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**Human lipodystrophies: genetic and acquired diseases of adipose tissue**

Jacqueline Capeau<sup>1,2,3</sup>, Jocelyne Magré<sup>1,2</sup>, Martine Caron-Debarle<sup>1,2</sup>, Claire Lagathu<sup>1,2</sup>,  
Bénédicte Antoine<sup>1,2</sup>, Véronique Béréziat<sup>1,2</sup>, Olivier Lascols<sup>1,2,3</sup>, Jean-Philippe Bastard<sup>1,2,3</sup>,  
Corinne Vigouroux<sup>1,2,3</sup>

<sup>1</sup> INSERM, U938, CDR Saint-Antoine, 75012 Paris, France

<sup>2</sup> UPMC University Paris 06, UMR\_S 938, CDR Saint-Antoine, 75012 Paris, France

<sup>3</sup> AP-HP Tenon and Saint-Antoine Hospitals, 75012 Paris, France

corresponding author : J Capeau, CDR Saint-Antoine UMRS938, Faculty of Medicine Saint-Antoine site, 27 rue Chaligny, 75571 Paris cedex 12, France

jacqueline.capeau@inserm.fr, tel: 33 1 40011332, fax 33 1 40011432

**Abstract**

Human lipodystrophies represent a heterogeneous group of diseases characterized by generalized or partial fat loss, with fat hypertrophy in other depots when partial. Insulin resistance, dyslipidemia and diabetes are generally associated, leading to early complications. Genetic forms are uncommon: recessive generalized congenital lipodystrophies result in most cases from mutations in the genes encoding seipin or the 1-acyl-glycerol-3-phosphate-acyltransferase 2 (AGPAT2). Dominant partial familial lipodystrophies result from mutations in genes encoding the nuclear protein lamin A/C or the adipose transcription factor PPAR $\gamma$ . Importantly, lamin A/C mutations are also responsible for metabolic laminopathies, resembling the metabolic syndrome and progeria, a syndrome of premature aging. A number of lipodystrophic patients remain undiagnosed at the genetic level.

Acquired lipodystrophy can be generalized, resembling congenital forms, or partial, as the Barraquer-Simons syndrome, with loss of fat in the upper part of the body contrasting with

accumulation in the lower part. Although their aetiology is generally unknown, they could be associated with signs of auto-immunity.

The most common forms of lipodystrophies are iatrogenic. In human immunodeficiency virus-infected patients, some first generation antiretroviral drugs were strongly related with peripheral lipoatrophy and metabolic alterations. Partial lipodystrophy also characterize patients with endogenous or exogenous long-term corticoid excess.

Treatment of fat redistribution can sometimes benefit from plastic surgery. Lipid and glucose alterations are difficult to control leading to early occurrence of diabetic, cardio-vascular and hepatic complications.

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## **Introduction**

Diseases of adipose tissue are present with a high prevalence in the global population; in particular those linked with fat expansion leading to obesity, metabolic syndrome or type 2 diabetes. The consequences of increased fat depots are markedly dependent upon their localization. Adipose tissue in the lower part of the body is able to expand and can therefore accumulate excessive energy from diet, stored as triglycerides: taken as a whole, it appears protective at the metabolic level [1]. By contrast, accumulation of fat in the upper part of the body is deleterious. Most abdominal fat is accounted for by subcutaneous fat (SAT) and, under physiologic conditions, only a minor part is represented by intra-abdominal visceral fat (VAT). Excessive SAT, and even more VAT, is strongly associated with metabolic alterations and insulin resistance. These alterations result from the increased release of free fatty acids (FFA) from insulin-resistant adipocytes but also from modified adipokine production with decreased production of adiponectin by adipocytes and increased production of pro-inflammatory cytokines (IL-6, IL-1 $\beta$ , TNF- $\alpha$ ) and chemokines (such as CCL2), in part by adipocytes, but mainly by macrophages invading adipose tissue [2].

Human lipodystrophies are far less common than obesity and characterized, at the opposite, by fat disappearance. However, at the metabolic level, common alterations are observed with insulin resistance, dyslipidemia and generally increased FFA and decreased adiponectin production. Recently, the genetic origin of some of these lipodystrophies has been clarified. However, a number of patients remain undiagnosed at the genetic level. Otherwise, some acquired forms are iatrogenic [3-6].

### **1. Definition and diagnosis**

Human lipodystrophies represent a heterogeneous group of diseases [4-6] characterized by the loss of body fat, which could be localized or generalized. If localized, it is often associated with fat hypertrophy in some other depots.

At the clinical level, peripheral lipoatrophy affecting SAT can be easily diagnosed when marked and affecting regions with a natural large fat thickness. Loss of fat into cheeks and temples gives a gaunt face and, in the limbs, makes muscles and veins highly visible. However, lipoatrophy can be difficult to diagnose if mild, in particular at the lower limb level in males, who can have physiologically a low fat amount. In those cases, a CT-scan at the thigh level is useful but requires comparisons with normal subjects. The diagnosis of visceral fat atrophy (or hypertrophy) requires imaging techniques: a CT-scan or a MRI at the lumbar L4 level allows precise evaluation of the SAT and VAT areas.

