Skeletal alterations in lipodystrophy

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ABSTRACT

Lipodystrophic syndromes are a heterogeneous group of congenital or acquired pathological clinical conditions that share, as a common feature, a generalized or partial lack of adipose tissue.

Recent data in the literature suggest a correlation between adipose and skeletal tissues. Indeed, since both adipocytes and osteoblasts derive from a common mesenchymal cell, it has been hypothesized that alteration of one of the above two tissue types might involve cross-alteration in the other. This brief review analyzes data in the literature illustrating the potential presence of skeletal alterations in patients affected by lipodystrophic syndromes.

KEYWORDS

Lipodystrophy, skeleton, muscle, adipose tissue, leptin.

Introduction

Lipodystrophic syndromes are a heterogeneous group of congenital or acquired pathological clinical conditions that share, as a common feature, a generalized or partial lack of adipose tissue. With regard to their etiology, lipodystrophies are divided into genetic or acquired forms and, on the basis of the degree of loss of adipose tissue, into generalized or partial forms, as illustrated in Table I [1-3]. The prevalence of lipodystrophic syndromes is estimated at around 3.0 cases per million individuals (0.23 cases per million for the generalized forms and 2.84 cases for the partial ones) [1]. Congenital forms include autosomal recessive and dominant inherited subtypes, while the acquired ones usually have an autoimmune cause (with the exception of those caused by antiretroviral therapy, in HIV-positive patients, or localized forms caused by subcutaneous injection of insulin or other drugs) [2,4]. In lipodystrophic subjects, the expandability of adipose tissue, and thus its ability to accumulate an energy surplus, is exceeded even with minimal caloric intake; this leads to accumulation of lipids in ectopic sites such as the liver, muscle, kidney, and pancreas, and, in contrast, a chronic reduction of circulating levels of the hormone leptin. Low levels of leptin stimulate the sense of hunger, thus driving a vicious circle that leads to progressive ectopic accumulation of fat [5]. At peripheral level, the action that favors the use of glucose and fatty acids by skeletal muscle is lost, resulting in lipotoxicity. Furthermore, the ectopic accu-

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Table I Classification of lipodystrophy (modified by Reff. 2,4,5).

GENERALIZED	CONGENIAL GENERALIZED (CGL) (Berardinelli-Seip)	ACQUIRED GENERALIZED (AGL) (Lawrence-Seip)
Lack of adipose tissue	Generally apparent at birth or in early childhood	loss in childhood or adolescence Occurs over weeks to years
Metabolic abnormalities	Usually appear in childhood Generally severe	
PARTIAL	**FAMILIAL PARTIAL (FPL) (Dunnigan, Köbberling)**	**ACQUIRED PARTIAL (APL) (Barraquer-Simons)**
Loss of adipose tissue	Around puberty Variable pattern of fat loss, usually lower body	In child ood or adolescence Occurs over months to years Usually upper body fat loss
Metabolic abnormalities	In adulthood Vary in severity	Vary in severity

mulation of intramuscular and hepatic fat contributes to the development of insulin resistance. Therefore, lipodystrophic syndromes are characterized by multiple hormonal and metabolic alterations, such as insulin resistance with early onset of diabetes mellitus, severe hypertriglyceridemia, non-alcoholic fatty liver disease, and a picture similar to that of polycystic ovary syndrome (PCOS) [1,6]. In some patients, these complications can lead to diabetic nephropathy and retinopathy, acute pancreatitis due to severe hypertriglyceridemia and chylomicronemia, liver cirrhosis, and early-onset cardiovascular disease. Congenital lipodystrophies are very rare and can be apparent at birth, in the case of classic congenital generalized lipodystrophy, the progeroid neonatal forms, and Keppen-Lubinski syndrome [7], while in other forms, such as partial lipodystrophy forms or mandibulo-acral dysplasia, the loss of adipose tissue can manifest itself later in life [1,8,9]. As indicated, the loss of adipose tissue can be generalized, with almost total loss of adipose tissue in the body, or affect only some areas of the body. The extent of the metabolic defect is generally related to the extent of the lack of adipose tissue [10].

Lipodystrophy diagnosis

The presence of lipodystrophy can be suspected in subjects with partial or generalized absence of adipose tissue and validated by anthropometric measurement techniques such as skin plicometry and/or instrumental examinations such as dual photonic beam densitometry and total-body magnetic resonance imaging [11]. The presence of specific physical characteristics, anamnestic data, and the presence of comorbidities can increase the suspicion of a diagnosis of lipodystrophy (Tab. I). It is important to remember that leptin levels are not critical for a diagnosis and, in the presence of a clear clinical suspicion, related genetic tests may be required: genotyping may include sequencing limited to a gene or a group of candidate genes. Finally, differential diagnosis includes conditions presenting with severe weight loss (malnutrition, anorexia nervosa, uncontrolled diabetes mellitus, adrenocortical insufficiency, neoplastic cachexia, HIV-associated atrophy, chronic infections). Furthermore, generalized lipodystrophies can be confused with acromegaly, while partial lipodystrophies might need a differential diagnosis with Cushing's syndrome or other forms of central obesity (Tab. I), such as those seen in young women with PCOS.

