



## Proceedings of the annual meeting of the European Consortium of Lipodystrophies (ECLip) Cambridge

Hélène Mosbah, Baris Akinci, David Araújo-Vilar, Juan Carrion Tudela, Giovanni Ceccarini, Philippe Collas, I. Sadaf Farooqi, Antía Fernández-Pombo, Isabelle Jéru, Fredrik Karpe, et al.

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**Proceedings of the annual meeting of the European Consortium of Lipodystrophies (ECLip) Cambridge, UK, 7-8 April 2022**

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## ABSTRACT:

Lipodystrophy syndromes are rare diseases with defects in the development or maintenance of adipose tissue, frequently leading to severe metabolic complications. They may be genetic or acquired, with variable clinical forms, and are largely underdiagnosed. The European Consortium of Lipodystrophies, ECLip, is a fully functional non-profit network of European centers of excellence working in the field of lipodystrophies. It provides a favorable environment to promote large Europe-wide and international collaborations to increase the basic scientific understanding and clinical management of these diseases. It works with patient advocacy groups to increase public awareness. The network also promotes a European Patient Registry of lipodystrophies, as a collaborative research platform for consortium members. The annual congress organized gives an update of the findings of network research groups, highlighting clinical and fundamental aspects. The talks presented during the meeting in Cambridge, UK, in 2022 are summarized in these minutes.

**Key words:** lipodystrophy syndrome, fatty acid, total body irradiation, encephalopathy, miRNA, caveolin-1, therapeutic education, EPHX1, seipin, registry, metreleptin, antibody.

## INTRODUCTION

The European Consortium of Lipodystrophies, ECLip, is a fully functional non-profit network of European centers of excellence in the field of lipodystrophies.

Lipodystrophy syndromes form a heterogeneous group of diseases characterized by defects in the development or maintenance of adipose tissue, frequently leading to metabolic complications associated with insulin resistance, in the absence of malnutritional or a catabolic state. They are classified into 4 major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPL), acquired generalized lipodystrophy (AGL) and acquired partial lipodystrophy (APL). Partial forms of lipoatrophy may be associated with regions of fat accumulation. Lipodystrophy can also occur as part of complex systemic diseases such as premature ageing syndromes (progeroid syndromes).

The ECLip network (<https://www.eclip-web.org/lipodystrophies/>) provides a favorable environment to promote and facilitate large Europe-wide and international collaborations to increase the basic scientific understanding and clinical management of lipodystrophy syndromes. It aims to improve diagnosis and prevention, to provide optimum medical care, and, in collaboration with patient advocacy groups, to promote public awareness in the domain of lipodystrophies. The ECLip Patient Registry of lipodystrophies was set up to extract and share data, and provide a collaborative research platform for consortium members [1].

The network organizes at least one annual meeting, updating the findings of network research groups and stimulating collaborations. The presentations given during the last ECLIP meeting in Cambridge, UK, in 2022 are summarized in these minutes.

## **ABSTRACTS of the ECLIP meeting Cambridge 2022**

### **Fatty acid trafficking regional adipose tissues, Professor Fredrik Karpe, University of Oxford, UK**

Prof. Fredrik Karpe coordinates several research programs in metabolic physiology and pathophysiology, based in particular on the Oxford Biobank general population cohort. He presented the results of his research assessing the storage capacities of excess energy in the form of lipids in adipose tissue. Measuring the entry of fatty acids into adipocytes, their esterification into triglycerides, and conversely, assessing the intra-adipocyte hydrolysis of triglycerides (lipolysis), the exit of fatty acids into the capillaries draining the adipose tissue, and the flow of fatty acids into the bloodstream (spillover) all require complex metabolic investigations. Fredrik Karpe discussed the interest and limitations of different methods: imaging (DEXA, PET-scan), and ingestion or intravenous administration of labeled fatty acids followed by measurement of labeled triglycerides in biopsy samples of adipose tissue. He presented the principles of measurement of arteriovenous difference in labeled fatty acids concentrations, enabling exploration of the flow of fatty acids in very precise anatomical territories, specific to abdominal and gluteal subcutaneous adipose tissue. This method makes it possible to dynamically explore the metabolic response of adipose tissue to several stimuli (for example, during a meal, or after an increase in insulin or other hormones). At the physiological level, it shows that femoro-gluteal adipose tissue is not very sensitive to lipolysis induced by catecholamines, but on the contrary very active in extracting fatty acids from circulating lipoproteins of hepatic origin (very low density lipoprotein: VLDL) and storing them as triglycerides. This method also allowed his team to show, in 5 patients with lipodystrophy linked to *LMNA* variants versus 5 control subjects, that lipodystrophic patients have a lower capacity to extract fatty acids from circulating lipoproteins (chylomicrons and VLDL) to feed the adipocyte triglyceride storage pathway. Conversely, they have an increased flow of fatty acids and triglycerides into the bloodstream (spillover), which results from a decreased adipocyte triglyceride storage capacity.

