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Disorders of adipose tissue and lipodystrophies: causes, consequences, and treatment perspectives

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ABSTRACT:
Lipodystrophies are rare metabolic disorders characterized by the loss of adipose tissue, which can manifest as generalized, partial, or localized. This condition is associated with metabolic complications such as insulin resistance, diabetes, hypertriglyceridemia, and liver steatosis. The paper discusses the classification of lipodystrophies by etiology and fat loss extent, including generalized and partial forms, both congenital and acquired. Special focus is placed on HIV-associated lipodystrophy due to the prevalence of antiretroviral therapy. The pathophysiology involves disrupted adipogenesis, leading to abnormal fat distribution and metabolic dysfunction. Diagnosis includes medical history, physical exams, and body composition analysis. Treatment focuses on managing metabolic issues and may involve therapies like metreleptin.
OBJECTIVE: This study aims to analyze the pathophysiology, diagnosis, and treatment of lipodystrophies, particularly focusing on congenital, acquired, and HIV-associated forms. It

explores the underlying metabolic mechanisms, diagnostic challenges, and current and future therapeutic approaches, including metreleptin and other strategies.
MATERIALS AND METHODS: The study relies on scientific research, review articles, and reports on lipodystrophy syndromes, primarily sourced from PubMed, Google Scholar, and Cochrane Library. It examines data related to diagnostics, etiology, and treatment options.
CONCLUSIONS: Lipodystrophies are rare and heterogeneous, making diagnosis challenging. Early detection is essential to prevent complications like diabetes and cardiovascular disease. Modern technologies such as dual-energy X-ray absorptiometry (DEXA) help assess body composition more accurately. Although therapies like metreleptin show promise, they remain expensive and difficult to implement. Further research is needed to improve understanding and management of lipodystrophies, and patient education is crucial for better outcomes.
KEYWORDS: Lipodystrophy, adipose tissue loss, metabolism, insulin resistance, diabetes, hypertriglyceridemia, HIV, metreleptin, adipogenesis, congenital lipodystrophy, acquired lipodystrophy

INTRODUCTION:

Lipodystrophies are a rare group of disorders characterized by the loss of adipose tissue. Fat loss can affect the entire body (generalized lipodystrophy), specific areas (partial lipodystrophy), or be limited to small localized regions under the skin (localized lipodystrophy). These diseases result from genetic mutations, autoimmune processes, or medication effects[1]. In both inherited and acquired lipodystrophies, increased oxidative stress in adipocytes has been observed, though its causality has not been definitively established[2]. The most commonly encountered forms are localized lipodystrophies and those associated with HIV, while genetic and acquired forms are less frequent[1].

Lipodystrophies can be classified by their causes and the extent of fat loss into four main types: congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPLD), and acquired partial lipodystrophy (APL)[3]. In most cases, generalized hereditary lipodystrophies are inherited in an autosomal recessive manner,

whereas partial forms are usually autosomal dominant[4]. HIV-associated lipodystrophy is a specific subtype of acquired partial lipodystrophy and is the most common. It is typically associated with the loss of peripheral subcutaneous fat (lipoatrophy) and/or central fat accumulation (lipohypertrophy)[5]. The pathophysiology of lipodystrophy involves abnormalities in adipocyte differentiation, triglyceride storage, and transcriptional and translational processes regulating adipogenesis[6]. In localized lipodystrophy, the risk of metabolic complications is minimal due to limited fat loss. In contrast, partial and generalized forms significantly increase the risk of metabolic disturbances[1]. A deficiency of adipose tissue leads to lipid deposition in the liver, muscles, and other organs, potentially causing insulin resistance, diabetes, hypertriglyceridemia, polycystic ovary syndrome (PCOS), and nonalcoholic fatty liver disease (NAFLD)[7]. A reduction in subcutaneous fat decreases leptin levels, disrupting satiety control mechanisms. Consequently, hyperphagia occurs, exacerbating metabolic changes and perpetuating a cycle of dysfunction[8].

Due to its rarity and heterogeneous symptoms, lipodystrophy often goes undiagnosed or is misdiagnosed. This is particularly concerning as the disease is progressive, and its complications can be fatal[9]. The most common causes of death include cardiac diseases (e.g., cardiomyopathy, heart failure, myocardial infarction, arrhythmias), liver disorders (failure, gastrointestinal bleeding, hepatocellular carcinoma), kidney failure, acute pancreatitis, and sepsis[7]. Among patients with lipodystrophy, various cardiac problems have been observed, including hypertension, cardiac conduction abnormalities, autonomic dysfunction of the cardiac system, coronary artery disease, and hypertrophic cardiomyopathy. The most common cardiac anomaly in individuals with generalized lipodystrophy is left ventricular hypertrophy (LVH), affecting approximately half of the patients[10].

