Diseases of adipose tissue: genetic and acquired lipodystrophies

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Abstract

Human lipodystrophies represent a group of diseases characterized by altered body fat amount and/or repartition and major metabolic alterations with insulin resistance leading to diabetic complications and increased cardiovascular and hepatic risk. Genetic forms of lipodystrophies are rare. Congenital generalized lipodystrophy or Berardinelli–Seip syndrome, autosomal recessive, is characterized by a complete early lipodystrophy and severe insulin resistance and results, in most cases, from mutations either in the seipin gene of unknown function or AGPAT2 encoding an enzyme involved in triacylglycerol synthesis. The Dunnigan syndrome (FPLD2, familial partial lipodystrophy of the Dunnigan type) is due to mutations in LMNA encoding the lamin A/C, belonging to the complex group of laminopathies that could comprise muscular and cardiac dystrophies, neuropathies and syndromes of premature aging. Some FPLDs are linked to loss-of-function mutations in the PPAR-γ gene (peroxisome-proliferator-activated receptor γ; FPLD3) with severe metabolic alterations but a less severe lipodystrophy compared with FPLD2. The metabolic syndrome, acquired, represents the most common form of lipodystrophy. HIV-infected patients often present lipodystrophies, mainly related to side effects of antiretroviral drugs together with insulin resistance and metabolic alterations. Such syndromes help to understand the mechanisms involved in insulin resistance resulting from altered fat repartition and could benefit from insulin-sensitizing effects of lifestyle modifications or of specific medications.

Introduction

Lipodystrophies represent a heterogeneous group of diseases characterized by generalized or partial alterations in body fat development or distribution and insulin resistance [1]. The main forms of lipodystrophies are classified according to their origin, either genetic or acquired, and to the clinical pattern of the lipoatrophy, either generalized or partial. Such an association of clinical and biological alterations was reported not only in human diseases but also in different models of transgenic animals and pointed to an important role for adipose tissue in glucose and lipid metabolism.

The pathophysiology of most human lipodystrophies is still unknown. However, murine models of lipoatrophic diabetes revealed that primary genetic alterations in fat development resulted in diabetes and dyslipidaemia and that diabetes could be reversed by fat transplantation in one model [2]. Leptin and adiponectin deficiencies, due to the absence of adipose tissue, are important determinants of the metabolic abnormalities in the mouse models. These pathophysiological mechanisms help to understand why these clinical and biological features are associated in most cases in the syndromes of lipodystrophy, whatever their origin [2].

Genetic forms of lipodystrophy

BSCL (Berardinelli–Seip congenital lipodystrophy)

BSCL is characterized by generalized lipoatrophy present at birth or occurring in early infancy. Lipoatrophy is associated with signs of insulin resistance: muscular hypertrophy, skin lesions of acanthosis nigricans, signs of hyperandrogenism and hepatomegaly. The patients show insulin resistance early in life, then hypertriglyceridaemia and altered glucose tolerance evolving towards diabetes after puberty.

This syndrome is transmitted according to a recessive pattern. In the typical BSCL, mutations in two genes are responsible for most cases [3]. The first gene to be identified, BSCL2 located on chromosome 11q13 and encoding seipin, is expressed in most human tissues with a higher level of expression in testes and in tissues of neuronal origin [4]. To date, 21 different mutations have been identified among 116 patients, generally leading to the synthesis of a null protein.

Interestingly, two heterozygous mutations in the seipin gene, N88S and S90L, have been recently reported to be responsible for dominant motor neuropathies: distal hereditary motor neuropathy type V and Silver spastic paraplegia.
syndrome [5]. It has been proposed that these mutations could modify an N-glycosylation site resulting in altered protein processing and the formation of aggresomes with a deleterious effect on neuronal cells.

The second gene found to be mutated in BSCL, located in 9q34, is AGPAT2 encoding the enzyme 1-acylglycerol-3-phosphate-acyl transferase 2 responsible for the synthesis of phosphatidic acid from lysophosphatidic acid in the pathway of TG (triaclyglycerol) synthesis [6]. To date, 30 different mutations have been recorded among 96 patients [3]. Lipatrophy could result from a decreased capacity of adipocytes to synthesize TG.

At the clinical level, the patients mutated on BSCL1 and BSCL2 exhibit very similar phenotypes but the disease is generally more severe and associated with mental retardation in patients mutated on the seipin gene [7].