### **Form vs function in adipose disorders: where does lipodystrophy stop?**

#### **Professor Robert Semple, University of Edinburgh, UK**

Professor Robert Semple, from the University of Edinburgh, discussed the challenge of developing sensitive and specific clinical diagnostic criteria for lipodystrophies: should the definition be based on adipose tissue anatomy? Or on its function? Or both? Organs are usually assessed both anatomically, on imaging and clinical examination, and functionally, by a direct measure of organ function, or by biochemical biomarkers of function. It is usually functional assessment that drives clinical decision making. A good example is the thyroid gland, with thyroid function more commonly determining treatment than thyroid anatomy.

Anatomically, lipodystrophies can readily be identified as long as patients are well nourished. In this case general or regional deficiency of adipose tissue is easily observed. However, this can be mimicked or masked by negative energy balance, which leads to “physiological” loss of adipose tissue. Where true lipodystrophy is present, important subtypes may be identified that help to identify underlying pathological processes. Decreased adipose tissue is associated with increased muscle mass and strength in several developmental forms of lipodystrophy, but with decreased muscle mass and bone density in lipodystrophies featuring accelerated mesodermal tissue ageing, for example. In diagnosing lipodystrophy anatomical abnormalities

must be assessed in the context of markers of adipose tissue dysfunction. These include low blood concentrations of leptin, and adiponectin, high concentrations of insulin, metabolic dyslipidaemia, increased liver lipid content, and systemic inflammation. None of these are specific for lipodystrophy, however.

The challenges in diagnosis were illustrated through discussion of two genetic disorders. *PIK3R1*-related SHORT syndrome features reduced adipose tissue amount and is commonly called a form of lipodystrophy. However, serum triglycerides and hepatic fat, serum leptin and adiponectin are usually normal. The mouse model similarly shows decreased adiposity but also decreased serum triglycerides, no systemic inflammation, and healthy adipose tissue histology and gene expression. It also has increased energy expenditure. Is reduced adiposity without evidence of functional adipose failure consistent with true lipodystrophy?

Conversely, Alström syndrome, a complex recessive syndrome, includes severe insulin resistance with low serum adiponectin, dyslipidemia and hepatic steatosis, and premature atherosclerosis, all closely mimicking the biochemical profile of adipose failure seen in severe lipodystrophy. However, adiposity is moderately increased. This suggests that Alström syndrome could be regarded as a *forme fruste* of lipodystrophy, but with relative rather than absolute adipose failure.

Thus, the definition of lipodystrophies cannot reliably be based on either form or function alone; lipodystrophies are a heterogeneous group of pathologies whose diagnosis would be accelerated by development of a better biochemical index of adipose failure.

### **Bone phenotype of familial partial lipodystrophy type 2 (FPLD2)**

**Professor MC Vantyghem, University of Lille, France**

FPLD2 combines partial lipoatrophy, muscle hypertrophy, and skeletal abnormalities such as relatively short fingers and lower limbs. The bone phenotype of lipodystrophic syndromes is controversial, especially in terms of the T-score measured in DEXA: No difference in T-score between FPLD2, FPLD1 and obese individuals [2], higher Z-score levels at least in one site, especially trabecular, in generalized lipoatrophy syndromes [3] or lower T-score in HIV-related lipodystrophies [4] Radiological abnormalities have also been described in generalized lipodystrophies [5] Given the links between adipocytes, myocytes, and chondrocytes, all of which are derived from a mesenchymal stem cell, the study of the bone phenotype of FPLD2 is of interest both for the individual management of these rare diseases and pathophysiologically.

Bone is an endocrine organ that secretes FGF23, a hormone that increases urine phosphates, and osteocalcin, a hormone that can increase insulin secretion, insulin sensitivity of adipose tissue, testosterone secretion in men and nutrients uptake by muscle. The main objective of this work was to evaluate the bone phenotype of FPLD2 women with *LMNA R482* mutation by studying blood markers of bone remodeling (osteocalcin and crosslaps), phosphate and calcium parameters, and by assessing body composition by DEXA and MRI, in comparison with age- and sex-matched obese and thin women. The second objective was to specify the determinants of this phenotype.

### **Lipodystrophy induced by total body irradiation**

**Dr Anna Stears, University of Cambridge, UK.**

Dr. Stears reported the case of 2 patients who presented with a lipodystrophy picture following total body irradiation in the setting of a hematologic malignancy. The first patient presented with a partial lipodystrophy, which started 2 years after irradiation. Eight years later, a picture of insulin resistance was revealed with hypertriglyceridemia, diabetes and hepatic steatosis. Management was based on reducing carbohydrate and fat intake, stopping enteral nutrition and oral nutritional supplements, and increasing physical activity. These lifestyle changes resulted in improvements in diabetes, triglycerides and insulin levels. At the last clinical evaluation, the hepatic steatosis had significantly improved, and the question of introducing metreleptin was raised. The second case is that of a patient who presented, in the aftermath

of total body irradiation, a severe insulin resistance picture with hypertriglyceridemia, acute pancreatitis, diabetes requiring high doses of ultraconcentrated insulin, and steatosis. In this context of uncontrolled metabolic situation despite very low fat diet, metreleptin treatment was introduced at 5 mg/d. The metabolic situation was partially improved with a decrease in triglycerides and a decrease in hunger. However, insulin doses remained very high. These two clinical situations illustrate the importance of early detection of metabolic complications following total body irradiation in pediatric cancers. The introduction of dietary measures such as a low-fat diet was effective. The place of metreleptin in these situations remains to be defined [6]–[9].

