Lipodystrophy United

Resources Patients, Stakeholders, and Patients to Understand the Burden of the Disease and Treatment Options

Basic Understanding of Lipodystrophy

A. "Nova." *PBS*, Public Broadcasting Service, 8 Apr. 2020, www.pbs.org/video/how-hormone-leptin-helps-regulate-appetite-tltl4x/.

In this PBS episode, the hormone leptin and how it helps regulate appetite is explained in the case of Troy, a Congenital Generalized Lipodystrophy (CGL) patient. **Because lipodystrophy patients do not have subcutaneous fat, they cannot produce leptin**. Low levels of leptin trigger an alarm to eat, providing a chemical explanation of why patients experience hyperphagia.

B. Sanders, Rebecca. "Lipodystrophy Stories: Personal Experiences and Insights." Lipodystrophy UK, 19 Jan. 2024, lipodystrophyuk.org/videos/living-with-lipodystrophy/

Lipodystrophy UK has crafted a thorough introductory resource on lipodystrophy, serving as a **valuable tool for the patient community**. This comprehensive guide incorporates **patient stories** spanning various lipodystrophy types, offering a nuanced understanding of their experiences. The resource includes informative videos covering diverse aspects of lipodystrophy, such as its **definition, physical manifestations, internal effects on patients, hormonal impacts, self-management strategies, and pertinent advice along with contact information**.

C. Stratton, Andra. "Lipodystrophy Explained." Check Rare, 4 Feb. 2020, https://www.youtube.com/watch?v=R9xfIkblIyA

Andra Stratton, a patient advocate, provides a basic understanding of lipodystrophy, a multi-system disease. In lipodystrophy, the absence of normally distributed adipose tissue leads to a **muscular appearance**. With no safe fat storage, it **accumulates** in the bloodstream, concentrates around organs, potentially causing organ failure. Due to the lack of body fat leading to low levels of leptin, lipodystrophy patients are in a constant state of **extreme hunger (hyperphagia)**.

D. National Organization for Rare Diseases (NORD), "Acquired Lipodystrophy," Last updated: June 16, 2015, https://rarediseases.org/rare-diseases/acquired-lipodystrophy/

Acquired Lipodystrophy refers to non-genetic forms of lipodystrophy, emerging during life and lacking a direct genetic cause. Subtypes include Acquired Generalized Lipodystrophy (AGL), Acquired Partial Lipodystrophy (APL), High Active Antiretroviral Therapy-Induced Lipodystrophy (LD-HIV), and Localized Lipodystrophy. **AGL involves varying fat loss patterns, often starting in childhood or adolescence**,

accompanied by severe insulin resistance, metabolic complications, and potential liver issues. **APL, typically appearing in childhood, leads to progressive fat loss in the upper body while sparing the lower body**, with some developing kidney disorders. LD-HIV arises in HIV patients receiving antiretroviral therapy, causing gradual fat loss in limbs and face. **Localized Lipodystrophy involves subcutaneous fat loss in specific body areas, often linked to drug injections**. Causes range from medications to autoimmune reactions, and underlying mechanisms remain complex. Diagnosis relies on symptoms, clinical evaluation, and specialized tests, with treatments addressing specific complications and often involving psychological support, dietary measures, and, in severe cases, cosmetic surgery or transplantation. Recent approvals include **metreleptin therapy for generalized lipodystrophies**, although its use involves careful consideration of risks and benefits.

E. Cleveland Clinic, "Lipodystrophy," https://my.clevelandclinic.org/health/diseases/23441-lipodystrophy

Lipodystrophy is a condition characterized by the loss or abnormal distribution of fat tissue in the body, impacting various metabolic functions. **There are genetic and acquired forms, with genetic types like congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPLD) often diagnosed in childhood**. Acquired forms, like acquired generalized lipodystrophy (AGL) and high active antiretroviral therapy (HAART)-induced lipodystrophy (LD-HIV), may develop later in life. **Lipodystrophy affects adipose tissue, leading to health issues such as diabetes, abnormal cholesterol levels, and metabolic syndrome**. Treatment involves managing associated conditions, including leptin replacement and medications for diabetes and cholesterol, while cosmetic procedures can address appearance-related concerns. The prognosis varies based on the specific type and associated complications.

F. https://drive.google.com/file/d/1lJNLx9MviByht0p_bnJEqiTfCYRDnm-C/view?usp=sharing

Sonia Rehal, a scientist with Familial Partial Lipodystrophy (FPL), provides insight into the metabolic complications of this condition. FPL entails partial fat loss, primarily affecting areas like the lower extremities, arms, legs, and buttocks, alongside variations of fat excess. **The absence of fat storage containers leads to fat accumulation around cells**, resulting in a lack of leptin, a crucial hormone. Moreover, **excess lipid droplets contribute to inflammation and dysfunction in endothelial cells lining blood vessels**, promoting ectopic lipid accumulation. Consequently, patients experience constant hunger due to leptin deficiency, leading to difficulties in functioning properly. Additionally, there's an increased risk of **insulin resistance, diabetes, and polycystic ovarian syndrome for women**. **Hypertension** arises from vessel malfunction, further

exacerbated by **fatty liver, hypertriglyceridemia, and pancreatitis** due to excess fat droplets. Muscle inflammation, termed myalgia, results from lipid droplet accumulation, while abnormal heart rhythms and cardiomyopathy pose significant risks, necessitating pacemakers and defibrillators. **Vascular dysfunction**, often associated with diabetes, heightens the risk of complications like kidney disease, accentuated by the leakier nature of kidneys in lipodystrophy patients.

G. European Consortium of Lipodystrophies (EClip), "Lipodystrophies," https://www.eclip-web.org/

European Consortium of Lipodystrophies is a network of lipodystrophy research groups. Their website provides basic information about the disease, monthly publications, and summaries of yearly meetings with researchers and patient advocacy groups making it a great general resource for the lipodystrophy community.