Human lipodystrophies are generally associated with severe insulin resistance. Therefore, clinical signs of insulin resistance can help diagnosis: the presence of skin lesions of acanthosis nigricans, a skin brownish lesion present in the axillae, neck and other body folds is an excellent indication of marked insulin resistance, in particular in normal-weight patients. Long-term insulin resistance can lead to acromegaloid features, striking in face and seen in particular in congenital forms. Insulin resistance can result in increased size of genital organs in prepubertal children, ovarian hyperandrogenism leading to virilisation and hirsutism with polycystic ovary syndrome and hyperthecosis in women. Insulin resistance is also commonly associated with hepatomegaly and steatosis.

At the metabolic level, lipodystrophies are characterized by glucose and lipid alterations which can be mild or even absent during childhood and increase in severity when patients age. Lipid alterations associate increased triglyceride (TG) level, which can be raised up to 100 mmol/l, leading to a high risk of acute pancreatitis, while HDL cholesterol is decreased. Glucose values could remain in the normal range in young patients, if insulin secretion is able

to compensate for insulin resistance, but increase progressively leading to glucose intolerance then diabetes, difficult to control.

The main acute complication is acute pancreatitis due to very high TG level. Chronic complications are related to long-term diabetic complications, microangiopathy, affecting retina, kidney and nerves, macroangiopathy, leading to early atherosclerosis, and to hepatic complications of steatosis leading to steatohepatitis and sometimes cirrhosis and portal hypertension.

The differential diagnosis with syndromes of insulin resistance due to alterations at the insulin receptor level (leprechaunism, type A and type B syndromes) could be difficult. However, in these latter syndromes, lipodystrophy and dyslipidemia are absent and very high adiponectin levels have been recently reported [7]. Lipomatosis represents localized fat tumors, different from lipodystrophies. They can be multiple, affecting mainly the proximal limbs areas and the neck in the familial lipomatosis, and are sometimes associated with mutations in mitochondrial DNA (*MERRF* mutations in particular). The Launois-Bensaude lipomatosis, of unknown origin, is often associated with peripheral neuropathy and increased alcohol intake.

## **2. Classification:**

Human lipodystrophies can be defined by the extent of fat loss (generalized or partial) and by their etiology, either genetic or acquired (table 1). Genetic forms of lipodystrophy are uncommon diseases and, up to now, only a few genes have been identified, the alteration of which is responsible for lipodystrophy and insulin resistance.

Genetic forms of complete lipodystrophy called Berardinelli-Seip congenital lipodystrophy (BSCL) or congenital generalized lipodystrophy are exceptional, with fat loss being generally recognized at birth or very early in infancy. It is associated with severe insulin resistance.

Most of the patients present recessive mutations in one of two genes, *BSCL2* encoding seipin or 1-acyl-glycerol-3-phosphate-acyltransferase 2 (*AGPAT2*). A third gene, *CAVI*, encoding caveolin 1, has been recently identified in one patient. At present, less than 5% of patients with congenital generalized lipodystrophy remain without identified genetic alteration.

In partial lipodystrophies, which are rare diseases, two major genes have been identified so far that present generally heterozygous mutations: *LMNA*, encoding lamin A/C and *PPARG*, encoding PPAR $\gamma$ . Mutations in *LMNA* are more frequent than those in *PPARG* and can lead to a number of phenotypes, among which a phenotype where severe insulin resistance is the dominant feature, now designed as “metabolic laminopathy” [8]. In an international effort searching for new disease-causative genes, mutations in *AKT2*, *LMNB2* encoding lamin B2 and *CAVI* were reported in a few patients which remain isolated cases. Numerous patients remain undiagnosed at the genetic level.

Those observed in human immunodeficiency virus (HIV)-infected patients and attributed to the antiretroviral treatment mainly represent acquired forms of lipodystrophy. Very recent data suggest that the chronic viral infection could be also involved. New antiretroviral drugs, with less adverse effects on adipose tissue, are now used. Therefore, lipodystrophy is now less prevalent in this population. However, a number of comorbidities related to insulin resistance and aging occur at an early age in these patients.

A number of acquired lipodystrophies have been recognized for a long time in some rare patients. These forms can be either generalized, as the Lawrence syndrome, or partial, as the Barraquer-Simons syndrome. Their origin is unknown even if immune alterations and signs of auto-immunity have been identified in some patients. Otherwise, patients with hypercortisolism, either endogenous or exogenous, often present fat redistribution with loss of fat in the limbs and buttocks and increased fat in the upper part of the body, and in particular at the back of the neck (buffalo hump).

Finally, fat redistribution with loss of fat in the periphery and increased fat at the central level, is a physiologic evolution during aging. This central fat redistribution is associated with metabolic alterations such as insulin resistance, increased prevalence of diabetes and dyslipidemia. This could represent a very mild and physiologic form of lipodystrophy with associated metabolic abnormalities. This central fat redistribution is exacerbated in the metabolic syndrome with associated metabolic alterations leading to an increased risk of cardiovascular disease and of diabetes.

