



Lipodystrophy a rare challenge

A focus on the debilitating, ultra-rare disease, lipodystrophy: perceptions across Europe, challenges that exist and steps that can be taken to help improve the lives of those affected.

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Foreword

Over the past decade, the understanding of ultra-orphan diseases has improved significantly across Europe. However, in many cases this now poses a new set of challenges: How do healthcare professionals work together to identify patients more efficiently? How can specialist centres be supported to implement protocols and share best practices? And how should the physical and emotional needs of patients and carers be addressed?

Lipodystrophies exemplify this issue. These are heterogeneous, ultra-rare and irreversible diseases where many patients – particularly those with partial lipodystrophy – can go undiagnosed for years. People suffering from lipodystrophy have a total or partial lack of fat under the skin (subcutaneous fat). This lack of fat can cause issues ranging from serious problems with metabolism and organ damage to chronic pain and insatiable hunger, and even social isolation as a result of dysmorphia. It is, however, also an area where real progress is being made. Across Europe, specialists are becoming more familiar with the disease, centres of excellence and patient groups are emerging and medical innovation is helping to improve lives.

This report comes at a pivotal time for this condition, as the lipodystrophy community seeks to build on what has been

achieved in recent years and make inroads into some of the most pressing challenges that remain.

The report content and recommendations reflect the real-world experiences of clinicians, patients and advocacy groups who have seen, first-hand, the debilitating effects of lipodystrophy over many years. We invite everyone reading to examine the recommendations closely and work with us and the wider lipodystrophy community to increase understanding of this disease and evolve clinical practice.

In a disease that is so rare, challenges can seem insurmountable; yet by implementing even small changes, significant progress can be made. By taking simple steps, we can help many of those affected by lipodystrophies to live better lives.

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Executive summary

Outside of a niche community, there is generally little recognition of lipodystrophies and the issues they present to patients and carers. This is despite the fact that this group of ultra-rare diseases are frequently debilitating and life-limiting. As a result, it can take years, or even decades for a patient to receive a correct diagnosis. Healthcare systems across Europe are often ill-equipped to effectively identify these patients and are inconsistent in referring them to specialist care where their long-term physical and emotional needs can be best met.

This report aims to prompt a change in this situation. The content draws upon real-life clinical perspectives, patient contributions and published literature. Insights and recommendations were gathered through a series of in-depth discussions with lipodystrophy clinicians from across Europe, that took place in July 2019. Each specialist provided their individual perspective on the most pressing issues surrounding the diagnosis and management of lipodystrophy. This then led to the collective identification of changes that may help improve the status quo. To complement insights from the medical community, the viewpoint of patients and carers have also been captured – ensuring that this report includes a perspective of those who know what it is really like to live with lipodystrophy.

The expert panel highlighted a range of ongoing challenges faced by both patients and healthcare professionals affected by lipodystrophies. The most prominent of these included:

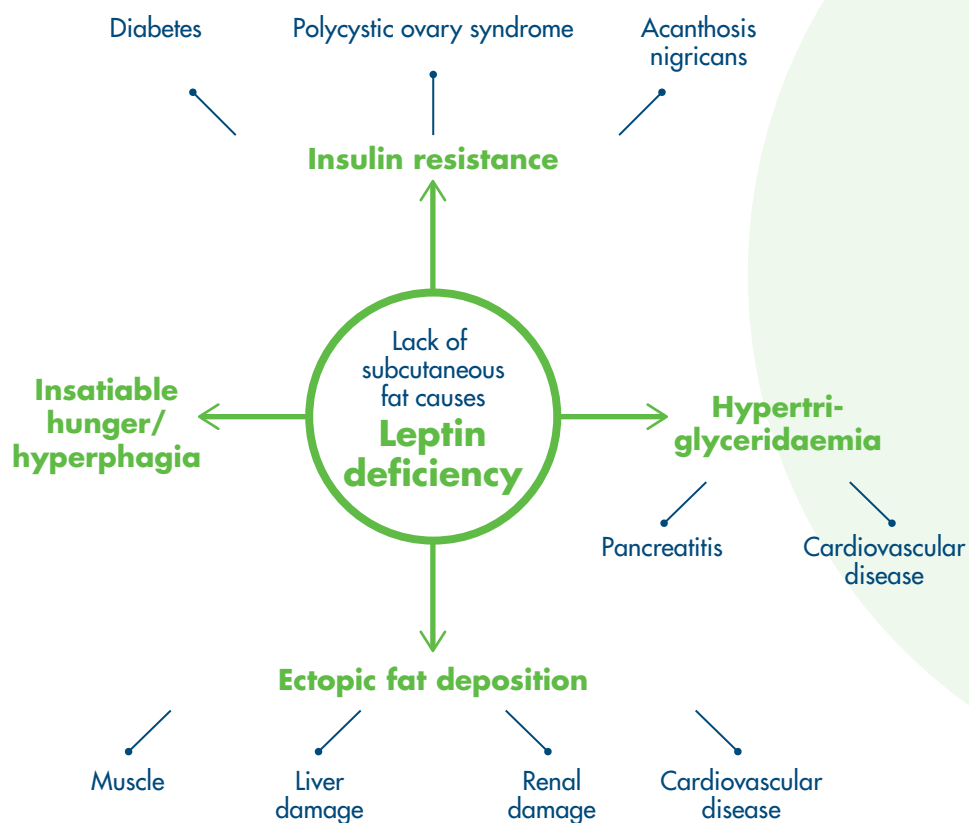
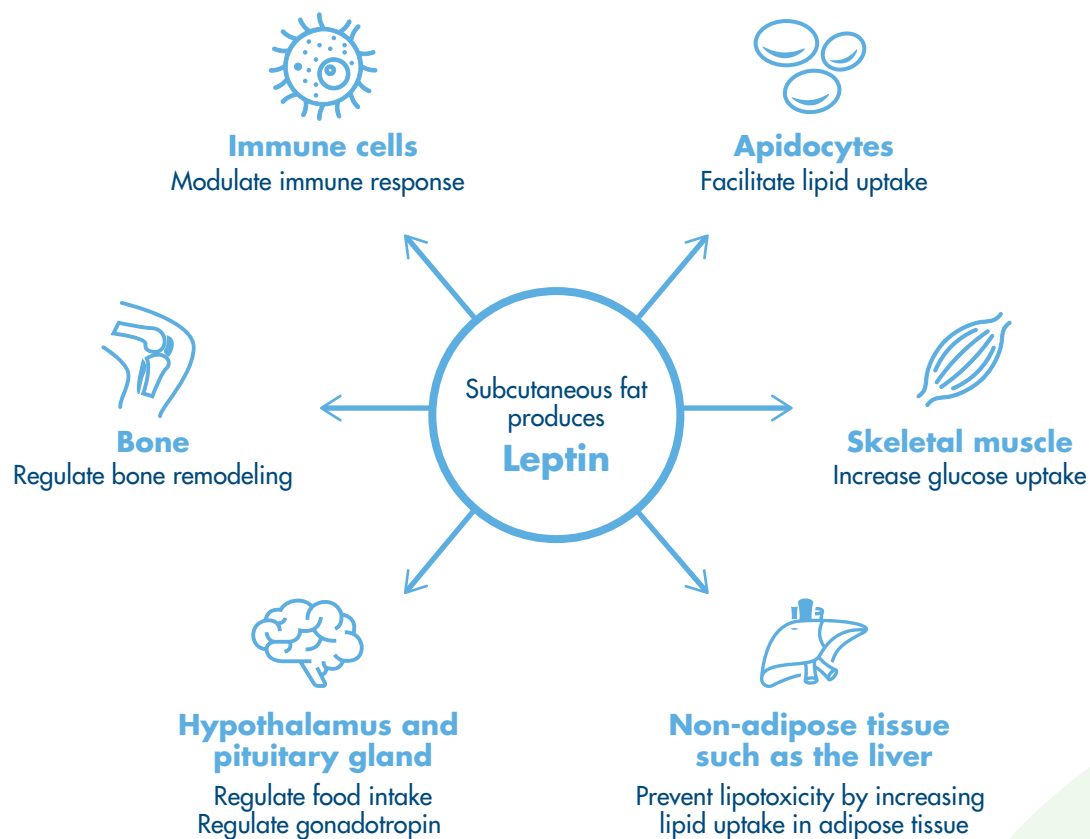
- Time to diagnosis remains disproportionately long, particularly for those with Partial Lipodystrophy (PL) who may wait over a decade for diagnosis
- Low disease awareness is causing patients – who may have prominent symptoms – to be missed or ‘lost’ in the system with an incorrect diagnosis
- The lack of awareness of specialist centres and a defined referral process means that patients with a suspected lipodystrophy may not receive appropriate care
- Social stigma is a significant burden and continues to be a serious concern for many patients, particularly in relation to body image
- Although medical innovation is helping to improve outcomes for patients, in some cases access remains very challenging

This report’s research prompted a number of suggestions for ways in which positive change can occur for people affected by lipodystrophy in both the short- and long-term; core recommendations include:

- Improve basic training resources and make these readily available online
- Enhance training/symptom awareness among non-specialist healthcare professionals (HCPs) who are likely to see lipodystrophy patients as part of the disease’s associated comorbidities
- Support specialist centres in working with local/non-specialist teams to establish clear protocols for referral so that patients are diagnosed more efficiently
- Ensure that specialist centres meet the holistic needs of patients, including their psychological wellbeing as well as treating the metabolic and endocrine complications of lipodystrophy
- Ensure that access to novel technologies is not restricted due to a lack of understanding of the ‘real world’ nature of this disease and the requirement to use inappropriate cost-effectiveness criteria



Consequences of leptin deficiency^{1,2,3,4,5}



What is lipodystrophy?