CLINICAL DIAGNOSIS

During a clinical examination, it is essential to conduct a detailed medical and family history. Key information should include the onset and duration of symptoms, history of cardiometabolic diseases, hyperphagia, and the presence of autoimmune diseases or HIV infection. These details help distinguish between subtypes of lipodystrophy and assess its severity. Additionally, information about the patient's reproductive history, puberty progression, and menstrual cycle regularity should be collected[11].

The physical examination should assess fat distribution. Areas of lipoatrophy are typically distinctive: subcutaneous fat is reduced, and muscles and veins are more prominent. Blood

pressure should also be measured, and signs of insulin resistance (e.g., acanthosis nigricans, hirsutism, acromegaloid features) and hypertriglyceridemia (e.g., eruptive xanthomas) should be noted. Dual-energy X-ray absorptiometry (DEXA) can be used for precise body composition assessment[11].

EPIDEMIOLOGY

The prevalence of lipodystrophy depends on data sources. A review of European literature and electronic databases since 2000 estimates the global prevalence of lipodystrophy at 1.3–4.7 cases per million people, with generalized forms at 0.23 per million and partial forms at 2.84 per million. However, partial forms are often underdiagnosed[12].

Growing awareness of lipodystrophy syndromes allows diabetologists to recognize genetic forms of lipodystrophy as a significant subtype of monogenic diabetes, similar to MODY diabetes. These disorders can also be identified by specialists in other fields, such as lipidology, endocrinology, gynecology, hepatology, and dermatology [3]. The low prevalence, phenotypic diversity, and genotypic variability hinder research on lipodystrophy in single centers, limiting the identification of new genetic and environmental factors, understanding the natural course of the disease, complications, treatment responses, and prognosis, including mortality[12].

HIV-ASSOCIATED LIPODYSTROPHY

The introduction of highly active antiretroviral therapy (HAART) has reduced HIV-related mortality by 50–80%[13]. However, HAART use is associated with the risk of developing acquired lipodystrophy, with a prevalence ranging from 10% to 83% among HIV patients[14]. Long-term treatment may lead to metabolic disturbances such as fat redistribution, dyslipidemia, insulin resistance, lactic acidosis, and bone metabolism changes[13]. Those using zidovudine, didanosine, stavudine, and most protease inhibitors (PIs) are particularly susceptible to these complications[15]. The first cases of this condition were described in 1997 among patients on antiretroviral therapy. HIV-associated lipodystrophy manifests as fat accumulation (lipohypertrophy), fat loss (lipoatrophy), or a combination of both. Lipoatrophy affects the face, buttocks, arms, and legs, while lipohypertrophy involves the trunk and can present as central obesity, breast enlargement, fat accumulation on the neck, or lipomas[16].

Patients with lipodystrophy often struggle with metabolic issues, reduced quality of life, low self-esteem, and difficulties adhering to treatment recommendations. Visible changes in

appearance, such as facial or limb wasting, can cause anxiety and fear of disclosing HIV status[14].

CONGENITAL GENERALIZED LIPODYSTROPHY (CGL)

Congenital generalized lipodystrophy (CGL) is one of the most common types of genetic lipodystrophy. This autosomal recessive disorder is most prevalent among children of consanguineous parents. Affected individuals almost completely lack adipose tissue, leading to prominent skeletal muscle visibility. In childhood, hepatosplenomegaly often develops, and metabolic complications such as diabetes emerge during adolescence[17].
Despite its distinctive phenotype, the disease is often misdiagnosed as malnutrition or an athletic physique. Early detection of CGL could significantly improve patient outcomes [18].

FAMILIAL PARTIAL LIPODYSTROPHY (FPL)

Familial partial lipodystrophy (FPL) is an autosomal dominant condition characterized by fat loss in the upper and lower extremities and the trunk. Many patients, particularly women, experience fat accumulation in the face, neck, perineal region, and abdomen. Typical features also include fat deposits in the dorsocervical region, known as a "buffalo hump," and in supraclavicular and submental areas, giving a "Cushingoid" appearance. Women with FPL may experience masculinization, irregular menstrual cycles, and reproductive problems such as infertility, miscarriages, gestational diabetes, or hypertension. Physicians should be aware of cases of polycystic ovary syndrome (PCOS) secondary to lipodystrophy, particularlyFPLD2,as these forms respond well to treatment[19]. The most common type, FPLD2 (Dunnigan variant), is associated with pathogenic variants in the *LMNA* gene, which is also implicated in dilated cardiomyopathy. These patients are at higher risk of cardiac arrhythmias, such as atrial fibrillation. Early diagnosis is crucial to prevent cardiovascular complications[20]. Currently, seven subtypes and four unclassified variants of FPL have been described, with FPLD2 and FPLD1 being the most common[21].