More Complicated Understanding of Lipodystrophy

A. Lipodystrophy UK, "Understanding the Genetics," https://lipodystrophyuk.org/lipodystrophy-understanding-the-genetics/

Lipodystrophy refers to a group of disorders characterized by the varying **loss of adipose tissue**. The **genetic basis** varies among different subtypes. This article explains the **gene mutations and the gene expression patterns** causing each type of Lipodystrophy.

B. Lipodystrophy: a paradigm for understanding the consequences of "overloading" adipose tissue, Koini Lim, Afreen Haider, Claire Adams, Alison Sleigh, and David B. Savage Physiological Reviews 2021 101:3, 907-993 doi: https://journals.physiology.org/doi/full/10.1152/physrev.00032.2020

The paper discusses the various **roles of adipose tissue** (AT), commonly known as body fat, and its involvement in different types of lipodystrophy, a condition characterized by abnormal fat distribution. Adipose tissue is not just a storage place for fat; it's a dynamic organ made up of different cell types like fat cells, immune cells, and others. It produces signaling molecules called adipokines, such as leptin and adiponectin. **Leptin helps regulate our eating habits and energy usage**, and a lack of it can lead to overeating and obesity. Adipose tissue can grow in two ways: by increasing the size of existing fat cells (hypertrophy) or by creating new ones (hyperplasia). This growth process, called adipogenesis, happens both before we're born and during our adult lives. Different parts of our body fat can behave differently, **influencing how our bodies store and use energy**. In recent years, scientists have found genetic mutations associated with lipodystrophies, suggesting a **connection between these disorders and the ability of fat cells to form properly**. Ectopic fat accumulation (fat in the wrong places) is a common

feature of lipodystrophies, and theories have been proposed to understand why it is **linked to insulin resistance**. The text mentions the significant benefits of bariatric surgery for both obesity and lipodystrophy-associated insulin resistance.

C. Zammouri J, Vatier C, Capel E, Auclair M, Storey-London C, Bismuth E, Mosbah H, Donadille B, Janmaat S, Fève B, Jéru I, Vigouroux C. Molecular and Cellular Bases of Lipodystrophy Syndromes. Front Endocrinol (Lausanne). 2022 Jan 3;12:803189. doi: 10.3389/fendo.2021.803189. PMID: 35046902; PMCID: PMC8763341. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8763341/

The focus is on genetic forms of lipodystrophies, **with over 20 genes identified as causative factors in monogenic lipodystrophy syndromes**. The review explores the **molecular and cellular bases of these syndromes, including altered adipocyte differentiation and premature cellular senescence**, highlighting their impact on adipose tissue functions and insulin response. Additionally, the review covers topics such as links between lipodystrophy and premature aging, immuno-inflammatory aggressions of adipose tissue, and the relationships between lipomatosis and lipodystrophy. Finally, the use of substitutive therapy with metreleptin, an analog of **leptin**, is discussed.

D. National Lipid Association, Guest Editorial: A Glimpse at Lipodystrophy – Diagnosis and Treatment, Jonathan Q. Purnell, Md, Eliot A. Brinton, Md, Fnla, Sergio Fazio, Md, Phd, Fnla, David R. Neff, Do, 2020, https://www.lipid.org/lipid-spin/summer-2018/guest-editorial-glimpse-lipodystrophy-—-diagnosis-and-treatment

The ability of clinicians to swiftly and accurately diagnose patients (**clinical acumen**) and **genetic testing** can confirm lipodystrophy type. Treatment involves a low-fat high-fiber diet, regular activity, and managing comorbidities. For severe cases, metreleptin, a leptin analog, is approved to address complications of leptin deficiency. **Lipidologists should consider lipodystrophies in patients with hypertriglyceridemia and severe insulin resistance**, distinguishing them from other conditions like familial chylomicronemia syndrome. Treatment includes lifestyle management, diabetes control, lipid-lowering medications, and, in generalized lipodystrophy with low leptin, metreleptin replacement.

E. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011 Feb;11(2):85-97. doi: 10.1038/nri2921. Epub 2011 Jan 21. PMID: 21252989; PMCID: PMC3518031. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21252989/

Adipose tissues, serving as fat storage, influence various organs like the brain, heart, blood vessels, liver, and muscles by **releasing adipokines**. These adipokines can either

induce inflammation or mitigate it, and **maintaining a proper balance is essential for overall health**. Dysfunctional fat cells can disrupt this balance, impacting inflammation response, metabolism, and cardiovascular health.

F. Fourman LT, Grinspoon SK. Approach to the Patient With Lipodystrophy. J Clin Endocrinol Metab. 2022 May 17;107(6):1714-1726. doi: 10.1210/clinem/dgac079. PMID: 35137140; PMCID: PMC9113814. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9113814/

Lipodystrophy conditions are more common than previously thought, and it's crucial to assess and manage cardiovascular risks in all lipodystrophy patients. Treatment includes replacing **leptin for those without HIV and using tesamorelin for HIV-associated lipodystrophy**, but there's still much to learn about optimizing care for these patients and gaining insights into fat biology and related diseases.

G. Akinci B, Oral EA, Neidert A, Rus D, Cheng WY, Thompson-Leduc P, Cheung HC, Bradt P, Foss de Freitas MC, Montenegro RM, Fernandes VO, Cochran E, Brown RJ. Comorbidities and Survival in Patients With Lipodystrophy: An International Chart Review Study. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5120-5135. doi: 10.1210/jc.2018-02730. PMID: 31314093; PMCID: PMC6760298. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31314093/

This international chart review conducted across multiple countries examined the natural history of non-HIV-related lipodystrophy syndromes in 230 patients who never received disease-specific therapies, providing crucial insights into the untreated course of the condition. **The study found a lifetime prevalence of diabetes/insulin resistance in 58.3%**, with **liver abnormalities** being the most common organ abnormality. The mean time to the first organ abnormality differed significantly between generalized lipodystrophy (GL) and partial lipodystrophy (PL), and while diabetes/insulin resistance occurred earlier in GL, **disease progression time was comparable between GL and PL**. The study also reported mean time to death in both groups, offering comprehensive, **long-term data** on the natural history of non-HIV-related lipodystrophy.