Lipodystrophies are a group of heterogenous, ultra-rare and irreversible conditions characterised by an absence of fat beneath the skin (subcutaneous fat).⁶ The pattern of this absence of fat can either be generalised (across the whole body) or partial (in specific areas) and so the conditions are often sub-categorised into generalised lipodystrophy (GL) and partial lipodystrophy (PL).⁷ Both forms of lipodystrophy may be either inherited or acquired, secondary to other conditions or of no known cause.

Generalised lipodystrophy (GL)

In GL, a near-total absence of subcutaneous fat may be present from birth. This form occurs in around one person per million people globally.⁶



Partial lipodystrophy (PL)

In contrast, PL patients have a partial loss of subcutaneous fat and fat accumulation where subcutaneous fat remains. These patients often do not experience symptoms until puberty. The incidence of this form is slightly more common at around three people per million people worldwide.⁶



Around **4 in every 1 million people** are thought to be affected by lipodystrophies globally
– **approximately 3,000 people across Europe.**⁶

Hard to find, but not invisible

Among the most distinct symptoms of this disease are the physical characteristics associated with the lack of subcutaneous fat. Presenting with little or virtually no subcutaneous body fat, GL patients can appear extremely muscular across their entire body from a young age.⁴ This is often despite the fact that patients frequently eat significant amounts of calorific food to counteract an extreme hunger, with consecutive hyperphagia, that can present as a debilitating symptom.³

In PL, the lack of subcutaneous fat may be less obvious and may be more prominent in the limbs and trunk.⁴ In certain cases, this can also be accompanied by a disproportionate accumulation of fat around the face and neck.⁸ For some patients – many of whom may be children or young adults – the distinct appearance caused by this condition can be its most distressing symptom.⁹



The psychological toll caused by concerns around body image in those with lipodystrophy can be incredibly profound on a patient's wellbeing, particularly in teenagers and young adults. I've seen saddening cases where people have become nearly totally socially isolated, even removing themselves from school as a result. This is a significant issue and one that healthcare professionals must be mindful of.

*Dr Ingrid Jazet,
Department of Endocrinology/Internal Medicine, Leiden University Medical Center, Netherlands*



A cause of serious metabolic complications

Apart from acting as a store for excess energy, an important role of subcutaneous fat is to produce the hormone leptin, which is vital in helping to control metabolic and endocrine processes across the body and in regulating appetite. As people with lipodystrophy lack much of their subcutaneous fat they become leptin deficient. This causes fat to be distributed to other locations in the body such as the muscles, liver and pancreas, in turn causing numerous complications, some of which are **potentially-life threatening. These include:**⁸

Severe insulin resistance as a consequence of fat in the muscles and a lack of leptin, resulting in hard-to-treat **diabetes mellitus** and potentially requiring high doses of insulin

Severe hypertriglyceridaemia which can increase the risk of heart disease, stroke and **acute pancreatitis**

Hepatic steatosis (fatty liver disease) which manifests as an accumulation of fat in the liver that can cause nonalcoholic fatty liver disease (NAFLD), scarring and finally liver cirrhosis

Polycystic ovary syndrome affecting reproductive cycles in women that may lead to reduced fertility

Acanthosis nigricans which presents as dark patches on the skin at the folds of the body, such as the neck or armpits

In addition to the severe impact on a patient's quality of life due to the associated conditions, lipodystrophies can also drastically reduce life expectancy – with some patients not living beyond childhood.^{4,10}

A significant burden to daily life

People living with lipodystrophy can find many aspects of their daily life affected, from the ability to work and carry out basic daily tasks, to how they socialise. Patients may experience pain and fatigue as a result of their lipodystrophy. It can also bring practical and fiscal challenges, with some of those who are diagnosed needing to travel significant distances for specialist treatment, often at their own expense.

Patients with lipodystrophy, particularly those with GL, can also experience symptoms of extreme or chronic hunger, with consecutive hyperphagia.³ While following an energy-restrictive diet can improve a patient's metabolic symptoms, in some people this urge to eat is simply too strong to overcome. Additionally, in children, a careful balance must often be struck to ensure they have enough energy for growth, while minimising metabolic complications.