### **3. Pathophysiology of adipose tissue loss**

Adipose tissue now appears as playing a leading role in energy metabolism and insulin sensitivity through the control of lipid metabolism and the secretion of numerous adipokines involved in important functions and in particular in insulin sensitivity (mainly adiponectin) and insulin resistance (pro-inflammatory cytokines). When fat depots are reduced due to lipodystrophy, as seen in these patients, TG present on circulating lipoproteins, chylomicrons and VLDL, can be only partially stored in fat depots leading to increased circulating TG [9]. In addition, the hydrolysis of TG on lipoproteins, occurring inside the vascular lumen, leads to increased circulating FFA levels. Reduced fat amounts result in reduced circulating leptin [10] levels that are strongly related to the total amount of fat and in particular of SAT. Very low levels of leptin are deleterious for metabolism and leptin replacement therapies were shown to markedly improve metabolic parameters in patients with severe lipodystrophies (see chapter 7 below). Adiponectin values are also generally greatly reduced [10] in association with strong insulin resistance. Adiponectin is important to oxidize FFA into mitochondria in the liver and muscles. Therefore, adiponectin deficiency impairs this oxidation leading to intracellular accumulation of fatty acid derivatives. Increased FFA and decreased adiponectin are two major actors in the process called lipotoxicity related to an ectopic accumulation of



TG associated with insulin resistance [11]. The mechanisms postulated for lipotoxicity imply the increased level of fatty acid derivatives, acyl-CoA, diglycerides, ceramides, present in the cytosol of some tissues such as the liver, muscle, heart and pancreas, due to the decreased ability of mitochondria to oxidize acyl-CoA. Accumulation of fatty acid derivatives leads to activation of stress and inflammatory kinases such as IKK- $\beta$  and some PKC isoforms, which phosphorylate on specific serine residues the insulin receptor substrate protein (IRS1). This phosphorylation blocks insulin signaling, resulting in decreased glucose transport inside muscles. Excessive fatty acids are directed towards TG, which depot in the cytosol leading to steatosis in the liver and intramyocellular fat deposits in the muscles and heart. This lipid deposition buffers excessive fatty acids derivatives and preserves tissues from further damage. It can be diagnosed by imaging methods as nuclear magnetic resonance spectroscopy. Other pathways could be altered resulting in increased gluconeogenesis and increased hepatic glucose production.

Altogether, this lipid deposit and associated alterations lead to insulin resistance, which could result in altered glucose tolerance then diabetes, when pancreatic insulin secretion is unable to fully compensate for insulin resistance. However, this post-receptor insulin resistance is selective, and the inability of insulin to suppress gluconeogenesis contrasts with the preserved capacity of the hormone to activate de novo lipogenesis through the SREBP-1 pathway. As a result, hyperinsulinemia increases de novo lipid production responsible for increased TG-rich VLDL production and hypertriglyceridemia [9].

#### **4. Genetic lipodystrophies**

##### **Berardinelli-Seip congenital generalized lipodystrophy**

The main genetic form of generalized lipodystrophy is a very rare disease, Berardinelli-Seip congenital lipodystrophy or BSCL, previously denominated lipoatrophic diabetes. Two main forms, BSCL1 and 2, have been described.

At the clinical level, lipoatrophy is neo-natal or very early and complete affecting both SAT and VAT. In early infancy, patients present with muscular hypertrophy and organomegaly, in particular cardiac hypertrophy, associated with an increased growth velocity. Metabolic complications generally appear progressively during childhood, with increased TG level, then glycemia leading to overt insulin-resistant diabetes at puberty. Insulin resistance is generally present during childhood, with skin acanthosis nigricans being present, but not always diagnosed if insulin levels are not measured. Early complications, in particular those related to diabetes, occur in adults.

The genetic origin of BSCL2 was identified at first by Magré et al. [12] in 2001 as resulting from mutations in *BSCL2* encoding seipin of unknown function. In most cases, patients have homozygous mutations but can also be compound heterozygotes. Up to now, 31 different mutations have been identified in 136 patients. All, but 3, are null mutations. BSCL2 patients are more severely affected than BSCL1 and often present mild mental retardation. Patients are often Caucasian with a higher prevalence of the disease in Europe and Middle East and Asia. In addition, patients from Brazil, probably of Portuguese origin, have been identified.

The function of seipin remained unknown up to recently when data obtained with yeast and human cells implicated this protein in lipid metabolism, more specifically in lipid droplet formation. Seipin deficiency results in severe alterations in lipid droplets morphology indicative of a defect in the formation or maturation of this organelle [3, 13]. In cells issued from patients with seipin mutations, this alteration in the pattern of lipid droplets was associated with a decreased activity of the stearoyl-CoA desaturase 1 (SCD1) reflected by an increase ratio of saturated to the corresponding monounsaturated fatty acids in cellular TG

and phospholipids [14]. Unsaturated but not saturated fatty acids, are able to induce the formation of new and/or increase the size of pre-existing lipid droplets. SCD1 plays a key role in this process by partitioning excess lipid into monounsaturated fatty acids that can be safely stored. The precise mechanism by which seipin works with SCD1 at the endoplasmic reticulum level to synthesize lipid droplets requires further investigation.

BSCL1, identified as linked to a locus on chromosome 9q34, was related latter on with mutations in *AGPAT2* by the group of Garg et al in 2002 [15]. This gene is mutated in about 50% of patients with typical BSCL and the disease is recessively inherited, most patients being homozygous. Thirty-three different mutations have been described in 110 patients: most are null mutations and 8 are missense mutations. This form is mainly observed in patients of African ancestry but also in Caucasian patients. At the clinical level, lipoatrophy implicates all fat depots but mechanical fat. Metabolic alterations are milder than those reported in BSCL2 patients and mental retardation is usually absent.