### **Progressive Encephalopathy with/without Lipodystrophy: an update.**

**Professor David Araujo-Vilar University of Santiago de Compostela, Spain**

Progressive encephalopathy with or without lipodystrophy (PELD), or Celia encephalopathy (10), is a neurodegenerative disease with a poor prognosis, associated or not with lipodystrophy. This genetic disease involves variants in the BSCL2 gene located on chromosome 11q12.3, and encoding the protein seipin, which has a highly conserved loop in the lumen of the endoplasmic reticulum, two transmembrane domains and a cytosolic C and N-terminal domain. Seipin forms oligomers to have an overall ring structure with the transmembrane domains in the periphery. There are 3 isoforms: BSCL2-203, BSCL2-205/207/210 and BSCL2-201. These isoforms are differentially expressed in tissues with 88% of the BSCL2-203 isoform in the brain, and 78% of the BSCL2-205 form in adipose tissue. Seipin is involved in lipid droplet formation, adipogenesis, lipid homeostasis, mitochondrial function, neuronal function, spermatogenesis. The natural history of PELD is the appearance (or not) of a generalized lipodystrophy (CGL) in the first months of life, with hypertriglyceridemia, hepatic steatosis, then psychomotor retardation around 2 years of age evolving to a neurodegenerative pathology around 4 years of age and convulsions around 4.5 years of age with death around 8 years of age.

Six BSCL2 variants have been identified in this syndrome: c.985C>T with 9 reported cases; c.974dupG with 11 cases and 100% CGL, c.1048C>T with 2 cases, 100% CGL and 100% neurodegenerative syndrome, c.1076dupC with one case, c.566T>A with 2 cases without CGL and c.445C>G with one case. When the mutation affects exon 7 (the Celia seipin), the oligomerization of the seipin is impaired, with formation of large aggregates localized in the nucleus and leading to activation of endoplasmic reticulum stress. This abnormal seipin may impair peroxisome function and biogenesis. Progressive encephalopathy with or without lipodystrophy has a varied phenotypic spectrum, it is of recessive or dominant origin and always has a neurological involvement of variable degree (from language delay to fatal epileptic encephalopathy). In recessive forms, generalized lipodystrophy is frequent, and overexpression of the short transcript of BSCL2 could be responsible for the neurological damage. The pathological mechanisms of these neurological abnormalities are due to the formation of aggregates of this small seipin isoform, leading to reticulum stress and neuronal damage due to intra-nuclear inclusions. The mechanisms of the dominant forms remain unknown.

### **Familial partial lipodystrophy syndromes in Spain.**

**Dr Antía Fernández-Pombo, University of Santiago de Compostela, Spain**

Between 2001 and 2020, 92 patients were diagnosed with familial partial lipodystrophy syndrome in the Lipodystrophy Unit of Santiago de Compostela, Spain. Dr Antía Fernández-Pombo described this cohort.

Of these 92 patients, 75 were followed for a median of 4.7 years (0.5-17.6); 82.7% were women and the median age was 42.7 years. A total of 66 patients had a pathogenic variant in the *LMNA* gene (FPLD2), 5 in the *PPARG* gene (FPLD3) and 4 in the *PLIN1* gene (FPLD4). 70.7% of this cohort had muscle hypertrophy, 64% had phlebomegaly, especially in FPLD2 patients (71.2% versus 20% in FPLD3 patients and 0% in FPLD4) and 41.3% had insulin resistance.

Among the FPLD2 patients, only those with the N466 variant had pancreatitis (20%), triglycerides were higher in the group of FPLD2 patients with the N466 variant and skinfolds were thinner in the FPLD2 R482 group compared to the N466 group. Thus, some phenotypic and metabolic characteristics within FPLD2 patients suggest heterogeneity even within forms due to *LMNA* exon 8 variants.

Adipose tissue loss was less severe in FPLD4 and FPLD3 patients, which may explain a diagnosis at a later age. FPLD3 patients had a higher prevalence of metabolic complications, suggesting that their metabolic severity is not solely due to the defect in adipose tissue expandability. The prevalence of metabolic complications in this cohort is consistent with that previously described in the literature. However, fewer cardiovascular complications were found in these subjects (the prevalence remaining higher than in the general population).