The symptoms of lipodystrophy affect so many aspects of my life, from extreme fatigue to severe muscle pain and even causing depression and anxiety. One of the most significant aspects of the disease is the relentless, chronic hunger which many patients experience. This is not the sort of hunger that comes with missing a meal, but an actual pain that does not subside no matter how much food you have eaten. This can have real knock-on effects on disease management as lipodystrophy is largely controlled through diet. However, the persistent hunger can make dietary choices hard to control.

*Dr. Rebecca Sanders,
Chair & Co-founder at Lipodystrophy UK (LDUK)*

Challenges facing patients today

A potentially long journey to diagnosis

Lipodystrophy is a complex disease with recognition often difficult due to it being a collection of syndromes with multiple different manifestations. This, coupled with a general lack of awareness amongst both clinicians and the general public, means patients are typically diagnosed very late. Importantly, this may only occur once secondary problems have been experienced, such as liver, kidney and cardiovascular damage resulting from poorly controlled diabetes and hypertriglyceridaemia.²

14 years is the average time from onset of symptoms to diagnosis in PL¹¹



Generalised and partial lipodystrophy can be easily recognised if you know what to look for. However, greater awareness is required among other healthcare professionals to help improve diagnosis, before the condition becomes even more serious. A priority should be to increase understanding among secondary healthcare professionals who encounter patients via their comorbidities. For cardiologists, paediatricians, gynaecologists, dermatologists and associated nurses a basic level of training should be routine.

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Santiago de Compostela, Spain*



It can be very difficult to distinguish between lipodystrophy, other metabolic conditions or Cushing's disease. What is extremely important is to conduct a complete physical examination of the patient, including without clothes, in order to fully assess their arms or legs and help identify visible aspects of lipodystrophy.

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Due to the physical manifestation of GL at a young age, many people who are born with the condition are diagnosed relatively early on.¹²

In PL, however, the change in physical appearance can often be wrongly attributed to consequences of metabolic symptoms that are common to diabetes, rather than the lesser known lipodystrophies.¹² It is also reported that there are likely to be more 'missed cases' in men as opposed to women, since a lean, muscular appearance in men may not be considered unusual.



“

Someone with partial lipodystrophy may have had diabetes and hypertension from childhood and been seen by various healthcare professionals for decades but still not been correctly diagnosed. I have seen patients who have been ‘lost’ in such a way for 40 or 50 years, sometimes misdiagnosed with conditions such as Cushing’s disease or type 1 diabetes, due to clinicians being uninformed. In extreme cases the patient may have undergone unnecessary treatment such as having their adrenal glands removed. It is devastating to know that when diagnosis is delayed, so much damage is likely to have been caused to the vascular system, kidneys and other organs.

Prof Vaia Lambadiari

Lipodystrophies and Lipid Disorders Clinic, 2nd Dpt of Internal Medicine. Research Unit and Diabetes Center, National and Kapodistrian University of Athens, Attikon Hospital, Athens, Greece

Patients are getting ‘lost’ in the system

A history of misdiagnosis, coupled with a poor, though slowly improving, awareness among healthcare professionals can mean that patients get ‘lost’ within the secondary care system and may wait many years before being diagnosed with lipodystrophy.¹¹ Although multiple healthcare professionals may come into contact with a lipodystrophy patient – such as diabetes specialists, cardiologists, paediatricians, gynaecologists and dermatologists – they often struggle to attribute prominent symptoms to this disease. As a consequence, patients may not see a specialist in treating lipodystrophy until they start to experience severe complications, including organ damage.

“

When people contact us they are really exhausted, they do not know where to go and who can help them. Our first objective is to reassure them and make contact with the proper referral centre. In the future we hope that diagnosis will become much faster, but this can only be done if we raise greater awareness of the disease.

Valeria Corradin,

Vice-President of Italian Association of Lipodystrophy (AILIP) and mother of lipodystrophy patient, Italy



“

Professor Grimaldi diagnosed me with Berardinelli-Seip syndrome, a form of generalised lipodystrophy at 55 years old, 27 years after the onset of diabetes. Although the final diagnosis took many years, I was relieved, as were my family, to be able to put a name to this disease which had previously been thought to be an unknown form of diabetes and a bone disease. Living with lipodystrophy is life-altering: everything must be prepared with rigor, from food choices to travel arrangements.

Mr Tréboz,

Vice President, French Association of Lipodystrophy (AFLIP), France

Challenges facing patients today

Earlier referral to specialist centres

A 'specialist' centre is a medical centre with recognised expertise in the diagnosis, care and management of a particular condition.

In a very rare disease like lipodystrophy, the role of the specialist centre is particularly important as it will generally have far more experience in dealing with a relevant cohort of patients. The best opportunity for a patient to receive a specific lipodystrophy diagnosis and the most appropriate care therefore tends to be within a specialist centre.

