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ABSTRACT

Lipodystrophy syndromes are rare diseases primarily affecting the development or maintenance of the adipose tissue but are also distressing indirectly multiple organs and tissues, often leading to reduced life expectancy and quality of life. Lipodystrophy syndromes are multifaceted disorders caused by genetic mutations or autoimmunity in the vast majority of cases. While many subtypes are now recognized and classified, the disease remains remarkably underdiagnosed. The European Consortium of Lipodystrophies (ECLip) was founded in 2014 as a non-profit network of European centers of excellence working in the field of lipodystrophies aiming at promoting international collaborations to increase basic scientific understanding and clinical management of these syndromes. The network has developed a European Patient Registry as a collaborative research platform for consortium members. ECLip and ECLip registry activities involve patient advocacy groups to increase public awareness and to seek advice on research activities relevant from the patients perspective. The annual ECLip congress provides updates on the research results of various network groups members.

1. Introduction

Lipodystrophy syndromes are progressive rare diseases characterized by a generalized or partial lack of adipose tissue. Loss of adipose tissue in lipodystrophy leads to reduced fat storage capacity and leptin deficiency, an essential adipocyte-derived hormone that plays a pivotal role in energy homeostasis and metabolism. People living with lipodystrophy are at high risk for severe metabolic disease and life-threatening organ complications. Metabolic abnormalities may develop at relatively early ages and include, but are not limited to, diabetes, severe hypertriglyceridemia, and hepatic steatosis. Also, molecular characteristics of lipodystrophy and associated autoimmune features in acquired lipodystrophies contribute to peculiar characteristics of each subtype of lipodystrophy and specific disease burden. Lipodystrophies are still remarkedly under-recognized.

The European Lipodystrophy Consortium (https://www.ECLip-web.org/lipodystrophies), founded in 2014, brings together more than 30 research groups from 19 European countries and from other parts of the World. In 2016, the consortium established the European Registry of Lipodystrophies, an international patient registry collecting clinical and molecular data from centres all over Europe and neighbouring countries. Currently, there are around 600 registered patients and the background and structure of the registry has been already described [1]. Some ECLip centers are also active members of Endo-ERN and MetabERN networks and contribute with their expertise to the improvement of care in the rare diseases field at the European Union level.

The ECLip network organizes a yearly meeting that brings together leading experts on the disease joining from all the continents. The annual ECLip congress gives an update on the research results of the various network groups. The talks presented during the meeting held in Pisa in September 2023 are summarized in an abstract form as presented by the leading authors.

2. Abstracts of the ECLip meeting, Pisa, 2023

2.1. Nuclear envelope-linked lipodystrophies

*2.1.1. E. Schena, A. Gambineri, G. Lattanzi**

*2.1.1.1. *Giovanna Lattanzi (lattanzi@area.bo.cnr.it).* Lipodystrophies linked to defects of the nuclear envelope include partial or generalized forms caused by mutations in *ZMPSTE24* or *LMNA* gene. Defects in their gene products elicit accumulation of prelamin A forms and/or production of mutant prelamin A. *LMNA*-linked partial lipodystrophies are type 2 Familial Partial Lipodystrophy (FPLD2) and type A Mandibuloacral Dysplasia (MADA), while generalized lipodystrophy is observed in type B Mandibuloacral Dysplasia (due to *ZMPSTE24* mutations), atypical-Werner syndrome, atypical Progeria and Hutchinson-Gilford Progeria. The pathogenesis of lipodystrophic laminopathies involves altered determination of adipocyte precursors. FPLD2 preadipocytes from the neck, a depot of brown adipose tissue, can aberrantly differentiate towards the white lineage [2].

Methods Our studies are currently aimed at investigating the pathways affected by mutant prelamin A, which alter preadipocyte

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fate. Our focus is on the mineralocorticoid receptor (MR), a protein of the nuclear receptor superfamily that has been implicated in adipose tissue determination [3].

Results Compared to brown adipocytes from healthy donors, where MR was retained in the cytoplasm, FPLD2 brown adipocytes showed MR accumulation at the nuclear envelope and in the nucleoplasm and formation of enlarged lipid droplets, a condition typical of white adipocytes. The MR inhibitor spironolactone reduced MR import in the nucleus of FPLD2 adipocytes and redirected their differentiation towards a brown-like phenotype. Preliminary clinical studies suggest a positive effect of spironolactone in FPLD2 brown adipose tissue.

Conclusion MR is a new player in FPLD2 pathogenesis and deserves further investigation as a disease effector and potential therapeutic target in nuclear envelope-linked lipodystrophies.

2.2. Defining the effects of GLP-1 receptor agonists in lipodystrophy

2.2.1. Justin J. Rochford (j.rochford@abdn.ac.uk)

Individuals with lipodystrophies typically suffer from significant metabolic diseases including lipoatrophic diabetes, hepatic steatosis and hyperphagia. Better therapies for affected individuals are urgently needed. Glucagon like peptide-1 receptor (GLP-1R) agonists are widely prescribed for type 2 diabetes. However, published studies of their use to treat lipodystrophy are limited. To understand in greater detail the potential benefits of these drugs in individuals with lipodystrophy we have examined the therapeutic effects of the GLP-1R agonist, liraglutide, in mice with congenital generalised lipodystrophy. Our work has revealed that liraglutide significantly improved insulin, glucose and pyruvate tolerance in seipin knockout mice. Once daily liraglutide injections for 14 days modestly reduced food intake and significantly improved hepatomegaly associated with steatosis. Moreover, liraglutide enhanced insulin secretion in response to glucose challenge and improved glucose control. Overall, these studies provide important insights regarding the effects of GLP-1R agonists for treating lipodystrophy, better informing their use to improve the health of individuals with this condition.

