**A Review Article on Lipodystrophy**

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**Abstract**

Lipodystrophy syndromes are a heterogeneous group of diseases, characterized by selective absence of adipose tissue. In one sense, these diseases are lipid-partitioning disorders, where the primary defect is the loss of functional adipocytes, leading to ectopic steatosis, severe dyslipidemia, and insulin resistance. These syndromes have attracted significant attention since the mid-1990s as the understanding of adipose tissue biology grew, initially spurred by the discovery of the pathways leading to adipocyte differentiation and maturation, and then by the discovery of leptin. Although lipodystrophy syndromes are known since the beginning of the 20th century, significant progress in understanding these syndromes were made in the last two decades, placing these syndromes at the forefront of the translational metabolism field. Currently, more than 20 distinctive molecular etiologies have been attributed to cause human diseases most of which map to adipocyte differentiation or lipid droplet pathways. Seemingly acquired syndromes are recently reported to have a genetic basis, suggesting that our “pre-genome” understanding of the syndromes was inadequate and that we need to likely change our classification schemes. Regardless of the etiology, it is the selective absence of adipose tissue and its function, leading to the reduced ability to store long-term energy that perturbs insulin sensitivity and lipid metabolism. The treatment of these syndromes has also attracted considerable interest. The most successful example of the treatment of these syndromes came from the demonstration that leptin replacement strategy improved insulin resistance and dyslipidemia in the most severely affected forms of the disease, leading to an FDA approved therapy for generalized lipodystrophy syndromes. In the partial forms of the disease, the phenotypes are more complex, and the efficacy of leptin is not as uniform. Currently, standard treatment-resistant partial lipodystrophy is an EMA-approved indication, and numerous trials are in progress, either evaluating the efficacy of leptin in familial partial lipodystrophy or aiming to develop potential new treatments for the partial forms of the disease. These rare metabolic diseases are likely to continue to fuel novel breakthroughs in the field of metabolism in the foreseeable future. For complete coverage of all related areas of Endocrinology

**Keywords :**

Lipodystrophy ,Lipoatrophy, Lipohypertrophy, congenital Generalised Lipodystrophy , familial Partial Lipodystrophy, Acquired Generalised Lipodystrophy, Highly active antiretroviral therapy, Metformin, Metreleptin

**Definition :**

Lipodystrophy syndromes are a group of genetic or acquired disorders in which the body is unable to produce and maintain healthy fat tissue. The medical condition is characterized by abnormal or degenerative conditions of the body’s adipose tissue.

It can involve loss of fat (lipoatrophy), accumulation of fat (lipohypertrophy), or both. This condition may be inherited (genetic lipodystrophy) or acquired due to factors like autoimmune disorders, infections, or prolonged use of certain medications, such as antiretroviral therapy for HIV.

**Types of Lipodystrophy**

**Genetic**

Congenital Generalised Lipodystrophy (CGL)

Familial Partial Lipodystrophy (FPLD)

**Acquired**

Acquired Generalised Lipodystrophy(AGL)

Acquired Partial Lipodystrophy (APL)

Highly active antiretroviral therapy( HAART)

**Genetic Lipodystrophy**

**Congenital Generalised Lipodystrophy (CGL)**

Congenital Generalised Lipodystrophy (CGL) , is also known as Berardinelli-Seip syndrome, is a rare genetic disorder characterized by the near-complete absence of adipose (fat) tissue from birth. This leads to a range of metabolic complications. CGL has four known types, each caused by mutations in different genes

**Causes**

**CGL Type 1 (AGPAT2 Mutation)**

**CGL Type 2 (BSCL2 Mutation)**

**CGL Type 3 (CAV1 Mutation)**

**CGL Type 4 (PTRF Mutation)**

**Symptoms**

The primary feature of CGL is a generalized lack of fat tissue, but this absence affects the body’s metabolism, leading to a range of symptoms:

**Near-total loss of body fat:** This is noticeable from birth or early infancy. The lack of subcutaneous fat gives individuals a muscular appearance with prominent veins, despite the absence of proper fat storage.

**Insulin resistance and diabetes :** Due to the lack of fat storage, excess lipids accumulate in non-adipose tissues (like the liver and muscles), causing insulin resistance. This often leads to early-onset diabetes (typically during childhood or adolescence).

**Treatment :**

**1.Dietary Modifications**

**Low-Fat, High-Protein Diet:** To reduce triglycerides and cholesterol levels, a low-fat diet is recommended. This helps prevent the liver from becoming overloaded with fats and reduces the risk of pancreatitis.