For lipodystrophy, specialist care is often provided through one or very few national centres. In some smaller European countries, specialist care may even be provided through referral to a centre based in another country.

“ Specialist centres are very important in the diagnosis and management of lipodystrophy. Having concentrated expertise in one place should ensure that all patients get the same high level of care. However, due to the distance patients may need to travel, some only visit their specialist centre once a year. For this reason, it is important for local healthcare professionals to have an awareness of the disease so that they can work closely with a specialist centre to follow care plans and, most importantly, understand the specific needs of a lipodystrophy patient.

*Dr. Rebecca Sanders,
Chair & Co-founder
at Lipodystrophy UK (LDUK)*

Although specialist centres typically exist nationally for the management of lipodystrophy, it is thought that many healthcare professionals do not know how or where to refer suspected lipodystrophy patients. In these cases, it is not uncommon for 'generalist' secondary care clinicians to continue to manage lipodystrophy patients under their own care. This vacuum means that referral to a national specialist centre may be delayed or simply not happen at all.

Alternative approaches to national specialist centres

There are some exceptions to the 'specialist centre approach' in lipodystrophy care. In France, an alternative 'hub and spoke' model of care is offered under the name PRISIS, where patients can receive ongoing care more locally with support offered centrally from the specialist centre.

In Portugal the 'specialist centre' model of care does not exist – instead individual experts manage small numbers of lipodystrophy patients, with concerted efforts made to connect treating healthcare professionals and establish a more formal network through email and meetings.



“ Given that lipodystrophy is a very rare disease it makes sense to have one or very few specialist centres highly attuned to a patient's pathology. At the very least it is important that an assessment is carried out by a specialist centre at least once in order to confirm (or not) the diagnosis and see if a patient can benefit from a more bespoke treatment for their condition. Alongside this, of course, there should be a network of people with an awareness of lipodystrophy who can support non-specialist healthcare professionals when the need arises.

*Dr. Giovanni Ceccarini
Obesity and Lipodystrophy Center, Endocrinology
Unit, University Hospital of Pisa, Italy*

Social stigma and inconsistent emotional support

In addition to the multiple comorbidities experienced by people with lipodystrophy, physical manifestations of the disease can often cause the most significant distress for patients. While affecting both sexes to some degree, women in particular frequently feel this burden and may find that it impacts their social or intimate relationships and self-esteem. Manifestations of this can range from patients being afraid of simple everyday activities such as swimming, to severe social isolation and mental health issues.

“To have a child with lipodystrophy is heart-breaking and very difficult to process. Although receiving a formal diagnosis provides some relief, your mind immediately jumps to wondering about your child's future; how everyone will react and whether the child's school will be prepared for their needs.

*Naca Pérez de Tudela,
President of Family Association Affected
by Lipodystrophies (AELIP) and mother
of lipodystrophy patient, Spain*

The impact of lipodystrophy on the perception of body image has been researched by experts in the UK, with patients describing themselves as “deformed”, “masculine” and being “stuck with what we've got”.¹³ Teenage years can be particularly problematic. Many patients with GL are diagnosed as children or young adults and bullying as a result of their physical appearance can occur. UK experts have noted that providing psychological support alongside medical management may be vital to help ensure people live well with such an appearance-altering condition.

The last few years have seen the emergence of more and more dedicated patient support organisations able to provide guidance to people affected by GL or PL. However, this is very much only in certain countries and many smaller EU regions not only have no specific patient support groups but are also limited by the fact that patients may not be able to join online groups or social network forums because of an inability to speak English.



“In Belgium there is currently no patient organisation to guide or to support patients for the psychological impact of lipodystrophy, nor is there any dedicated psychiatric support service. In our centre, individuals with lipodystrophy can contact a psychologist, a dietitian, a nurse or a social assistant, affiliated with the obesity/diabetes centre.

*Prof Ann Mertens
Department of Endocrinology, University
Hospitals Leuven, Belgium*

In Spain, patient organisation AELIP provides broader, holistic support to patients via phone, online and face-to-face services aimed at reducing emotional suffering, enhancing self-esteem and support around social rejection. In addition to psychological support, the group also provides legal, dietary and sexual advice to patients.

Challenges around access to innovative medicines

A diagnosis of GL or PL is an encouraging step forward for a patient. Yet once this occurs, access to an appropriate treatment can remain a challenge.

Few medical innovations have emerged for lipodystrophy, with the majority addressing only the symptoms, not the cause of the disease. Additionally, in such a rare condition, the collection of large data sets and the evaluation of conventional clinical trial endpoints – which are traditionally used when considering the approval and reimbursement of new medicines – may be exceptionally limited.