2.3. Loss of PLAAT3 phospholipase induces a mixed lipodystrophic and neurological syndrome due to an alteration of the PPARγ signaling pathway

*2.3.1. N. Schuermans, S. El Chehadeh, D. Hemelsoet, J. Gautheron, M.C. Vantyghem, S. Nouioua, M. Tazir, C. Vigouroux, M. Auclair, E. Bogaert, S. Dufour, F. Okawa, P. Hilbert, N. Van Doninck, M.C. Taquet, T. Rosseel, G. De Clercq, E. Debackere, C. Van Haverbeke, F.R. Cherif, J. Andoni Urtizberea, J.B. Chanson, B. Funalot, F.J. Authier, S. Kaya, W. Terryn, S. Callens, B. Depypere, J. Van Dorpe, Program for Undiagnosed Diseases (UD-PrOZA), B. Poppe, F. Impens, N. Mizushima, C. Depienne, B. Dermaut, I. Jéru**

*2.3.1.1. *Isabelle Jéru (isabelle.jeru@aphp.fr).* *Introduction* PLAAT3 is a phospholipase, mainly expressed in adipose tissue and in the nervous system. It is a potential therapeutic target for metabolic syndrome, as PLAAT3 deficiency in mice protects against obesity.

Methods Exome and genome sequencing led to the identification of *PLAAT3* pathogenic variants in humans. The metabolic consequences of PLAAT3 deficiency on murine and human adipose tissue were determined by a multi-omics approach (transcriptomics, proteomics and lipidomics). The impact of the loss of PLAAT3 activity on human adipocyte differentiation and functions was assessed using a CRISPR-Cas9 genome editing approach.

Results We identified seven patients from four independent consanguineous families carrying homozygous truncating *PLAAT3* variants. These patients presented with a lipodystrophic syndrome, associating adipose tissue loss and metabolic complications, as well as variable neurological damage, including demyelinating peripheral neuropathy and/or intellectual disability. Multi-omic analysis of adipose tissue from *Plaat3*$^{-/-}$ mice and patients showed on the one hand a membrane enrichment in phospholipids, and on the other hand an inhibition of the PPARγ signaling pathway, one of the main transcription factors controlling adipocyte differentiation. We also observed that inactivation of PLAAT3 by CRISPR/Cas9 in human adipocyte stem cells induced insulin resistance and impaired PPARγ-mediated adipocyte differentiation.

Conclusion These results demonstrate the involvement of PLAAT3 in a complex autosomal recessive lipodystrophic syndrome combining loss of adipose tissue, metabolic manifestations and neurological signs. At the adipocyte level, PLAAT3 deficiency induces an alteration of the lipid profile and a major defect in cell differentiation. The consequences of PLAAT3 inactivation at the neurological level remain to be evaluated.

This work has been accepted for publication in *Nature Genetics* in September 2023.

2.4. Molecular basis of acanthosis nigricans in genetic syndromes of severe insulin resistance

*2.4.1. S. Sánchez-Iglesias, S. Cobelo-Gómez, A. Antelo-Abeijón, A. Níñez-Diaz, L. Rodríguez-Sobrino, A. Tahoces-Rodríguez, E. Díaz-López, T. Prado-Moraña, A. Fernández-Pombo, D. Araújo-Vilar**

*2.4.1.1. *David Araújo-Vilar (david.araujo@usc.es).* Acanthosis nigricans (AN) is a skin lesion related to conditions associated with insulin resistance (IR), and, therefore, hyperinsulinemia. In general, the severity of these lesions is linked to plasma insulin levels, being especially severe in disorders related to variants in the insulin receptor (Rabson-Mendenhall syndrome, R-M) or in congenital generalized lipodystrophy (CGL). The pathogenetic mechanisms of AN are not known, but it has been postulated that insulin activation of the IGF-1 receptor is involved in the hyperproliferation of keratinocytes and dermal fibroblasts in these skin lesions.

Aim To evaluate the role of the IGF-1 receptor in AN and its relationship with the MAPK, PI3K-AKT-mTOR and Wnt-beta-catenin pathways in dermal fibroblasts from patients with severe IR syndromes [4–6].

Methods Primary dermal fibroblasts were obtained from a healthy subject, a patient with R-M syndrome, a patient with CGL type 2, and 2 patients with CGL type 2 chronically treated with metreleptin. Fibroblasts were cultured under three conditions: basal, insulin, and insulin plus linsitinib (an insulin and IGF-1 receptor inhibitor). The proliferation rate was quantified with Ki67 staining. Using Real-Time qPCR, the expression of the following genes was quantified: *MAP3K5*, *MAPK1*, *ELK1*, *CCNC*, *PI3KR1*, *MTOR*, *GSK3B* and *CTNNB1*.

Results Under basal conditions, only R-M fibroblasts showed a higher proliferation rate (60%), while in those from CGL2 patients previously treated with metreleptin the proliferation rate was significantly lower (–41%). Insulin treatment induced greater proliferation only in fibroblasts from CGL2 patients not treated with metreleptin (21%). Linsitinib treatment reduced the proliferation rate in all fibroblast lines studied (21–43%). In the basal situation, the expression of all the genes studied was markedly increased in the R-M fibroblasts (300–3000%), and in some, and to a lesser extent (39–260%), of those from CGL2, while it was significantly reduced in CGL2 fibroblasts pretreated with metreleptin (–46–80%). Treatment with insulin increased the expression of all the genes studied in control fibroblasts and linsitinib reduced such expression in almost all of them. In R-M fibroblasts, insulin increased the expression of *MAP3K5*, *ELK1* and *GSK3B*, while linsitinib reduced the

expression of *ELK1*, *PI3KR1*, *MTOR* and *GSK3B*. In CGL2 fibroblasts, insulin increased the expression of *MAP3K5* and *GSK3B*, while linsitinib reduced the expression of *GSK3B*. In CGL2 fibroblasts from patients treated with metreleptin, insulin increased the expression of *ELK1*, *CCNC*, *PI3KR1*, *MTOR*, *GSK3B*, and *CTNNB1*, while linsitinib decreased the expression of *ELK1*, *CCNC*, *PI3KR1*, and *MTOR*.