H. Chiquette E, Oral EA, Garg A, Araújo-Vilar D, Dhankhar P. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. Diabetes Metab Syndr Obes. 2017 Sep 13;10:375-383. doi: 10.2147/DMSO.S130810. PMID: 29066925; PMCID: PMC5604558. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604558/

This study aimed to quantitatively estimate the prevalence of non-human immunodeficiency virus (HIV)-associated lipodystrophy (LD) syndromes, a rare group of disorders characterized by abnormal fat distribution. Using electronic medical record

(EMR) databases and literature searches, the **prevalence** of all LD, generalized lipodystrophy (GL), and partial lipodystrophy (PL) was assessed. The range of worldwide prevalence estimates for all LD, GL, and PL was found to be smaller and narrower (1.3–4.7 cases/million, 0.2–1.0 cases/million, and 1.7–2.8 cases/million, respectively) than previously reported estimates (~0.1–90 cases/million). The study emphasizes the ultra-rare nature of LD and **highlights the need for standardized diagnostic criteria** and coding to enhance accuracy in future prevalence estimates.

I. Zachary T. Bloomgarden; Gut Hormones, Obesity, Polycystic Ovarian Syndrome, Malignancy, and Lipodystrophy Syndromes. Diabetes Care 1 July 2007; 30 (7): 1934–1939. https://doi.org/10.2337/dc07-zb07

This study looks at insulin resistance and its associations with gut hormones, obesity, polycystic ovarian syndrome (PCOS), malignancy, and lipodystrophy syndromes. It discusses the **role of gut hormones like PYY and oxyntomodulin in appetite regulation**, explores obesity and insulin resistance interventions such as bariatric surgery and ghrelin regulation, and examines the link between PCOS and metabolic health. Lipodystrophy syndromes are considered as natural experiments **providing insights into the genesis of insulin resistance and potential treatment approaches**.

Quality of Life and Lipodystrophy

A. Demir, T., Simsir, I.Y., Tuncel, O.K. et al. Impact of lipodystrophy on health-related quality of life: the QuaLip study. Orphanet J Rare Dis 19, 10 (2024). https://doi.org/10.1186/s13023-023-03004-w https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-03004-w#citeas

The QuaLip study is a prospective observational real-world investigation focusing on the impact of lipodystrophy on the quality of life (QoL) and **psychoemotional well-being of both adult and pediatric patients**. Over the 24-month follow-up period, **27.69% of adult patients were diagnosed with various psychiatric disorders, such as depressive episodes, anxiety disorders, and adjustment disorders**. The disease burden was notable, affecting aspects like physical appearance, fatigue, and pain, as indicated by lipodystrophy disease and QoL questionnaires. Additionally, a significant proportion of patients reported symptoms of depression and hunger. Lower QoL scores were associated with psychiatric disease and poor metabolic control. The study highlights the **underdiagnosis of psychiatric disorders among lipodystrophy patients and emphasizes the substantial impact of the condition on both QoL and psychoemotional well-being**.

Patient Stories

A. Sanders, Rebecca, "An interview with Becky Sanders, Chair of Lipodystrophy UK," Lipodystrophy UK, 29 Mar. 2021, https://www.youtube.com/watch?v=Dcic7xBYkTo

Becky, Chair of Lipodystrophy UK, shares her personal journey with Familial Partial Lipodystrophy (FPL), emphasizing its **pervasive impact on daily life**, including symptoms like fatigue and hyperplasia. Her diagnostic journey, though swift, was unique in being referred to endocrinology due to a halted menstrual cycle. **Becky founded Lipodystrophy UK to address the lack of community and support for those with lipodystrophy**. The organization's future goals include tailored psychological support, research into treatment options addressing the root cause, and patient involvement in research. **Becky underscores the need for increased awareness within the medical community to prevent misdiagnosis**. Lipodystrophy UK's significant achievement is collaborating on the approval of metreleptin, and Becky stresses the importance of **building a supportive community** for individuals facing similar challenges.

B. "Interview with Snehal," Lipodystrophy UK, 30 Mar, 2021, https://www.youtube.com/watch?app=desktop&v=sxwoUBg-1TM

Snehal, diagnosed with Familial Partial Lipodystrophy (FPL) at 19, shares her journey. The **shared diagnosis with relatives** added pieces to their family's diagnostic puzzle. She faced bullying, impacting her marriage prospects in a traditional Indian setting. **Snehal advocates maintaining a positive mindset, prayer, taking things one day at a time, and finding supportive physicians as coping strategies. She stresses the importance of self-advocacy, engaging in joyful activities, and not letting the disease define one's identity.** As a doctor, she gained insight into the disease. Snehal's advice highlights resilience and a positive approach to navigating the challenges of living with lipodystrophy.

C. "Interview with Catherine," Lipodystrophy UK, 30 Mar. 2021, https://www.youtube.com/watch?app=desktop&v=UVovhTRjxBg

Catherine discusses the **emotional challenges of familial partial lipodystrophy**, where societal misunderstandings and judgments contribute to feelings of frustration. She highlights the **burden of constant inquiries about her weight** and the associated self-consciousness, leading to mental health issues like **depression and loneliness**. Despite daily struggles, Catherine finds vital support in the empathetic community of fellow patients who share similar experiences.