### **Lipodystrophy UK, Dr Rebecca Sanders**

The UK Lipodystrophy Association, represented by Dr Rebecca Sanders, presented the objectives of its organization: 1) to increase awareness of the condition so that an appropriate diagnosis can be made as early as possible, in order to improve the prognosis in the longer term 2) to help improve the quality of life of patients and their families 3) to build a sustainable and active organization. The association has set up a website [www.lipodystrophyuk.org](http://www.lipodystrophyuk.org). It participates in various research projects. For example, an evaluation of chronic fatigue is proposed to lipodystrophy patients in collaboration with the Pain Institute, using mixed quantitative and qualitative methods. The objective is to include 50 patients, who will be evaluated 3 times over a period of 6 to 9 months. This study will start in the summer of 2022. In addition, a survey was conducted to evaluate the care pathway of patients with lipodystrophy. Twenty-five patients and 17 clinicians were interviewed (UK, USA, Canada). Patients reported a difficult journey to final diagnosis. Outside of the specialized service, the patients described the lack of local care. They also express the lack of coordination between care services. Patients most often have to explain to the health professional what lipodystrophy is. The main conclusions of this work are the need for a better knowledge of lipodystrophy within the health care community, and the need for better coordination between the different actors in the care of these patients [11]

### **Reading WAT dysfunction and lipodystrophy through the lens of dysregulated miRNA Dr Margherita Maffei, National Research Council, Institute of Clinical Physiology, Pisa, Italy**

The general objective of this work is to uncover novel signatures of lipodystrophic (LD) syndromes by identifying differentially expressed circulating microRNAs (DE cmiRNAs) and, in turn, to exploit these novel biomarkers to correlate their abundance with typical metabolic derangements of the disease and with WAT/adipocyte dysfunction.

An unbiased approach based on miRNOME profiling performed in a small cohort of LD subjects and matched controls (n=8) allowed to identify 8 DE cmiRNAs. Subsequent step of validation and characterization were performed in larger cohorts (n=30) by quantitative PCR and the results on 6 miRNAs are presented in more detail including 5 member of the miRNA family 320 (a-e) and miRNA 196a5p.

Members a-3p, b, c, e of the 320 family were upregulated, while 320d and 196a-5p were downregulated in LD subjects. The difference remained statistically significant when analysis were performed for subsets of patients defined by specific LD subtypes (e.g CGL, APL, FPLD2 etc), except for FPLD1 which showed a distribution of circulating miRNAs 320 and 196a-5p totally overlapping with that of the controls. Expression of the 6 miRNAs was detected in the adipocyte.

CmiRs-320a-3p showed significant inverse relationships with plasma leptin, typically low in LD, while downregulation of cmiR-320d predicts an altered hepatic profile and higher inflammation.

Gene ontology analysis revealed cell-cell adhesion as a process regulated by 320 miRNAs targets.

Interestingly, the expression of miR196a-5p was not only reduced in the circulation of LD subjects but also found to be lower in LD adipose tissue biopsies. Further, its expression was regulated during the adipogenesis of the human preadipocyte cell line SGBS and transfection of a miR 196a5p mimic in normal condition or upon exposure to protease inhibitors, a treatment reported to impair adipogenesis, resulted in upregulation of typical markers of adipocyte terminal differentiation.

In conclusion we established a correlation between the presence of LD syndromes and an altered abundance of specific circulating miRs 320a-e and 196a-5p. Their expression by WAT and the adipocyte is demonstrated and studies are ongoing to better elucidate the specific source(s) of their dysregulation and to understand if they may constitute molecular switches implied in LD pathogenesis.

### **Genome architecture during adipogenesis**

**Professor Philippe Collas, University of Oslo, Norway**

**Prof. Philippe Collas** works on the **dynamic remodeling of chromatin during the process of adipogenesis** (differentiation of precursor cells into adipocytes). His work shows that chromatin dynamically interacts with the nuclear submembrane protein network of A- and B-type lamins, defining specific functional regions called LADs (lamina-associated domains). LADs, located at the periphery of the cell nucleus, are poor in genes and enriched in heterochromatin, i.e. DNA regions with little transcriptional activity (generating little gene expression). During adipocyte differentiation, LADs are repositioned along chromosomes and can be modified, leading to the expression of genes that were repressed in undifferentiated stem cells, and conversely to the extinction of pluripotency genes. These "waves" of specific gene expression changes induce the commitment of the undifferentiated cell to a specific differentiated lineage (e.g. adipocyte or endothelial). Mutations in the *LMNA* gene, by modifying the structure of LADs, also modify these waves of epigenetic regulation of gene expression, which disrupts cell differentiation, not only into adipocytes, but also into endothelial cells.

### **Dissociating obesity and metabolic complications**

**Professor Antonio Vidal-Puig, University of Cambridge, UK**

Professor Vidal-Puig's work focuses on the study of the expansibility of adipose tissue. The expansion capacity of adipose tissue is not infinite. If this point of maximum expansion is reached, fatty acids are stored ectopically, leading to metabolic complications, this is the concept of lipotoxicity. Adipose tissue fibrosis is linked to local inflammation, leading to an imbalance between collagen synthesis and degradation. GWAS (Genome Wide Association Studies) techniques have allowed the identification of regions of the genome involved in insulin resistance, such as the locus near the *PEPD* (*Peptidase D*) gene. The protein produced by this gene is a peptidase that plays a role in the degradation of collagen, and it is also a ligand of *EGFR* (*Epithelial Growth Factor Receptor*). Decreased expression of this enzyme in human adipose tissue (especially visceral) is associated with release of this enzyme, fibrosis and type 2 diabetes. In mouse models, pharmacological inhibition of *PEPD* is associated with an increase in fibrosis, blood glucose and insulin resistance. *PEPD* is also expressed in macrophages, immune cells involved in adipose tissue inflammation. The decrease in the enzymatic activity of *PEPD* in macrophages contributes to adipose tissue dysfunction, hepatic steatosis and insulin resistance. In adipose tissue, the release of this protein by macrophages leads, via its role as an *EGFR* ligand, to an alteration of adipogenesis, fibro-inflammation and insulin resistance of adipose tissue (autocrine and paracrine pathways) [12], [13].