Improving care for people with lipodystrophy

In looking at how outcomes can be improved for people with lipodystrophy, some key themes remain prominent. These include:

IMPROVING CLINICAL PRACTICE

Achieving better, faster diagnosis and referrals in lipodystrophy will require the effective education, training and support of more healthcare professionals across Europe.

Training the right healthcare professionals

While patients may interact with many layers of the health system over the course of their disease, certain 'generalist' secondary care healthcare professionals remain on the front line of spotting the signs of lipodystrophy:

- Cardiologists
- Dermatologists
- Endocrinologists
- Diabetologists
- Gynaecologists
- Hepatologists
- Paediatricians
- Nurses working within the above teams



Lipodystrophy specialists are a small but engaged expert community. However, a reality is that we often cannot visit meetings or events that would allow us to learn from others or share our experiences. It is therefore vital that we look to expand the use of online channels for training and best practice sharing.

Dr Ingrid Jazet

Department of Endocrinology/Internal Medicine, Leiden University Medical Center, Netherlands



As parents, we went through various stages: grief, acceptance and fear when we received our daughter's lipodystrophy diagnosis. We immediately told ourselves that we now understand what we are fighting against and committed ourselves to doing so. For us, this means focusing on gathering as much information as possible and finding the best help and treatment for our little girl. As there is so little information out there, it is critical that the patient community is able to access it as easily as possible.

*María Fernanda de Amorím,
Delegate of Family Association Affected by
Lipodystrophies (AELIP) in Portugal and mother
of lipodystrophy patient, Portugal*

Broadening content available online

The fact that the lipodystrophy expert community is small, dispersed and time-limited highlights the considerable role for online and digital content to be made available. This is particularly helpful for content relating to disease recognition and patient referral/support.

Where possible, content is particularly helpful when made available in languages beyond English and using language that is simple to understand.

Sharing best practice

As well as experts sharing advice between each other, two-way dialogue should be established between specialist and non-specialist centres to aid information flow and best practice.

Allocating time for physical examination in high-risk patients

Spotting lipodystrophy can be very difficult without a physical examination. Ensuring that a full physical examination is given to 'high-risk' lipodystrophy patients (such as those with insulin resistant diabetes) may help clinicians in seeing the visible physical characteristics of lipodystrophy and support diagnosis/referral.

Enhancing the impact of specialist centres

Early diagnosis and referral are critical in helping prevent irreversible organ damage and other long-term issues. It is therefore important that awareness of specialists and/or specialist centres is improved – both nationally and internationally.

Where possible, it would be valuable to establish national guidelines or local protocols around lipodystrophy. These would then potentially assist healthcare professionals in identifying potential cases of lipodystrophy and what to then do in terms of referral to a specialist centre. This would be most beneficial for departments who are more likely to encounter lipodystrophy patients, such as diabetic, cardiology or paediatric clinics to identify potential patients and promptly refer suspected cases to specialist centres.

“ In Germany, a challenge for doctors can be referring the patient into our care once a diagnosis has been confirmed. There is certainly a need for greater working between different specialisms, such as paediatricians and endocrinologists, as well as better visibility of the specialist centre.

*Prof Dr Annette Richter-Unruh,
Clinic for Paediatric and Adolescent Medicine,
the Ruhr-Universität Bochum in the St. Josef-
Hospital, Bochum, Germany*



“ Having waited almost 30 years for my own diagnosis with lipodystrophy, I know what a frustrating time this can be for patients and their families. This frustration can be amplified further when a diagnosis is actually received, as you wonder why the physical appearance – a key indicator of lipodystrophy – did not result in being diagnosed sooner. Raising awareness of the disease to prevent such drastic delays is of the utmost importance so that patients can receive the care they need and be connected with patient organisations who can give them the information and support that they need.

*Genevieve Charriot,
President, French Association of Lipodystrophy
(AFLIP), France*

Improving care for people with lipodystrophy

MEETING THE HOLISTIC NEEDS OF PATIENTS

As well as addressing the metabolic complications of lipodystrophy, it is important to explore how the wider psychological and practical needs of patients and carers can be met.

Providing support beyond medical treatment

The widespread impact of lipodystrophy means that there may be value in routinely exploring whether patients and carers should be offered counselling or psychological, dietary and chronic pain management support.

An evaluation of existing psychological services may help provide a clearer picture of how specialist centres can best support patients in the future.

Where patient groups exist, they can be supported in providing expert-backed guidance to patients and families through existing channels, including phonelines and social media forums.



Enhancing the role of ECLIP

The European Consortium of Lipodystrophies (ECLIP) plays an important role in facilitating disease understanding among healthcare professionals in different countries, especially those that do not have a good referral centre or access to treatment.