D. Lipodystrophy: The Importance of Awareness, News Medical Life Sciences, Rebecca Sanders, Interview conducted by Alina Shrourou, B.Sc. (Editor), Apr 3 2018, https://www.news-medical.net/news/20180403/Lipodystrophy-The-Importance-of-Awareness.aspx

Lipodystrophy UK, founded by Rebecca Sanders, aims to enhance awareness, fund research benefiting patients directly, collaborate with global lipodystrophy groups, and organize a worldwide conference for knowledge exchange. More information can be found on Lipodystrophy UK's Twitter account (@lipodystrophyuk).

E. "Lipodystrophy is Often Misdiagnosed," Check Rare, 2020, https://www.youtube.com/watch?v=GpwfoS8VRSk

Andra Stratton discusses misdiagnoses by highlighting that **patients are often underdiagnosed and misdiagnosed**. Generalized Lipodystrophy in women is generally diagnosed because lack of adipose tissue is usually recognized by doctors. However, **diagnosis can take many years and a lot of effort**. Generalized Lipodystrophy in men is potentially more difficult to diagnose because it is more typical for men to be more muscular and vascular than women. Partial lipodystrophy patients do not usually get diagnosed until their 30's and 40's when there is significant organ damage. **Partial lipodystrophy patients feel pretty defeated, and a diagnosis can lead to a confirmation that "they are not crazy."**

F. University of Michigan, "Advocating for Her Own Rare Disease: Andra's Story," February 28, 2017, https://www.michiganmedicine.org/health-lab/advocating-her-own-rare-disease-andras-story

Andra Stratton, diagnosed with familial partial lipodystrophy, **faced a lack of information** about her rare disease. Motivated by this gap, she founded Lipodystrophy United (LU), a foundation aimed at creating awareness and supporting those affected. The organization focuses on **addressing the challenges of lipodystrophy**, including severe insulin resistance and high lipids, while **providing a sense of community for patients worldwide**. Collaborating with specialists like Dr. Elif Oral at the University of Michigan, the foundation advocates for increased awareness among physicians and offers support to combat isolation. Stratton's efforts extend to nominating Dr. Oral for the Rare Champion of Hope Award, highlighting the collaborative work needed in the rare disease community. The foundation remains **committed to easing the path for individuals dealing with lipodystrophy by offering resources, information, and a supportive community**.

G. Mass Bio, "Patient Story: A Long Road to Diagnosis," OCT 04, 2017, https://www.massbio.org/news/recent-news/patient-story-a-long-road-to-diagnosis/

Andra Stratton, diagnosed with familial partial lipodystrophy, reflects on the signs of her rare condition that appeared in **childhood, including asthma, pneumonia, and increasing thinness**. Despite facing various health issues, a diagnosis remained elusive until her first pregnancy when **elevated blood sugar levels and eclampsia raised**

concerns. Stratton's second pregnancy further highlighted health risks, leading to an abnormal mammogram and, eventually, an endocrinologist's diagnosis of familial partial lipodystrophy at age 37. **Motivated by the lack of information and resources, Stratton co-founded Lipodystrophy United, dedicated to raising awareness, providing support, and aiding in patient diagnosis**. Despite the absence of a cure, Stratton emphasizes the importance of management tools and increasing awareness and treatment options for lipodystrophy.

H. "'FaceBook Friends Saved my Life' - A Lipodystrophy Story, Rare Disease Report," 2017, https://www.youtube.com/watch?v=MxbpEdh-xvk

Natalie Embry talks about her long journey to diagnosis. She demonstrates the power of the patient community, as **finding the Lipodystrophy facebook group ultimately led to her diagnosis**. She lives in a rural area, so she **managed the burden of the disease through support from her patient group**, periodically traveling to Michigan to Dr. Oral but otherwise educating her own doctors about lipodystrophy. **Patients ultimately have the power to educate other patients and doctors about lipodystrophy**, indicating that the larger reach of our patient community, the better.

I. "Interview with Karen," Lipodystrophy UK, 2022, https://www.youtube.com/watch?app=desktop&v=vfgcQ-nnN1M

Karen, a patient diagnosed with Familial Partial Lipodystrophy (FPL), found relief and empowerment in understanding the cause of her symptoms after a **lengthy diagnostic process** due to the condition's rarity and complexity. Despite facing misdiagnoses and societal judgments, she embraces her uniqueness and focuses on **what she can control, supported by her family and a positive mindset**. Metreleptin treatment has significantly improved her quality of life by reducing extreme hunger and aiding in weight management. Despite challenges, Karen emphasizes the importance of **advocacy, self-awareness, and tailored dietary plans** in navigating life with lipodystrophy, stressing that the condition doesn't define her but requires adaptation and resilience.

J. "Interview with Trish," Lipodystrophy UK, 2022, https://www.youtube.com/watch?v=kT1E5gUeGww

Trish, initially diagnosed with diabetes at 32 and later with Familial Partial Lipodystrophy (FPL), grapples with the profound fatigue and dietary restrictions imposed by her condition, **often feeling misunderstood by others who cannot grasp its severity**. Struggling with body image issues and psychological challenges like borderline personality disorder and body dysmorphia, Trish faces a love/hate relationship with food and endures judgment from medical professionals, who often misdiagnose or inadequately understand lipodystrophy. Coping with the guilt of eating and navigating the complexities of managing her health, Trish finds solace in exercise, rest, and open

communication with doctors, emphasizing the importance of advocating for oneself and seeking support within the lipodystrophy community. Despite the ongoing challenges, Trish maintains a positive attitude, **embracing acceptance as a pathway to happiness** amid the constant battle of living with lipodystrophy.

K. "Make-A-Wish: Kyleigh Dean," Carolina Panthers, 2019, https://www.youtube.com/watch?v=mjxvMlm9Y9M

Kyleigh, football player and wrestler, talks about her experience with Congenital Generalized Lipodystrophy with the Carolina Panthers through Make a Wish Foundation. Kyleigh feels very badly every day but **fights through the fatigue and pain through her love for sports**. She's not afraid to be different, and wants to be the best at everything that she does despite fighting for her life with pancreatitis weeks earlier.