ACQUIRED GENERALIZED LIPODYSTROPHY (AGL)

Acquired generalized lipodystrophy (AGL), also known as Lawrence syndrome, is a rare disorder that develops later in life[22]. Acquired lipodystrophy is often classified as idiopathic. Although an immunological basis is suspected, biomarkers such as autoantibodies are usually

absent[23]. AGL is characterized by fat loss, which typically begins in childhood or adolescence, with females being three times more likely to develop the condition than males. Children with AGL often exhibit increased appetite due to low plasma leptin levels, accelerated linear growth, and, less commonly, acromegaloid features. Acquired lipodystrophy can also manifest as a paraneoplastic symptom of brain tumors in infants and young children[22].

TREATMENT OF LIPODYSTROPHY

Treatment of lipodystrophy is based on medical nutritional support, physical activity, and the use of medications to regulate blood glucose and lipid levels. A promising development in managing metabolic disturbances associated with lipodystrophy is the use of metreleptin asreplacementtherapy[24]. The goal of lipodystrophy treatment is to improve or prevent long-term metabolic complications and organ damage. Standard approaches include lifestyle modifications, such as a low-fat diet and regular physical activity (if there are no contraindications), as well as medications to lower glucose, lipids, and support cardiovascular health[25].

METRELEPTINTHERAPY

Metreleptin is the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe metabolic disturbances associated with generalized lipodystrophy[26]. Metreleptin improves glucose tolerance, insulin secretion, reduces insulin resistance caused by lipotoxicity, hyperphagia due to leptin deficiency, dyslipidemia, and hepatic steatosis. It also enhances the quality of life. In children treated with metreleptin, improvements in the hypothalamic-pituitary-gonadal axis function have been noted without accelerating puberty[27]. Despite its efficacy, metreleptin requires daily injections, which can be painful for patients due to a lack of subcutaneous fat tissue. Additionally, the therapy is expensive and not universally accessible, underscoring the need for more affordable, widely available, and oral treatment options[28]. The FDA has included a warning about metreleptin use due to the risk of T-cell lymphoma in patients with AGL. AGL is associated with a high risk of lymphoma, which may occur in patients both treated and untreated with metreleptin. This suggests that metreleptin likely is not a direct cause of lymphoma development, though its potential role in cancer progression remains theoretical. Nonetheless, for most patients with AGL and severe metabolic disturbances, the benefits of metreleptin in improving metabolic status outweigh the potential theoretical risks of lymphoma[29].

GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor (GLP-1R) agonists offer an alternative, improving insulin sensitivity, reducing appetite, decreasing obesity, and delaying gastric emptying. However, lipoatrophic diabetes in patients with lipodystrophy differs from type 2 diabetes. Studies in mice with genetically induced lipodystrophy have shown that daily liraglutide administration for two weeks improved hepatomegaly, reduced liver fibrosis markers, and enhanced glycemic control [28]. Ongoing research highlights potential benefits of thiazolidinediones, insulin-like growth factor-1 (IGF-1), leptin, and growth hormone-releasing hormone in treating lipodystrophy. However, none of these approaches have been approved for reversing fat loss or treating severe insulin resistance caused by the condition [30].

SUMMARY

Lipodystrophies constitute a group of rare, heterogeneous disorders that lead to abnormalities in fat distribution and storage, resulting in significant metabolic consequences. This paper presents the classification of lipodystrophies, including both congenital and acquired forms, as well as specific cases associated with HIV infection. These conditions are linked to multiple metabolic complications, such as insulin resistance, diabetes, dyslipidemia, and nonalcoholic fatty liver disease, as well as an increased risk of cardiovascular disorders.

In terms of therapy, the paper outlines current treatment methods, such as the use of metreleptin, which represents the only approved substitution therapy, as well as alternative therapeutic approaches, including glucagon-like peptide-1 receptor (GLP-1R) agonists and thiazolidinediones. Although the treatment of lipodystrophy is challenging, emerging therapies hold promise for improving patients' quality of life and reducing the risk of metabolic complications.

In summary, lipodystrophies are complex diseases requiring a multidisciplinary diagnostic and therapeutic approach. Early diagnosis, appropriate medical care, and tailored treatment can significantly improve patients' prognosis and quality of life.

Author's contribution

Conceptualization, KR ; methodology, EJJ; software, EJJ, KR, JNS, MN; check, MN, MR; formal analysis EJJ, KR; investigation, JNS, MN; resources, EJJ, MR; data curation, KR;

writing– rough preparation MN, MR ; writing-review and editing, EJJ, KR,; visualization, JNS, KR,; supervision, MN, EJJ, JNS ; project administration, MR

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