**2. Medications**

**Insulin Sensitizers**: Metformin or thiazolidinediones are often prescribed to improve insulin sensitivity and control blood glucose levels.

**Lipid-Lowering Medications:** Statins, fibrates, or omega-3 fatty acids are commonly used to lower cholesterol and triglyceride levels.

**Familial Partial Lipodystrophy (FPLD ):**

Familial Partial Lipodystrophy (FPLD) is a rare genetic disorder characterized by the selective loss of body fat in specific areas, while fat may accumulate in other regions. This condition can have multiple subtypes, with varying genetic causes and patterns of fat loss.

**Causes**

FPLD is usually inherited in an autosomal dominant pattern, meaning one copy of the altered gene in each cell is sufficient to cause the disorder. Several gene mutations are associated with different forms of FPLD, such as mutations in the LMNA, PPARG, AKT2, PLIN1, and CIDEC genes. These genes are involved in fat storage, metabolism, and energy regulation, and their mutations disrupt normal fat distribution and lipid metabolism.

**Symptoms**

**Localized Fat Loss:** Fat is often lost in the limbs, buttocks, and face, while fat may remain or accumulate around the neck, face, and intra-abdominal areas.

**Insulin Resistance:** Due to the abnormal fat distribution, individuals are prone to insulin resistance, often leading to Type 2 diabetes.

**Treatment :**

**Medications**

**Insulin-Sensitizing Agents:** Metformin is often prescribed to improve insulin sensitivity and control blood sugar levels.

**GLP-1 Agonists:** Medications like liraglutide can help with weight loss and glycemic control.

**Statins or Fibrates**: These may be used to manage high cholesterol and triglycerides, common in FPLD patients.

**Acquired Generalised Lipodystrophy (AGL)**

Acquired generalized lipodystrophy (AGL), also known as acquired generalized lipoatrophy, is a rare disorder characterized by the progressive loss of body fat from various parts of the body, especially under the skin. Unlike congenital lipodystrophy, which is inherited, AGL develops later in life, often due to an autoimmune or inflammatory trigger.

**Causes**

The exact cause of AGL is not fully understood, but several potential triggers and associated conditions have been identified:

**Autoimmune or Inflammatory Conditions:** Many patients with AGL have a history of autoimmune diseases, such as lupus, rheumatoid arthritis, or juvenile dermatomyositis.

**Symptoms**

**Loss of Subcutaneous Fat:** Fat loss often occurs throughout the body, leading to a muscular or thin appearance, particularly in areas like the face, arms, legs, and torso.

**Muscle Hypertrophy:** Due to the loss of fat, the muscles might appear more prominent, which can give an athletic appearance despite other symptoms.

**Treatment**

**Management of Metabolic Abnormalities:**

**Insulin Resistance:** This is often a significant problem, and management with insulin sensitizers like metformin or thiazolidinediones (e.g., pioglitazone) may be considered.

**Acquired Partial Lipodystrophy**

Acquired partial lipodystrophy (APL) is a rare disorder characterized by the selective loss of subcutaneous fat, typically affecting the upper body while preserving fat in the lower body. Here are the causes and symptoms:

**Causes**:

**Autoimmune Disorders:** APL is often associated with autoimmune conditions like systemic lupus erythematosus (SLE) and other connective tissue diseases, where the immune system attacks the body’s tissues, including fat.

**Genetic Factors:** Though most cases are acquired, some may have a genetic predisposition. Certain mutations could contribute to the condition.

**Symptoms:**

**Fat Loss in Upper Body:** The primary symptom is the loss of subcutaneous fat from the upper limbs, face, neck, and trunk.

**Fat Accumulation in Lower Body:** In contrast, fat tends to accumulate in the lower body, including the thighs, buttocks, and lower abdomen.

**Treatment :**

**Management of Metabolic Complications:**

**Hypertriglyceridemia and Hyperlipidemia:** APL is often associated with elevated triglyceride levels, which can increase the risk of cardiovascular diseases. Medications such as fibrates (e.g., fenofibrate) or statins may be prescribed to control lipid levels.

**Highly Active Antiretroviral Therapy (HAART)**

HAART Lipodystrophy : refers to the body fat changes and metabolic complications that can occur in people receiving Highly Active Antiretroviral Therapy (HAART) for HIV/AIDS .

**Causes**

HAART lipodystrophy is primarily caused by the long-term use of certain antiretroviral medications. These drugs can interfere with the body’s fat metabolism, leading to abnormal fat distribution and metabolic changes. The following are the mechanisms thought to contribute to the condition:

**Symptoms**

HAART lipodystrophy is characterized by a combination of lipoatrophy (fat loss) and Lipohypertrophy (fat gain), along with associated metabolic changes. Symptoms can vary in severity, and not all individuals experience both fat loss and fat gain.