*AGPAT2*, the most expressed *AGPAT* adipocyte isoform, catalyzes acylation of lysophosphatidic to phosphatidic acid in the pathway of triglycerides synthesis [3]. Accordingly, its reduced level or absence could explain decreased TG accumulation and altered adipocyte differentiation. In addition, the modified levels of lysophosphatidic and phosphatidic acids, which exert important signaling functions, could also play a role.

Apart from these two genes, a homozygous nonsense mutation, Glu38X, in a third gene, *CAVI*, encoding caveolin 1, was recently identified in a Brazilian patient by Magré and coworkers [16]. The phenotype is very similar to that of BSCL1 and BSCL2 patients. Because caveolin 1 plays an important role in the entry of lipids towards intracellular lipid droplets in

adipocytes, its absence could explain decreased fat. In addition, a role for caveolin in insulin signaling has been reported which could explain the phenotype of severe insulin resistance.

Taken as a whole, the mutations in these three genes account for 98% of the patients we investigated: among 117 patients, 62 are mutated in the seipin gene, 60 in *AGPAT2* and 1 in *CAVI*. Only 3 patients remain undiagnosed at the genetic level.

To explain the severe insulin resistance associated with lipodystrophy, it can be hypothesized that lipotoxicity is particularly severe in these patients, completely unable to store fat in adipose tissue and with massive ectopic lipid depots in the muscles, heart and liver. In addition, very low leptin levels are involved in severe metabolic alterations and could possibly be reverted by a treatment with recombinant leptin. Decreased levels of adiponectin were also previously reported, at least in patients with mutations in *AGPAT2* and *CAVI* [10, 16].

Therefore, whatever the mechanism leading to fat loss, the almost complete absence of fat in humans is associated with severe insulin resistance and metabolic alterations leading to early complications and reduced lifespan.

### **Partial lipodystrophies linked to *LMNA* mutations**

Partial lipodystrophies dominantly inherited are often denominated familial partial lipodystrophy or FPLD and two main forms have been identified at the genetic level. At first, mutations in *LMNA* were recognized as responsible for the FPLD of the Dunnigan type (also called FPLD2). Then, in a few patients, mutations in the gene encoding PPAR $\gamma$  were found, responsible for FPLD3.

The story of *LMNA* mutations is fascinating. In less than 10 years, 10 different diseases were shown to be linked to a number of mutations in the gene encoding lamin A/C: the phenotypes cover a large spectrum, some of them overlapping each other, resulting in a continuum of

diseases collectively called laminopathies, affecting in priority tissues of mesenchymal origin. The story began in 1999 by the discovery by G. Bonne working in the group of K. Schwartz in Paris that this gene was responsible for the dominantly inherited Emery-Dreyfuss myopathy [17]. Later on, other forms of myopathies and of cardiomyopathies were found to be related to *LMNA* mutations. In 2000, the Canadian group of Robert Hegele and the English group of Richard Trembath found that the dominantly inherited FPLD of the Dunnigan type was also due to *LMNA* mutations, most of them being located in exon 8, coding for the globular C-terminal domain of the protein, with a hot-spot at residue 482 replacing arginine by a neutral residue in 90% of FPLD2 patients [17]. Further studies on the patients' phenotype were performed by our group [18] and others. Indeed, the typical FPLD2 phenotype due to the R482 *LMNA* substitution is absent in prepubertal children. The clinical and biological signs appear after puberty associating fat loss at the limb and abdominal subcutaneous level together with increased fat in the face and neck giving a cushingoid appearance. The clinical phenotype is generally obvious in women, who often complain also of hirsutism, but can be very mild in men, which could make the diagnosis difficult. Metabolic alterations also occur after puberty leading to severe hypertriglyceridemia, insulin-resistant diabetes and early atherosclerosis.

The pathophysiology of the disease is not well understood. Lamin A/C together with lamin B are intermediate filaments present inside the nucleus where they form a meshwork under the inner nuclear membrane, the nuclear lamina. Lamina is associated to the membrane through interactions with different proteins embedded in the inner nuclear membrane that also interacts with other partners across the nuclear envelope, like nesprin, linking the nucleus to the actin cytoskeleton in the cytosol. In addition, some lamin A/C is present inside the nucleoplasm and probably plays important functions at that level: lamin A/C is able to interact

with other proteins controlling nuclear functions such as LAP2 $\alpha$ , the retinoblastoma protein Rb, cFos controlling the transcription factor AP-1 and SREBP-1 a transcription factor playing an important role in adipocyte and controlling PPAR $\gamma$ .

Mature lamin A is obtained after a complex process of maturation. During this process, prelamin A gains a farnesyl anchor, which allows the movement of the protein to the inner nuclear envelope. The maturation then requires the action of a specific protease called ZMP-STE24 or FACE1, which removes the C-terminal end of the protein including the farnesyl anchor. Thus the link between lamin A and the nuclear membrane is weakened allowing lamin A to be partially localized in the nucleoplasm.