**FPLD2 (familial partial lipodystrophy of the Dunnigan type)**

FPLD2, dominantly inherited, is a rare disease characterized by the disappearance, after puberty, of subcutaneous peripheral adipose tissue with fat accumulation in the neck and face and other signs of insulin resistance. Metabolic alterations associated with FPLD are responsible for the severity of the disease with insulin resistance, glucose intolerance or diabetes, dyslipidaemia with marked hypertriglyceridaemia that can lead to acute pancreatitis. Although this disease affects males and females, both clinical traits and metabolic alterations associated with FPLD are responsible for the severity of the disease with widespread phenotypic features resembling insulin resistance without clinical lipodystrophy [21]. Our study suggests that primary alterations in insulin signalling could also result from LMNA mutations.

Close to FLPD, another form of familial lipodystrophy has a slightly different phenotype, difficult to differentiate from the metabolic syndrome, the Köbberling familial partial lipodystrophy or FPLD1. Its genetic origin is unknown [1].

**Other laminopathies with premature aging and lipodystrophy**

Different patients with LMNA mutations associating lipatrophy together with insulin resistance and signs of premature aging have been described in [22,23].

The premature aging syndrome MAD (mandibuloacral dysplasia), associating osteodysplasia with micrognatia, lipodystrophy and scleroderma-like skin lesions [1,24] could also be linked to mutations in either LMNA or ZMPSTE24, encoding a zinc metalloprotease involved in lamin A maturation.

Hutchinson–Gilford progeria syndrome is a rare genetic disease with widespread phenotypic features resembling premature aging. The characteristic features include short stature, bone pathology together with lipatrophy. Features of premature atherosclerosis leading to death are observed. A heterozygous de novo single base substitution G608G within exon 11 of LMNA was shown to be responsible in the activation of a cryptic splice site resulting in the production of the truncated lamin A protein with an in-frame deletion of 50 amino acids near the C-terminus [25,26]. This deletion impairs the normal processing of prelamin A to lamin A.
by ZMPSTE24. It has been proposed that the accumulation of the abnormally processed and truncated lamin (called progerin) leads to the disruption of the lamin-linked functions [14].

**Metabolic syndrome due to PPAR-γ (peroxisome-proliferator-activated receptor γ) mutations**

Otherwise, in a few patients, heterozygous mutations in PPAR-γ result in a phenotype of FPLD (FPLD3) close to the ‘metabolic syndrome’ with lipodystrophy affecting limbs and buttocks but sparing abdominal subcutaneous fat, severe insulin resistance, diabetes, dyslipidaemia with high TGs and decreased HDL (high-density lipoprotein) and severe hypertension. Hepatic steatosis and ovary polycystic syndrome are often present [27].

Four heterozygous mutations have been reported: V290M, F360L, R397C and P467L, according to the PPAR-γ1 sequence [27–29]. Two of the PPAR-γ mutations were shown to act through a dominant-negative mechanism and/or to decrease PPAR-γ transcriptional activity. The lipodystrophic phenotype is less severe than in LMNA-mutated patients but the metabolic alterations are more severe pointing to a role for PPAR-γ not only in adipose tissue but also in other tissues.

In addition to diet interventions and classical drugs required for the treatment of diabetes and dyslipidaemia, therapeutic options can use insulin sensitizers (metformin and thiazolidinediones). Leptin was shown to markedly improve metabolic alterations in patients with low leptin levels [30].

**Acquired forms of lipodystrophy**

**Metabolic syndrome**

Metabolic syndrome – also called syndrome X, insulin resistance syndrome, or dysmetabolic syndrome – was defined, according to the World Health Organization [31], by the presence of:

(a) impaired glucose regulation or insulin resistance;
(b) at least two of the following criteria: TG >1.7 mmol/l, HDL <0.9 mmol/l for men or <1.0 mmol/l for women, SBP/DBP >140/90 mmHg (where SBP stands for systolic blood pressure and DBP for diastolic blood pressure), body mass index (BMI) >30 kg/m² or waist-to-hip ratio (WHR) >0.9 for men and 0.85 for women, urinary albumin/creatinine ratio >30 mg/g.

Recently, a new International Diabetes Federation (IDF) definition has been proposed. The metabolic syndrome is defined by central obesity (waist circumference >94 cm for Europid men and >80 cm for Europid women, with ethnicity-specific values for other groups) plus any two of the following four factors: raised TG >1.7 mmol/l (or specific treatment), reduced HDL cholesterol <1 mmol/l in males and <1.3 mmol/l in females (or specific treatment), increased blood pressure (SBP/DBP >130/85 mmHg) (or specific treatment), raised fasting plasma glucose >5.6 mmol/l or previously diagnosed Type II diabetes.

