatments targeting~~for~~ specific metabolic abnormalities ~~are~~have been developed ~~being invented~~ (Araújo-Vilar and Santini 2019). For example, Metreleptin (Recombinant methionyl human leptin) is a drug invented specifically for lipodystrophy. It targets leptin deficiency in patients~~. Leptin is a hormone that regulates energy metabolism~~. Leptin~~It~~ is secreted by adipose tissue, and it regulates a person's appetite and food intake (Tsoukas, Farr, and Mantzoros 2015). Since lipodystrophy patients lack functional adipose tissue, leptin secretion also decreases. This causes patients to show extreme hyperphagia, which means the excessive intake of food. This worsens insulin resistance and creates excess fat that must be stored in internal organs or muscles. Metreleptin's main purpose is to mimic the naturally occurring leptin hormone, and it must be administered at least once daily (Rodriguez, Mastronardi, and Paz-Filho 2015). It helps reduce patients' appetite and decreases the intake of calories, which contributes to the accumulation of lipid droplets. The use of metreleptin in FPLD patients is not approved by the FDA since it does not work as efficiently in FPLD patients as in CGL patients~~. Metreleptin is found to be more efficient in Generalized lipodystrophy patients due to the low levels of leptin that are produced~~(Gilio, Foss-Freitas, and Oral 2025). Individual cases of FPLD could be evaluated for whether the requirements for the metreleptin treatment are met. However, the risk of using Metreleptin for special groups of people with generalized lipodystrophy, such as pregnant women, ~~are~~is not certain. Other common drugs, such as insulin or metformin, can also help patients control their symptoms; however, they are not a cure for LD~~D~~. ~~.~~ Cosmetic surgery is also an option for patients to minimize the psychological discomfort and to have a better quality of life (Table 2).



	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.

Table 2: Possible medications to control metabolic issues that arises with lipodystrophy. Including the objectives, possible challenges, and other considerations (Reproduced from (Patni et al., 2024) ~~(Patni et al. 2024)~~ under the terms of the CC BY license)

5.2 Lifestyle Modification~~Change in Daily Routine~~

Although Metreleptin can generally help with metabolic dysfunctions, lifestyle modification also plays a significant role in managing lipodystrophy. A low-fat diet is recommended for patients. Carbohydrate intake is also restricted to control diabetes. Since the body cannot store excess energy properly, it would be beneficial for patients to reduce the intake of food that will be metabolized into excess fat or energy. Physical exercises are also encouraged. However, patients with cardiovascular issues should avoid ~~doing too much~~excessive exercise to prevent ~~the development of other serious~~further complications (Akinci et al. 2024).

5.3 Limitations and Possibility of Gene Editing

Although Metreleptin is an effective way for LD patients to manage metabolic complications, it is not able to cure ~~it~~them. In the future, gene editing could be applied to treating ~~the treatment of~~ this disease. Preclinical trials have been conducted on mouse models with CGL2, which has a gene mutation at the BSCL2 gene. Seipin knockout (SKO) mice, which generally show similar metabolic symptoms to CGL2 patients, were generated~~,~~ and ~~were~~ injected with adeno-associated virus (AAV) vectors (Sommer et al. 2022). A~~A~~V can be engineered to ~~,~~transduce~~targets~~ adipocytes, enabling ~~which act as a~~ targeted ~~in~~ gene therapy for lipodystrophy. The results of the trials show that gene therapy effectively restores adipose tissue development and function (Tiwari et al. 2024). However, even

though AAVV is commonly used in clinical trials, it hasn't been used to directly target adipose tissue. Novel AAVV serotypes that targets adipose tissue or an alternative promoter are critical for the development of an improved gene therapy strategy for LD patients. Therefore, there isn't enough evidence currently to suggest that the results from mouse models can be translated to humans. Continued research on LD and advances in gene therapy are necessary to develop a more effective therapeutic strategy for this rare disorder.

6. *Conclusion and the Future*

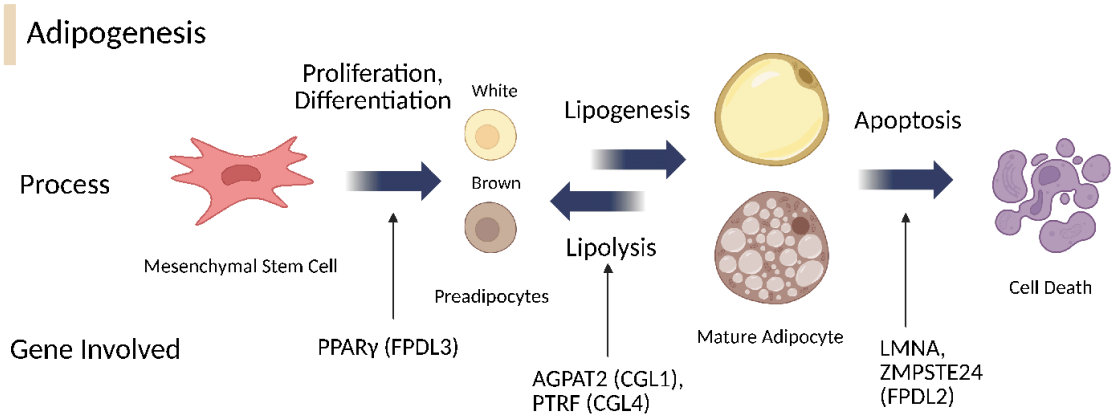


Figure 4: Steps of adipogenesis. Starting from mesenchymal stem cells, after proliferation and differentiation, it develops into preadipocytes. Then, through lipogenesis, preadipocytes grow into mature adipocytes. When a person is fasting, adipocytes go through lipolysis to produce energy by breaking down triglycerides into glycerol and free fatty acids. The last step is apoptosis, which ultimately leads to cell death. (Made with BioRender)

GAlthough genes involved in lipodystrophy syndromes affect various cellular processes, such as lipid synthesis, signal transduction, and nuclear structure. They, they all lead to a common outcome: impaired adipocyte development and function. The examples discussed in this review, including CGL1, CGL4, FPLD2, and FPLD3, demonstrate how different stages of adipogenesis and gene mutations that are involved in adipogenesis all lead to similar consequences (Figure 4). In addition to genetic causes, acquired factors can also contribute to adipocyte dysfunctions, as seen in AGL.

LD highlights the essential role of adipose tissue as an endocrine and metabolic organ. It not only stores energy but also maintains metabolic homeostasis and regulates hormones. The absence of adipocytes, as shown in this review, could cause

life-threatening disorders. Understanding this condition not only helps people recognize the role of adipose tissue in metabolism but also helps raise awareness of rare diseases. For conditions like lipodystrophy, many patients remain undiagnosed throughout their lives. Not only is conducting research with so few samples challenging, but scientists may be less willing to dedicate time to studying rare diseases compared to diseases that affect a larger population. Increased awareness and improved diagnostic tools not only help identify individuals affected by this disease earlier but also give them a chance to manage their condition in a more effective way.

Since the discovery of lipodystrophy syndromes in ~~around~~ the mid-20th century~~, lots of~~, significant progress has been made in ~~to get a better~~ understanding ~~of~~ lipodystrophy. From ~~the~~ phenotypes and ~~to the~~ metabolic abnormalities to ~~and the~~ underlying genetic causes, research ~~have~~ has been conducted ~~done~~ to find ~~seek for~~ ways to reduce patient's' pain and suffering. Having a deep understanding of lipodystrophy, such as the mechanisms of various genes and their relationship with adipogenesis, will be crucial to the development of a more effective and targeted therapeutic strategy.

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Dear reviewer,

Thank you very much for your meaningful insights, thoughtful comments, and suggestions on my manuscript “Molecular Basis of Lipodystrophy: Gene Mutations, Pathophysiology, and Therapy”. Below, I address the comments point by point.

Major Comments

1. Mechanistic Inaccuracy in FPLD3 Pathophysiology: The authors state that mutations in the PPARG gene "might cause excess differentiation and growth of adipocytes," leading to cellular stress. This contradicts established molecular biology. Pathogenic variants in PPARG associated with FPLD3 are typically loss-of-function or dominant-negative mutations that fundamentally impair adipogenesis. This fundamental error should be corrected to accurately reflect the disease's molecular basis.
Response: I thank the reviewer for this thoughtful suggestion. I agree that fixing this error is important for the accuracy of the molecular mechanisms. I have revised the manuscript as requested to ensure the accuracy of this section.

2. Omission of CGL2 (BSCL2) in Section 3: While the authors appropriately discuss BSCL2 (seipin) in the context of preclinical gene therapy models, they entirely omit CGL2 from the main "Genetics and Pathophysiology" section, focusing only on CGL1 and CGL4. Given that BSCL2 mutations cause the most severe and globally prevalent form of CGL, a dedicated subsection explaining seipin's role in lipid droplet biogenesis is mandatory.
Response: I appreciate this helpful comment. I agree that adding a section explaining CGL2 strengthens the overall scope of the manuscript. Therefore, I have added a section in the discussion dedicated to CGL2.

3. Conflation of FPLD2 and ZMPSTE24 Pathology: In Section 3.3, the authors state that ZMPSTE24"is also considered to be one of the factors that causes lipodystrophy" in the context of FPLD2. The authors should clarify this distinction: classic FPLD2 is caused by heterozygous missense mutations in the LMNA gene itself. Mutations in ZMPSTE24 (which impair prelamin A processing) cause distinct, more severe syndromic forms of lipodystrophy (e.g., Mandibuloacral Dysplasia). Blurring the lines between these genetic etiologies creates confusion both clinically and molecularly.
Response: I thank the reviewer for this valuable insight. I agree that distinguishing the difference between them is important. I have added details addressing their difference.

4. Incomplete Methodology Results: The authors include a "Method" section outlining their literature search strategy, keywords, and inclusion/exclusion criteria. However, they fail to report the actual results of this search. There is no mention of how many articles were initially retrieved, screened, or

ultimately included. To ensure scientific rigour and reproducibility, the authors should provide these numbers.
Response: I appreciate the thoughtful comment about the completeness of the method section. I agree that this helps with the overall clarity and scientific rigour. I have added details on the number of articles retrieved, screened, and included.

5. Superficial Explanation of Lipotoxicity: While the manuscript notes that lipodystrophy leads to metabolic dysfunctions such as insulin resistance and fatty liver, it fails to provide a detailed molecular explanation of lipotoxicity. The paper needs to clearly explain how the inability to store triglycerides in adipocytes leads to ectopic lipid deposition in the liver and skeletal muscle, which directly interferes with insulin receptor signalling pathways.
Response: I appreciate this helpful feedback. To improve clarity of the relationship between insulin resistance and lipotoxicity, I have added a paragraph to the diagnosis and clinical features section explaining the underlying mechanisms.