### **Natural history and disease progression in generalized lipodystrophy**



**Dr. Baris Akinci, Dokuz Eylul University, Turkey**

Dr. Baris Akinci presented findings from the Turkish Lipodystrophy Registry regarding the natural history of congenital (CGL) or acquired generalized lipodystrophy (AGL). Unfortunately, Turkey has little access to treatments to help control metabolic disorders in patients with lipodystrophy. In particular, in Turkey, the prescription of GLP1 agonists is conditional on the presence of obesity, which prevents patients with lipodystrophy from benefiting from them. Metreleptin is also difficult to access. Thus, the longitudinal description of Turkish patients with lipodystrophy is somewhat similar to that of the spontaneous course of the disease. The study of the Turkish cohort, comprising more than 70 patients with different forms of generalized lipodystrophy (GL) (of acquired or genetic origin, over 60% women), indicates that the disease is severe, leading to early metabolic complications (diabetes in more than half the patients, hypertriglyceridemia in nearly 90% of patients, liver steatosis in more than 80% of patients; all commonly diagnosed in the first decades of life). Also, end-organ complications are quite prevalent in GL and can develop early in life. These organ complications may lead to serious morbidity and mortality at relatively young ages. Patients with CGL2 generally have an earlier and more severe liver disease than patients with CGL1. In the CGL1 group, women are younger than men at diagnosis of diabetes and have higher HbA1c and triglyceride concentrations. In contrast to what has been previously reported, patients with CGL4 may have overt diabetes. Bone cysts associated with CGL can be complicated by fractures. The most common causes of mortality are related to metabolic and/or infectious complications.

**The International Association of Families and Patients with Lipodystrophy, AELIP, Mrs. Naca Perez de Tudela and Mr. Juan Carrion Tudela**

AELIP is an International Association of Relatives and People Affected by Lipodystrophies that was created in 2012 to continue the legacy of Celia Carrión Pérez de Tudela and whose main objective is to improve the quality of life of people and families living with Lipodystrophy in the world.

To this end, it develops 2 priority areas around which the work and efforts of this entity revolve. AELIP supports and promotes research into Lipodystrophies, assigning 75% of its annual budget to the 2 lines of research that currently exist in Spain. Since its foundation, AELIP has donated a total of €240,000 to Lipodystrophy research projects.

2. AELIP implements and develops a portfolio of services that aims to respond to all the social and health needs that people and families affected by an infrequent lipodystrophy syndrome. Its main services are: information and orientation in Lipodystrophies, psychological support, dietetic counseling and legal advice support. AELIP works hand in hand with a committee of experts at an international level that responds to the medical consultations it receives and positions it as a reference entity at a global level.

AELIP considers networking to be essential, which is why it has been coordinating and implementing World Lipodystrophy Day since its foundation, which has been commemorated since 31 March 2013.

AELIP is also a member of the Spanish Federation of Rare Diseases (FEDER), the Spanish Society of Lipodystrophies (SEL), the Spanish Society of Endocrinology and Nutrition (SEEN), EURORDIS and the European Consortium of Lipodystrophies (ECLIP) at the European level and at the international level of the Ibero-American Alliance of Rare Diseases (ALIBER) and the World Network of Rare Diseases (RDI). MORE INFO at [www.aelip.org](http://www.aelip.org) [14].

**Caveolin-1, caveolae and congenital generalized lipodystrophy****Professor Corinne Vigouroux, CRM PRISIS, Paris, France**

The *CAV1* gene encodes caveolin-1, a major protein of caveolae, which are plasma membrane microdomains involved in cell signaling. Until recently, only one patient had been described with a homozygous null variant of *CAV1*, associated with generalized congenital lipodystrophy (CGL3, Kim et al, JCEM 2008). We explored a consanguineous family referred for generalized

congenital lipodystrophy by next-generation sequencing, and clinical, radiological and metabolic investigations were performed. We studied skin fibroblasts from the index case and the previously reported patient. We identified a novel homozygous *CAV1* p.(His79Glnfs\*3) variant, which predicts the synthesis of a protein truncated in its N-terminal portion, in 4 patients aged 8 months to 18 years with generalized lipodystrophy, insulin resistance, low HDL cholesterol and/or high triglycerides. Dysphagia due to esophageal achalasia was diagnosed in the two affected adolescents, aged 15 and 18 years. The heterozygous relatives (n=9) were asymptomatic. We showed, in cultured fibroblasts from two patients, a complete absence of caveolae at the plasma membrane and a loss of protein expression of caveolin-1 and its partners caveolin-2 and cavin-1. These abnormalities were accompanied by insulin resistance with increased oxidative stress and premature cell senescence. This study shows that pathogenic variants of *CAV1* lead to a syndrome of congenital lipodystrophy with metabolic complications, of autosomal recessive transmission. The defect in caveolin-1 expression and/or the absence of caveolae induce specific clinical manifestations, including esophageal achalasia requiring specific management. In addition, other heterozygous variants of the *CAV1* gene, which predict alterations of the C-terminal protein, have been associated with other phenotypes: partial lipodystrophy with neurological disorders (one family), pulmonary arterial hypertension (a few families), and neonatal progeroid syndrome in two patients (heterozygous *de novo* variants) [15].

