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Lipodystrophic Syndromes:

when the lack of adipose tissue affects diabetes control

Lipodystrophies comprise a group of rare and heterogeneous diseases characterized by the loss of adipose tissue. They may be generalized, when fat loss affects the entire body, or partial, when fat loss involves only certain body regions, with possible accumulation in others. Other distinct forms of lipodystrophy, perhaps the most widely recognized, include localized lipodystrophies, which are characterized by adipose tissue loss in a very small area of the body and are commonly associated with the use of medications such as insulin; however, these will not be addressed in this article. Lipodystrophies may also be of genetic or acquired origin (1). In Spain, the Thyroid and Metabolic Diseases Unit (UETeM), affiliated with Universidad de Compostela (A Coruña, Spain), serves as the national reference center for the diagnosis and treatment of patients with these conditions. Our research group has estimated a prevalence in Spain of 2.78 cases of lipodystrophy per million inhabitants (0.51 cases per million for generalized lipodystrophies and 2.28 cases per million for partial forms) (2).

Although the full classification is considerably more complex, four main subtypes of lipodystrophy can be distinguished: congenital generalized lipodystrophy or Berardinelli–Seip syndrome (A), familial partial lipodystrophy (B), acquired generalized lipodystrophy or Lawrence syndrome (C), and acquired partial lipodystrophy or Barraquer–Simons syndrome (D). In the figure, blue indicates body regions where adipose tissue loss occurs, whereas red indicates regions of fat accumulation.

To understand the pathophysiology of lipodystrophies, it is helpful to consider the best-known adipose tissue disorder: obesity. In obesity, excess nutrients are initially stored in adipose tissue. However, when the capacity of adipocytes (specialized fat-storing cells) to continue accumulating fat becomes saturated, nutrients begin to deposit in organs where they should not accumulate (ectopic fat deposition), such as the liver or muscle. In lipodystrophies, a similar situation of ectopic fat accumulation occurs; however, in this case it is due to the absence or dysfunction of adipocytes. That is, because there is insufficient functional adipose tissue, the body lacks an appropriate site for nutrient storage, resulting in their deposition in other organs. In acquired generalized lipodystrophy, an autoimmune component is also believed to exist, whereby the immune system chronically attacks and destroys adipose tissue. The adaptations resulting from adipose tissue loss, the inability to store excess nutrients, their ectopic deposition, and abnormal adipocytokine production (molecules produced by fat tissue that help regulate metabolism) impair insulin signaling, leading to insulin resistance and various metabolic signs, most notably diabetes. These alterations are often accompanied by other complications, such as hypertriglyceridemia, fatty liver disease, and reproductive abnormalities. Collectively, these factors may lead to damage of vital organs, cardiovascular disease, and increased mortality in these patients (3).

Considering these distinctive mechanisms, diabetes associated with lipodystrophy is included in the most recent American Dia- »