Conclusions Fibroblast proliferation is much more pronounced in extreme IR syndromes (R-M) and inhibition of the IGF-1 receptor reduces it. Our results suggest that different pathways regulated by this receptor and involved in cell proliferation are overactivated especially in R-M syndrome. Strikingly, prior chronic treatment with metreleptin reduces the proliferation rate and normalizes the expression of the studied genes.

2.5. Short stature, lipodystrophic syndrome, and cilia defects: clinical and cellular findings

2.5.1. C. Vigouroux, E. Capel, K. Perge, M. Nicolino*
*2.5.1.1. *Corinne Vigouroux (corinne.vigouroux@inserm.fr).* This study, performed with the team of Prof. Marc Nicolino (Department of Pediatric Endocrinology, Lyon University Hospital, France), aims to describe the endocrinological and metabolic features associated with SOFT syndrome and to decipher their pathophysiological mechanisms. SOFT syndrome (Short stature, Onychodysplasia, Facial dysmorphism, hypoTrichosis) is due to biallelic variants in the *POC1A* gene encoding a centriolar protein involved in the formation of primary cilia and centrosomes. Insulin resistance was already reported in several affected patients [7–9] but the cellular mechanisms involved remain poorly known. Two female patients of 9.75 and 19 years-old, investigated for severe growth retardation with dysmorphic features, were diagnosed with SOFT syndrome due to novel biallelic *POC1A* mutations. Apart from the classical signs of the disease, both patients showed signs of resistance to IGF1 and to insulin, with glucose tolerance abnormalities, liver steatosis, and dyslipidaemia. They presented a central distribution of body fat, but total fat mass and leptinemia were not decreased. Skin fibroblast cultures from both patients showed the absence of POC1A protein expression, with primary cilia abnormalities, decreased cellular proliferation, senescence, and impaired activation of insulin and IGF1 signaling pathways. Primary cilia were previously shown to be involved in the recruitment of insulin and IGF1 receptors to the plasma membrane [10,11]. Immunoprecipitation studies showed that the amount of insulin and IGF1 receptors associated with cilia in the patients' fibroblasts was decreased as compared to control cells. The ability of insulin to bind to its receptor, which was studied in fibroblasts from one patient, was also decreased. CRISPR/Cas9-mediated deletion of *POC1A* was performed in human adipocyte stem cells (collaboration Dr Jérémie Gautheron, Saint-Antoine Research Center, Paris). This cell model recapitulated the defects in ciliogenesis, insulin and IGF1 signaling, and cellular proliferation and senescence observed in patients' fibroblasts. Importantly, it also showed that the absence of POC1A expression impairs adipocyte differentiation. This study shows that *POC1A* null variants could result not only to the morphological abnormalities associated with SOFT syndrome, but also to insulin and IGF1 resistance and adipocyte dysfunction. Abnormalities in protein transport and adipose tissue dysfunction have been reported in other ciliopathies (Bardet-Biedl syndrome, Alström syndrome) [12,13]. In addition, variants in *PCNT* encoding the centrosomal pericentrin protein are responsible for a syndrome combining growth retardation, osteodysplasia, insulin resistance and adipocyte differentiation defects [14]. This suggests that the metabolic phenotype associated with SOFT syndrome and other ciliopathies could result from similar pathophysiological mechanisms.

2.6. Results and conclusions of the first study of quality of life in patients with lipodystrophy in Europe and Iberoamerica

*2.6.1. Jose Jerez Ruiz, Juan Carrion Tudela, Naca Perez De Tudela, Asociación AELIP**
*2.6.1.1. *Asociación AELIP (siolip@aelip.org).* *Introduction* Infrequent lipodystrophies (classified as rare, ultra-rare and, in short, chronic diseases) cause a deterioration in the quality of life of the people who suffer from them, as they end up affecting different personal areas such as work or social life, among others. Frequently, the limitations of the disease increase dependency and provoke crisis situations that end up triggering, in the worst cases, various hospital admissions. These limitations vary according to the type of lipodystrophy, as well as the profile of the people who suffer from it. Quality of Life has become an indicator of the evolution of the state of health of these patients, as an expression of a strategy aimed not only at prolonging life, but also at alleviating the symptoms of the disease and maintaining, as far as possible, vital functioning [15,16].

Objectives The main objective of this study, is to know the impact that psychosocial aspects have on the health/quality of life of people affected by Lipodystrophy and their families.

Methods The study was developed using the SF-36 questionnaire and a specific complementary annex on well-being and needs of people with lipodystrophy, elaborated by the AELIP research team. Participation was completely voluntary and anonymous. The questionnaires were administered electronically using a generic survey platform (GoogleForms).

Results From the sample of 167 patients who had participated in this study, the following results were extracted. On a scale of 0–1, the SF36 questionnaire on the state of health reflects a mean of 0.52, which is considered remarkably low when compared to 0.90 in the general population and 0.80 in mild pathologies. 40% of the participants lived in Spain, 18% in Europe and the remaining 42% in Latin America. Congenital lipodystrophy (CGL) Berardinelli Seip syndrome is the most common type of lipodystrophy, representing 48.5% of the total sample. The prevalence of this disease was higher in females than in males. The symptoms of disease suffering had begun in childhood in 61.7% of the cases receiving a diagnosis before the age of 3 years. The remaining 39.3% reported having been diagnosed after the age of 5 years, which shows a "diagnostic delay". The distance to the referral hospital was a determining factor for patients when it came to undergoing more than one annual medical check-up. 82.6% of patients said that their financial situation allowed them to eat a balanced diet. 55% of patients indicated that they followed a treatment that had allowed them to slow down the disease and the associated metabolic complications, improving their quality of life. 48% of those surveyed considered that social relationships had been greatly affected since they had been diagnosed. Information and guidance about the pathology was of vital importance in 92.8% of cases. 86% of the responders had a reference professional in their country to whom they turned in case of need.