6. Clarification of Metreleptin Indications: The manuscript presents metreleptin as the "primary choice for LD patients", but later notes it is "more efficient in Generalised lipodystrophy patients". The authors should explicitly clarify current clinical guidelines. Metreleptin is strictly indicated and FDA-approved for generalised lipodystrophy; its use in partial lipodystrophy is highly restricted and heavily scrutinised due to varying efficacy and risk profiles.
Response: Thank you for pointing out this mistake. I agree that addressing this error improves the quality of the manuscript. I have fixed the problem mentioned above to improve the accuracy of the information regarding metreleptin.

7. Omission of APL in Pathophysiology: The introduction introduces Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome). However, APL is entirely ignored in the subsequent "Genetics and Pathophysiology" section, which only covers AGL. APL should be discussed to provide a comprehensive overview of acquired forms.
Response: Thank you for this valuable feedback. I agree that adding APL provides a more complete review of lipodystrophy. Therefore, I added details about APL to the “acquired lipodystrophy” section, which discusses both AGL and APL.

Minor Comments
1. Overuse of Acronyms in Single Paragraphs: The authors correctly define acronyms such as HAART and NRTI upon their first use. However, since these terms appear only twice and within the same

paragraph, introducing the acronyms is unnecessary and clutters the text. It is standard practice to write out the full terms if they are not used frequently throughout the remainder of the manuscript.
Response: I thank the reviewer for this helpful insight. I agree that the use of acronyms is excessive in this paragraph. Therefore, I have replaced the acronyms with their full terms to improve the paragraph's flow.

2. Scientific Phrasing and Grammar: Several sentences lack scientific precision or contain grammatical errors. For instance, the phrases "The storage of adipocytes is limited" and "Except for CGL2, in which patients generally do not acquire both kinds of fat tissues" require language editing for clarity and grammatical correctness.
Response: I appreciate this considerate comment. I agree that fixing the grammar errors will improve the clarity of the paper as a whole. Therefore, I have fixed the issues mentioned above and other phrases that also need clarification.

3. Unsubstantiated Claims: The authors state that "around 200 clinical trials are in progress, trying to discover a new way to treat or cure lipodystrophy, especially targeting leptin deficiency". This specific claim requires a reference or a citation from a clinical trial registry to verify the figure.
Response: I appreciate this helpful suggestion. I have included a citation to the website ClinicalTrials.gov

4. Figure Formatting: References to figures within the text should be capitalised for consistency with academic formatting (e.g., change "(figure 1)" and "(figure 2)" to "(Figure 1)" and "(Figure 2)").
Response: Thank you for noticing this minor detail. I have fixed them as required.

Dear reviewer,

Thank you very much for your meaningful insights, thoughtful comments, and suggestions on my manuscript "Molecular Basis of Lipodystrophy: Gene Mutations, Pathophysiology, and Therapy". Below, I address the comments point by point.

Grammar and Style: The writing is generally clear and understandable, and the overall flow of ideas is logical. The main issue here is consistency in tone. Some sections are written in a strong academic voice, while others shift into more conversational phrasing. Maintaining a consistent scientific tone throughout will strengthen the professionalism of the manuscript. There are also a few recurring grammar issues, including sentence structure, verb agreement, and phrasing, which can be addressed with a careful final pass.
Response: Thank you for this thoughtful suggestion. I agree that maintaining a consistent tone and fixing the grammatical mistakes would help the readability of this manuscript. Therefore, I have revised some sections to improve the quality and readability.

Scientific Framing: The manuscript shows a good grasp of the literature and includes appropriate gene targets and pathways. A notable strength is the inclusion of both genetic and acquired forms of lipodystrophy, which gives the paper a more complete scope. The paper would become even stronger by more consistently linking molecular mechanisms to clinical presentation. In the strongest sections, this connection is clear and effective, and applying that same level of explanation across all sections would improve overall coherence.
Response: I appreciate this helpful feedback. I agree that linking molecular mechanisms to clinical phenotypes would improve the quality of this review. I have revised parts of the manuscript that would benefit from adding the connection between them.

Organization: The overall structure is logical and appropriate for a review article, moving from classification to mechanisms, then to diagnosis and treatment. This organization works well and helps guide the reader through complex material. Some paragraphs, particularly in the introduction and diagnosis sections, are quite dense and would benefit from being divided into smaller sections. The Methods section is functional but could be more clearly organized to match the level of detail seen in the rest of the paper.
Response: I appreciate this helpful comment. I agree that dividing those sections into smaller paragraphs will improve clarity, and that the method section would benefit from adding more details to it. I have reorganized the introduction and diagnosis section. As for the method section, I have added the results of my search and reorganized it to improve clarity.

Scholarly Tone: The paper demonstrates strong content knowledge and clear effort in engaging with the material. The tone is effective in many sections, particularly in the mechanistic discussions. To elevate the manuscript further, it would help to maintain that same level of academic tone throughout and avoid occasional conversational phrasing. This adjustment would better align the writing with the strength of the scientific content.

Response: Thank you for this thoughtful insight. I agree that maintaining a consistent tone throughout the paper is important. Therefore, I have revised the parts of the manuscript that show conversational phrasing tp improve consistency.

Dear Reviewer,

Thank you for your thorough and valuable suggestions. These detailed editorial corrections helped me improve the overall quality of this review. Below, I respond to the comments by sections.

Title page and abstract

· Page 1, Title ("Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy"): The title is clear and appropriate for the paper's scope. You may want to consider whether "disease progression" is the most precise phrase here, since the paper is centered more on mechanisms, classification, and treatment than on longitudinal progression. A term such as "pathophysiology" may better match the content.

· Page 1, Abstract, opening sentence ("Lipodystrophy syndromes are rare diseases that are often characterized…"): The opening sentence introduces lipodystrophy well, but the wording is somewhat repetitive. "Rare diseases that are often characterized" could be made more concise.

· Page 1, Abstract, sentence beginning "Fat tissues are also known as adipose tissues…": This reads more like a general definition than part of a scientific abstract. You may want to replace this with a sentence emphasizing the metabolic role of adipose tissue instead.

· Page 1, Abstract, sentence containing "a series of metabolic issues": This is broad. It would be stronger if it named a few specific complications, such as insulin resistance, hepatic steatosis, or hypertriglyceridemia.

· Page 1, Abstract, sentence beginning "They are all factors that determine…": This is a bit unclear. It would help to specify whether you mean the clinical phenotype, the molecular defect, or the pattern of adipose loss.

· Page 1, Abstract, sentence beginning "Due to the rarity of this disorder…": This would read better as "these disorders," since you are discussing lipodystrophy syndromes rather than a single disease entity. The sentence also becomes somewhat repetitive with "this disease" later in the same thought.

· Page 1, Abstract, sentence beginning "In this article, we first consider…": This feels more narrative than review style. It may read more professionally if you state the review's scope directly rather than walking the reader through it step by step.

· Page 1, Abstract, final sentence beginning "Future direction of study…": This needs a small grammatical correction. The sentence would also benefit from a more precise phrasing of how genetic understanding may inform future therapies.

· Page 1, Abstract, overall: The abstract does a good job covering the paper's main sections, but it could become stronger by making the connection between gene mutations and metabolic outcomes more
explicit. Right now, the abstract introduces the topics clearly, but it does not fully show the mechanistic thread that becomes important later in the paper.

Response for comments on the title page and abstract: I appreciate these thoughtful suggestions. I have implemented the corrections suggested.

Introduction and Background

· Page 1–2, Introduction, Paragraph 1, sentence containing "inability to store body fat and excess nutrients": The introduction establishes the topic clearly, though this phrase could be made more precise. Since one of the key consequences is ectopic lipid storage, naming that directly may strengthen the scientific framing.

· Page 2, Introduction, Paragraph 1, sentence beginning "Adipose tissues are formed through a process called adipogenesis…": The explanation of adipogenesis is useful, but some of this material reads more like a textbook definition than an introduction to a review article. You may want to move more quickly from defining adipogenesis to explaining why it is relevant to lipodystrophy.

· Page 2, Introduction, Paragraph 1, sentence beginning "This process also includes the triacylglycerol (TAG) fatty acid cycle…": The TAG cycle discussion is informative, but the sentence is fairly dense and contains several concepts at once. It may help to simplify the structure so the role of lipid storage and mobilization stands out more clearly.

· Page 2, Introduction, Paragraph 1, sentence beginning "It is the process where the lipid droplets…": This is slightly unclear, as the referent for "It" is not immediately obvious. Clarifying the subject of the sentence may improve readability.

· Page 2, Introduction, Paragraph 1, sentence beginning "However, if a gene mutation…": The statement about gene mutations affecting adipogenesis is conceptually strong. It may be worth stating more explicitly that these disruptions impair adipocyte differentiation, lipid droplet formation, or adipose maintenance, depending on the gene involved.

· Page 2, Introduction, Paragraph 2, paragraph beginning "LD can be either congenital or acquired…": This classification paragraph contains important material, but it is doing a great deal at once. It may be easier for the reader if you divide it into one paragraph on congenital versus acquired forms and a second paragraph on subtype distinctions within CGL and FPLD.

· Page 2, Introduction, Paragraph 2, sentence beginning "CGL (also called Berardinelli-Seip syndrome)…": This sentence is clear, although it may help to define "mechanical and metabolic fat tissues" more carefully. Some readers may not immediately know how you are distinguishing these categories.

· Page 2, Introduction, Paragraph 2, sentence beginning "CGLs are autosomal recessive…": This is understandable, but the phrasing could be made more formal.

· Page 2, Introduction, Paragraph 2, sentence beginning "Same as CGL…": This sounds conversational. A more formal transition would improve continuity.

· Page 2, Introduction, Paragraph 2, sentence beginning "Since the body is not able to store excess energy…": The FPLD description is one of the stronger parts of the introduction because it links adipose
redistribution to metabolic consequences. This would become even stronger if you clarified that the

apparent “gain” of fat in other regions often reflects abnormal redistribution rather than normal adipose expansion.

· Page 2, Introduction, Paragraph 2, sentence beginning “Proteins or enzymes that are encoded…”: This is a bit heavy structurally. The main point is good, but the sentence could be made clearer by emphasizing function first.

· Page 2, Introduction, Paragraph 2, phrase “and sometimes idiopathic”: The acquired forms are introduced clearly, although this phrase could be smoothed slightly to fit the tone of the rest of the paragraph.

· Page 3, Introduction, Paragraph 3, paragraph beginning “Not only will the lack of excess energy…”: This paragraph introduces metabolic complications well. The figure reference is useful, and the transition into treatment is natural, though the opening sentence itself is somewhat broad and could be made more concise.

· Page 3, Introduction, Paragraph 3, sentence containing “It currently the only FDA-approved treatment”: The metreleptin discussion is appropriate here, but there is a small grammar issue in this sentence.

· Page 3, Introduction, Paragraph 3, prevalence sentences containing “3/million,” “0.23/ million,” and “2.84/million”: The prevalence numbers are helpful. You may want to make sure units are presented consistently, for example “per million” rather than “/million.”

· Page 3, Introduction, Paragraph 3, sentence beginning “It is also estimated to shorten a patient’s lifespan…”: This is important and strengthens the clinical significance of the review.