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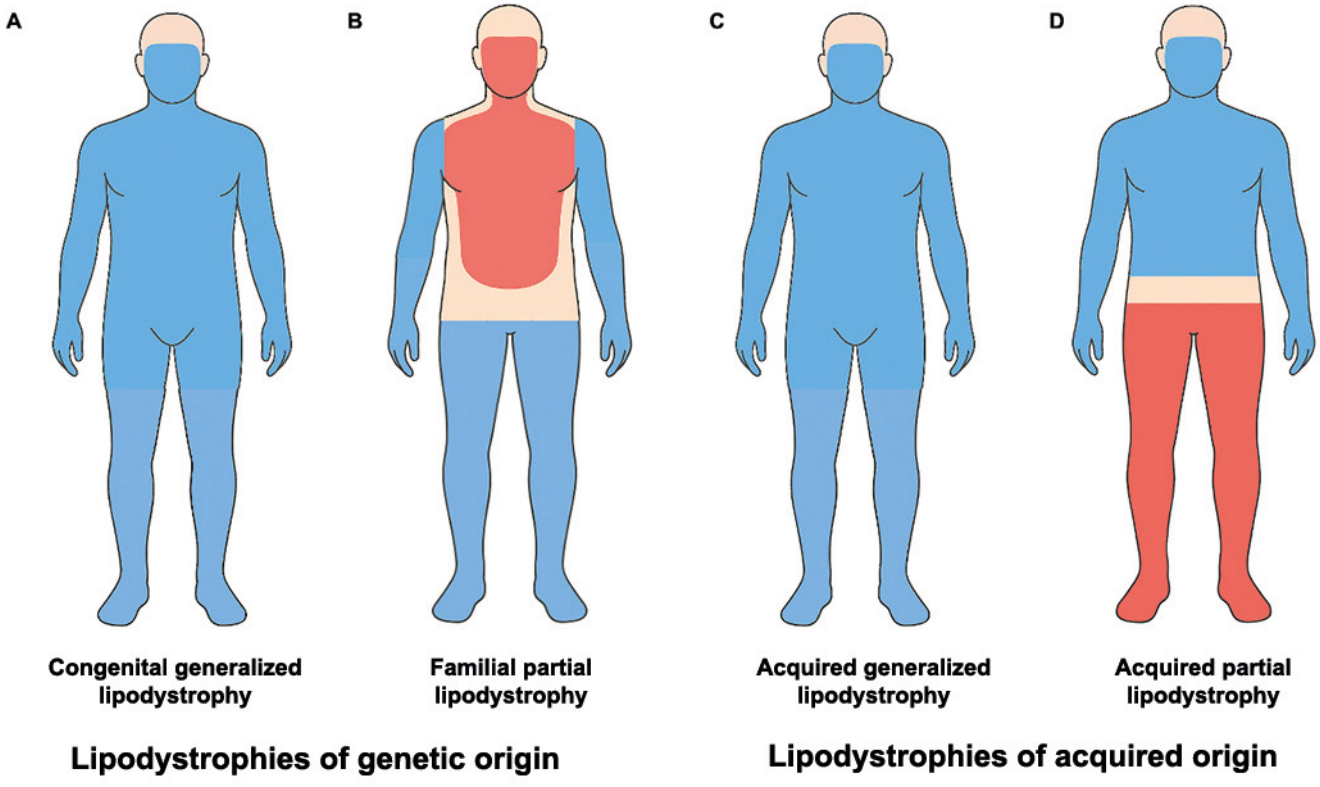

FIGURE. Main types of lipodystrophy. Author's own elaboration.

TO DATE, THERE IS NO CURE FOR LIPODYSTROPHIES. HOWEVER, MORBIDITY AND MORTALITY ASSOCIATED WITH THESE CONDITIONS IMPROVE WITH EARLY INTERVENTION; THEREFORE, TREATMENT SHOULD BE PRIMARILY DIRECTED AT CONTROLLING ASSOCIATED METABOLIC COMORBIDITIES, SUCH AS DIABETES

betes Association (ADA) classifications as another specific type of diabetes attributable to underlying syndromes or diseases (in this case, lipodystrophy). For the reasons outlined above, type 1 diabetes mellitus has also been described in some patients, particularly those with acquired generalized lipodystrophy, in whom autoimmune destruction of pancreatic beta cells leads to insulin deficiency. This may result in a mixed phenotype, with features of type 1 diabetes mellitus and severe insulin resistance, often translating into very high insulin requirements (4). Overall, according to a recent study conducted by our group, the prevalence of diabetes among patients with any lipodystrophy subtype is 43.5%, with a mean time to diagnosis of approximately 30 years (12 years in patients with generalized lipodystrophy and 35 years in those with partial lipodystrophy) (2).

In 2016, the Multisociety Clinical Practice Guidelines for the diagnosis and management of lipodystrophic syndromes summarized the criteria and screening frequency for the main associated comorbidities. Accordingly, all patients with lipodystrophy should undergo a comprehensive metabolic evaluation to detect diabetes, hypertriglyceridemia, and nonalcoholic fatty liver disease, as well as cardiovascular and reproductive dysfunction. Diabetes screening should be performed annually following ADA recommendations (fasting plasma glucose, oral glucose tolerance test, or glycated hemoglobin). Autoantibody testing may help clarify the diagnosis of type 1 diabetes mellitus, particularly in patients with acquired generalized lipodystrophy (5).

Currently, there is no cure for lipodystrophies. Nevertheless, morbidity and mortality associated with these diseases improve with early intervention; therefore, treatment should be primarily focused on controlling associated metabolic comorbidities, such as diabetes. In this context, diet and physical exercise are integral components of the treatment plan. Given the physical appearance of individuals with lipodystrophy (especially in generalized forms), they may be mistakenly diagnosed with malnutrition. Despite low body weight in many cases, increasing food intake or administering nutritional supplements is not appropriate, as fat loss is generally not reversible and may instead worsen diabetes (3, 5).