The pathophysiology of the lipodystrophic phenotype observed in FPLD2 patients remains unknown. The C-terminal domain of lamin A/C has been shown to interact with DNA and the transcription factor SREBP-1, thus playing a scaffolding function. When lamin A/C is mutated on the residues responsible for FPLD2, all located at the surface of the globular domain, a decreased interaction with DNA and SREBP-1 has been reported which could explain altered adipose tissue differentiation. We showed that some cultured skin fibroblasts issued from FPLD2 patients presented nuclei with abnormal shape with blebs and an abnormal repartition of lamin A/C and B [19]. Then, the presence of nuclear blebs has been reported in cells from all patients with mutations in LMNA and are now considered as a hallmark of laminopathies. Interestingly, we have recently shown that adipose tissue issued from hypertrophic neck fat, presented a number of abnormalities indicating the presence of a mitochondrial dysfunction together with increased fibrosis. Adipocytes were not hypertrophied as expected but on the contrary reduced in size [20]. Therefore, *LMNA* mutations result in all fat depots in abnormal adipose tissue with defective differentiation.

In addition to the canonical *LMNA* mutations observed in patients with the typical form of FPLD2, several *LMNA* mutations have been reported in patients with atypical forms of lipodystrophies but severe insulin resistance. Since, in some of these patients, lipodystrophy is very slight, this new syndrome was denominated “metabolic laminopathies” [8]. Some patients presented other signs of laminopathies with muscle and/or cardiac alterations. Their diagnosis is not obvious since these patients resemble those with the common metabolic syndrome. However, it is important to diagnose them in order to prevent early complications including cardiac rhythm or conduction disturbances that can be present in patients with typical FPLD2 [21]. In addition, since the disease is generally dominant, it is important to perform a familial screening in order to provide the patients with an adequate and early treatment. We propose to screen for mutations in *LMNA* in patients with lipodystrophy, even mild, if familial antecedents are present or in the case of associated muscular signs or cardiac disturbances. CT scan of the abdomen and/or thigh can help diagnosis so as the regional evaluation of body fat amount by DEXA.

The discovery in 2003 that a syndrome of premature aging called the Hutchinson-Gilford progeria resulted from a mutation in *LMNA* opened a new field of investigation on the role of lamin A/C [17]. Importantly the *LMNA* G608G mutation does not modify the postulated sequence of prelamin A but alters a splice site resulting in the deletion of 50 amino acids including the site of proteolysis by the protease ZMP-STE24. Therefore, this truncated prelamin A, called progerin, remains farnesylated and strongly anchored in the nuclear membrane. In addition to mutations in the lamin gene being responsible for progeria, other diseases with severe premature aging were discovered due either to mutations in *LMNA* or in the gene encoding ZMP-STE24 resulting in an increased level of farnesylated prelamin A. A number of studies tried to understand why the presence of progerin or farnesylated prelamin

A is toxic for the cell. Some data outlined the important role of lamin A/C in the recruitment of DNA repair factors [22]. When altered, this results in genomic instability and p53 activation leading to cell senescence and accelerated aging. Very recent studies revealed that progerin could affect mesenchymal stem cells leading to altered differentiation of the cell lineage issued from these cells [23] including bone, muscle, adipose tissue, skin, all tissues affected in priority in laminopathies.

Interestingly, lipodystrophy, insulin resistance and early cardiovascular complications are features common both to premature aging syndromes and to typical or atypical lamin-linked lipodystrophies, suggesting some similar pathophysiological mechanisms. We thus searched for the presence of prelamin A in fibroblasts from patients with metabolic laminopathies and FPLD2. Farnesylated prelamin A was indeed present and *LMNA*-mutated cells presented features of early senescence [24].

### **Familial partial lipodystrophies linked to mutations in *PPARG***

The first patient described with a mutation in the gene encoding PPAR $\gamma$  was identified with a severe insulin resistance and hypertension but lipodystrophy, which was mild, was only diagnosed secondarily [25]. Since that, several patients with *PPARG* mutations were recognized, all characterized by mild forms of lipodystrophy, affecting the lower limbs and the buttocks but sparing the abdominal SAT, together with severe hypertension and metabolic abnormalities. About 15 different mutations have been identified, all heterozygous, leading to a dominant transmission of the disease [6].

The pathophysiological mechanisms involve alterations of the transcriptional activity of PPAR $\gamma$ , which is important for adipose tissue differentiation, but also plays a role in other tissues. The mutations identified could induce a dominant-negative effect but could also be deleterious due to haploinsufficiency [6]. The fact that patients with FPLD mutated on



*PPARG* present a less severe lipodystrophy than those mutated on *LMNA* but more severe metabolic alterations suggests that PPAR $\gamma$  plays important roles outside adipose tissue.

### **Other partial inherited lipodystrophies**

A third gene encoding the protein kinase B, *AKT2*, has been involved in FPLD. This kinase, playing an important role as an intermediate in insulin signaling, was mutated in several members of a family with hyperinsulinemia and diabetes, indicating a dominant transmission of insulin resistance [26]. The proband presented with partial lipodystrophy [9]. However, this gene was not found mutated in other patients and two other missense mutations in *AKT2* do not clearly segregate with insulin resistance in the families and do not alter Akt2 kinase activity. In addition, heterozygous *CAVI* frameshift mutations have been reported in atypical forms of partial lipodystrophy. However, the phenotype is heterogeneous and the functional consequences of the different genetic alterations difficult to understand [3].

A number of patients with familial forms of partial lipodystrophies are at present undiagnosed. Recent studies from a large international collaboration indicate that some other genes could be involved in a few of them. Nevertheless, a number of cases remain unidentified at the genetic level.