· Page 3, Introduction, final sentence beginning “In addition, the treatment developed…”: This could be made slightly more polished. It feels incomplete in structure and would be a good place to state clearly that the review will examine both current therapies and emerging directions.

Response for comments on Introduction and background: Thank you for the helpful feedbacks. I have corrected them as requested.

Methodology

· Page 3, Section title (“2. Method”): Consider changing “Method” to “Methods” to align with standard scientific formatting.

· Page 3, Methods paragraph, sentence beginning “The search included following keywords…”: The literature search description is straightforward, though it would read more smoothly if this were changed to “included the following keywords.”

· Page 3, Methods paragraph, keyword list: The keyword list is useful and appropriately targeted to the paper’s focus.

· Page 3, Methods paragraph, sentence beginning “Only publications in English language were considered”: This would read more naturally as “Only English-language publications were considered.”

· Page 3, Methods paragraph, sentence containing “comprehensive reviews”: The inclusion criteria are generally clear, though this phrase might benefit from a little more specificity if you want to distinguish narrative reviews from systematic reviews.

· Page 3, Methods paragraph, sentence beginning “Case studies with relevant insights…”: This is understandable, though the basis for relevance could be clarified slightly.

· Page 3, Methods paragraph, sentence beginning “Non peer reviewed sources…”: “Non peer reviewed” should be hyphenated. Also, the phrase “case reports with only quantitative data and without further analysis” is a little difficult to interpret. You may want to clarify the reasoning behind that exclusion.

· Page 3, Methods paragraph, final sentence beginning “Full article was reviewed…”: This should be plural.

· Page 3, Methods, overall: This section is functional, but it may become clearer if organized under brief subheadings such as Search Strategy, Inclusion Criteria, and Exclusion Criteria.

Response to comments on methodology: I thank the reviewer for the valuable comments. I have revised the manuscript as requested.

Discussion – Section 1: Genetics and Pathophysiology

· Page 4, CGL1, opening paragraph beginning “Type 1 Congenital Generalized Lipodystrophy…”: The AGPAT2 section contains strong mechanistic content. The explanation is scientifically valuable, but the sentence structure is quite dense. Breaking some of the longer sentences may make the biochemical pathway easier to follow.

· Page 4, CGL1, sentence beginning “AGPAT2 is the gene coding for…”: This would be more standard scientifically as a direct statement that the gene encodes the enzyme.

· Page 4, CGL1, sentence beginning “It is an important precursor…”: The explanation of phosphatidic acid synthesis is detailed, which is good for the review’s depth. You may want to make the link to adipocyte dysfunction slightly more explicit at the end of the paragraph so that the reader sees why this biochemical step matters clinically.

· Page 4, CGL1, sentence beginning “The AGPAT family consists of 11 isomers…”: This is useful, though a little hard to follow because several ideas are packed together.

· Page 4, CGL1, sentence beginning “The presence of mechanical adipose tissue…”: The contrast between AGPAT2 and other isomers is interesting and relevant. This may be one place where an extra citation or a more explicit mechanistic link would strengthen the section further.

· Page 4, CGL1, sentence beginning “Defects in AGPAT2 genes also impact insulin signaling…”: This point is important. It may be helpful to clarify whether this effect is direct or secondary to impaired adipocyte function, since the sentence currently reads somewhat definitive.

· Page 4, CGL4, opening sentence beginning “Type four Congenital Generalized Lipodystrophy…”:

The opening sentence is clear. The subsection would benefit from more consistent capitalization and formatting in the disease name.

· Page 4, CGL4, sentence beginning “Caveolae are one of the most abundant invaginations…”: The explanation of caveolae is strong, though “lots of mammalian cells” reads conversationally. A more formal phrasing would strengthen tone.

· Page 4, CGL4, sentence beginning “Cavin-1 starts the whole process…”: This phrasing feels informal. A more academic wording would match the rest of the review.

· Page 4, CGL4, sentence containing “caveolin 1,2”: The discussion of caveolin isoforms is useful, but the formatting should be standardized.

· Page 4–5, CGL4, sentence beginning “Absence of caveolae causes the cell…”: The sentence describing cellular consequences would benefit from slightly more precision. Instead of “not be able to develop properly,” you may want to emphasize membrane organization, signal transduction, or adipocyte stability.

· Page 5, CGL4, paragraph beginning “Some symptoms that are uniquely associated…”: The clinical phenotype discussion is useful and helps connect molecular defects to patient presentation.

· Page 5, CGL4, final sentence beginning “These symptoms can be explained…”: This could be made more explicit in showing how tissue-specific expression relates to muscle and cardiac findings.

· Page 5, FPLD2, opening sentence beginning “The gene LMNA…”: The LMNA subsection is scientifically important, and the topic choice is strong. The first sentence is somewhat heavy structurally and may benefit from division into two shorter sentences.

· Page 5, FPLD2, sentence beginning “Specifically…”: This appears incomplete and may need revision into a full sentence.

· Page 5, FPLD2, sentence beginning “One way that Lamin A can affect cell development…”: The ZMPSTE24 discussion is relevant. This would be even stronger if you briefly clarified whether you are describing laminopathy-related processing defects more broadly or specifically FPLD2-associated mechanisms.

· Page 5, FPLD2, sentence beginning “Not only will the lack of Lamin A…”: The point about prelamin A accumulation is well made and adds mechanistic depth.

· Page 5, FPLD2, paragraph beginning “A high risk of cardiovascular diseases…”: This paragraph is interesting, though the transition from nuclear structure to epicardial adipose tissue is fairly abrupt. One bridging sentence may help.

· Page 5, FPLD2, final sentence beginning “Other studies will also need to be done…”: This reads somewhat informal. The idea is good, but the phrasing could be more academic.

· Page 5–6, FPLD3, opening sentence beginning “Type 3 Familial Partial Lipodystrophy…”: The

PPARG subsection is relevant and well chosen. There is a small phrasing issue with “encodes for.”

· Page 6, FPLD3, sentence beginning “PPARγ has three isoforms…”: The mechanism is clearly described and fits well within the paper. Some small reductions in repetition may help readability.
· Page 6, FPLD3, sentence beginning “After binding, PPARγ induces many targeted genes…”: “induces many targeted genes” might be expressed more precisely, since this is really about transcriptional regulation of downstream targets.

· Page 6, FPLD3, sentence beginning “Mutations in PPARG might cause excess differentiation…”: This appears to be an oversimplification. Many pathogenic PPARG variants impair adipocyte function rather than simply increasing growth, so this phrasing may be misleading and should be reconsidered for accuracy.

· Page 6, FPLD3, paragraph beginning “Compared to FPLD2…”: The comparison with FPLD2 is useful and adds real value to the review. This is a strong section because it moves beyond listing mechanisms and begins comparing phenotypes.

· Page 6, FPLD3, final sentence beginning “However, FPLD3 patients also show…”: This is good, though it may help to clarify why a milder loss of adipose tissue can still be associated with more severe metabolic disease.

· Page 6, AGL, opening sentence beginning “As we can see…”: The opening sentence introduces acquired disease appropriately, but “As we can see” sounds conversational and could be removed.

· Page 6, AGL, paragraph beginning “Adverse effects of highly active antiretroviral therapy…”: The HAART discussion is interesting and clinically relevant. Some of the sentence structure is slightly long, but the content is strong.

· Page 7, AGL, sentence beginning “Proteins such as thymidine analog nucleoside reverse transcriptase inhibitors…”: This is not accurate. NRTIs are pharmacologic agents, not proteins, and this distinction is important for maintaining scientific accuracy. This sentence should be revised to reflect the correct classification and mechanism.

· Page 7, AGL, sentence beginning “It decreases the expression of adiponectin…”: The adiponectin and mitochondrial toxicity points are relevant and help ground the section mechanistically.

· Page 7, AGL, paragraph beginning “Another possible cause of AGL…”: The autoimmune mechanism is a good addition. The perilipin discussion is especially useful because it broadens the review beyond purely genetic forms.

· Page 7, AGL, sentence beginning “It leads to an increase in lipolysis activities…”: This is conceptually good, though it may help to clarify whether you mean uncontrolled lipolysis due to loss of lipid droplet protection.

Response for discussion section 1: I appreciate the thoughtful comments. I have fixed the mistakes mentioned to improve quality and clarity.

Diagnosis and Clinical Features

· Page 7–8, Diagnosis, Paragraph 1 beginning "Since lipodystrophy is such a rare disease…": This paragraph includes important diagnostic material, but it is quite long and would benefit from being divided into smaller units.
· Page 7, Diagnosis, opening phrase "not well known to the public": This point about underrecognition is important and clinically relevant, though this phrasing may be less useful than a more clinician-focused one.

· Page 7–8, Diagnosis, sentence beginning "Although patients with CGL show symptoms…": The contrast between CGL and FPLD diagnosis is helpful.

· Page 8, Diagnosis, sentence beginning "It could be easily mixed up with…": "mixed up with" would benefit from more formal wording.

· Page 8, Diagnosis, paragraph beginning "Some phenotypes that are associated…": The phenotype paragraph is detailed and generally useful. There is a small typo in "in charge or energy storage."

· Page 8, Diagnosis, sentence beginning "Metabolic adipose tissues are in charge…": The explanation of metabolic versus mechanical adipose tissue is useful, but the wording could be made more precise.

· Page 8, Diagnosis, sentence beginning "Although patients still in some degrees lack…": This is difficult to follow and appears structurally incomplete. This portion may benefit from being rewritten for clarity.

· Page 8, Diagnosis, final sentence beginning "Next, we will be discussing…": The transition into treatment is smooth and works well, though this phrasing reads somewhat narrative for a review

article.

Response for Diagnosis and Clinical Features: I thank the reviewer for these helpful feedbacks. I have revised this section as mentioned.

Treatments

· Page 8, Treatments, opening sentence beginning "Currently, there isn't a definite treatment…": This sounds somewhat informal. The idea is correct, though the phrasing could be slightly more formal.

· Page 8–9, Metreleptin subsection overall: The metreleptin discussion is one of the strongest applied sections of the paper. It explains the rationale for therapy clearly and appropriately ties it to leptin deficiency.

· Page 9, Metreleptin subsection, sentence beginning "Leptin is a hormone…": This explanation is useful, though some of this material repeats ideas already implied in the section. You may be able to reduce repetition.

· Page 9, Metreleptin subsection, sentence beginning "This causes patients to show extreme hyperphagia…": The connection between hypoleptinemia, hyperphagia, and ectopic fat storage is

well stated and clinically meaningful.

· Page 9, Metreleptin subsection, sentence beginning “Metreleptin’s main purpose is to mimic…”: This is fine, though it may be worth noting whether the treatment’s benefit is metabolic, symptomatic, or both.

· Page 9, Metreleptin subsection, sentence beginning “Metreleptin is found to be more efficient…”: This might be adjusted slightly to reflect clinical response rather than efficiency.

· Page 9, Metreleptin subsection, sentence beginning “However, the risk of using Metreleptin…”: This contains a subject-verb agreement issue and could be clarified to improve readability.