**Lipoatrophy (Fat Loss):**

**Face:** Loss of fat in the cheeks, temples, and around the eyes, leading to a sunken or gaunt appearance.

**Limbs :** Loss of fat in the arms and legs, causing veins to become more prominent and muscles to appear more defined.

**Abdomen :** Accumulation of visceral fat in the abdominal area, leading to a “pot belly” or central obesity .

**Neck and Upper Back :** Development of a “buffalo hump” (excess fat on the back of the neck or upper back).

**Treatment**

**Modifying Antiretroviral Therapy:**

**Switching Medications :** If possible, changing to antiretroviral drugs with a lower risk of lipodystrophy, such as newer NRTIs (tenofovir and emtricitabine) or integrase inhibitors, may help prevent further fat changes.

**Stopping Mitochondrial-Toxic Drug :** Discontinuing medications like stavudine and zidovudine, which are most associated with lipoatrophy, may prevent worsening of fat loss.

**Diagnosis of Lipodystrophy :**

**1.Clinical Evaluation:**

A detailed medical history and physical examination are crucial. Doctors will assess symptoms such as fat loss from limbs or face, abnormal fat accumulation in the abdomen or upper back, and insulin resistance.

**2.Laboratory Tests**:

Blood Tests to evaluate cholesterol, triglycerides, insulin levels, glucose, and other metabolic indicators.

**Genetic Testing**

If a genetic cause is suspected, such as mutations in the LMNA, PPARG, or AGPAT2 genes.

**3.Imaging Studies:**

MRI or CT scans can be used to assess fat distribution in the body and help confirm the presence of abnormal fat loss or accumulation.

**4.Biopsy:**

In some cases, a skin biopsy or fat biopsy may be performed to examine fat cells and confirm the diagnosis.

**FDA APPROVED DRUGS**

The FDA has approved a few drugs specifically for the treatment of lipodystrophy, especially for rare forms such as generalized lipodystrophy. These include:

**Metreleptin (Myalept)**

**Approval :** FDA-approved in 2014.

**Indication** : For the treatment of complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy .

**Mechanism :** It is a recombinant leptin analog that replaces the deficient hormone leptin, which plays a key role in regulating fat distribution, energy balance, and metabolism.

**Tesamorelin (Egrifta)**

**Approval :** FDA-approved in 2010.

Indication : For the reduction of excess abdominal fat in HIV-associated lipodystrophy

Mechanism : A growth hormone-releasing factor (GHRF) analog that stimulates the production and release of growth hormone, leading to a reduction in visceral fat.

**Indication :** For the reduction of excess abdominal fat in HIV-associated lipodystrophy

These are the two main FDA-approved drugs for lipodystrophy. Other treatments such as antidiabetic and lipid-lowering agents, while not specifically approved for lipodystrophy, are commonly used off-label to manage metabolic complications associated with the condition.

CONCLUSION

Lipodystrophy syndromes are a group of fascinating diseases that are caused by mechanisms that disrupt predominantly adipocyte differentiation or lipid droplet formation. LMNA gene defects, the most common single gene defects leading to the development of lipodystrophy syndromes, leads to lipodystrophy possibly due to inducing adipocyte apoptosis or death, but more work is needed on this front. Regardless of the mechanism and whether the diseases present with generalized or partial fat loss, common metabolic complications include severe insulin resistance, hypertriglyceridemia, and ectopic fat deposition, especially hepatic steatosis. This common theme is recapitulated in numerous animal models as well. The diseases are typically progressive and lead to multi-organ involvement and increased mortality. Molecular advances in the understanding of disease mechanisms may lead to better and specific treatments for lipodystrophy syndromes. So far, the most exciting therapeutic development for the treatment of lipodystrophy syndromes has been the approval of leptin replacement therapy for generalized lipodystrophy in the form of Metreleptin which started a new era in lipodystrophy research; leading to the launch of registries and natural history studies (e.g. the LD Lync Study-Natural History Study of Lipodystrophy Syndromes (NCT03087253) (294-296), organization of research consortia around the world (e.g., European Consortium of Lipodystrophies (ECLip) (297) and country specific patient advocacy foundations or organizations. All these efforts will contribute to discovery of new disease forms and disease mechanisms, understanding of the natural course of lipodystrophy diseases, development of improved treatment options and possibly cures

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