In France, the prevalence of metabolic syndrome in the population is approx. 9 and 6% in adult men and women respectively, while in the U.S.A. it is approx. 24% of adults [32].

This syndrome is also associated with increased small dense LDL (low-density lipoprotein) particles, increased uric acid, and plasminogen activator inhibitor-1 levels together with insulin resistance, which appears to play a central role [33]. The accumulation of fat in the abdomen, at the visceral level, results in visceral obesity. The major risks concern the cardiovascular system, with the development of atherosclerosis and the occurrence of cardiovascular complications and the liver, with the occurrence of NASH (non-alcoholic steato-hepatitis) and the possible evolution towards cirrhosis.

**HIV-related lipodystrophy linked to ART (antiretroviral therapy)**

HAART (highly active ART) with NRTIs and NRTIs (nucleoside analogue inhibitors of viral reverse transcriptase) allowed a major reduction in the severity and morbidity of HIV infection; however, it was associated with the occurrence of secondary effects collectively termed ‘HAART-related lipodystrophy’.

This lipodystrophic syndrome is frequently observed in HIV-infected patients (~50%) and often but not always associates peripheral lipodystrophy, central hypertrophy and metabolic disorders (dyslipidaemia, impaired glucose tolerance and diabetes) [34]. In addition to factors related to the infection and to the patient, the treatment plays a major role in the occurrence of these alterations.

Clinical results suggest that NRTI therapy is mainly responsible for peripheral lipatrophy while treatment with PIs increases the severity of lipodystrophy and favours central hypertrophy and metabolic disorders [35]. To better approach the pathophysiology of the drug effects, *in vitro* adipocyte cell models were used. We observed that thymidine analogues, d4T and ZDV, contrary to other NRTIs, can alter mitochondrial functions [36]. Some PIs but not all were capable of strongly affecting adipocyte differentiation possibly by targeting the step of the adipogenic differentiation factor SREBP-1. This could result from an altered structure of the nuclear lamina network due to impaired maturation of the prelamin A to lamin A [37,38] that could contribute to a phenotype of premature aging in these patients. Thymidine analogues did not impair adipocyte differentiation but altered adipocyte lipid content [36]. PIs, contrary to NRTIs, induced insulin resistance. Finally, some PIs and thymidine analogues markedly altered adipokine expression and secretion: while IL-6 (interleukin-6) and TNFα (tumour necrosis factor α) were increased by the drugs, adiponectin was decreased. The altered secretion of IL-6 and TNFα was parallel to the extent of drug-induced apoptosis [39]. Thus, *in vitro*, NRTIs and PIs could alter different adipocyte functions and could act in synergy to induce lipid loss and apoptosis, ultimately leading to fat loss.
In vivo studies revealed that NRTIs could play an important role in lipodystrophy [35] not only by decreasing mitochondrial DNA but also by other mechanisms. Lipotoxic adipose tissue from patients presented major histological alterations with decreased adipocyte size, increased fibrosis and macrophage infiltration [40–42]. This tissue had an altered differentiation and insulin sensitivity. The profile of adipokines was markedly altered with increased TNFα and IL-6 and decreased adiponectin and leptin expression [42,43]. In addition, as in vitro expression of TNFα and IL-6 was parallel to the level of cell apoptosis suggesting that these cytokines play an important role in fat loss. These results, together with in vitro results, suggest that HAART-induced lipodystrophy could result from the synergistic effect of NRTIs and PI, which could alter adipogenic transcription factors, adipokine secretion, mitochondrial function resulting in decreased differentiation, adipose insulin resistance and apoptosis ultimately leading to lipodystrophy. Visceral fat hypertrophy could be explained by the different physiology of visceral adipocytes that could become hypertrophied due to increased local cortisol synthesis [44].

Metabolic alterations observed in ART-treated patients could result from the direct effect of drugs on lipid metabolism or insulin sensitivity. In addition, due to lipodystrophy and fat-insulin resistance, decreased adiponectin and increased release of non-esterified (free) fatty acids will aggravate metabolic disorders and whole body insulin resistance [44,45].

In conclusion, human lipodystrophies result from different pathophysiological mechanisms either genetic, or acquired and in particular linked to drugs. However, the main concern with most of these diseases is the high prevalence of cardiac (atherosclerosis) and hepatic complications (NASH) due to altered fat repartition and insulin resistance. A major concern is also the presence of signs of premature aging that will increase local cortisol synthesis [44].

References


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