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Editorial

Lipodystrophy: Time for a global registry and randomized clinical trials to assess efficacy, safety and cost-effectiveness of established and novel medications

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ABSTRACT

1. Introduction

Lipodystrophy is a group of clinically heterogeneous inherited or acquired disorders characterized by complete (generalized lipodystrophy) or partial (partial lipodystrophy) absence of subcutaneous fat (lipoatrophy) that may or may not occur simultaneously with the pathological accumulation of adipose tissue (lipohypertrophy) in other regions of the body [1]. Congenital lipodystrophy is extremely rare, whereas acquired lipodystrophy (especially those cases associated with the human immunodeficiency virus [HIV] infection and the related highly active antiretroviral therapy [HAART]) are much more common [2]. Approximately 1000 cases of congenital (familial or sporadic) lipodystrophy have been reported in the literature [1,3]. Based on the assumption that only one fourth of the patients may be reported, the prevalence of congenital lipodystrophy may be estimated to be approximately less than one in a million [3].

Familial partial lipodystrophy (FPLD) is a group of usually monogenic, autosomal dominant disorders characterized by loss of fat affecting the limbs, buttocks and hips. There is no universally accepted clinical signs and no objective criteria to establish the diagnosis. We have recently summarized the clinical manifestations of lipodystrophy elsewhere [4,5]. Regionally excessive fat accumulation is frequent, but varies by subtype and may result in a Cushingoid appearance in some cases. Muscular hypertrophy is also common. Fat distribution is typically normal in early childhood, with loss of fat occurring around puberty [6]. Patients with FPLD exhibit severe insulin resistance (IR) and IR-related co-morbidities,

Abbreviations: BBB, blood-brain barrier; DM, diabetes mellitus; FPLD, familial partial lipodystrophy; GLP, glucagon-like peptide; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IR, insulin resistance; LMN, lamine; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic fatty liver disease; PARL, presenilin associated rhomboid-like protein; PINK, PTEN-induced kinase; PPAR, peroxisome proliferator activated receptor; PTEN, phosphatase and tensin homolog; RCT, randomized control trial; SGLT, sodium-dependent glucose cotransporter; TNF, tumor necrosis factor; TuLip, Turkish Lipodystrophy Study Group.

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including diabetes mellitus (DM), hypertriglyceridemia and low high-density lipoprotein cholesterol, and nonalcoholic fatty liver disease (NAFLD). Typically, the severity of these metabolic derangements is associated with the degree of adipose tissue loss [7].

2. What is New in "Metabolism"

Two new articles are being published in this issue of "*Metabolism*", one on adipocyte differentiation [8] and another one on a case series of patients with FPLD [9].

2.1. A Novel Pathway in Adipocyte Differentiation

Shiau et al. [8] provides evidence on the role of presenilin associated rhomboid-like protein (PARL) – phosphatase and tensin homolog (PTEN)-induced kinase (PINK)1 – Parkin pathway in adipocyte differentiation. Based on their results from 3T3-L1 pre-adipocytes and male C57BL/6 mice, the authors concluded that when pre-adipocytes are switched to differentiation, PARL cleaves the full-length-PINK1, thus generating fragments of PINK1 (s-PINK1); at this early stage of differentiation (day 0–4), mitochondrial mass is increased to cover the increased energy demands of cellular remodeling. At the second stage (day 5–6), s-PINK1 accumulates in mitochondria and translocates into cytoplasm to mediate Parkin degradation; at this stage, mitochondria are fragmented, thus their mass is decreasing. At the late stage (day 7–8), excess mitochondria have been eliminated, so as to maintain the lower energy demands of the mature adipocytes [8].