### **5. Acquired lipodystrophies**

The occurrence of lipodystrophy can be delayed in some genetic forms of lipodystrophy such as FPLD2, in which the phenotype appears after puberty. Otherwise, in some patients, lipodystrophy occurs during childhood and adulthood, without familial antecedents or mutations in genes known to be responsible for lipodystrophy, and in the context of an acute disease. At the clinical level, lipodystrophy can be complete or partial, very similar to that

observed in genetic forms. Metabolic alterations are also very similar, arguing for the causative role of fat loss in metabolic disturbances.

### **Generalized acquired lipodystrophy**

Also called the Lawrence syndrome, lipodystrophy occurs during childhood or adulthood sometimes preceded by an acute viral illness. The origin is unknown. However, in a number of patients, fat disappearance is preceded by a local inflammatory panniculitis. Also, signs of auto-immunity are sometimes present [27]. Therefore, in some patients, it is possible that fat is aggressed by an immune process leading to adipocyte destruction: when searched for, the presence of anti-adipocyte immune reactivity in patients' serum was found occasionally. Otherwise, the clinical and biological signs and the complications are very similar to those observed in BSCL [5, 6].

### **Acquired partial lipodystrophy**

Among the different forms of partial acquired lipodystrophy, with no known etiology, one form can be identified since its phenotype is the reverse of that found in FPLD. Patients with the Barraquer-Simmons syndrome, more frequent in women, present a normal or decreased fat amount in the upper part of the body (face, upper part of the trunk, arms) while fat in the lower part is in excess (buttocks, hips, legs). The etiology is unknown, even if auto-immunity has been reported in some cases. A membrano-proliferative glomerulonephritis affects one third of the patients and more than half of them show signs of activation of the alternative complement pathway: low circulating levels of C3 and presence of C3 nephritic factor. Heterozygous alterations in *LMNB2* encoding lamin B2 have been reported by the group of Hegele et al. [6] but were not confirmed by the other groups involved in the genetics of lipodystrophies.

Interestingly, while patients with loss of fat in the lower part of the body present severe metabolic alterations, patients with the reverse phenotype do not generally present such alterations, in agreement with the beneficial role of lower limbs fat at the metabolic level.

### **Lipodystrophies linked to HIV infection**

Patients with HIV infection benefit since the late 1990s of different classes of antiretroviral drugs, that resulted in the control of the viral infection in most cases. In particular, the introduction in 1996 of the class of HIV protease inhibitors (PI) given in association with the class of nucleoside reverse transcriptase inhibitors (NRTI) led, in most patients, to an efficient control of the viral infection on the long term together with immune recovery of the CD4 T lymphocytes number.

However, at the time when PIs were introduced, a number of patients underwent lipodystrophy, with severe peripheral lipoatrophy and, in some patients, excessive visceral fat accumulation. These alterations in fat distribution were associated with metabolic disturbances, insulin resistance, diabetes, dyslipidemia [4-6, 28].

The prevalence of HIV-related lipodystrophies in the early 2000s was very high, affecting more than half of the patients and about 70-80% in some groups, such as the French ANRS APROCO cohort.

The pathophysiology of this lipodystrophy led to extensive clinical and fundamental studies [29]. A number of researches evaluated the ability of individual antiretroviral drugs to alter adipocyte functions in cultured cells. At first, the deleterious impact of first generation PI such as nelfinavir and indinavir was clearly demonstrated, these drugs being able to inhibit differentiation, induce insulin resistance and increase the production by adipocytes of pro-inflammatory cytokines [30]. More recently, second generation PIs were also evaluated for their ability to modify adipocyte phenotype: ritonavir and lopinavir exerted deleterious effects

through the induction of an oxidative stress and the modification of adipokine secretion while atazanavir and amprenavir used alone were mainly devoid of an effect in that setting [31]. The ability of some PIs to induce IL6 secretion through the activation of the NF- $\kappa$ B pathway was seen in human adipose tissue explants. Importantly, this effect was observed in explants from SAT but not VAT, in accordance with the clinical observation of preferential atrophy of SAT in HIV-infected patients [32]. A major pathway, which could also explain the effect of PIs, results from their ability to inhibit the enzyme ZMP-STE24 therefore leading to the accumulation of farnesylated prelamins A, to increased oxidative stress and to induction of an early cellular senescence [24]. This point is important to consider given the phenotype of premature aging which is frequently observed in HIV-infected patients.

The second class of antiretroviral drugs which is now suspected to play the leading role in lipoatrophy is the class of thymidine analogue NRTI and in particular the two first very active molecules, stavudine and zidovudine. These drugs were able to markedly alter adipocyte function in vitro through altered mitochondrial potential and increased oxidative stress [33] leading to decreased adiponectin secretion. They also increased MCP-1 and IL6 production [31]. Thus, these two NRTIs but not the second-generation NRTIs were able to induce cellular premature senescence [33].

Clinical studies clearly revealed that the two thymidine NRTIs, mainly stavudine, were involved in priority in patients' lipoatrophy. PI could act in synergy with these NRTIs but could also impact on visceral fat and induce fat hypertrophy together with metabolic alterations, some PI being deleterious on lipids, with increased VLDL production by the liver, while others affect in priority insulin sensitivity and glucose metabolism. The demonstration of the toxic effects of antiretroviral drugs on adipose tissue was investigated in HIV-infected patients who were able to stop any antiretroviral treatment for at least 6 months. In this ANRS study, Lipostop, initial adipose tissue inflammation was markedly decreased, this

improvement being related to the interruption of stavudine or zidovudine. However, both PI and thymidine analogues negatively impacted on different other adipocyte function [34].