· Page 9, Metreleptin subsection, final sentence beginning “Other common drugs…”: The closing sentence on adjunctive therapies and cosmetic surgery is appropriate. This gives the treatment section a more complete and realistic scope.

· Page 9, Lifestyle subsection title (“Change in Daily Routine”): This feels somewhat informal as a heading. A more standard heading may fit better with the rest of the paper.

· Page 9, Lifestyle subsection, paragraph beginning “Although Metreleptin can generally help…”: This section is brief but useful. It might be strengthened by explaining why a low-fat or carbohydrate-restricted diet is recommended in metabolic terms, rather than only listing the recommendations.

· Page 9, Lifestyle subsection, sentence containing “doing too much exercise”: This is understandable but may be rephrased more formally.

· Page 9–10, Gene Editing subsection, opening paragraph: This section is forward-looking and adds value to the paper. The discussion of gene therapy is a strong choice for the final treatment subsection.

· Page 10, Gene Editing subsection, sentence beginning “The results of the trials show…”: The mouse model example is useful and helps ground the idea in actual preclinical work.

· Page 10, Gene Editing subsection, sentences containing “AVV”: The acronym “AVV” appears to be used in place of “AAV” (adeno-associated virus). This should be corrected consistently throughout the section. In addition, phrases such as “AVV targets adipocytes” read somewhat absolute and may benefit from more precise wording.

· Page 10, Gene Editing subsection, sentence beginning “Therefore, there isn’t enough evidence…”: The translational caution here is important and scientifically appropriate. This section benefits from the fact that it does not overstate clinical readiness.

· Page 10, Gene Editing subsection, final sentence beginning “Continued research on LD…”: This conclusion is good and appropriately cautious.

Response for Treatments: Thank you for these helpful feedbacks. I have implemented these suggestions as requested.

Conclusion and Future Directions

· Page 10–11, Conclusion, opening sentence beginning "Although genes involved in lipodystrophy syndromes…": This contains the paper's central idea and is conceptually strong, but it is fairly long. Breaking it into two sentences may improve readability.

· Page 11, Conclusion, phrase "common outcome -impaired adipocyte development and function": This contains a spacing and punctuation issue. It should be corrected for clarity and consistency with standard formatting.

· Page 11, Conclusion, paragraph beginning "LD highlights the essential role…": This paragraph does a good job emphasizing adipose tissue as an endocrine and metabolic organ. That is one of the manuscript's central strengths.

· Page 11, Conclusion, sentence beginning "For conditions like lipodystrophy…": The discussion of awareness and diagnostic delay is relevant and provides a meaningful clinical takeaway.

· Page 11, Conclusion, sentence beginning "Since the discovery of lipodystrophy syndromes…": "lots of progress has been made" reads somewhat informal.

· Page 11, Conclusion, sentence containing "research have been done": This is a grammar issue.

· Page 11, Conclusion, final sentence beginning "Having a deep understanding…": The final sentence is appropriate, though it may be strengthened by tying future therapy more directly to the specific mechanisms discussed earlier.

Response for Conclusion and Future Directions: I thank the reviewer for the thoughtful comments. I have revised the conclusion as requested.

Figures and Tables

· Table 1 / Page 2: The table is useful and supports the classification section well. Make sure the labeling and formatting remain consistent with the journal's style.

· Figure 1 / Page 3: The comparison figure is a helpful visual aid. The caption contains multiple grammatical issues, including "The storage of an adipocytes is limited" and "increase glucose level in blood streams." These should be revised for clarity and correctness.

· Figure 2 / Page 4: The figure is relevant and supports the CGL1 discussion appropriately.

· Figure 3 / Page 5: The caveolae figure is helpful, though the caption could be a bit more precise scientifically. Also, "Biorender" should be standardized to "BioRender."

· Table 2 / Page 9: This table adds practical value to the treatment section. Make sure the reproduced source and licensing note are formatted exactly as required by the target venue.

· Figure 4 / Page 10: This is one of the stronger figures in the manuscript because it helps unify the review conceptually. The caption is informative and supports the final conclusion well.

Response for Figures and Tables: I appreciate these helpful comments. I have fixed the details that are mentioned above.

The student has clearly put a lot of effort into addressing our comments, and the paper is in a much stronger position now.

Because the student has made such substantial improvements, I do not think we need to send this out for another full round of peer review. I recommend **acceptance with minor edits**, provided the student addresses a few final, specific critiques outlined below.

Here is my post-review critical feedback.

Strengths and improvements:
The author did an excellent job expanding the scope and scientific rigour of the review. The addition of the CGL2/seipin section provides crucial context for the most severe form of congenital lipodystrophy. Furthermore, the newly added explanation of lipotoxicity (specifically how excess free fatty acids accumulate in the liver and skeletal muscle to disrupt insulin signalling) bridges a major mechanistic gap that was missing in the first draft. The methodological transparency has also been appropriately addressed with the inclusion of screening numbers , and the clinical indications for metreleptin are now accurately represented.

Constructive critiques and areas for final polish:
While the manuscript is vastly improved, there are a few remaining scientific and structural issues that need to be resolved before publication:

1. Biologically contradictory sentence in FPLD3. In an attempt to address my previous comment on FPLD3, the author merged their original flawed premise with my correction, resulting in a contradictory sentence: *"Loss-of-function or dominant-negative mutations in pathogenic variants of PPARG cause excess differentiation and growth in adipocytes, fundamentally impairing adipogenesis."* The author should delete the phrase *"cause excess differentiation and growth in adipocytes"* entirely. Impaired adipogenesis means the cells *fail* to differentiate and grow; they cannot do both simultaneously.
2. Missing link in the APL/C3NeF mechanism: The addition of the APL section is great, but the explanation of the C3NeF pathway misses a vital physiological link. The author states that continuous C3 breakdown activates the terminal pathway, leading to adipocyte lysis. To deepen this manuscript, the author should briefly mention *why* adipocytes are targeted: adipose tissue produces high levels of Factor D (adipsin), making it uniquely susceptible to localised alternative complement pathway activation.
3. Numbering and formatting typos: The author added the new CGL2 section but accidentally duplicated the numbering. There is currently "3.2 Type 2 Congenital Generalised Lipodystrophy (CGL2)" followed immediately by "3.2 Type four Congenital Generalised Lipodystrophy (CGL4)". This needs to be corrected to 3.2, 3.3, 3.4, etc.
4. Awkward phrasing in the diagnosis section: The sentence, *"Only CGL2 patients do not acquire both mechanical and metabolic adipose tissues",* remains awkwardly phrased. In a medical context, "acquire" implies catching an infectious disease. This should be rephrased to *"Only CGL2 patients fail to develop both..."* or *"Only CGL2 patients are born without..."* to maintain a strict academic tone.

Molecular Basis of Lipodystrophy: Gene Mutations, Disease Progression, and Therapy- Accept with minor edits.

The revised manuscript shows clear improvement in organization, clarity, and overall scientific presentation. Many of the earlier concerns were addressed thoughtfully, particularly in the areas of structure, terminology, and explanation of key concepts. The paper now reads more cohesively, and the progression between sections is easier to follow. The introduction and abstract are both stronger in this version and do a better job establishing the scope and clinical relevance of the review from the beginning.

One of the stronger aspects of the revision is the improved discussion of the molecular and metabolic basis of lipodystrophy. Several sections now provide clearer explanations of how disruptions in adipocyte biology contribute to disease development and metabolic complications. The paper also does a better job balancing scientific detail with readability, which helps the review feel more focused and organized overall. The inclusion of both genetic and acquired forms of lipodystrophy continues to strengthen the scope of the manuscript and gives the review broader clinical relevance.

The treatment section has improved as well and now feels more integrated into the overall discussion of disease mechanisms and patient outcomes. The figures and tables also contribute more effectively to the manuscript in this version and support the written discussion more clearly than before. Overall, the paper now reads more like a complete review article rather than a collection of summarized information.

There are still a few smaller areas that could continue to be refined. Some sentences remain slightly long or dense, particularly in sections discussing molecular pathways, and simplifying a few of these sentences may further improve readability. In a few places, mechanistic explanations could also be phrased somewhat more cautiously to avoid sounding overly definitive when discussing pathways that are still under investigation. Adding a small number of additional citations in sections with more detailed mechanistic discussion may also help strengthen scientific support in those areas.

Overall, this is a strong revision that reflects clear effort and attention to feedback. The manuscript is substantially more polished, better organized, and more scientifically focused than the earlier version. Following revision, the manuscript is scientifically sound, well organized, and appropriate for publication pending minor editorial refinement.

Molecular Basis of Lipodystrophy: Gene Mutations, ~~Disease Progression,~~Pathophysiology, and Therapy

Abstract

Lipodystrophy syndromes are a group of ~~are~~ rare diseases ~~that are often~~ characterized by a general or partial absence of body fat~~.~~, caused by the inability to properly store and utilize ~~Fat tissues are also known as~~ adipose tissues~~.~~; ~~and the~~The lack of adipose tissue~~s~~ would lead to serious consequences and the development of a series of metabolic issues, including insulin resistance, leptin deficiency, and hypertriglyceridemia. Lipodystrophy~~These~~ syndromes are genetically and clinically heterogeneous, with different phenotypes influenced by underlying molecular defects. Both fat distribution and the molecular defect play a role in ~~They are all factors that~~ determine~~e~~ing the type of lipodystrophy a patient has. Due to the rarity of these~~is~~ disorders, not many studies have been conducted~~done~~ on ~~it~~them. This~~, which~~ results~~leads to~~in the public's~~people's~~ lack of ~~knowledge~~awareness, increasing the difficulty of diagnosing and treating these conditions~~about this disease and increases the difficulty of treating it~~. T~~ In t~~his article ~~article, we first~~ examine~~consider~~s the classification and clinical aspects of lipodystrophy syndromes, covering the onset and the differences in phenotypes of patients. ~~Then, we~~ It further discusses the molecular and cellular mechanisms of several types of lipodystrophies and the role they play in the development of adipose tissues. In addition~~Next~~, this review addresses ~~we focus on~~ other metabolic dysfunctions caused by lipodystrophy, such as insulin resistance, fatty liver, and hypertriglyceridemia. Lastly, we evaluate therapeutic strategies aimed at improving metabolic control and quality of life in affected patients. Future ~~direction of~~ research~~study~~ and potential therapy~~ies~~ may be improved with a deeper and more thorough understanding of the genetic and mechanistic basis of lipodystrophy, as it is critical for identifying key mechanisms and developing a more targeted treatment.