### **Set-up of a patient therapy education program on lipodystrophy syndromes.**

#### **Dr Camille Vatie, Sorbonne University Paris**

Therapeutic education (TVE) has been defined by the World Health Organization as helping patients acquire or maintain the skills they need to manage their lives with a chronic disease. The WHO estimates that 80% of patients followed in the city have a chronic disease, so the challenge of TPE is major. Numerous publications have shown the beneficial effect of TVE on objective parameters and on patients' quality of life in many chronic diseases, including diabetes, with a decrease in HbA1c from 0.1 to 0.9%, better compliance with treatment and a better quality of life. For rare diseases, few data exist to date. Lipodystrophic syndromes combine metabolic and cardiovascular complications, low self-esteem, and a significant impact of the disease on quality of life. In France, the rare disease plan has allowed the financing of FTE projects, including the "LIPEA" program for children and adults with lipodystrophic syndromes in France. This program was developed jointly with the medical, nursing, dietetic and psychology teams of the endocrinology departments of Saint Antoine and Robert Debré in Paris, the regional hospital of Lille and the University Hospital of La Réunion. Based on the needs of the patients, identified through a questionnaire distributed by the patient association AFLIP, this program was built around 4 axes, proposing a whole day in small groups (4 to 6 patients), suffering from CGL or FPL, of the same sex and age group. The first workshop is a medical workshop to understand the disease, with adipocytes to be placed on body diagrams of non-lipodystrophic and lipodystrophic patients. The second is a dietetic workshop to define together how to eat healthily and to elaborate recipes; the third is a psychological workshop to talk about the disease with emoticons as tools, and the last one is a socio-aesthetic workshop to work on the body image. Since 2021, 17 patients have participated in this program in Paris. The impact of this program will soon be evaluated on metabolic parameters but also on quality of life, anxiety, self-image and self-esteem.

### **Metabolic effects of metreleptin in patients with lipodystrophy: a real-life experience in the French cohort**

#### **Dr Hélène Mosbah, PRISIS, Hôpital Saint Antoine, Paris**

This is a French retrospective study, conducted within the PRISIS network, in patients with lipodystrophy who were treated with metreleptin between 2009 and 2020 [16]. Clinical and biological data were collected before treatment initiation, 1 year after treatment initiation, and in the long term. Forty-seven patients were included in this work, 28 with generalized lipodystrophy and 19 with partial lipodystrophy. The median overall follow-up time was 37

months. In patients with generalized lipodystrophy, HbA1c and triglycerides decreased significantly at 1 year and longer. Body mass index (BMI), liver enzymes and albuminuria were significantly reduced at 1 year. In patients with partial lipodystrophy, the course was different. HbA1c did not decrease. Triglycerides and BMI decreased significantly at 1 year. Patients with uncontrolled diabetes and/or high triglycerides were mostly responsive to treatment. In patients with partial lipodystrophy, patients who responded to diabetes were less often on insulin and had lower serum leptin levels than non-responders.

### **EPHX1 mutations cause a lipotrophic diabetes syndrome due to impaired epoxide hydrolysis and increased cellular senescence**

**Dr Isabelle Jéru, National Reference Centre for Rare Diseases of Insulin Secretion and Insulin Sensitivity, Assistance Publique-Hôpitaux de Paris, France**

The discovery of the first epoxide hydrolase (EH), EPHX1, dates back more than 40 years and today 5 genes encoding EHs are known. EHs are enzymes that regulate cellular homeostasis by hydrolyzing various epoxide substrates into less reactive diols. The functions of EHs remain partly unknown and no pathogenic variants in this class of genes have been reported in humans to date. This study describes two independent families that were subjected to trio exome analyses. The effect of the identified EPHX1 variants was modeled in different cell systems: HEK293 cells expressing normal and mutated forms of the protein, murine 3T3-L1 pre-adipocyte cells and human adipocyte stem cells (ASCs) in which EPHX1 was inactivated by a CRISPR-Cas9 system, as well as patient fibroblasts. The authors identified two de novo pathogenic variants located in the catalytic site of EPHX1 in patients with complex lipotrophic diabetes characterized by adipose tissue loss, insulin resistance, and multiple other organ involvement. Analysis of HEK293 cells revealed that these variants led to aggregation of the protein in the endoplasmic reticulum and a loss of its epoxide hydrolysis activity. Knockout of *Ephx1* in 3T3-L1 and ASCs abolishes adipocyte differentiation and inhibits the insulin response. The study of these two cell types also reveals a major oxidative stress and cellular senescence, observations confirmed on patient fibroblasts. Finally, a beneficial effect of metreleptin treatment was observed in patients. This translational study underlines the importance of epoxide regulation in adipocyte function and insulin resistance and provides new insights into the physiological roles of EHs in humans.