Pleiotropic effects of lipodystrophy: skeletal alterations

As mentioned, lipodystrophy is caused by several different mutations which impair adipose tissue development, quantity and function [12,13]. Since adipocytes derive from a mesenchymal progenitor cell [14-16] shared with other mesenchymal-derived cells, such as chondrocytes, osteoblasts, and muscle cells, it might be hypothesized that other mesenchymal-derived tissues could be compromised as a consequence of adipose tissue damage [17]. Considering that a correlation between fat and skeletal tissue exists, several studies have also suggested that an increase in abdominal fat tissue is often related to decreased skeletal density [14-16], likely due to decreased osteogenesis and bone formation, and increased bone resorption as a result of osteoclast activity [14]. Indeed, some data have started to be collected on skeletal alterations in subjects affected by lipodystrophic syndromes.

Since the first description, by Bandeira *et al*., of altered bone density [18] in subjects affected by Berardinelli-Seip syndrome, more recent reports have shown that children affected by this syndrome grow rapidly and also have advanced bone age [19]. Moreover, several mutations have been described in different genes which might also lead to alterations in several different tissues, including the skeleton. In particular, mutations in the lamin A/C gene (*LMNA*) have been linked to a broad spectrum of tissue-specific disorders, named laminopathies, which include familial partial lipodystrophy type 2, cardiomyopathies, muscular dystrophies, neuropathies, and overlapping phenotypes [8,13]. Interestingly, laminopathies can also lead to diseases with features of accelerated aging, named progerias (from the Greek words πρό, "premature" and γέρων, "old"). These conditions, associated with *LMNA* mutations, are recognized in different progeroid syndromes, both typical (Hutchinson-Gilford progeria syndrome, type A mandibulo-acral dysplasia, restrictive dermopathy) and atypical forms, including Werner syndrome [9,12]. The possible involvement of skeletal alterations in these conditions might be due, among other reasons, to the fact that lamin A/C is an intermediate protein from the nuclear lamina, encoded by the *LMNA* gene, that plays a key role in facilitating the mechano-signaling of cytoskeletal from cell membrane into the nucleus. Indeed, this intracellular transduction system plays a crucial role in guaranteeing the correct functioning of other tasks also linked to lamin A/C, such as structural support of the nucleus and regulation of gene expression. Thus, within skeletal regulation, lamin A/C plays a pivotal role in the migration and differentiation of mesenchymal stem cells, progenitors of osteoblasts, and may therefore potentially be involved in altered bone homeostasis [8]. In fact, bone formation is a complex process regulated by hormonal, but also chemical and mechanical signals, deriving from the surrounding extracellular matrix [14].

Indeed, the increased bone mass often described in Berardinelli-Seip congenital generalized lipodystrophy (CGL) strongly suggests that alteration of fat mass in these subjects might indeed regulate skeletal homeostasis, leading to bone changes. Interestingly, a recent report [20] on bone imaging findings in patients affected by lipodystrophy demonstrated a peculiar skeletal alteration characterized by osteosclerosis, osteolytic lesions in the axial skeleton, and pseudo-osteopoikilosis. In particular, among the different images, the authors evaluated the radiographic images of a patient with CGL1 in early childhood, hypothesizing that the first lesion appeared as cortical and trabecular bone sclerosis. Also, later in life, during adolescence, the young patient showed osteolytic lesions which appeared and propagated mainly in the long bones, suggesting that these lesions might be an early sign of lipodystrophy. The presence and progression of bone alterations in CGL has also been described in another interesting study that reviewed 24 cases of genetic

CGL; on the basis of all these reports, frequent and peculiar imaging features of skeletal abnormalities, described in generalized lipodystrophic syndromes, are osteosclerosis [20], lytic lesions, and/or pseudo-osteopoikilosis, often associated with transformation of the bone marrow as also described in a recent review of the literature [19].

Moreover, individuals affected by progeroid syndromes, either typical or atypical, show significant skeletal alterations associated with adipose tissue loss and other clinical and metabolic alterations [9,12,21]. An experimental animal model, i.e., fat-free (FF) mice mimicking Berardinelli-Seip patients, showed potent osteoblastic activity, leading to increased trabecular and cortical bone volume. Moreover, FF mice, like Berardinelli-Seip patients, are diabetic and normalization of glucose tolerance and decreasing the circulating insulin failed to correct the skeletal phenotype. Even more importantly, in terms of providing insight into the mechanisms of action linked to the altered bone features, the skeletal phenotype of these FF mice was completely rescued by transplantation of adipocyte precursors or white or brown fat depots, indicating that adipocyte-derived products regulate bone mass [20]. In conclusion, current evidence strongly indicates a correlation between altered fat tissue function and skeletal homeostasis in subjects affected by lipodystrophic syndromes. However, more studies are needed to fully characterize the molecular and cellular mechanisms underlying these alterations.

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