2.7. Activities of Lipodystrophy UK

2.7.1. Rebecca Sanders (lipodystrophyuk@hotmail.com)

The Lipodystrophy UK Charity, represented by Rebecca Sanders, presented activities over the last year, in particular, their fully funded patient day. Highlights included more than 90 patients and family in attendance, provision of travel expenses, accommodation, and lipodystrophy-friendly meals, a full agenda of speakers including clinical experts, dieticians, research, mental health, body image, fatigue, and patient stories. A break-out room for children with educational and fun activities, plus recording sessions to capture individual patient stories. In addition, it participates in various

research projects. For example, its study, "A patient-led assessment of chronic fatigue in Lipodystrophy using Fatigue Evaluations (LiFE)", in collaboration with the University of Cambridge and the Newcastle Centre for Fatigue Research, is underway. Lipodystrophy UK is involved in the Scottish Medicines Consortium (SMC) application for drug funding. Resources include a recipe book and disability application support. They are also participating in the Global Patient Leaders collaboration, which includes UK, Germany, Spain, Italy, France, USA, Canada, and Brazil. The association has a website: www.lipodystrophyuk.org. The presentation was ended with a call to action – collaboration – between clinicians, researchers, and patient groups, at all stages of study development, from research proposals to study design, and participation to data dissemination. Everyone needs a seat at the table. Patients want more treatment options, research that impacts patients QoL, and a holistic approach to well-being.

2.8. Activities of Ailip Italy

2.8.1. Valeria Corradin (corradin73@gmail.com)

Over the years we have realized that there is a very relevant clinical question that specialist in the field found themselves very puzzling to answer: what is the best nutritional regimen for a patient affected by lipodystrophy? These question include how is best to combine foods, what do we need to systematically avoid and is there anything we can do to alleviate the hunger? Leaving the big questions to the experts, we decided to start from designing a small practical guide, rich of useful suggestions, a small book containing: lists of foods that should be avoided, suggestions on how to mix and combine nutrients, easy recipes with the appropriate cooking methods together with little tricks to keep hunger at bay and triglycerides, cholesterol, glucose levels under control. We were lucky enough to meet a highly rated chef who recently joined our Association (Ailip), hence the easiest and closest collaboration to be able to give little help to all those who have less experience with food, perceived by many of us as enemy and friend at the same time. With the support of the Lipodystrophy Center of the University Hospital of Pisa we are developing this project which we have temporarily, although improperly, called the Recipe Book. Something that can really serve to be as a small help and aid in being able to offer practical suggestions in managing the kitchen, so that food can become more of an ally than something to fight and become obsessed with.

2.9. The adipocyte response to ionizing radiations

2.9.1. M. Maffei*, G. Scabia

*2.9.1.1. *Margherita Maffei (m.maffei@ifc.cnr.it). Background* Precocious exposure to ionizing radiations is a risk factor for the onset of lipodystrophy. This concept is supported by anecdotal clinical observations as well as systematic cohort studies, pointing to a exposure to radiotherapy (RT) as a crucial determinant for higher risk of developing metabolic syndrome and alterations of white adipose tissue (WAT) gene expression profile, with increased inflammation and fibrosis and decreased presence of adipocyte precursors [17]. Work conducted on cell and animal models did not lead so far to conclusive results regarding the mechanisms for the observed *liaison* between RT and WAT dysfunction, partly due to high heterogeneity in the experimental set-ups adopted and in the poor control of the radiation energy reaching the target. RT can be administered through a conventional mode (CONV) or with an innovative protocol defined as FLASH which implies ultrafast delivery of radiation at ultra-high dose rates, this being reportedly less damaging for the healthy tissues [18].

Aim of the present study is to investigate how RT administered through CONV or FLASH mode impacts on survival, damage and differentiation of the human preadipocyte SGBS preadipocytes, a cell line able to undergo adipose conversion when exposed to an appropriate cocktail.

Methods Cells were irradiated both as adipocytes and preadipocytes with different dosage (4, 8, 16 Gy) using a prototype of electron linear accelerator, able to switch between the conventional and the FLASH mode.

Results Our data, collected 72 hrs after RT treatment, indicate that adipocytes survival is not affected by irradiation, whereas cell death, as evidenced by the presence of picnotic nuclei (apoptosis) or by propidium iodide staining (necrosis) and senescence show a dose dependent increase, more pronounced in CONV compared to FLASH RT. When preadipocytes were irradiated their capacity to differentiate into adipocytes was greatly impaired at high does. At medium doses (8 Gy) the effect of CONV was more pronounced compared to FLASH RT.

Conclusions In a set up allowing tightly controlled irradiation conditions SGBS preadipocytes and adipocytes show signs of damage, which are dose dependent, this being consistent with the contribution of RT to the etiopathogenesis of lipodystrophy. SGBS model could then be exploited for further investigation of the underlying mechanism relating ionizing radiations with AT dysfunction.

2.10. Assessing tissue-specific gene therapies in a pre-clinical mouse model of lipodystrophy

2.10.1. George D. McIlroy (g.mcilroy@abdn.ac.uk)

Introduction Congenital generalised lipodystrophy (CGL) is a rare and life-threatening disorder. Individuals with CGL fail to develop appropriate adipose tissue stores. This causes severe metabolic complications, including hepatic steatosis and lipoatrophic diabetes. There is currently no cure for CGL, and treatment options remain limited. Adipose tissue has emerged as a target for adeno-associated virus (AAV) vectors [19]. We recently revealed that systemic AAV-mediated gene therapy restores visceral adipose development and metabolic health in a pre-clinical mouse model of CGL [20]. We have subsequently investigated whether tissue-specific AAV vectors can provide a more targeted form of therapeutic intervention for CGL.