### **An update on Lipodystrophy Research from Michigan: two evolving stories.**

**Professor Elif Oral, University of Michigan, USA**

Professor Elif Oral reported on the 3 missions of his research group: to discover new forms of lipodystrophy, to discover new mechanisms and to discover new treatments.

In total through 2018, 269 patients were referred to his center for "lipodystrophies." Among them, 191 were patients with lipodystrophies or relatives, 43 had no real lipodystrophy and 35 patients had other atypical pathologies. From these patients, his team was able to highlight the discovery of new clinical phenotypes with variants of known genes: *LMNA*, *PPARG*, *MFN2*, (lipodystrophy, lipomatosis), *MC4R* (monogenic obesity); the discovery of new variants of known genes: *PI3KR1*, *FBN1* (lipodystrophies), *SH2B*, *SRC1* (heterozygous monogenic obesity), groupings of phenotypes but without gene association (acquired generalized lipodystrophy with immune dysregulation, abrupt onset obesity with autoimmune terrain, patients with supra sellar tumors and fat distribution abnormalities), or new target genes among families or index cases (*EBF2*, whose expression is thought to be important for adipogenesis).

### **Investigating potential therapeutic approaches and molecular pathophysiology in lipodystrophic seipin deficient mice**

**Professor Justin Rochford, University of Aberdeen, UK**

Prof. Rochford presented the recent results obtained by his research group using the seipin gene-validated mouse model. This model mimics the phenotype of congenital generalized

lipodystrophy, with the exception of hypertriglyceridemia, which is not observed in the mouse model of the disease. The increase in beta-pancreatic cell mass in this model is indicative of the pancreatic response to extreme insulin resistance. Concerning the increased susceptibility to bacterial infections, which has been described as an important cause of mortality in patients with CGL, it was not found in the mouse model in which seipin invalidation was restricted to myeloid cells. This suggests that the infectious pathologies in these patients are not due to seipin deficiency, and more likely result from underlying metabolic disorders. This mouse model has also allowed to explore several therapeutic avenues in congenital generalized lipodystrophy.

#### **Anti-metroleptin antibody: what do we know?**

**Professor Ferruccio Santini and Professor Giovanni Ceccarini, Obesity and Lipodystrophy Center at the University Hospital of Pisa, Italy**

The Italian team recalled that any protein treatment could potentially induce the production of antibodies, even if the treatment was initiated when the said protein is not totally absent from the organism (examples of hormonal treatments by insulin, ACTH, PTH, EPO or by cytokines: TNF, interferons). The antibodies produced are polyclonal, of different isotypes (IgM, Ig G, IgE) and of different subclasses. They are observed in up to 70% of patients and can bind to the protein and sometimes neutralize its activity. Metreleptin is a 16kDa protein synthesized by *E. Coli*. In the American cohort FHA101 (obese or lipodystrophic), treated with metreleptin, antibodies measured by ELISA were found in a large majority of patients: 96-100% of obese patients and 86-92% of patients with lipodystrophy. The peak of the antibody concentration usually occurs between 3 and 6 months after the beginning of the treatment but can occur even after two years of treatment and the concentration decreases thereafter. The presence of antibodies affects the measurement of leptin concentration. 3 patients with obesity developed neutralizing antibodies concomitantly with weight regain. Four patients with generalized lipodystrophy also developed neutralizing antibodies concomitantly with worsening of metabolic control, one of whom had disappearance of neutralizing antibodies during metreleptin treatment.

The Italian team discussed clinical cases characterized by the appearance of neutralizing antibodies and reported one case of disappearance of these antibodies after continuing the treatment at increased dose of metreleptin. Because of the difficulty of standardizing the measurement of leptin antibodies, an alternative would be to measure the concentration of leptin in serum after precipitation with polyethylene glycol (PEG), an easy and rapid method. Many questions remain concerning these antibodies: do they interfere with the half-life of metreleptin? Do they induce leptin-resistance and, if so, by what mechanisms (blood-brain barrier transport? binding to its receptors)? When and how is it necessary to measure them and what is the best strategy to encompass leptin resistance induced by neutralizing antibodies ? [17], [18]

#### **Seipin localizes at Endoplasmic-reticulum/mitochondria contact sites to control mitochondria calcium import and metabolism in adipocytes,**