Keywords: Lipodystrophy syndromes, adipose tissue, adipogenesis, gene mutations, metabolic dysfunctions

1. *Introduction*

Lipodystrophy syndromes (LD) are a heterogeneous group of rare disorders characterized by the partial or complete loss of mature adipose tissue in localized or generalized areas. This results in the inability to store body fat, ectopic lipid storage, ~~-~~and excess nutrients (Fourman and Grinspoon 2022). Two main classes of lipodystrophy are Congenital Generalized Lipodystrophy (CGL) and Familial Partial Lipodystrophy (FPLD). ~~Adipose tissues are formed through a process called adipogenesis, and it is crucial for the adipose tissue to function normally.~~

For adipose tissues to function normally, adipogenesis is crucial for the differentiation of the precursor cells. Adipogenesis starts with ~~Adipogenesis is the~~

process by which mesenchymal stem cells differentiatinge into mature adipose tissue. DuringThis adipogenesisprocess, lipid storage and mobilization is regulated by also includes the triacylglycerol (TAG) fatty acid cycle.; which regulates lipid storage and mobilization in adipocytes. It is the processL where the lipid droplets undergo lipolysis (the breakdown of lipid droplets) and lipogenesis (the synthesis of new lipid droplets)(Poulos et al. 2016). However, if a gene mutation or other factors affect the components that play a roleinvolved in the regulation ofregulating adipogenesis, thisit would lead to impaired adipocyte differentiation, lipid droplet formation, and adipocyte functions.to serious, life-threatening consequences.

LD can be either congenital or acquired. Congenital Lipodystrophy, and it is classified based on the location of lost adipose tissue, and further divided into subtypes according to the gene segment that is mutated (Akinci, Gular, and Oral 2024) (Table 1). Meanwhile, acquired lipodystrophy is caused by external factors or side effects of other treatments.

CGL (also called Berardinelli-Seip syndrome) is characterized by the near-complete absence of adipocytes, both mechanical and metabolic fat tissues (Oswiecimska n.d.). CGLs are inherited in an autosomal recessive manner, and thewith symptoms typicallyoften presenting start showing shortly after birth. It is further divided into CGL1, CGL2, CGL3, and CGL4, which link to four different gene mutations. FPLD presents as an abnormal distribution of adipose tissue, with fat loss around the limbs, torso, and hips. It can be autosomal recessive or dominant depending on the genee that is involved. Since the body is not able to store excess energy in those areas, other body parts, such as the face, neck, and internal organs like the liver, gain extra adipose tissue (Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic n.d.). This results in the abnormal distribution of adipose tissues. As with Same as CGL, FPLDit is furtheralso divided into several subtypes, including FPLD1 (Kobberling-type lipodystrophy), FPLD2 (Dunnigan Variety lipodystrophy), FPLD3, FPLD4, FPLD5, and FPLD6. The development of adipocytes is tightly regulated by various proteins and enzymes. The genes that encode these proteins or enzymes are often the genes associated with lipodystrophy.Proteins or enzymes that are encoded by the genes associated with any kind of lipodystrophy all play important roles in the development of adipocyte.

As for Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome), they have similar symptoms as CGL and FPDL. However, they are caused by autoimmune diseases, side effects of antiretroviral therapy (ART) for HIV patients, or even idiopathic reasons (Misra and Garg 2003).Acquired Generalized Lipodystrophy (AGL, Lawrence Syndrome) and Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome) have similar symptoms, respectively; however, they can be caused by autoimmune diseases, the side

~~effects of antiretroviral therapy (ART) for HIV patients, and sometimes idiopathic (Misra and Garg 2003).~~ ¶

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
Generalized Lipodystrophy Syndrome					
Congenital Generalized Lipodystropy (Berardinelli-Seip syndrome)	CGL1	AGPAT2	Autosomal recessive	Near total absence of adipose tissue, generalized musularity, metabolic abnormalities. Starts showing symptoms shortly after birth.	Loss of metabolic fat, retains mechanical fat tissues
	CGL2	BSCL2	Autosomal recessive		Mild mental retardation
	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
Acquired Generalized Lipodystrophy (Lawrence Syndrome)	NA	NA	NA	Near total absence of adipose tissue, metabolic issues. Develops during childhoold/ puberty.	Could be caused by autoimmune diseases, panniculitus, idiopathic or immunotherapy
Partial lipodystrophy syndromes					
Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/ adolescense.	Palpable "ledge" between normal and lipodistrophic areas
	FPLD2 (Dunnigan)	LMNA	Autosomal dominant		High risks of cardiovascular diseases
	FPLD3	PPARG	Autosomal dominant		Less severe and distal fat loss
	FPLD4	PLIN1	Autosomal dominant		Increased fibrosis of adipose tissue, small lipid droplets in adipocytes
	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

Type	Subtype	Gene Involved	Inheritence	Clinical Phenotype	Commonly associated Features
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	CGL3	CAV1	Autosomal recessive		Vitamin D resistance
	CGL4	PTRF	Autosomal recessive		Myopathy, pyloric stenosis
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Familial Partial Lipodystrophy	FPLD1 (Kobbering)	Unknown	Polygenic	Absence of fat around the limbs and buttock, excess adipose tissues around face, neck, and abdomen. Also shows sign of metabolic issues. Develops during purberty/adolescense.	Palpable "ledge" between normal and lipodistrophic
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	FPLD5	CIDEC	Autosomal recessive		
	FPLD6	LIPE	Autosomal recessive		Increased visceral fat
Acquired Partial Lipodystrophy (Barraquer-Simons syndrome)	NA	NA	NA	Lost of subcutaneous fat around the face, neck, upper limbs and abdomen. Low limbs are not effected.	Causes could be autoimmune, MPGN-associated, immunotherapy or idiopathic

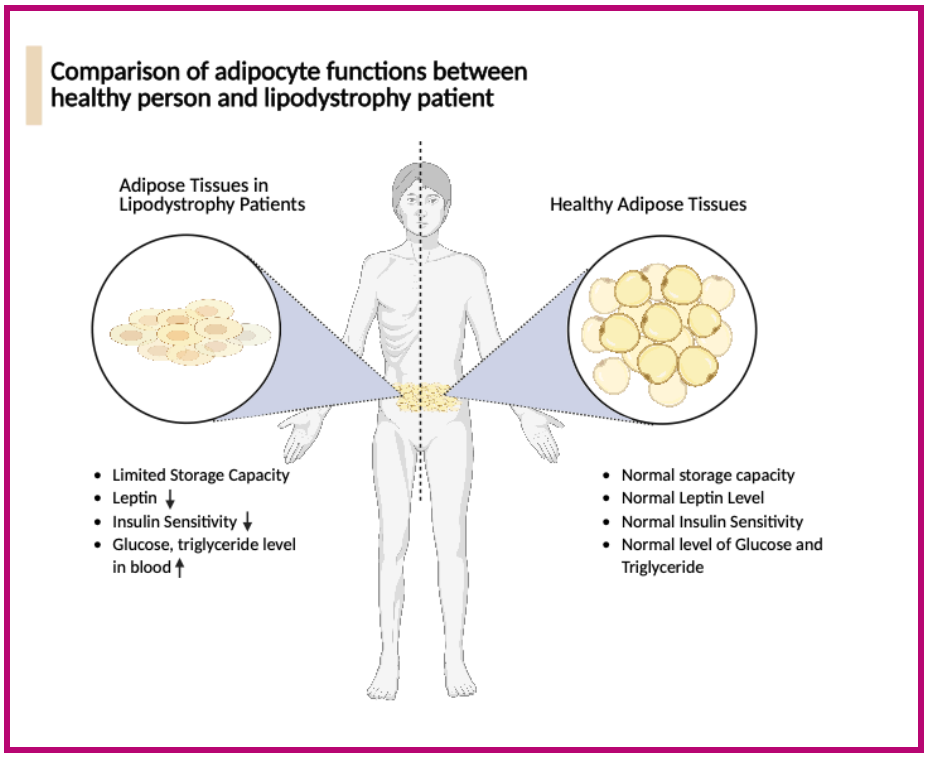
▲ Table 1: Classification, clinical features, and molecular basis of lipodystrophies (Made with Google Sheet)

Not only will the lack of excess ~~energy~~body fat ~~affect~~affect the body's normal functions, but ~~other~~ complications ~~t~~associated~~hat arise~~ with lipodystrophy also have a significant~~big~~ effect on patients' lives. Some common metabolic abnormalities include leptin deficiency, insulin resistance, diabetes, hypertriglyceridemia, and fatty liver disease (F~~f~~igure 1). Currently, around 200 clinical trials are ~~in progress, trying~~underway to discover a new way to treat or cure lipodystrophy, with a particular focus on ~~especially targeting~~ leptin deficiency (*Search ClinicalTrials.Gov For*, n.d.)~~ncy~~.

Metreleptin, for example, is a treatment created specifically for acquired or congenital generalized lipodystrophy ~~LD~~ patients. It is a targeted treatment for leptin deficiency, which is a common metabolic issue associated with LD~~D~~ (Araújo-Vilar & Santini, 2019)~~. (Araújo-Vilar e Santini 2019)~~. It is currently the only FDA- approved treatment for generalized lipodystrophy ~~LD~~ patients.~~.~~ However, conventional treatment, such as special diets, is still optimized before metreleptin (Meehan et al., 2016). Due to the rarity of this disease, limited research has been done, making Metreleptin the primary choice for CGL and AGL patients ~~LD patients~~ (Ajluni et al., 2016). As for FPLD patients, the use of Metreleptin is highly restricted. Therefore, they will need to maintain ~~Patients will still need to have~~ an appropriate ~~healthy~~diet and require other medications for the ~~other~~ metabolic complications~~issues~~.

According to studies, only about 3 per ~~/~~million people around the world are affected by some type of lipodystrophy syndrome. While the prevalence of CGL is estimated to be 0.23 per ~~/~~million people, the prevalence of FPLD is around 2.84 per ~~/~~million people (Chiquette et al. 2017). It is also estimated to shorten a patient's lifespan by 30 or more years. The main cause of death is shown to be liver diseases and infections caused by adipose tissue dysfunction, but also varies from type to type of lipodystrophy (Lima et al. 2018).

This literature review aims to highlight the molecular mechanisms underlying~~of~~ lipodystrophy, ~~focusing~~ with a focus on the genetic causes, differences between types of lipodystrophies, and other metabolic conditions caused by adipose tissue abnormalities, as well as ~~. In addition,~~ the treatment developed and future directions of study, and the ~~other~~ possibilities for ~~a~~ fundamental treatments.~~cure~~.



Comparison of adipocyte functions between healthy person and lipodystrophy patient
Adipose Tissues in Lipodystrophy Patients
Healthy Adipose Tissues
Limited Storage Capacity
Leptin ↓
Insulin Sensitivity ↓
Glucose, triglyceride level in blood ↑
Normal storage capacity
Normal Leptin Level
Normal Insulin Sensitivity
Normal level of Glucose and Triglyceride

▲ Figure 1: Comparison of adipocyte functions between a healthy person and a lipodystrophy patient. Adipocyte storage ~~The storage of adipocytes~~ is ~~is limited~~decreased in lipodystrophy patients. Common metabolic abnormalities include leptin deficiency, insulin resistance, and elevated blood~~increased~~ glucose levels in the bloodstream. (Made with BioRender)

2. Methods

Search Strategy

A literature search was conducted using PubMed and Google Scholar databases. The search included the following keywords: “lipodystrophy genetics”, “adipocyte differentiation”, “AGPAT2”, “PTRF Cavin-1”, “LMNA mutation”, “PPARγ mutation”, “lipodystrophy metabolic abnormalities”. Titles and abstracts were first screened for relevance. Full articles were reviewed to see if they met the inclusion criteria. 97 articles were initially screened, and 55 papers were ultimately referenced in this review.