Methods We generated AAV8 vectors containing the mini/aP2 or thyroxine-binding globulin promoter to specifically target adipose tissue or the liver, respectively. AAV-mini/aP2 vectors also contained four copies of the liver-specific microRNA-122 target sequence to limit hepatic transgene expression.

Results Systemic delivery of adipose or liver specific AAV vectors restored adipose tissue development and improved metabolic health in mice with CGL. Insulin resistance assessed by HOMA-IR was normalised eight weeks post-treatment ($P < 0.01$, $n = 5$/AAV vector) compared to AAV-CMV-eGFP treated controls. Circulating Fgf-21 ($P < 0.0001$, $n = 5$/AAV vector) and alanine transaminase ($P < 0.05$, $n = 5$/AAV vector) levels were significantly improved, and liver weights were significantly reduced in both treatments ($P < 0.0001$, $n = 5$/AAV vector). Surprisingly, hepatic steatosis was only improved with AAV-mini/aP2 vector administration ($P < 0.0001$, $n = 5$), indicating divergent effects were apparent depending on promoter selection.

Conclusions We identify that tissue-specific AAV-mediated gene therapy is feasible and may offer an effective form of therapeutic intervention to correct metabolic dysfunction in patients with CGL.

2.11. Leptin secretion from human adipocytes is dependent on glucose availability

2.11.1. D. Tews*, S. Brandt, J. von Schnurbein, P. Fischer-Posovszky, M. Wabitsch
2.11.1.1. *Daniel Tews (Daniel.Tews@uniklinik-ulm.de). *Background* Leptin is produced by adipocytes and regulates central hunger and satiety sensation. While the central leptin effects are well understood, little is known about the regulation of peripheral leptin production. Clinical data demonstrate that leptin levels are rapidly declining upon fasting, suggesting that leptin secretion is acutely regulated by nutrient availability [21]. Although it has been previously shown that leptin secretion is under control by insulin and glucocorticoids in human adipocytes [22], the interplay between nutrients and hormones in this context has not been studied in detail. We thus aimed to study leptin expression and secretion in a human adipocyte cell model under chemically defined conditions.

Methods Human SGBS preadipocytes were differentiated into adipocytes for 14 days. The expression of leptin in response to different stimuli were determined by qRT-PCR and Western Blot. Secretion of leptin to the cell culture medium was measured by ELISA after 48 hours. ATP production rates were quantified by quantified using a Seahorse XFe96 flux analyzer.

Results As expected, both leptin expression and secretion were strongly enhanced by cortisol in mature adipocytes. Treatment with different glucose concentrations (0–10 mM) revealed a dose-dependent effect on leptin secretion, which peaked at physiological glucose levels (5.5 mM). Complete glucose deprivation or inhibition of glycolysis by 2-desoxy-glucose completely blocked leptin expression and secretion, indicating that glucose metabolism is a driver of leptin production. As expected, cellular ATP production was lower in absence of glucose, thus we were interested whether leptin secretion in response to glucose was mediated via common energy sensing pathways. We therefore either activated AMP-dependent protein kinase by AICAR or inhibited mTOR activity using rapamycin. Indeed, both treatments resulted in an inhibition of leptin expression and secretion, indicating that leptin production is dependent on glycolytic energy supply.

Conclusion Our data indicate that leptin production in human adipocytes is mediated by intracellular glucose availability, suggesting a direct link between glycolytic energy supply and leptin production. These findings may contribute to understand the rapid regulation of leptin levels upon fasting.

2.12. A single subcutaneous injection of recombinant leptin increases hepatic triglyceride secretion in patients with lipodystrophy

2.12.1. M. Beghini*, M. Metz, C. Baumgartner, P. Wolf, M. Bastian, M Hackl, S. Baumgartner-Parzer, R. Marculescu, M. Krebs, J. Harreiter, J. von Schnurbein, S. Brandt-Huenemann, K. Miehle, G. Ceccarini, S. Magno, C. Pelosini, C. Tran, A. Gambineri, C. Cecchetti, M. Krssak, L. Pfleger, M. Trauner, A. Kautzky-Willer, M. Stumvoll, M. Wabitsch, F. Santini, I. Turan, B. Akinci, Herbert Stangl, C. Fürnsinn, T. Scherer
2.12.1.1. *Marianna Beghini (marianna.beghini@meduniwien.ac.at). *Background* Metreleptin ameliorates hepatic steatosis in patients with lipodystrophy via a mechanism that is partially independent of leptin's anorexic effect [23]. We hypothesized that metreleptin increases the secretion of hepatic very-low density lipoprotein triglyceride (VLDL1-TG), a key mechanism that protects the liver from steatosis, as we recently described in healthy male individuals [24].

Methods In this randomized, placebo-controlled, crossover trial (EudraCT Nr. 2017-003014-22) we assessed the effects of a single acute subcutaneous metreleptin/placebo injection in patients with lipodystrophy on hepatic VLDL1-TG secretion (primary outcome parameter) and hepatocellular lipid content (HCL%, secondary outcome parameter) measured by ^{1}H-magnetic resonance spectroscopy before and 3 hrs after the injection.

Results We recruited ten patients (8 females, 2 males; mean age ± SD: 49 ± 14 yrs) with familiar partial (n = 9) or generalized (n = 1) lipodystrophy. Acute hyperleptinemia increased hepatic VLDL1-TG secretion by approximately 75% (mean ± SEM: 291 ± 44 mg/hr vs. 510 ± 56 mg/hr after placebo vs. metreleptin; P = 0.001). HCL% showed a trend to rise under placebo conditions, whereas it did not after metreleptin.

Conclusions Acute hyperleptinemia increases hepatic VLDL1-TG secretion in patients with lipodystrophy offering an explanation for its anti-steatotic action independent of its anorexic effects.