Where possible, countries should strive to send representatives to attend the regular ECLIP meetings (either face to face or remotely). Since 2014, attendance is growing year on year which is positive; however, countries outside of the EU could, in particular, benefit from participation.

Uniting the efforts of healthcare professionals, patient groups and pharmaceutical companies

Multiple stakeholders have a role in disseminating information about lipodystrophy and groups should aim to work closely together where possible.

LOOKING AT THE WIDER VALUE OF NEW MEDICINES

Where there is expert clinical consensus to do so, it could be advisable for reimbursement authorities to adopt novel, or more flexible approaches to the assessment of new medical innovations or technologies – ensuring that the full value of any significant advance in care is taken into account.



Priority recommendations

Based on the collective feedback of the experts convened in this report, primary recommendations that should be considered a priority include:

Improve disease awareness among healthcare professionals most likely to encounter lipodystrophy, specifically: diabetologists, gynaecologists, endocrinologists, internists, hepatologists, cardiologists, paediatricians and nurses

- Establish a basic set of picture-led materials to aid training around disease recognition
 - Disease-recognition checklists
 - Case histories
- Leverage materials to create web-based training modules
- Include lipodystrophy on training syllabuses of relevant specialities
- Invite presentations from specialist centres or encourage staff to attend relevant sessions at national/international meetings



Underscore the importance of a prompt referral to a specialist lipodystrophy centre

- Educate relevant specialities on the value of referral to specialist lipodystrophy centres, including the threat of serious metabolic complications caused by unnecessary delay
- Ensure relevant specialities are aware of specialist centres that exist for lipodystrophy nationally and have an established protocol for referral in place
- Spread awareness of diagnosis and treatment guidelines among healthcare professionals across Europe

Consider the holistic needs of patients

- Where possible, every lipodystrophy patient should have access to additional support to meet their psychological, physical and practical needs. At a base level, access to a counsellor or psychologist should be possible at each specialist centre

Improve recognition of the wider value of new medical innovations

- Examine criteria being used to assess novel technologies and, where needed, ensure they take into account the wider outcomes for patients, carers, healthcare professionals and society



Expertise and resources across Europe

Specialist centres

Italy	Obesity and Lipodystrophy Center, Endocrinology Unit, University Hospital, Pisa
France	Co-ordinating Centre of the National Reference Network For Rare Pathologies of Insulin Secretion and Insulin-Sensitivity, AP-HP Hôpital Saint-Antoine, Paris
United Kingdom	National Severe Insulin Resistance Service, Institute of Metabolic Science, Cambridge University Hospital NHS Foundation Trust, Cambridge
Spain	Lipodystrophy Unit, Division of Endocrinology, Complejo Hospitalario Universitario de Santiago de Compostela
Germany	Clinic for Paediatric and Adolescent Medicine, Ruhr-Universität Bochum in the St. Josef-Hospital, Bochum Institute of Human Genetics Martin Luther University Halle-Wittenberg, Halle Department of Endocrinology, University Hospital Leipzig, Leipzig Clinic for Transplantation Medicine, University Hospital Münster, Münster Department of Paediatric and Adolescent Medicine, Ulm University Hospital, Ulm
Greece	Lipodystrophies and Lipid Disorders Clinic, 2nd Dpt of Internal Medicine. Research Unit and Diabetes Center, National and Kapodistrian University of Athens, Attikon Hospital, Athens
Belgium	Department of Endocrinology University Hospitals Leuven Leuven
Netherlands	Department of Endocrinology/Internal Medicine Leiden University Medical Centre, Leiden
Denmark	Clinic for Obesity and Related Metabolic Diseases, Department of Endocrinology and Internal Medicine, MEA, Aarhus University Hospital, Aarhus

Patient support groups



Associazione Italiana Lipodistrofie
www.ailip.it



Association Française des Lipodystrophies
<https://bit.ly/2Lkm6uG>



Lipodystrophy UK
<http://lipodystrophyuk.org/>



Asociación de Familiares y Afectados
por Lipodistrofias
www.aelip.org

European professional groups

European Consortium of Lipodystrophies
www.eclip-web.org/

For further information about lipodystrophy please visit

Lipodystrophy.eu
www.lipodystrophy.eu/en

French Network of Rare Diseases of Insulin Secretion
and Insulin Sensitivity
<http://endocrino-sat.aphp.fr/prisis/>
Email: prisis.sat@aphp.fr