Inclusion/Exclusion Criteria

Articles published between 2000 and 2026 were included. Only ~~publications in the~~ English language publications were considered. Studies were included if they were peer-reviewed primary research articles or comprehensive reviews, including both narrative reviews and systematic reviews, that focused ~~focusing~~ on the genetic, molecular, or metabolic mechanisms underlying ~~of~~ lipodystrophy syndromes. Case studies were included if they provide~~with~~d relevant insights, such as pathological or mutation analyses or clinical findings ~~were also included~~. Non-~~peer~~-peer-reviewed sources and ~~,~~articles published before 2000 are excluded.~~;~~ Ccase reports that only report~~with~~ descriptive ~~only~~ quantitative data~~-~~, without the discussion of mechanistic interpretation, are also excluded, as clinical data are not the focus of this review.~~and without further analysis were excluded. Titles and abstracts were first screened for relevance. Full article was reviewed if they met the inclusion criteria.~~

3. Discussion

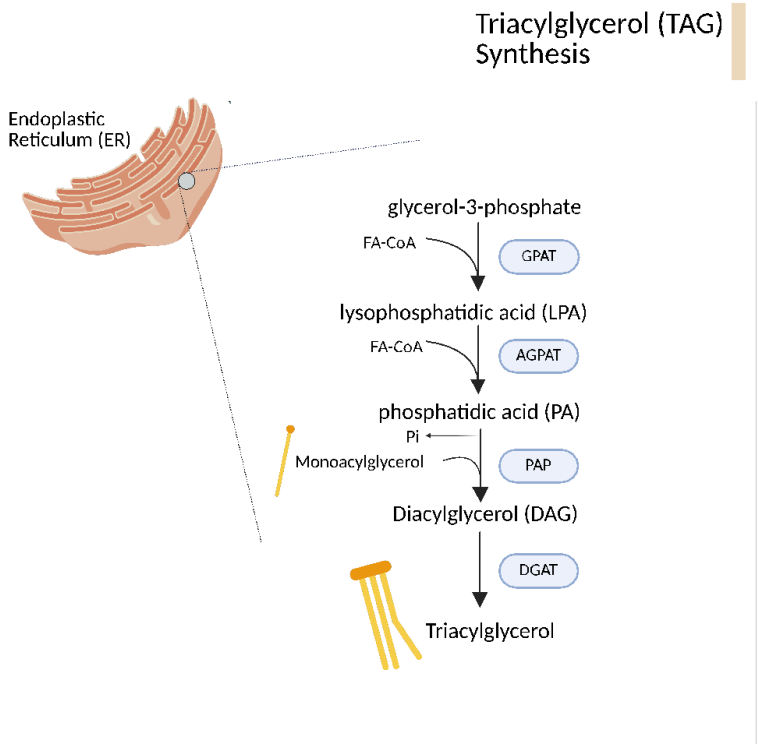
Genetics and Pathophysiology

3.1 Type 1 ~~1~~ Congenital Generalized Lipodystrophy (CGL1)

Type one~~1~~ Congenital Generalized Lipodystrophy (CGL1) is caused by a mutation in the gene AGPAT2. AGPAT2 is the gene that ~~coding for~~ encodes the ~~a specific~~ enzyme ~~,~~ 1-acylglycerol-3-phosphate O-acyltransferase 2. It~~, which~~ catalyzes the acylation of lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1,2 diacylglycerol-3-phosphate)(Gale et al. 2006) (F~~f~~igure 2). It is an important precursor for~~of~~ the biosynthesis of triacylglycerol (TAG) and phospholipid~~s synthesis~~ from glycerol-3-phosphate. This step esterifies a second fatty acyl group at the sn-2 position of the glycerol backbone. Phosphatidic acid is further acylated by other enzymes, creating triacylglycerol and phospholipids. Impaired formation of phosphatidic acid results in the absence of triacylglycerol production, thereby disrupting the normal adipose tissue development.

The AGPAT family consists of 11 isomers.~~;~~ Among the isomers, ~~however,~~ AGPAT2 is expressed at higher levels in adipose tissue than the other isomers. The presence of

mechanical adipose tissue can be explained by the increased expression of the other isomers (Broekema et al., 2018). However, studies have shown that the expression of AGPAT2 is required for the accumulation of triacylglycerol, especially in metabolic adipose tissues. Defects in the AGPAT2 genes also impact insulin signaling, which is a direct effect of impaired adipocyte dysfunction (Santoro et al., 2021). ~~meaning~~ This also causes~~that~~ gluconeogenesis ~~will~~to be unrestricted, which leads to the development of hyperglycemia and diabetes(de Melo et al. 2025).



▲ Figure 2: The process of Triacylglycerol synthesis. In the second step, where LPA is acylated to PA, AGPAT is the enzyme that catalyzes this reaction. Without it, the reactions after it will not occur properly, meaning that adipocytes can't develop properly. (Made with BioRender)

3.2 *Type 2 Congenital Generalized Lipodystrophy (CGL2)*

Type 2 Congenital Generalized Lipodystrophy (CGL2) is caused by pathogenic variants of the BSCL2 gene. It encodes the protein seipin, which is found in the endoplasmic reticulum (ER) (Akinci et al., 2024), Seipin plays an important role in the regulation of lipid droplet biogenesis. It interacts with proteins involved in TAG synthesis to facilitate adipogenesis. For instance, it binds with AGPAT2 to regulate PA metabolism. Seipin deficiency could lead to abnormal accumulation of PA. This increases the surface tension of the ER and decreases its line tension, disrupting the unidirectional lipid droplet

budding. It causes the accumulation of newly synthesized neutral lipids in the ER, leading to severe ER stress and potentially being toxic to the cells (Li et al., 2022).

CGL2 is the most common type of congenital lipodystrophy. But mutations in the BSCL2 also lead to the most severe symptoms. Patients are born without any fat, including mechanical and metabolic adipose tissues. They also have an earlier onset of diabetes mellitus than other types of lipodystrophies. Other than adipocytes, seipin is also expressed in the brain and testis. This leads to mild mental disability, developmental language disorders, and an impaired reproductive system.

3.3 Type four Congenital Generalized Lipodystrophy (CGL4)

Type four Congenital Generalized Lipodystrophy (CGL4) is associated with the gene mutation in the PTRF gene (Polymerase I and Transcript Release Factor)(Salle-Teyssières et al. 2016). The PTRF gene encodes cavin-1, which is one of the essential proteins that is required for the biogenesis of caveolae. Caveolae are the most abundant invaginations of the plasma membrane across a wide range of mammalian cells (Figure 3). Cavin-1 plays a critical role in the initiation of caveolae by recruiting other structural proteins, such as caveolins. Without it, cells won't be able to produce caveolae. Although it is abundant, its functions have only been understood in the past few decades. It plays a role in signal transduction, endocytosis, and mechanotransduction (Stea and D'Alessio 2025). Cavin-1 binds with the caveolins to form Caveolae. There are three members in the caveolin family: caveolin-1, caveolin-2, and caveolin-3. They are expressed in a variety of cells, like smooth muscle cells, fibroblasts, and adipocytes. Caveolin 3 is expressed exclusively in cardiac and skeletal muscle. It is shown that the lack of PTRF-CAVIN doesn't affect the level of caveolin expressed (Rajab et al. 2010). However, it affects caveolin's ability to localize to the cell's surface, which makes the formation of caveolae impossible. The absence of caveolae causes abnormalities and dysfunctions, including impaired signal transduction and a lack of mechanoprotection. Without the extra membranes acting as a buffer against the force of mechanical stretching, cardiac cells are at a greater risk of rupturing (Grivas et al., 2020).

Clinical features uniquely associated with CGL4 are myopathy, which affects skeletal muscle structure, and distal metaphyseal deformation, causing bone stiffness and limited range of motion (Ardissone et al. 2013). Cardiac arrhythmias are also one of the symptoms caused by the lack of PTRF-CAVIN, and they could be life-threatening, showing the serious consequences of cavin-1 deficiency (Rajab et al. 2010). These symptoms can be explained by the location where caveolins 1, 2, and 3 are expressed.

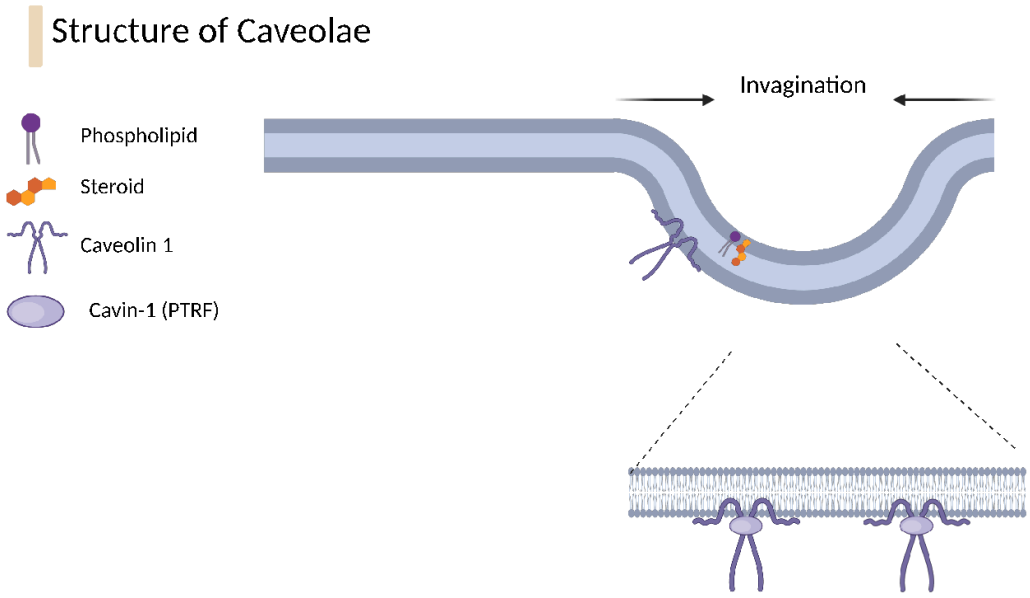


Figure 3: ~~The~~ structure and formation of caveolae. Caveolae are invaginations~~clusters~~ of~~in~~ the ~~cell~~ plasma membrane. Cavin-1 first binds with the plasma membrane, initiating caveolae synthesis. C~~and~~ caveolin 1 binds with cavin-1, which stabilizes its structure ~~together~~ and forms caveolae. (Made with BioRrender)

3.4 Type ~~two~~2 Familial Partial Lipodystrophy (FPLD2)

The gene LMNA~~, which~~ encodes the protein called Lamins.~~,~~ It is the gene that ~~causes~~ is associated with Type ~~two~~2 Familial Partial Lipodystrophy (FPLD2). ~~It~~ FPLD2 is ~~is also~~ the most common type of lipodystrophy syndrome (Corsa et al. 2021). In cells, Lamin A and Lamin C are expressed predominantly. The main functions of Lamin A/C are the regulation of nucleus shape, providing structural stability to the nuclear envelope and cytoskeleton, and also controlling gene regulation (Maung et al. 2026)(Bagias et al. 2020). They are important intermediate filament proteins forming the nuclear lamina. They also play a role in ~~Specifically,~~ organizing~~the nuclear lamina and~~ chromatin~~, and the interaction between them~~. Mutations in Lamin A/C can lead to premature aging syndrome (Hutchinson-Gilford Progeria Syndrome). The mutated LMNA gene produces a mutant product called progerin. As progerin accumulates in the nucleus, it destabilizes DNA, triggers premature senescence, and alters the shape of the nucleus (Gonzalo et al., 2017).