More recently, a role for HIV infection has been also postulated, given that HIV can act on adipocytes, possibly by infecting them when adipocytes are in an inflammatory context [35] but also through the release by infected resident macrophages inside adipose tissue of viral proteins, which alter adipocyte phenotype ([36]. In addition, when infected by HIV, macrophages shift their phenotype from a mainly anti-inflammatory M2 towards a M1 phenotype, resulting in the release of pro-inflammatory cytokines [37] and thereby in adipocyte insulin resistance and altered adipokine production. Therefore, taken as a whole, the severity of HIV-related lipodystrophy observed when patients were treated with first generation antiretrovirals, could result from different factors, all aggressing adipocytes: the simultaneous use of drugs able to negatively impact on adipose tissue but also the long term HIV infection, with probably, in most patients, the constitution of virus reservoirs in macrophages inside adipose tissue.

At present, the toxicity of the new drugs in the different antiretroviral classes is markedly decreased and the occurrence of the lipodystrophic phenotype reduced in HIV-infected patients. In most patients switched from first towards second generation antiretrovirals, lipodystrophy improved but the reversion is slow and sometimes incomplete. Plastic surgery could provide a valuable improvement at least for facial lipoatrophy when severe.

However, HIV-infected patients, even well-controlled with an undetectable viral load and a high number of CD4 lymphocytes, encounter the early occurrence of a number of comorbidities classically associated with aging: increased cardio-vascular disease, hypertension, osteoporosis, neurocognitive decline, dyslipidemia, diabetes, renal and liver failure, sarcopenia and motor decline, frailty, non-acquired immunodeficiency syndrome defining malignancies. These alterations could reveal the occurrence in these patients of

premature aging. Studies have to be performed to identify the reason for this process, which probably results from the chronic infection, leading to a long-term low grade inflammation, from immune senescence, leading to immune depletion, and from the adverse effect of some antiretroviral drugs. In addition, personal factors such as smoking, junk food, excessive alcohol intake and lack of exercise probably accentuate the infection-related alterations.

### **Lipodystrophies linked to excess cortisol**

It has long been recognized that patients with excess cortisol, either with a Cushing syndrome or disease or treated for a while with corticoids, present fat redistribution, with fat loss in the limbs and fat gain in the upper part of the trunk, including moon-like face, buffalo hump in the back and increased VAT. In addition, these subjects undergo bone loss, hypertension, hyperandrogenism and metabolic alterations with insulin resistance, linked to the effect of cortisol: altered glucose tolerance and even corticoid-induced diabetes, lipid alterations and increased cardio-vascular risk. Therefore, this phenotype is clearly a cortisol-induced lipodystrophic syndrome.

The role of cortisol in adipose tissue is important to consider, since fat is able to convert inactive cortisone into active cortisol due to the presence of the enzyme  $11\beta$ -hydroxysteroid dehydrogenase. It has been observed that abdominal SAT is able to secrete cortisol while the role of visceral fat in that setting has been recently questioned in men. Cortisol increases adipocyte size leading to insulin resistant large adipocytes while it inhibits adipocyte proliferation. However, the mechanism by which cortisol induces lipodystrophy remains unclear.

### **And what about aging?**

During the process of physiological aging, fat depots present a physiologic redistribution towards central parts of the body, with loss of fat in the limbs and increased waist circumference, particularly seen in postmenopausal women. This redistribution is associated with age-related deterioration of insulin sensitivity, glucose and lipid parameters. In the context of increased body weight, this redistribution is more marked and the phenotype linked with central obesity has been individualized as the metabolic syndrome. Increased central fat, both subcutaneous and visceral, probably plays a leading role in the occurrence of the other alterations associated in the metabolic syndrome: decreased HDL, increased LDL cholesterol, TG, blood pressure, glycaemia. Therefore, the metabolic syndrome could represent a mild form of acquired human lipodystrophy

## **6. Treatment of lipodystrophies**

The altered body fat repartition can benefit from plastic surgery. Patients with FPLD2 sometimes undergo successful removal of excess fat at the neck and face level. In patients with HIV-related facial lipoatrophy, plastic surgery is able to provide amelioration, even if often transitory: the Coleman technique consists in injection into the cheeks of autologous fat. Otherwise, correction with resorbable polyacrylamide gels or with non resorbable fillers such as alkylamide allows partial correction. In some patients with severe hypertrophy of fat as a buffalo hump, fat removal can be proposed but with a risk of recurrence.

Some medications could possibly ameliorate lipoatrophy: a treatment with troglitazone, a first generation thiazolidinedione (TZD), was initially shown to restore some fat in the limbs in patients with generalized lipodystrophy not related to HIV infection [38]. In patients with HIV-related lipodystrophy, TZD revealed poor efficacy on fat restoration. This was probably due to the presence of stavudine in the patients' treatment, which impeded fat restitution.

When pioglitazone was given to patients not treated by stavudine, an improvement in peripheral fat was reported [39].