The Power of Patient Engagement

A. McCray AT, LeBlanc K; Undiagnosed Diseases Network. Patients as Partners in Rare Disease Diagnosis and Research. Yale J Biol Med. 2021 Dec 29;94(4):687-692. PMID: 34970107; PMCID: PMC8686769. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8686769/

Active partnership with patients in the Undiagnosed Diseases Network (UDN) has significantly enhanced research outcomes, building patient communities, addressing unmet needs, and advocating for research funding. **Patients' direct experiences have been crucial in shaping the work of clinicians and researchers, bringing valuable perspectives to the forefront**. While progress has been made, ongoing efforts aim to involve patients even earlier in the research process and address power dynamics among clinicians, researchers, and patients.

B. Young, K., Kaminstein, D., Olivos, A. et al. Patient involvement in medical research: what patients and physicians learn from each other. Orphanet J Rare Dis 14, 21 (2019). https://doi.org/10.1186/s13023-018-0969-1

The study focused on the Vasculitis Patient-Powered Research Network (VPPRN) to explore the **mutual learning experiences of patients and investigators collaborating in rare disease research**. Qualitative interviews with patients, investigators, and study managers revealed key insights into the benefits of effective communication, openness to listening, and the importance of setting realistic expectations. The findings emphasize that direct engagement of patient-partners in research design and development, coupled with shared learning between patients and investigators, **positively influences the dynamics of medical research teams**, impacting research design, participant recruitment, and study subject retention.

C. Levitan B, Getz K, Eisenstein EL, Goldberg M, Harker M, Hesterlee S, Patrick-Lake B, Roberts JN, DiMasi J. Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. Ther Innov Regul Sci. 2018 Mar;52(2):220-229. doi: 10.1177/2168479017716715. Epub 2017 Jul 17. PMID: 29714515; PMCID: PMC5933599. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5933599/

Researchers investigated whether involving patients in the development of new medicines is financially beneficial using a method called Expected Net Present Value (ENPV). They focused on cancer medicine development in phases 2 and 3. **The results showed that increased patient involvement led to significant financial gains, speeding up the development process and saving substantial money**. For instance, a $100,000 investment in patient engagement could yield returns exceeding 500 times that amount. Not only is patient involvement beneficial for healthcare, but it also makes **strong financial sense for medicine developers**.

D. ISBOR Improving Healthcare Decisions, "Increasing Patient Involvement in Drug Development," Lowe, Maria M. et al.Value in Health, Volume 19, Issue 6, 869 - 878 https://www.valueinhealthjournal.com/article/S1098-3015(16)30432-6/fulltext

This study investigates the **current state of patient involvement in drug development processes, aiming to identify opportunities, barriers, and examples of patient engagement**. Through interviews with senior leaders in the pharmaceutical industry, patients, research funders, regulators, and advocacy groups, the research reveals a **lack of widespread patient involvemen**t despite recognition of its potential benefits. Barriers include concerns about representativeness, added burden on patients, and perceived costs. The study underscores the need for **pharmaceutical companies to innovate and prioritize patient involvement** throughout the product lifecycle to align with evolving healthcare systems and meet patient needs effectively.

E. Next Avenue, "The Importance of Having, or Being, a Patient Advocate," Kerri Fivecoat-Campbell and SCAN Foundation, Sept. 7, 2018, https://www.nextavenue.org/importance-patient-advocate/

Acting as her mother's patient advocate, the narrator navigated through the complexities of her mother's healthcare journey, **identifying and addressing critical issues that medical professionals initially overlooked**. This advocacy proved instrumental in identifying adverse drug reactions and ensuring **appropriate medical interventions**, ultimately leading to significant improvements in her mother's condition and quality of life. Expert insights underscore the **importance of having a patient advocate**, emphasizing the need for informed decision-making, organizational skills, and active engagement in medical care to optimize patient outcomes and navigate the complexities of the healthcare system.

Congenital Generalized Lipodystrophy

A. National Organization for Rare Disorders (NORD), Congenital Generalized Lipodystrophy, Last updated: December 15, 2022, https://rarediseases.org/rare-diseases/congenital-generalized-lipodystrophy/

Congenital Generalized Lipodystrophy (CGL), or Berardinelli-Seip syndrome, is a rare genetic disorder marked by **near-total body fat loss and heightened muscularity**. Linked to insulin resistance, glucose intolerance, and diabetes, CGL manifests in four subtypes with distinct gene mutations. It affects approximately 500-600 individuals globally, with a prevalence ranging from **1 in a million to 1 in 10 million**. Diagnosis involves recognizing symptoms and genetic testing, while treatment focuses on managing individual complications, including dietary interventions, leptin replacement therapy, and, in severe cases, cosmetic surgery or liver transplantation.

Acquired Generalized Lipodystrophy

A. Fernandez-Pombo A, Prado-Moraña T, Diaz-Lopez EJ, Sanchez-Iglesias S, Castro AI, Cobelo-Gomez S, Araujo-Vilar D. Clinical Characterisation and Comorbidities of Acquired Generalised Lipodystrophy: A 14-Year Follow-Up Study. J Clin Med. 2023 Nov 27;12(23):7344. doi: 10.3390/jcm12237344. PMID: 38068396; PMCID: PMC10706961. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10706961/

Acquired Generalized Lipodystrophy (AGL) is a rare disorder characterized by gradual fat loss, and this study **examines seven patients over 14 years to enhance understanding of the condition**. Onset of the phenotype varied, occurring during childhood/adolescence in five cases and in adulthood in two cases, with some patients reporting infections or vaccine administration prior to lipodystrophy development. **Clinical features** included phlebomegaly (varicose veins), umbilical protrusion/hernia, acanthosis nigricans, and metabolic comorbidities such as diabetes, hypertriglyceridemia, and autoimmune conditions, emphasizing distinctive diagnostic criteria for AGL.