2.13. Referral of patients with rare insulin-resistance syndromes to a national reference center for rare diseases: key milestones assessed from the french national rare disease database

2.13.1. B. Donadille*, S. Janmaat-Salim, C. Vatier, C. Vigouroux
2.13.1.1. *Bruno Donadille (bruno.donadille@aphp.fr). *Background* Rare syndromes of lipodystrophy and insulin-resistance display heterogeneous clinical expressions. Their early recognition, diagnosis and management are required to avoid long-term complications [25–27].

Objective We aimed to evaluate the patients' age at referral to our dedicated national reference center in France and their elapsed time from first symptoms to diagnosis and to specialized care.

Patients and methods We analyzed the data from patients with lipodystrophy and insulin-resistance syndromes referred to the PRISIS coordinating reference center (Adult Endocrine Department, St-Antoine Hospital, AP–HP, Paris), prospectively recorded between 2018 and 2023 in the French national rare disease registry (BNDMR) [28].

Results We collected data from a cohort of 292 patients, including 208 women. The diagnosis were Familial Partial Lipodystrophy (FPLD, n = 124, including n = 67 FPLD2/Dunnigan Syndrome); Acquired lipodystrophy syndromes (n = 98, with n = 13 Acquired Generalized Lipodystrophy, AGL); Symmetric cervical adenolipomatosis (n = 27, Launois-Bensaude syndrome, LB), Congenital generalized lipodystrophy (n = 18, CGL) and rare severe insulin-resistance syndrome (n = 25). The median age at referral was 47.6 years [IQR: 31–60], ranging from 25.1 (CGL) to 62.1 years old (LB) and was significantly younger in women (P < 0.01), illustrating the gender-specific consequences of lipodystrophy and insulin-resistance. Patients were referred to our center 4.4 [IQR: 0.7–11] years after their diagnosis. Delay from first symptoms to referral was 15.0 years [IQR: 6.1–26.8].

Conclusion Improving knowledge and care pathways for rare insulin-resistance syndromes is necessary in France, and French national rare disease registry is an important tool in assessing diagnosis delays and access to specialized care at the PRISIS reference center.

2.14. Dunnigan lipodystrophy in Reunion Island: an exceptional prevalence

2.14.1. Estelle Nobécourt (estelle.nobecourt@chu-reunion.fr)

Familial Partial Lipodystrophy (FPLD2) [MIM#151660] is a rare genetic lipodystrophy due to pathogenic variants in *LMNA* encoding Lamin A/C. Although the global prevalence of FPLD2 was previously estimated at 1.3 to 4.7 per million, recent studies reported that it is probably largely underdiagnosed. In the genetic isolate of Reunion Island, a French overseas territory located in the Indian Ocean, we reported the largest cohort of patients bearing the same founder *LMNA* p.(Thr655Asnfs*49) pathogenic variant.

Actually, 154 patients were diagnosed in Reunion bearing FPLD2 (prevalence, 1/5500). The *LMNA* "Reunionese" variant consists of a G insertion at codon 654 in the prelamin-A-specific exon 11 (NM_170707.4: c.1961dup) that causes the synthesis of an abnormal, extended form of prelamin A lacking its C-terminal CSIM farnesylation motif. This pathogenic variant causes a lipodystrophic disease in both heterozygous (HTZ) and homozygous (HMZ) forms. We reported that subjects carrying the Reunionese variant share similar metabolic complications with patients bearing the "typical" LMNA p.(Arg482Trp/Gln) variants. We also confirmed, in this cohort, that alteration of blood glucose tolerance is a major complication of FPLD2. To detect early defects of glucose tolerance, an oral glucose tolerance test should be performed. As reported previously, the phenotype and complications of FPLD2 is more pronounced in women than in men. Working with the associations of patients is essential to adapt our care and answer patient preoccupations.

2.15. National recommendations for diagnosis and care of Dunnigan syndrome and congenital generalized lipodystrophy, and educational initiatives: recent achievements from the French lipodystrophy network

2.15.1. C. Vatier, H. Mosbah, B. Donadille, S. Janmaat, E. Nobécourt, E. Bismuth, M.C. Vantyghem, C. Vigouroux*
*2.15.1.1. *Camille Vatier (camille.vatier@aphp.fr).* *Background* Rare disease networks in France are developed according to the National Rare Diseases Plan initiated by the French Ministry of Health since 2005, with the creation of the national health network for rare endocrine diseases, called FIRENDO in 2011. The rare disease network FIRENDO has a national vocation to group together the clinical centers with expertise in rare endocrine diseases and to enable exchanges between the different members of the diagnostic, research, education and associative sectors via collaborative thinking. Since 2017, the rare conditions linked to abnormalities in insulin secretion and receptivity are an integral part of FIRENDO in the PRISIS group with one coordinating reference center (Saint-Antoine Hospital, Paris) and 21 Competence center in mainland France and La Réunion.

Objective Since 2017, we developed the PRISIS network to improve and harmonize patient management in France, to enable exchange between physicians, researchers and patient associations and to continue the collaboration with the European network ECLip (European Consortium of Lipodystrophy) and to integrate the Endo-ERN network particularly concerning lipodystrophic syndromes.

Results Regarding lipodystrophy syndromes, we have written and published Diagnostic and Care Protocols for familial partial lipodystrophy [29,30] and for congenital generalized lipodystrophy [31]. The objective is to inform health professionals about the diagnosis, reference treatments and monitoring of these diseases based on the study of existing scientific data and the experience of the people involved. We also developed a therapeutic education program for patients living with lipodystrophy from childhood to adulthood, together with patients' association. This is a multicenter program involving physicians, dietitians, psychologists, nurses, socioestheticians. The objective is to grow the patient's autonomy by facilitating their adherence to prescribed treatments and improving their quality of life. We also organize an annual scientific day of "Clinical-research meetings" for the patients and/or the physicians from the rare disease network PRISIS.