~~One way that Lamin A can affect cell development is t~~The interference with the cleavage step of post-translational regulation of Lamin A could also affect the patient. ZMPSTE24 plays an important role in this step, and it is also considered to be one of the factors that causes lipodystrophy. However, mutations in ZMPSTE24 cause another distinct form of lipodystrophy (mandibuloacral dysplasia), showing different symptoms and increased severity. ~~This m~~Nevertheless, modification is crucial and ensures that Prelamin A (the precursor of Lamin A before ~~the~~ post-translational regulation) ~~will~~

~~function~~functions normally. Not only will the lack of Lamin A affect cell functions, but the accumulation of Prelamin A could also be toxic to cells (Varlet, Helfer, and Badens 2020), which could affect the cell's ability to develop properly.

These cellular abnormalities contribute to broader systemic symptoms. This includes a~~A~~ higher risk of cardiovascular diseases ~~is also associated with FPLD2~~. It is found that FPLD2 patients have higher Epicardial adipose tissue (EAT) volume than type two diabetes patients (Talman et al. 2014) (Godoy-Matos et al. 2015). However, it is not related to other metabolic issues that are also presented in lipodystrophy (Lamothe et al. 2025). ~~Other~~ Additional studies will ~~also~~ need to be conducted~~done~~ to gain a~~have a~~ clearer insight into this condition and ~~the~~its correlation ~~between them~~.

3.5 Type ~~three~~3 Familial Partial Lipodystrophy (FPLD3)

Type ~~three~~3 Familial Partial Lipodystrophy (FPLD3) is caused by pathogenic variants of the PPARG gene. PPARG encodes ~~for~~ PPARγ (Peroxisome proliferator-activated receptor γ), a member of a superfamily of nuclear receptors. PPARγ is known as the master regulator of adipocyte differentiation, maintenance, and functions(Broekema et al. 2019). It ~~PPARγ~~ has three isoforms: ~~,~~PPARγ1, PPARγ2, and PPARγ3. Among them, PPARγ2 is predominantly expressed in adipocytes. PPARγ acts as a ligand-activated transcription factor. It binds to its target gene as a heterodimer with PPAR-response elements (PPREs)(Madsen et al. 2022). After binding, PPARγ regulates the transcription of downstream target genes ~~induces many targeted genes~~involved in the development of adipose tissue. Including t~~T~~he TAG cycle, which is ~~also~~ upregulated by PPARγ for the development of adipocytes. Loss-of-function or dominant-negative m~~M~~utations in pathogenic variants of PPARG ~~migh~~fundamentally impair adipogenesis. Therefore, leading ~~it leads~~ to increased cellular stress and dysfunctions in adipocytes(Soares et al. 2024).

Compared to FPLD2, FPLD3 patients show less severe fat loss. One way to explain this is that more large adipocytes are preserved since mutations in PPARG could lead to excess cell growth. Fat accumulation in areas such as the face and neck ~~are~~is also not observed (Bagias et al. 2020). However, FPLD3 patients also show more severe metabolic symptoms, specifically hypertriglyceridemia, diabetes, and insulin resistance. One possible explanation is that although patients still preserve large adipocytes, they only have a few small, insulin-sensitive adipocytes (Soares et al. 2024).

3.6 Acquired ~~Generalized~~ Lipodystrophy ~~(AGL)~~

A ~~s we can see, a~~ wide ~~variety~~ range of gene mutations that affect different cellular functions could all lead to LD. However, gene mutations are not the only cause of lipodystrophy. Other environmental factors can also trigger the onset of lipodystrophy. Acquired Generalized Lipodystrophy (AGL~~, also called Lawrence Syndrome~~) and Acquired Partial Lipodystrophy (APL) are forms ~~is another form~~ of lipodystrophy~~, which has similar symptoms to CGL but is~~that are not caused by genetic mutations(Al-Jawad et al. 2025).

Despite having different mechanisms, they have similar symptoms to congenital lipodystrophy.

¶

Acquired lipodystrophy is characterized by the gradual loss of fat tissue starting from childhood or adolescence. AGL patients show a generalized loss of adipose tissue, while APL patients show loss of adipose tissue from the upper body. This includes the face, neck, upper extremities, and upper trunk. They also share similar causes, including autoimmune diseases, panniculitis-associated causes, and idiopathic causes. However, while about 25% of AGL cases are associated with panniculitis, it is rare in APL patients (Hussain & Garg, 2016).

Adverse effects of highly active antiretroviral therapy ~~(HAART)~~ in patients with HIV are among~~one of~~ the factors that lead to acquired lipodystrophy~~AGL~~. The mechanism by which antiretroviral drugs play a role in the development of lipodystrophy is not fully understo~~od completely~~. One possibility is ~~Proteins such as~~ the use of t~~t~~hymidine analog nucleoside reverse transcriptase inhibitors ~~(NRTI), which are used~~ in highly active antiretroviral therapies~~HAART~~. They~~,~~ ~~are~~have been shown to disrupt adipose tissue functions (Guzman and Vijayan 2025). It decreases the expression of adiponectin, which regulates the oxidation of glucose and fatty acids. Nucleoside reverse transcriptase inhibitor ~~NRTI~~ also induces mitochondrial toxicity, which also plays a role in the development of ~~AGL~~acquired lipodystrophy. Lipodystrophy in HIV-infected patients is characterized by the loss of subcutaneous fat at the extremities and face.¶

~~Another possible cause of AGL is A~~autoimmune disease~~s~~ are also a significant cause of acquired lipodystrophy.~~:~~ ~~Specifically~~In particular, perilipin 1 ~~(PLIN1)~~ autoantibodies are found in AGL ~~AGL~~ patients (Corvillo et al. 2022). Anti-perilipin is also found in patients with ~~panniculitis associated~~panniculitis-associated AGL ~~AGL~~. Perilipin is found only in adipose tissue and forms a layer that coats lipid droplets. Under normal conditions, perilipin forms a barrier between lipase and the surface of lipid droplets. However, when the autoantibodies are present, it disrupts the normal function of perilipin. It leads to an increase in lipolysis activities, which ~~decreases~~ contributes to the gradual loss of adipose tissue in ~~the fat storage in t~~AGL patients ~~he body~~(Corvillo et al. 2018).

In APL patients, the presence of C3 nephritic factor (C3NeF) is commonly associated. It acts as an autoantibody against the body's own complement system, particularly complement component C3. When C3NeF binds with C3 convertase, it stabilizes the C3 convertase and prevents its natural decay. Since the function of C3 convertase is to cleave C3 into its active fragment, prolonged activation leads to a low level of C3 (*Nephritic Factor - an Overview | ScienceDirect Topics*, n.d.). In adipose tissues, the production of Factor D (adipsin) makes them more susceptible to the activation of the alternative pathway. Factor D plays an important role in the cleavage of factor B (C3bB), resulting in fragments Ba and Bb. The fragment Bb then forms the enzyme C3 convertase,

also known as C3bBb. As the breakdown of C3 continues, it activates the terminal pathway. It ultimately leads to the lysis of adipocytes, which explains the fat loss. However, the factor that limits fat loss to the upper body remains unclear (Corvillo & López-Trascasa, 2018). ¶

4. Diagnosis and Clinical Features

Since lipodystrophy is s~~uch a~~ rare ~~disease and not well known to the public~~, it is often misdiagnosed or left undiagnosed by clinicians. It heavily relies on clinical history and physical examinations that reveal the composition of adipose tissues. Metabolic dysfunctions are also important markers when diagnosing lipodystrophy. Although patients with CGL show symptoms such as a lack of body fat shortly after birth, it is often left undiagnosed until their childhood or adulthood, when they start showing metabolic abnormalities. As for FPLD, it is even more commonly unrecognized due to patients only losing adipose tissue partially. It could ~~be easily mixed up with~~be easily misdiagnosed as other types of common metabolic diseases, like obesity or severe diabetes mellitus. Presentations of AGL and APL are generally similar to CGL and FPLD, also including the metabolic issues that come with it (Lima et al. 2025).

Lipotoxicity is a direct consequence of adipose tissue dysfunction. Since adipose tissues aren't able to store as many lipid droplets as are produced, excess lipid droplets circulate in the bloodstream as free fatty acids. As the level of circulating free fatty acids elevates, it becomes toxic for non-adipose tissues, resulting in increased oxidative stress (Engin, 2017; Sies, 2020). Since the liver is the major organ that maintains the body's homeostasis, excess fatty acid accumulates at the liver, leading to fatty liver (Kikuchi & Takamura, 2017; Liu et al., 2010). This imbalance of fatty acids in the liver interferes with the insulin signaling pathways. In addition, the body stores excess fat in skeletal muscles, as it is the organ responsible for most of the energy uptake (Merz & Thurmond, 2020). Without skeletal muscles, glucose isn't consumed properly, which also disrupts the insulin signaling pathways.