Treatment of metabolic alterations can benefit from diet recommendations that can ameliorate insulin sensitivity and hypertriglyceridemia. When diabetes is present, it is generally insulin resistant and difficult to control. Insulin sensitizers are used at first, metformin and TZD. A treatment with TZD resulted in favourable effects on glucose control in several patients, even those with mutations in *PPARG*. Very high doses of insulin are frequently required. In some cases, medium chain fatty acids supplementation can contribute to lower TG. Otherwise, hypolipidemic drugs are required.

Since these patients often present very low leptin levels, replacement of leptin with recombinant human leptin has been evaluated and in adults resulted in markedly improved metabolic values and regression of liver steatosis [40].

## **7. Conclusion**

Lipodystrophies represent a heterogeneous group of severe diseases leading to early diabetic, cardio-vascular and hepatic complications. Alterations in adipose tissue distribution could result from mutations in several genes: the presence of lipodystrophy outlines the importance of these genes in adipose tissue function. The role of lipid droplets as a new organelle playing a leading role in adipocyte functions is shown by the discovery that several genes mutated in lipodystrophies act at that level [3]. Active researches are looking for mutations in other candidate genes. Even if the pathophysiology of lipodystrophies remains largely unknown, it is obvious that all situations with fat loss, in particular in the lower body fat depots, are associated with severe metabolic disturbances and insulin resistance, while the only lipodystrophic syndrome with the reverse repartition of fat (the Barraquer-Simons syndrome) is generally not associated with metabolic alterations. This is reminiscent of the android



obesity associated with abnormal metabolic parameters while the gynoid form is largely devoid of them.

Human partial lipodystrophies commonly associate loss of fat in some depots while others are increased. This points to the different physiology of the different fat depots, since the same genetic alteration or drug-induced toxicity results in opposite phenotypes depending on the fat localization.

The presence of mitochondrial dysfunction in lipodystrophies has been revealed in adipose tissue from patients with FPLD2 and other *LMNA* mutations but also in HIV-related lipodystrophies. Interestingly, some forms of lipomatosis result from mutations in mitochondrial DNA. Therefore, the relation between mitochondria and adipose tissue is probably important and complex and could result either in lipoatrophy but also in hypertrophied fat. Mitochondrial dysfunction has been also implied in muscular insulin resistance found during aging and in diabetic patients.

The specific role of lamin A/C in adipose tissue is important to consider. Accumulation of farnesylated prelamin A is involved in diseases associated with premature aging but also in *LMNA* and HIV-linked lipodystrophies, which also present signs of premature aging. During normal aging a fat redistribution is observed. Whether there is a link between lamin and normal aging remain to be demonstrated.

Therefore, studies on human lipodystrophies help to understand the complex physiology and pathology of fat. They point to new genes and new targets, which could lead to the discovery of new therapeutic clues in order to help treatment of patients with lipodystrophies but also, more generally, of patients with common forms of fat redistribution as observed in the metabolic syndrome and type 2 diabetes.

		Transmission	Protein encoded by the altered gene or causal agent	Age at onset lipodystrophy	Adipose distribution	Clinical and Biological parameters
<b>Genetic</b>	<b>Generalized</b> BSCL1 BSCL2 BSCL3	AR AR AR	AGPAT2 Seipin Caveolin 1	{Birth or early infancy	{Complete lipoatrophy	{Acanthosis nigricans, Dyslipidemia, Diabetes
	<b>Partial</b> FPLD2	AD	Lamin A/C	Puberty	Limbs and buttocks lipoatrophy, increased fat in the face and neck	{Acanthosis nigricans, Dyslipidemia, Diabetes
	Metabolic laminopathy	Generally AD	Lamin A/C	Puberty	Mild or absent lipodystrophy	
	<b>Partial</b> FPLD3	AD	PPAR $\gamma$	Puberty	Lower body lipoatrophy	Hypertension Acanthosis nigricans Dyslipidemia Diabetes
	<b>Partial</b> AKT2-linked	AD	AKT2/PKB		Partial lipodystrophy	Hypertension Acanthosis nigricans Diabetes
<b>Acquired</b>	<b>Generalized</b> Lawrence syndrome		Unknown Sometimes autoimmune disorders	Childhood or adulthood	Complete lipoatrophy	Sometimes panniculitis Acanthosis nigricans Dyslipidemia Diabetes
	<b>Partial</b> Barraquer-Simmons syndrome		Unknown Lamin B2 proposed but not confirmed	Adolescence or early adulthood	Upper body lipoatrophy Lower body fat accumulation	Uncommon metabolic alterations Sometimes low C3 and membranoproliferative glomerulonephritis
	<b>Generalized or partial</b> HIV-related		Some antiretroviral drugs: stavudine, zidovudine, first generation protease inhibitors	Generally adulthood	Peripheral lipoatrophy Central lipoatrophy or fat accumulation	Dyslipidemia Sometimes diabetes

	<b>Partial</b> related to hypercorticism		Endogenous or exogenous excess cortisol	Generally adulthood	Lower body lipoatrophy` Upper body fat accumulation	Dyslipidemia Often diabetes
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AR: autosomal recessive, AD: autosomal dominant

BSCL: Berardinelli Seip congenital lipodystrophy, FPLD: Familial partial lipodystrophy, HIV: human immunodeficiency virus

Table 1: Classification and main clinical features of lipodystrophies

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