Conclusion The French national network of rare disease helps the management of rare disease and the development of new tools to improve quality of life of patients. In 2023, the rare disease network for insulin secretion and insulin sensitivity disease (PRISIS) will grow up with more competence centers, and three reference centers.

2.16. Barraquer-Simons syndrome our (shared) experience

2.16.1. S. Magno, G. Ceccarini, F. Corvillo, C. Pelosini, D. Gilio, M. Paoli, S. Fornaciari, G. Pandolfo, S. Sanchez-Iglesias, P. Nozal, M. Curcio, M.R. Sessa, M. López-Trascasa, D. Araújo-Vilar, F. Santini*
*2.16.1.1. *Giovanni Ceccarini (giovanni.ceccarini@unipi.it).* Barraquer-Simons syndrome (BSS) is a very rare acquired form of lipodystrophy characterized by progressive loss of upper body subcutaneous fat, which affects face, upper limbs, and trunk. The pathogenesis of the disease is not entirely known and may involve autoimmune mechanisms. To date, despite the numerous case reports, only two studies have attempted to systematically investigate this disorder [32,33]. This study aimed at providing a comprehensive picture of the clinical, immunological, and metabolic features of a large cohort of BSS patients. Twenty-six patients diagnosed with BSS recruited in one Italian Center and two Spanish Centers were studied. Anthropometric parameters, biochemical tests, organ- and non-organ-specific autoantibodies, HLA status, and screening of the *LMNB2* gene were performed. Our patients cohort was predominantly composed by females (3/4); as previously reported, fat loss occurred mostly during childhood at a median age of 8 years. Most of the patients (75%) had at least one organ- and/or non-organ-specific autoantibody positive although not always the disease was clinically overt. Among various anthropometric measures, the ratio between the proportion of fat mass in upper limbs/lower limbs assessed by DEXA showed the best predictive value for diagnosis. Seventy-five percent of the children and 50% of the adults had C3 hypocomplementemia, a factor that is used as a supportive diagnostic criterion. Our results suggest that the prevalence of C3 hypocomplementemia may be lower than previously thought. HLA-DRB1 11:03 had higher allelic frequencies in patients compared to the general population. It has been proposed that *LMNB2* gene variants confer a high risk of developing the disease; in our study only 1 in 22 patients was found to carry a single (benign) variant in the *LMNB2* gene. The prevalence of the principal comorbidities was found superimposable to what has been previously described. This work has been accepted for publication in the JCEM in November 2023.

2.17. Natural history of generalized lipodystrophy following early vs. Late metreleptin treatment

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*2.17.1.1. *Rebecca J. Brown (brownrebecca@mail.nih.gov).* Generalized lipodystrophy (GLD) is characterized by near total loss of subcutaneous fat resulting in low leptin concentrations. Patients with GLD exhibit metabolic abnormalities such as severe insulin resistance, diabetes mellitus, hypertriglyceridemia, proteinuria, and non-alcoholic fatty liver disease (NAFLD), that are progressive over time [34]. Leptin replacement therapy using metreleptin is effective in improving these metabolic abnormalities [35]. It is unknown if starting metreleptin therapy prior to (early) versus after (late) the development of clinically significant metabolic disease will change the natural history of this disease. We hypothesized that starting metreleptin early versus late will lead to better long-term control of diabetes, hypertriglyceridemia, and proteinuric nephropathy. This is a single-center retrospective analysis of subjects with congenital and acquired generalized lipodystrophy ($n = 65$). Fasting serum insulin, glucose, lipids, HbA1c (A1c), and 24 hr urine protein excretion, and insulin and C-peptide areas under the curve (AUC) from oral glucose tolerance tests were assessed at baseline, after 6 months of metreleptin, and at 12-month intervals thereafter. For each outcome parameter, subjects were divided into early and late treatment groups. For A1c, early treatment was defined as < 7%. For all other parameters, early treatment was defined as < the upper limit of normal for that parameter.

The effect of early vs late treatment for each parameter was analyzed using linear mixed models adjusted for age and genetics and excluding baseline metabolic parameters. Follow-up diabetes control was better with early metreleptin treatment as assessed by both glucose and A1c. Fasting glucose was 42 mg/dL lower during follow-up with early (< 100 mg/dL) vs. late (≥ 100 mg/dL) treatment ($P = 0.0008$) and A1c was 1.5% lower with early (< 7%) vs. late (≥ 7%) treatment ($P < 0.0001$). At baseline, the early group defined by A1c had 57% higher C-peptide AUC ($P = 0.0008$) and 64% higher insulin AUC ($P = 0.0029$). At follow-up, the early group maintained a 33% higher C-peptide ($P = 0.03$) and 57% higher insulin AUC ($P = 0.0005$). Triglycerides were 92 mg/dL lower during follow-up in the early (< 150 mg/dL) vs. late (≥ 150) groups ($P = 0.005$). Urine protein excretion was 916 mg/24hr lower during follow-up in the early group (< 300 mg/24hr) vs. late group (≥ 300 mg/24hr) ($P = 0.04$). In conclusion, patients with generalized lipodystrophy treated with metreleptin prior to the onset of clinically significant metabolic disease showed better age-adjusted metabolic control over time for diabetes, hypertriglyceridemia, and proteinuria. Lower insulin and C-peptide secretion in the late treatment group suggest that worse diabetes control after metreleptin in this group may be attributable to irreversible loss of beta cell function prior to metreleptin.