Familial Partial Lipodystrophy

A. National Organization of Rare Diseases (NORD), “Familial Partial Lipodystrophy,” Last Updated Jun. 16, 2015, https://rarediseases.org/rare-diseases/familial-partial-lipodystrophy/

Familial partial lipodystrophy (FPL) is a rare genetic disorder characterized by the **progressive, selective loss of subcutaneous fat, often beginning around puberty, which leads to abnormal fat accumulation in other body areas**. FPL is associated with various metabolic complications, including glucose intolerance, hypertriglyceridemia, and diabetes, with severity depending on the extent of adipose tissue loss. It encompasses six subtypes, each caused by mutations in different genes, with four inherited as

autosomal dominant traits, one as an autosomal recessive trait, and the mode of inheritance for the Kobberling variety remains unknown. Individuals with FPL may exhibit a range of additional symptoms, and the disorder's recognition is more evident in women due to more pronounced metabolic complications. Diagnosis involves clinical evaluation, symptom identification, genetic testing, and managing complications through dietary modifications, exercise, cosmetic surgery for fat redistribution, and medications to address metabolic issues.

B. PTC Therapeutics, "Familial partial lipodystrophy (FPL)," https://www.ptcbio.com/therapeutic-areas/familial-partial-lipodystrophy/

Familial Partial Lipodystrophy (FPL) is a rare genetic disorder marked by the progressive loss of body fat, leading to **metabolic complications like insulin resistance and fatty liver disease**. Despite its low prevalence, FPL poses significant health risks, often presenting with comorbidities such as polycystic ovarian syndrome and diabetes. PTC Therapeutics is addressing FPL through the commercialization of Waylivra® (volanesorsen), aiming to alleviate its metabolic burden and improve patient outcomes.

C. Ajluni N, Meral R, Neidert AH, Brady GF, Buras E, McKenna B, DiPaola F, Chenevert TL, Horowitz JF, Buggs-Saxton C, Rupani AR, Thomas PE, Tayeh MK, Innis JW, Omary MB, Conjeevaram H, Oral EA. Spectrum of disease associated with partial lipodystrophy: lessons from a trial cohort. Clin Endocrinol (Oxf). 2017 May;86(5):698-707. doi: 10.1111/cen.13311. Epub 2017 Mar 27. PMID: 28199729; PMCID: PMC5395301.https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/28199729/

This cross-sectional study investigates partial lipodystrophy (PL) in 23 patients, emphasizing genetic, clinical, and laboratory characteristics. Most patients had heterozygous pathogenic variants in LMNA or a novel variant in POLD1. Metabolic parameters, such as liver fat content, were correlated with clinical features, revealing a complex multi-system disorder. **The study suggests that assessing body composition indices, particularly the fat mass ratio, may aid in PL diagnosis**. Additionally, nuclear disorganization and atypia may serve as potential biomarkers, even in the absence of LMNA pathogenic variants.

D. Garg A, Vinaitheerthan M, Weatherall PT, Bowcock AM. Phenotypic heterogeneity in patients with familial partial lipodystrophy (dunnigan variety) related to the site of missense mutations in lamin a/c gene. J Clin Endocrinol Metab. 2001 Jan;86(1):59-65. doi: 10.1210/jcem.86.1.7121. PMID: 11231979. https://academic.oup.com/jcem/article/86/1/59/2841085?login=false

The study identifies mutations in the lamin A/C (LMNA) gene, specifically in exon 8 and exon 11, associated with typical Familial Partial Lipodystrophy, Dunnigan variety (FPLD). Twelve families with exon 8 mutations (R482Q, R482W, G465D) exhibit typical

FPLD characteristics, while an atypical FPLD family with an exon 11 mutation (R582H) shows unique phenotypic features. **Phenotypic differences include less severe subcutaneous fat loss in specific body regions for atypical FPLD, alongside similar excess fat deposition in other regions compared to typical FPLD**. Atypical FPLD individuals also demonstrate tendencies toward lower serum triglycerides and higher high-density lipoprotein cholesterol levels. **The study suggests disrupted lamin A protein interaction in atypical FPLD**, contributing to distinct phenotypes compared to the disruption of both lamin A and C interactions in typical FPLD. Overall, this research enhances understanding of genetic and phenotypic heterogeneity within FPLD, **emphasizing the intricate role of lamin A/C mutations in body fat distribution and metabolic outcomes**.

E. Donadille B, D'Anella P, Auclair M, Uhrhammer N, Sorel M, Grigorescu R, Ouzounian S, Cambonie G, Boulot P, Laforêt P, Carbonne B, Christin-Maitre S, Bignon YJ, Vigouroux C. Partial lipodystrophy with severe insulin resistance and adult progeria Werner syndrome. Orphanet J Rare Dis. 2013 Jul 12;8:106. doi: 10.1186/1750-1172-8-106. PMID: 23849162; PMCID: PMC3720184. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23849162/

This study investigates the **connection between lipodystrophy, extreme insulin resistance, and Werner syndrome, a form of adult progeria associated with WRN gene mutations**. Two women initially diagnosed with partial lipodystrophic syndrome were later confirmed to have Werner syndrome, characterized by a distinctive lipodystrophic phenotype, severe insulin resistance, and additional features like cataracts and skin atrophy. Biallelic WRN null mutations (p.Q748X homozygous and compound heterozygous p.Q1257X/p.M1329fs) were identified. **Despite reduced ovarian reserve, pregnancies were achieved with insulin-sensitizers, complicated by cervical incompetence**. The study suggests a link between WRN mutations, lipodystrophy, and premature aging, shedding light on the molecular mechanisms involved. WRN-mutated fibroblasts displayed oxidative stress, lamin B1 overexpression, nuclear dysmorphies, and premature senescence, highlighting the potential role of DNA replication/repair in lipodystrophy etiology.

F. Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM. Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. Am J Hum Genet. 2000 Apr;66(4):1192-8. doi: 10.1086/302836. Erratum in: Am J Hum Genet 2000 Sep;67(3):775. PMID: 10739751; PMCID: PMC1288186. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10739751/

Familial partial lipodystrophy (FPLD), Dunnigan variety, is a genetic disorder characterized by **fat loss from the limbs and trunk, with excess fat deposition in the**

head and neck. It often leads to insulin resistance, dyslipidemia, and diabetes. Genetic mutations in the lamin **A/C gene, particularly in exons 8 and 11**, have been identified in families with FPLD, **impacting the globular C-terminal domain of the lamin A/C protein**. The study also notes clinical heterogeneity within affected individuals and emphasizes the need for further research to understand the specific mechanisms behind FPLD and how different genetic alterations contribute to distinct clinical outcomes.

G. Akamnonu C, Ueda M, Shah A. Rare Diagnosis of Familial Partial Lipodystrophy in a Patient With Life-Threatening Pancreatitis due to Hypertriglyceridemia. AACE Clin Case Rep. 2021 Jun 16;8(1):11-14. doi: 10.1016/j.aace.2021.06.005. PMID: 35097194; PMCID: PMC8784711. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8784711/

This report discusses a case of Familial Partial Lipodystrophy Type 2 (FPLD2), a rare genetic condition characterized by partial loss of subcutaneous tissue, which can lead to complications such as hypertriglyceridemia, insulin resistance, and diabetes. **The 32-year-old patient experienced recurrent pancreatitis, requiring multiple surgeries and resulting in various complications**. The diagnosis was achieved through careful history-taking, examination, and subsequent genetic testing. The case emphasizes the importance of **thorough physical examinations and detailed medical and family histories in diagnosing rare conditions like FPLD2, enabling appropriate counseling, family testing, and multidisciplinary care**.

Other Types of Lipodystrophy

A. Kristina I. Rother, Rebecca J. Brown; Novel Forms of Lipodystrophy: Why should we care?. Diabetes Care 1 August 2013; 36 (8): 2142–2145. https://doi.org/10.2337/dc13-0561

Recent advancements highlight the co-occurrence of lipodystrophy with obesity and the potential synergistic metabolic effects, alongside promising therapeutic interventions like leptin replacement therapy. Improved understanding of lipodystrophy's genetic underpinnings, varied clinical presentations, and associated comorbidities underscores the importance of accurate diagnosis, genetic counseling, and tailored medical management strategies.

Membranous Lipodystrophy

B. Akpinar F, Demir E, Apa DD. Membranous lipodystrophy: case report and review of the literature. An Bras Dermatol. 2015 May-Jun;90(3 Suppl 1):115-7. doi: 10.1590/abd1806-4841.20153677. PMID: 26312691; PMCID: PMC4540525. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540525/

Membranous lipodystrophy is a condition involving the **formation of cysts in the fatty tissue beneath the skin**. It can be associated with various diseases, including vascular

disorders. The reported case describes a patient with membranous lipodystrophy linked to both hypertension and venous insufficiency. **The diagnosis was made by examining tissue samples, revealing cysts surrounded by abnormal membranes, likely caused by reduced blood flow to the fatty tissue**. This condition can manifest as tender or nontender nodules, ulcers, or swelling. In this case, the patient had indurated plaques, and the underlying causes were identified as high blood pressure and venous insufficiency, emphasizing the **role of impaired blood flow in membranous lipodystrophy**.

HIV-Associated Lipodystrophy

C. Baril JG, Junod P, Leblanc R, Dion H, Therrien R, Laplante F, Falutz J, Côté P, Hébert MN, Lalonde R, Lapointe N, Lévesque D, Pinault L, Rouleau D, Tremblay C, Trottier B, Trottier S, Tsoukas C, Weiss K. HIV-associated lipodystrophy syndrome: A review of clinical aspects. Can J Infect Dis Med Microbiol. 2005 Jul;16(4):233-43. doi: 10.1155/2005/303141. PMID: 18159551; PMCID: PMC2095035. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095035/

Around two years after introducing **highly active antiretroviral therapy (HAART) for treating HIV, noticeable changes in body shape and metabolism, collectively known as lipodystrophy syndrome, were observed**. Initially linked to protease inhibitors, it later became clear that nucleoside reverse transcriptase inhibitors (NRTIs) also contribute to these changes. Lipodystrophy syndrome encompasses alterations in body fat distribution, including loss (lipoatrophy) and accumulation (lipoaccumulation), but a direct connection between these changes is unclear. Despite its prevalence and causes being challenging to define, this article reviews the current understanding of lipodystrophy, covering its definition, symptoms, risk factors, causes, diagnosis, and treatment, **emphasizing its association with HIV and antiretroviral drugs**.

D. Guzman N, Vijayan V. HIV-Associated Lipodystrophy. [Updated 2022 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493183/

HIV-associated lipodystrophy is a syndrome resulting from antiretroviral therapy (ART) characterized by body shape changes, **presenting as either lipoatrophy (fat loss) or lipohypertrophy (fat accumulation)**. Thymidine analog NRTIs, particularly stavudine and zidovudine, are linked to lipoatrophy. This condition adversely affects patients' physical appearance, self-esteem, and quality of life. Management involves ART adjustments, lifestyle modifications, and pharmacological interventions, with complications including metabolic abnormalities. **Regular monitoring is crucial**, and an interprofessional team approach, encompassing healthcare providers, nurses, pharmacists, and mental health professionals, is essential for comprehensive patient care and optimal outcomes.