Regarding glucose-lowering drugs, as in the general diabetic population, metformin is usually the first-line therapy, as it improves insulin sensitivity and is considered safe. In some cases of partial lipodystrophy, other medications such as thiazolidinediones may be used to enhance the function of residual subcutaneous fat; however, their use requires caution because of potential adverse effects, particularly in patients with certain cardiac conditions (eg, cardiomyopathy). More recent agents, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), may improve insulin resistance, reduce ectopic fat accumulation (eg, in the liver), and consequently improve fatty liver disease. However, experience with these agents in lipodystrophy remains limited, and in patients at high risk of pancreatitis or with very high triglyceride levels, GLP-1 RAs should be used with extreme caution. Experience with tirzepatide in patients with lipodystrophy is even more limited, although recent reports suggest it may improve insulin sensitivity, lower triglyceride levels, and reduce ectopic fat accumulation. Insulin therapy is frequently required, especially in severe cases of generalized lipodystrophy or when adequate glycemic control cannot be achieved with the aforementioned agents. In addition, when fat loss is generalized, intramuscular insulin administration may be necessary, as the absence of subcutaneous fat can impair normal insulin absorption (3, 5).

In cases in which metabolic signs (diabetes, hypertriglyceridemia) are not adequately controlled despite conventional treatment, therapy with recombinant human leptin (metreleptin) is indicated, particularly in generalized lipodystrophies, but also in selected cases of partial forms. Metreleptin helps regulate appetite, improve insulin sensitivity and glycemic control, reduce triglyceride levels, and normalize certain hepatic parameters, often allowing a reduction in the need for high doses of insulin or other medications. Nevertheless, its extremely high cost and restricted availability remain major barriers to widespread use (3, 5, 6).

Despite advances in the understanding and treatment of lipodystrophies, significant gaps persist in the scientific evidence regarding optimal diabetes management in these patients. Most current recommendations are based on

» observational studies, case series, and extrapolation from the general population, given the limited availability of clinical trials specifically designed for this population. Moreover, access to specific therapies such as metreleptin remains limited in many settings. Increasing awareness of these diseases among health care professionals and the general population, as well as the development of personalized therapeutic strategies, should be considered a priority. D

CONCLUSIONS

1. Lipodystrophies are a group of rare and heterogeneous diseases characterized by the loss of adipose tissue.
2. Loss of adipose tissue and its ectopic accumulation in organs where it should not be present lead to various metabolic manifestations, including diabetes.
3. According to the most recent ADA considerations, this form of diabetes is classified as "other specific types of diabetes attributable to underlying syndromes or diseases." Type 1 diabetes mellitus has also been described in some patients, particularly those with acquired generalized lipodystrophy.
4. All patients with lipodystrophy should undergo annual diabetes screening in accordance with ADA recommendations.
5. Diabetes management is based on appropriate diet and physical activity, together with pharmacologic therapy such as metformin (first-line), thiazolidinediones in selected cases of partial lipodystrophy, and consideration of SGLT2 inhibitors, GLP-1 receptor agonists, and tirzepatide (limited evidence). Insulin therapy is often required, and in cases of poor control despite prior management, metreleptin may be necessary.

REFERENCES:

1. Asociación Internacional de Familiares y Afectados de Lipodistrofias (AELIP). Material formativo en lipodistrofias [Internet]. AELIP; [citado 2025 jul 27]. Disponible en: https://aelip.es/material-formativo-en-lipodistrofias/
2. Fernández-Pombo A, Sánchez-Iglesias S, Castro-Pais AI, Ginzo-Villamayor MJ, Cobelo-Gómez S, Prado-Moraña T, Díaz-López EJ, Casanueva FF, Loidi L, Araújo-Vilar D. Natural history and comorbidities of generalised and partial lipodystrophy syndromes in Spain. Front Endocrinol (Lausanne). 2023 Nov 16;14:1250203. doi: 10.3389/fendo.2023.1250203.
3. Fernández Pombo A. Natural course and comorbidities of lipodystrophy syndromes in Spain [tesis doctoral]. Santiago de Compostela: Universidade de Santiago de Compostela; 2022.
4. Fernandez-Pombo A, Prado-Moraña T, Diaz-Lopez EJ, Sanchez-Iglesias S, Castro AI, Cobelo-Gomez S, Araujo-Vilar D. Clinical Characterisation and Comorbidities of Acquired Generalised Lipodystrophy: A 14-Year Follow-Up Study. J Clin Med. 2023 Nov 27;12(23):7344. doi: 10.3390/jcm12237344.
5. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother KI, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. J Clin Endocrinol Metab. 2016 Dec;101(12):4500-4511. doi: 10.1210/jc.2016-2466.
6. Araújo-Vilar D, Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest. 2019 Jan;42(1):61-73. doi: 10.1007/s40618-018-0887-z.