Glossary

Generalised lipodystrophy ⁷	a sub-category of lipodystrophies, characterised by the near-total absence of subcutaneous fat, usually from birth. Generalised lipodystrophy can be further divided into congenital generalised lipodystrophy, which is a genetic condition, and acquired generalised lipodystrophy which is often an autoimmune disorder or of no known cause.
Heterogeneous condition ¹⁴	a condition which may have a number of different manifestations and subtypes.
Hyperglycaemia ¹⁵	scientific term for high blood sugar.
Hyperphagia ¹⁶	a chronic hunger or abnormally increased appetite for food.
Leptin ¹⁷	a hormone produced by fat cells which, in the long term, acts to regulate food intake and control the body's energy expenditure and metabolism.
Orphan medicine ¹⁸	in Europe, orphan designation is given to a treatment that meets the following criteria: – is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating – the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development – no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.
Partial lipodystrophy ⁷	a sub-category of lipodystrophies characterised by the partial loss of subcutaneous fat. Partial lipodystrophy can be further divided into familial partial lipodystrophy, which is a genetic condition where symptoms often first appear at puberty and acquired partial lipodystrophy, which is often an autoimmune disorder.
Specialist centre	a medical centre with a recognised expertise in the diagnosis, care and management of a particular condition.
Subcutaneous ¹⁹	a type of tissue that is the innermost layer of the skin. This layer typically houses blood vessels, nerves, connective tissue and fat.
Ultra-orphan medicine ²⁰	a term used to refer to medicines for very rare conditions. The Scottish Medicines Consortium defines the prevalence of ultra-orphan diseases as 1 in 50,000 people.

References

1. Fiorenza CG, et al. Lipodystrophy: pathophysiology and advances in treatment. *Nat Rev Endocrinol* 2011;7:137–50.
2. Faggioni R, et al. Leptin regulation of the immune response and the immunodeficiency of malnutrition. *Faseb J* 2001;15:2565-71.
3. Brown R, et al. Diagnosis and Management of Lipodystrophy. *J Clin Endocrinol Metab*, 2016. 101(12):4500-4511.
4. Gupta N, et al. Clinical Features and Management of Non-HIV-Related Lipodystrophy in Children: A Systematic Review. *J Clin Endocrinol Metab*, 2017. 102(2): p. 363-374.
5. Weston N, et al. Hypertriglyceridaemia-induced pancreatitis. *BMJ Case Rep* 2013;27:2013.
6. Chiquette E, et al. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. *Diabetes Metab Syndr Obes*, 2017. 10: p.375-383.
7. Cambridge University Hospitals, Lipodystrophy, available at: https://www.cuh.nhs.uk/sites/default/files/publications/Lipodystrophy_v4.pdf. Last accessed September 2019.
8. Garg A. Lipodystrophies: Genetic and Acquired Body Fat Disorders. *J Clin Endocrinol Metab*, 2011. 96(11):3313–3325.
9. Addenbrooks Hospital, How lipodystrophy affects patients' lives, available at: <https://www.act4addenbrookes.org.uk/Aboutus/News/ArtMID/605/ArticleID/211/How-lipodystrophy-affects-patients'-lives>. Last accessed September 2019.
10. Dhankar P, et al. Estimating Quality of Life of Patients with Lipodystrophy. *Value in Health*, 2015. 18(3): A292.
11. Eldin A, et al. The LD Lync Study: Natural History Study of Lipodystrophy Syndromes: Early Lessons from the Pilot Data. *Journal of the Endocrine Society*, 2019. Volume 3, Issue Supplement 1.
12. Handelsman Y et al. The Clinical Approach To The Detection Of Lipodystrophy – An AACE Consensus Statement. *Endocr Pract*, 2013. 19(1): 107-116.
13. Adams C et al. "We're stuck with what we've got": the impact of lipodystrophy on body image. *J Clin Nurs*, 2018. 27(9): 1958-1968.
14. Wallstrom G, et al. Biomarker Discovery for Heterogeneous Diseases. *Cancer Epidemiol Biomarkers*, available at <https://cebp.aacrjournals.org/content/early/2013/04/12/1055-9965.EPI-12-1236.full-text.pdf>. Last accessed September 2019.
15. NHS. Hyperglycaemia, available at <https://www.nhs.uk/conditions/high-blood-sugar-hyperglycaemia/>. Last accessed September 2019.
16. Diamond G, et al. Hyperphagia In Foster Care Children. *Paediatric Research*, 1987. 21:180.
17. Friedman J, et al. Leptin and the regulation of body weight in mammals. *Nature*, 1998. 395:763-770.
18. European Medicines Agency. Orphan designation: Overview, available at: <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview>. Last accessed September 2019.
19. Verywell Health. Subcutaneous Tissue: The Innermost Layer of Skin, available at <https://www.verywellhealth.com/subcutaneous-tissue-1068882>. Last accessed September 2019.
20. Scottish Medicines Consortium. Revised process – ultra-orphan medicines for extremely rare conditions, available at <https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/>. Last accessed September 2019.