2.18. Clinical factors leading to serious morbidity and mortality in congenital generalized lipodystrophy type 4

2.18.1. G. Akinci, S. Alyaarubi, N. Patni, N. Alhashmi, A. Al-Shidhani, F. Prodam, N. Gagne, F. Babalola, A. Al Senani, K. Muniraj, S.M. Elsayed, M. Beghini, B. Ozgen Saydam, M. Allawati, M.S. Vaishnav, E. Can, I.Y. Simsir, E. Sorkina, F. Dursun, C. Kamrath, U. Cavdar, P.P. Chakraborty, O. Akgun Dogan, A. Al Hosin, A. Al Maimani, N. Comunoglu, A. Hamed, T. Scherer, J. Curtis, R.J. Brown, H. Topaloglu, V. Simha, M. Wabitsch, B. Tuysuz, E.A. Oral, B. Akinci, A. Garg*

*2.18.1.1. *Baris Akinci (barisakincimd@gmail.com).* Congenital generalized lipodystrophy type 4 (CGL4) is an ultra-rare autosomal recessive disorder characterized by near-total loss of adipose tissue and distinct clinical characteristics (e.g., myopathy, cardiac arrhythmias, congenital pyloric stenosis, skeletal abnormalities). CGL4 is a complex disease with several organ system dysfunction contributing to morbidity and mortality. On the other hand, whether patients with CGL4 develop as severe metabolic complications as seen in more common subtypes of CGL remains unclear. Previous case reports indicate absence of or only mild metabolic abnormalities at the time of diagnosis of CGL4. During the ECLip 2023 meeting, we presented an international cohort study that reports on the prevalence of various morbidities and causes of mortality in CGL4. This international cohort study is the largest reporting clinical outcomes in CGL4. Also, many centers were able to submit longitudinal data that helped us to describe the natural history of CGL4 better than the previous case reports. In this work, we identified major causes of serious morbidity and mortality in a relatively large group of patients with CGL4 from multiple international centers. Our results highlight the importance of regular monitoring for several organ systems in CGL4 and the urgency to treat the consequences of these abnormalities as they can be presently serious or may easily progress to life-threatening clinical presentations. This work has recently been submitted for publication as a full-text article.

2.19. Immunophenotype of PLIN1*-mutated patients compared to* LMNA*-mutated subjects, obese and healthy controls*

*2.19.1. L. Stienne, M.C. Vantyghem**

*2.19.1.1. *Marie-Christine Vantyghem (mcvantyghem@gmail.com).* Lipodystrophic syndromes are a group of rare diseases characterized by a generalized or partial lack of subcutaneous adipose tissue resulting in a metabolic syndrome and possible cardiovascular complications [26] and fertility disorders [36]. They may be congenital or acquired. The aim of this study was to compare the clinical, metabolic, anthropometric and immuno-haematological characteristics of patients with a familial partial lipodystrophy syndrome linked to a variant of perilipin 1 (*PLIN1* gene, named FPLD4) or lamin (*LMNA* gene, named FPLD2), with lean healthy or non-diabetic obese controls.

Methods This retrospective study of 74 patients divided into 4 groups was led in the context of a clinical trial (NCT01784289).

Results Compared to lean healthy controls, both FPLD4 and FPLD2 groups showed higher BMI, intraabdominal fat, HbA1c, triglycerides, ALAT and fatty liver. Compared to FPLD2, only leptin differed significantly with lower levels in the *PLIN1* mutated group. An increase of eosinophils was observed in both FPLD groups, an increase of leukocytes and neutrophils and a decrease of NK in FPLD2 group, and an increase of basophils in FPLD4, correlated with metabolic markers.

Conclusion The immuno-haematological changes observed in the two FPLD groups suggest a role in adipose tissue remodeling, with a dysfunction that could lead to insulin resistance.

2.20. Current status of the ECLip registry 2023

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Introduction The ECLip Registry was founded at the end of 2017 by the European Consortium of Lipodystrophy (ECLip) with the aim to register as many patients living with lipodystrophy in Europe and beyond as possible to learn more about the natural course of these rare diseases, to identify prognostic factors and to find new therapeutic options [1]. In addition, the ECLip registry hosts the European part of a post-authorization study from Amryt Pharma, now Chiesi Farmaceutici (MEASuRE EU). The registry is run by the ECLip Registry Board on behalf of the ECLip Registry Members who hold their regular meeting at the ECLip meetings. At this time point the members receive an update on the current status of the registry by the ECLip Registry Board, presented by Julia v. Schnurbein.

Current status As of February 2023, 583 patients have been recruited in 18 centres. Eight further centres are in the process of becoming recruiting members. For MEASuRE EU, 19 patients have currently been recruited. In 2023, the planned bi-annual plausibility checks for the core data set have been implemented and the first benchmarking report has been forwarded to the recruiting centres. 54% of all patients in the registry live with familial partial lipodystrophy (FPLD; FPLD 1: 35%, FPLD 2: 13%, FPLD 3 and 4: both 3%), 17% have a congenital generalized lipodystrophy (CGL; CGL 1: 8%, CGL 2: 3%, the rest rarer forms). The most common comorbidities were dyslipidaemia (73%), fatty liver disease (66%), and diabetes (53%), followed by hypertension (36%) and cardiac comorbidities (29%).

Outlook A core writing group is in the process of preparing the first cross-sectional analysis of the complete registry. In addition, multiple data evaluation applications are currently being processed. At the end of 2023, regular status reports on the data contend within the registry will be made public.

3. Conclusion and perspectives

In the follow-up of our last meeting [37], this publication allows the ECLip network to accomplish one of its missions: to increase knowledge in the field and in cooperation with patient advocacy groups.

New forms of lipodystrophy and mechanisms of insulin resistance have been described. Cohort studies focusing on very rare

subtypes of lipodystrophy have also presented before being published. Studies on novel therapeutic developments and on the effects of leptin hormonal replacement in lipodystrophy syndromes were also discussed with great emphasis.

Data from the international registries were anticipated showing the terrific potential that studies based on registry may exhibit. The ECLip network is continuously growing and increasing its collaboration activities across continents. Future directions of joined research programs and dissemination activities were also planned.

Disclosure of interest

The authors declare that they have no competing interest.

Ethics

Presented studies are all approved by appropriate institutional research ethics boards.

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