**Professor Xavier Prieur, University of Nantes, France**

Loss-of-function variants of the *BSCL2* gene encoding the endoplasmic reticulum (ER)-localized seipin protein lead to generalized lipodystrophy. The objective of this work is to better understand the associated physiopathological mechanisms, which remain poorly understood. The presented work describes mitochondrial abnormalities and altered oxygen consumption in cells of seipin-deficient patients. Seipin enrichment is observed at ER-mitochondrial contact sites (MAM) in human and mouse cells. Immunoprecipitation followed by mass spectrometry analysis showed an interaction between seipin and calcium regulators, in particular SERCA2, IP3R and VDAC. In a 3T3-L1 cell model with *BSCL2* gene siRNA, it was shown that loss of seipin results in a defect in mitochondrial calcium import accompanied by a generalized reduction in Krebs cycle metabolites and ATP levels. The authors then sought to determine the effect of nutritional status on seipin function using a proximity ligation assay. Association

of seipin with MAM calcium regulators is stimulated by fasting-type stimuli, whereas association of seipin with lipid droplets is promoted by lipid loading. In a KO mouse model, inducible deletion of seipin results in mitochondrial dysfunction preceding the development of metabolic complications. Taken together, these data suggest that seipin controls mitochondrial energy metabolism by regulating mitochondrial calcium influx at MAMs. In seipin-deficient adipose tissue, the reduced production of ATP alters the properties of adipocytes, and could thus contribute to the pathogenesis of lipodystrophy.

#### **Natural course of Lipodystrophy syndromes: a 10 year-observational study**

**Dr Ekaterina Sorkina, MD, PhD, Endocrinology Research Centre, Moscow, Russia**

In 2011 the first family with familial partial lipodystrophy type 2 (FPL2) was diagnosed by Pr Sorkina's team in Russia. Since 2012, an active search for patients with different lipodystrophy syndromes was started and by 08.04.2022, 100 patients had been identified, 70 of which are still being actively followed-up. Among them, 7 died and 23 were lost of follow-up. To the present date, only 1 of the patients with congenital generalized lipodystrophy type 4 (CGL4) receives metreleptin therapy, 5 FPL patients are in the process of getting access to this therapy.

So, the aim of this project was to identify the main types of lipodystrophy syndromes in Russia and the main causes of death in this population.

The structure of lipodystrophy syndromes in the 70 surviving patients in this cohort was the following:

- Generalized lipodystrophy (GL):10 patients, among them 5 with CGL (3 genetically proved among whom 2 *AGPAT2*, 1 *BSCL2*) and 5 with acquired GL (AGL)
- Partial lipodystrophy (PL): 50 patients, 4 of them with APL, 46 with FPL - 23 of which were genetically proven among whom 11 FPL2 (*LMNA*), 7 FPL3 (*PPARG*), and 5 FPL4 (*PLIN1*).
- Multiple symmetric lipomatosis - 2
- Lipodystrophy Associated with progeroid syndromes: 8, among which 5 *LMNA*, 1 *WRN*, 1 *POLD1*, and 1 another type

The causes of death in the 7 deceased patients were:

- gastrointestinal bleeding in a 40 y.o. CGL4 female with gigantic trophic ulcers
- acute thrombosis after COVID-19 in a 45 y.o. *WRN* patient
- acute respiratory insufficiency due to H1N1-associated pneumonia in a 5 y.o. male with AGL and APS1
- pancreatic cancer - FPL of unknown etiology, male, 52 y.o.
- multiple organ system failure - AGL + neurofibromatosis type 1, male, 36 y.o.
- acute myocardial infarction, heart failure - FPL2 (*LMNA* p.R482W), male, 60 y.o., father of the patients
- extensive myocardial infarction - FPL3, (*PPARG* p.R212Q), male, 65 y.o., uncle of the patient

#### **Four-year results of the ECLip Registry**

**Professor Martin Wabitsch and Dr Julia von Schnurbein, University of Ulm, Germany**

**Dr Julia Von Schnurbein** presented some results about the European ECLip registry, which she coordinates with Prof Martin Wabitsch at the University of Ulm (Germany) and Prof David Araujo-Vilar (Santiago de Compostela, Spain). The establishment of the ECLip lipodystrophy registry started at the end of 2017, and the principles of its operation have been published in Orphanet Journal of Rare Diseases [1]. Currently 17 European clinical centers contribute to the registry, and 517 patients have been included. Six new centers will join the project soon. Eighty percent of the patients included are women, 54% have familial partial lipodystrophy and 18% have congenital generalized lipodystrophy. At the molecular level, the main etiological form of lipodystrophy represented is partial lipodystrophy related to *LMNA* variants (FPLD2), which represents 39% of the patients included. Metabolic complications are frequent, with nearly 80% of patients presenting with dyslipidemia, more than 50% with diabetes, and more

than 50% with liver steatosis. Cross-sectional data from the registry will be published in the future under the auspices of ECLip.

## CONCLUSION and PERSPECTIVES

This publication allows the ECLip network to achieve one of his mission, which is to increase knowledge in the field in cooperation with the patients advocacy groups. Clinical experience and fundamental research presented during the Cambridge meeting show the advances in the field with cooperation from Eastern to Western parts of the world. Noticeably, the data from each country registry and from the European registry are now sufficient to show that lipodystrophy syndromes are present everywhere, with a wide clinical and genetic heterogeneity, but are often underdiagnosed. New specific causes of lipodystrophy and mechanisms of insulin resistance have been identified and further research is ongoing. The ECLip network is currently working on a new classification of lipodystrophy syndromes aiming to help diagnosis. Future collaborations aim to improve the therapeutic strategies. and define new approaches based on better understanding of the mechanisms involved.

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