Some phenotypes ~~that are~~ associated with lipodystrophy ~~are~~ include a muscular appearance, prominent veins, and ~~the~~ a lack of body fat. Two main types of fat tissue serve different functions in the body: metabolic and mechanical adipose tissue. Metabolic adipose tissue is responsible for energy storage and hormone secretion, while mechanical tissue, also known as subcutaneous fat, is found under the skin and internal organs to provide protection and support. For CGL patients, the ~~absence~~ loss of metabolic adipose tissues is more severe~~common~~ than the loss of mechanical tissues. Yet~~. Although~~ patients still, to ~~in~~ some degree,~~s~~ lack functional mechanical fat tissues. ~~Metabolic adipose tissues are in charge or energy storage and hormone secretion, while the mechanical tissues, also known as subcutaneous fat tissue, are found under the skin and internal organs to provide protection and support. Although patients still in some degrees lack functional~~

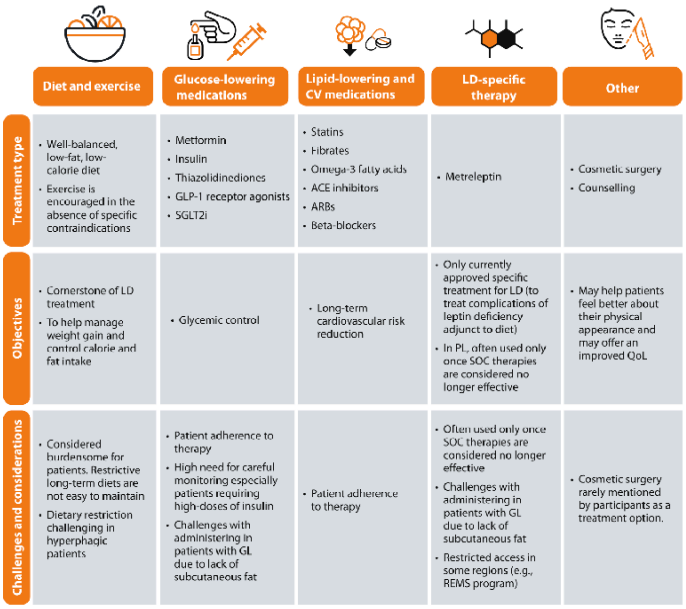
~~mechanical fat tissues.~~ Only CGL2 patients ~~Except for CGL2, in which patients generally~~ are born without mechanical and metabolic adipose tissues~~kinds of fat tissues~~ (Garg 2011).

In contrast, FPLD is ~~characterized~~characterized by the abnormal distribution with a slight loss of adipose tissue, meaning that patients still acquire most of their functional fat tissues. In addition, as mentioned before, the onset of CGL is often shortly after birth, but for FPLDs, its onset is usually around puberty or adolescence. In general, CGL patients lack the ability to build up mature adipose tissue~~s~~, while FPLD patients can't store or regulate adipose tissue properly. ~~Next, we~~ The following section will address potential treatments and their underlying mechanisms. ~~will be discussing some potential treatments for lipodystrophy and the mechanisms behind them.~~

5. Treatments

5.1 Metreleptin

Currently, there isn't a definitive~~e treatmen~~cure~~t~~ for lipodystrophy, but some treatments targeting~~for~~ specific metabolic abnormalities ~~are~~have been developed ~~being invented~~ (Araújo-Vilar and Santini 2019). For example, Metreleptin (Recombinant methionyl human leptin) is a drug invented specifically for lipodystrophy. It targets leptin deficiency in patients~~. Leptin is a hormone that regulates energy metabolism~~. Leptin~~It~~ is secreted by adipose tissue, and it regulates a person's appetite and food intake (Tsoukas, Farr, and Mantzoros 2015). Since lipodystrophy patients lack functional adipose tissue, leptin secretion also decreases. This causes patients to show extreme hyperphagia, which means the excessive intake of food. This worsens insulin resistance and creates excess fat that must be stored in internal organs or muscles. Metreleptin's main purpose is to mimic the naturally occurring leptin hormone, and it must be administered at least once daily (Rodriguez, Mastronardi, and Paz-Filho 2015). It helps reduce patients' appetite and decreases the intake of calories, which contributes to the accumulation of lipid droplets. The use of metreleptin in FPLD patients is not approved by the FDA since it does not work as efficiently in FPLD patients as in CGL patients~~. Metreleptin is found to be more efficient in Generalized lipodystrophy patients due to the low levels of leptin that are produced~~(Gilio, Foss-Freitas, and Oral 2025). Individual cases of FPLD could be evaluated for whether the requirements for the metreleptin treatment are met. However, the risk of using Metreleptin for special groups of people with generalized lipodystrophy, such as pregnant women~~, are~~is not certain. Other common drugs, such as insulin or metformin, can also help patients control their symptoms; however, they are not a cure for LD~~D~~. ~~.~~ Cosmetic surgery is also an option for patients to minimize the psychological discomfort and to have a better quality of life (Table 2).



	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.

▲ Table 2: Possible medications to control metabolic issues that arises with lipodystrophy. Including the objectives, possible challenges, and other considerations (Reproduced from (Patni et al., 2024) ~~(Patni et al. 2024)~~ under the terms of the CC BY license)

5.2 Lifestyle Modification~~Change in Daily Routine~~

Although Metreleptin can generally help with metabolic dysfunctions, lifestyle modification also plays a significant role in managing lipodystrophy. A low-fat diet is recommended for patients. Carbohydrate intake is also restricted to control diabetes. Since the body cannot store excess energy properly, it would be beneficial for patients to reduce the intake of food that will be metabolized into excess fat or energy. Physical exercises are also encouraged. However, patients with cardiovascular issues should avoid ~~doing too much~~excessive exercise to prevent ~~the development of other serious~~further complications (Akinci et al. 2024).

5.3 Limitations and Possibility of Gene Editing

Although Metreleptin is an effective way for LD patients to manage metabolic complications, it is not able to cure ~~it~~them. In the future, gene editing could be applied to treating ~~the treatment of~~ this disease. Preclinical trials have been conducted on mouse models with CGL2, which has a gene mutation at the BSCL2 gene. Seipin knockout (SKO) mice, which generally show similar metabolic symptoms to CGL2 patients, were generated, and ~~were~~ injected with adeno-associated virus (AAV) vectors (Sommer et al. 2022). AAV can be engineered to transduce~~targets~~ adipocytes, enabling ~~which act as a~~ targeted ~~in~~ gene therapy for lipodystrophy. The results of the trials show that gene therapy effectively restores adipose tissue development and function (Tiwari et al. 2024). However, even

though AAVV is commonly used in clinical trials, it hasn't been used to directly target adipose tissue. Novel AAVV serotypes that targets adipose tissue or an alternative promoter are critical for the development of an improved gene therapy strategy for LD patients. Therefore, there isn't enough evidence currently to suggest that the results from mouse models can be translated to humans. Continued research on LD and advances in gene therapy are necessary to develop a more effective therapeutic strategy for this rare disorder.

6. *Conclusion and the Future*

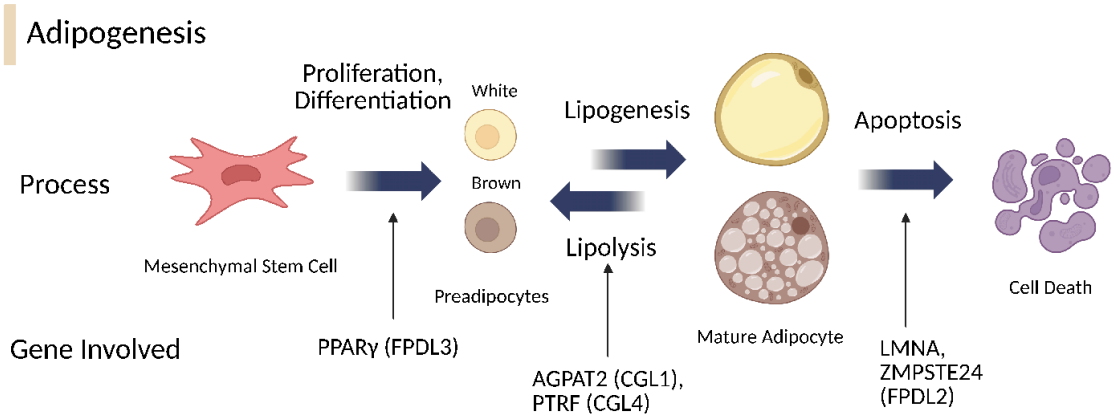


Figure 4: Steps of adipogenesis. Starting from mesenchymal stem cells, after proliferation and differentiation, it develops into preadipocytes. Then, through lipogenesis, preadipocytes grow into mature adipocytes. When a person is fasting, adipocytes go through lipolysis to produce energy by breaking down triglycerides into glycerol and free fatty acids. The last step is apoptosis, which ultimately leads to cell death. (Made with BioRender)

GAlthough genes involved in lipodystrophy syndromes affect various cellular processes, such as lipid synthesis, signal transduction, and nuclear structure. They, they all lead to a common outcome: impaired adipocyte development and function. The examples discussed in this review, including CGL1, CGL4, FPLD2, and FPLD3, demonstrate how different stages of adipogenesis and gene mutations that are involved in adipogenesis all lead to similar consequences (Figure 4). In addition to genetic causes, acquired factors can also contribute to adipocyte dysfunctions, as seen in AGL.

LD highlights the essential role of adipose tissue as an endocrine and metabolic organ. It not only stores energy but also maintains metabolic homeostasis and regulates hormones. The absence of adipocytes, as shown in this review, could cause

life-threatening disorders. Understanding this condition not only helps people recognize the role of adipose tissue in metabolism but also helps raise awareness of rare diseases. For conditions like lipodystrophy, many patients remain undiagnosed throughout their lives. Not only is conducting research with so few samples challenging, but scientists may be less willing to dedicate time to studying rare diseases compared to diseases that affect a larger population. Increased awareness and improved diagnostic tools not only help identify individuals affected by this disease earlier but also give them a chance to manage their condition in a more effective way.

Since the discovery of lipodystrophy syndromes in ~~around~~ the mid-20th century~~, lots of~~, significant progress has been made in ~~to get a better~~ understanding ~~of~~ lipodystrophy. From ~~the~~ phenotypes and~~to the~~ metabolic abnormalities to~~and the~~ underlying genetic causes, research ~~have~~ has been conducted ~~done~~ to find~~seek for~~ ways to reduce patient~~'s~~s' pain and suffering. Having a deep understanding of lipodystrophy, such as the mechanisms of various genes and their relationship with adipogenesis, will be crucial to the development of a more effective and targeted therapeutic strategy.

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9. Author Biography

Chiao Yun Cheng is a high school junior at Great Hearts Anthem Prep in Anthem, Arizona. She is a young researcher with a deep interest in biochemistry, genetics, and chemical engineering. She plans to pursue a degree in biochemistry or a related field, such as chemical engineering, in college. Through this research project, Chiao Yun developed a deeper passion for lab research and gained a deeper understanding of people with rare diseases. In the future, she hopes to develop more treatments for individuals with rare diseases and aims to solve existing problems in medical and scientific areas.

Beyond her studies and research, Chiao Yun is passionate about playing piano and drawing. She uses them as a way to relax and generate ideas. She also enjoys traveling and learning about different cultures, which helps broaden her perspective on the world.

10. Mentor Contribution Statement

Dr. Hamidreza Shaye provided guidance throughout the research and writing process by offering conceptual advice, academic direction, and methodological choices. In addition, he offered guidance on choosing research questions and identifying relevant and appropriate sources for citation. He advised on using academic tools to produce images and analyze information. He helped refine the paper's tone and scope by giving advisory feedback.

Dr. Lauren Tetz served as an advisor to the research project. She gave suggestions on how to structure the paper and strengthen the academic rigor. She also provided resources that helped structure the paper's content.

Dr. Shaye and Dr. Tetz did not participate in the writing process of the manuscript or the production of the images. The student determined the aim of this research and conducted the literature review independently.