To-date, the PARL-PINK1-Parkin system has been associated with neurogenerative diseases, including the Parkinson's disease. In this regard, PINK1 is released by healthy mitochondria to trigger neuron differentiation [10]. Furthermore, the system has been linked to IR, since PINK1 has been shown to alleviate IR in hepatocytes [11]. Therefore, the article by Shiau et al. [8] highlights the PARL-PINK1-Parkin system as a potential link among adipogenesis, IR and neurogenerative diseases. It would be of importance to show whether derangements of this system may result in failure of pre-adipocytes to differentiate to mature adipocytes, thus being associated with some forms of lipodystrophy. If this is validated, the PARL-PINK1-Parkin system may be a novel therapeutic target for lipodystrophy in the future.

2.2. Metabolic Abnormalities in Patients with FPLD

Akinci et al. described the clinical presentation and metabolic derangements in patients with FPLD in Turkey [9]. Based on a registry, named Turkish Lipodystrophy Study Group (TuLip), data from 56 patients (28-53 years old; 36 women) with FPLD, derived from 18 independent Turkish families were collected prospectively in the context of a multicentre effort between 2006 and 2016 [9].

FPLD was clinically diagnosed based on fat loss in selected areas and the diagnosis was supported by mapping fat distribution using whole body magnetic resonance imaging. Variants of genes associated with FPLD were identified in 12 families. More specifically, variants of the *lamine (LMN) A/C (LMNA)* gene were identified in 38 members of 9 families and of *peroxisome proliferator activated receptor (PPAR)-γ* gene in 9 members of 3 families [9]. A variant of *LMNB2* gene also identified in 1 family, but it was not possibly related to lipodystrophy. No variant in the sequenced genes was identified in 5 families, suggesting the existence of yet unknown genes associated with FPLD [9].

Interestingly, fat loss, documented by whole body magnetic resonance imaging, was less prominent and leptin levels higher in patients with variants of the *PPAR-γ* gene than those with variants of the *LMNA* gene [9]. Derangements associated with IR were observed in all patients. DM or prediabetes were evident in 83% of patients with variants of *LMNA* gene, 78% with variants of *PPAR-γ* gene and 89% with no detected variant. Hypertriglyceridemia was evident in 94%, 100% and 100% of patients, respectively, and low high-density lipoprotein-cholesterol in 85%, 78% and 89%, respectively. NAFLD was evident in 97%, 89% and 100% of patients, respectively. Interestingly, polycystic ovary syndrome was also evident in high rates in women of reproductive age [9]. Despite the relatively young age of the presented patients, end-organ complications, included coronary artery disease, retinopathy and nephropathy were also observed, with nephropathy being relatively more common (53%, 56% and 56% of patients, respectively) [9].

This case series is one of the largest published cohorts of FPLD patients. This study not only confirms the phenotypic heterogeneity of patients with FPLD, but also highlights IR as a central aspect of the disease and links specific gene variants with the disease. Furthermore, it points out that other variants or mutations of yet unrecognized genes are responsible for FPLD.

TuLip is one of the largest databases focused on lipodystrophy, either congenital or acquired. Apart from the current publication on FPLD [9], at least another two similar publications on patients with acquired partial lipodystrophy [12] and congenital generalized lipodystrophy [13] have been based on TuLip database. Due to the rarity of lipodystrophy, especially its congenital forms, TuLip and other similar databases are considered of importance, not only because they provide valuable observations on the clinical presentation and the natural history of a rare disease, but also because their formation may provide the basis for performing well-designed clinical trials in the future, which are in turn expected to alter future treatment options for the disease.

3. Lipodystrophy and Leptin

Leptin is the first described adipocyte-secreted hormone or adipokine (1994), which radically changed our understanding of the physiology and pathophysiology of adipose tissue, providing thus new opportunities for the treatment of the adipose tissue-related diseases [14]. Leptin deficiency is closely associated with lipodystrophy. Some patients have very low or practically null leptin levels (especially those with generalized lipodystrophy), but most patients with partial lipodystrophy have moderate hypoleptinemia (fasting serum leptin of 3-5 ng/ml), varying not only according to different