E. Singhania R, Kotler DP. Lipodystrophy in HIV patients: its challenges and management approaches. HIV AIDS (Auckl). 2011;3:135-43. doi: 10.2147/HIV.S14562. Epub 2011 Dec 14. PMID: 22267946; PMCID: PMC3257972. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257972/

HIV-associated lipodystrophy encompasses body composition and metabolic changes, such as lipoatrophy, lipohypertrophy, dyslipidemia, and insulin resistance, commonly observed with highly active antiretroviral therapy (HAART). Although resembling metabolic syndrome, these alterations can occur independently. Various factors, including host, disease, and treatment-related elements, contribute to these changes. Recent drug developments aim for metabolically safer regimens. The body composition shifts can lead to **psychological distress and impact treatment adherence**. Managing dyslipidemia and glucose alterations follows standard approaches. Lipoatrophy is addressed through **antiretroviral selection or switching, and sometimes plastic surgery**. Lifestyle modifications are key in lipohypertrophy management, and a **growth hormone releasing factor has emerged as a treatment option for central fat reduction**. Overall, addressing HIV-associated lipodystrophy involves a multifaceted approach considering both medical and psychological aspects.

How to Detect and Treat Patients with Lipodystrophy

A. "What Clinicians Need to Know About Lipodystrophy," Rare Disease Report, 2018, https://www.youtube.com/watch?v=ZuBaLXpNCf0

Andra Stratton talks about the **need for clinicians to work with patient organizations in disease research**. Keeping the patient involved in every step of their research is vital to treating patients more successfully. Clinicians usually focus on the metabolic effects of the disease, but **lipodystrophy is a multi-system disease**. Knowing that, patients are focusing on **urging clinicians to focus on hormone imbalances that lead to excessive hunger, sleep issues, pain, and neurological issues**.

B. Bruder-Nascimento T, Kress TC, Belin de Chantemele EJ. Recent advances in understanding lipodystrophy: a focus on lipodystrophy-associated cardiovascular disease and potential effects of leptin therapy on cardiovascular function. F1000Res. 2019 Oct 16;8:F1000 Faculty Rev-1756. doi: 10.12688/f1000research.20150.1. PMID: 31656583; PMCID: PMC6798323. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6798323/

This article explores lipodystrophy, a rare condition characterized by the absence of adipose tissue, **causing metabolic issues like insulin resistance and cardiovascular problems such as cardiomyopathy and hypertension**. The study delves into murine models of lipodystrophy to understand the cardiovascular consequences and presents metreleptin, a synthetic analog of the hormone leptin, as a treatment. While **metreleptin** has proven effective in improving metabolic functions, concerns about potential

cardiovascular risks arise due to previous associations between leptin and hypertension. The article emphasizes the **need for further research to determine metreleptin's impact on cardiovascular health in lipodystrophy patients**, considering both metabolic improvements and potential direct effects on the heart and blood vessels.

C. Lipodystrophy Syndromes: Presentation and Treatment, Baris Akinci, Melis Sahinoz, and Elif Oral., Last Update: April 24, 2018, https://www.ncbi.nlm.nih.gov/books/NBK513130/

Lipodystrophy syndromes, characterized by the selective absence of adipose tissue, represent **lipid-partitioning disorders resulting in ectopic steatosis, severe dyslipidemia, and insulin resistance**. Recent decades have witnessed significant advancements in understanding these syndromes, with over 15 molecular etiologies identified, predominantly associated with adipocyte differentiation and lipid droplet pathways. Notably, **seemingly acquired syndromes are now recognized to have genetic roots, challenging previous classification paradigms**. Despite diverse etiologies, **the common denominator is the absence of adipose tissue, disrupting insulin sensitivity and lipid metabolism**. Treatment strategies, exemplified by leptin replacement for generalized lipodystrophy syndromes, have shown success in improving insulin resistance and dyslipidemia, leading to FDA approval. Ongoing trials target potential therapies for partial forms, indicating a **promising avenue for novel breakthroughs in the metabolism field**. Current treatments for lipodystrophy syndromes involve lifestyle modifications, medications like metformin and fibrates, and cosmetic interventions. Bariatric surgery, particularly Roux-en-Y Gastric Bypass, has shown efficacy in weight loss and metabolic improvements. Investigational therapies, including antisense oligonucleotides and receptor agonists, are being explored in clinical trials, signaling potential advancements in targeted treatments for lipodystrophy.

D. Araújo-Vilar D, Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest. 2019 Jan;42(1):61-73. doi: 10.1007/s40618-018-0887-z. Epub 2018 Apr 27. PMID: 29704234; PMCID: PMC6304182. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6304182/

Lipodystrophy is a rare condition where the body lacks normal fat tissue, often leading to metabolic issues like **diabetes and high cholesterol**. This article aims to help doctors identify and treat lipodystrophy by **providing steps for diagnosis and management**. Lipodystrophy can be genetic or acquired, and it can affect the entire body or just parts of it. Recognizing lipodystrophy is crucial as it can be **misdiagnosed or overlooked**. The article suggests a diagnostic algorithm and emphasizes the importance of managing associated health problems. It also mentions leptin replacement therapy, which has shown positive effects on metabolic issues in lipodystrophy patients. The article concludes by

highlighting the need for a better understanding and recognition of lipodystrophy in clinical settings.

E. Brown RJ, Gorden P. Leptin therapy in patients with lipodystrophy and syndromic insulin resistance. In: Dagogo-Jack S, ed. Leptin: Regulation and Clinical Applications. Cham, Switzerland: Springer International Publishing; 2015:225–236. https://link.springer.com/chapter/10.1007/978-3-319-09915-6_18

This text discusses the use of recombinant human methionyl leptin (metreleptin) in the treatment of lipodystrophy, a condition characterized by a deficiency of subcutaneous adipose tissue. Leptin, a hormone discovered in 1994, plays a crucial role in regulating energy balance, and its deficiency in lipodystrophy leads to severe metabolic complications.

F. Oral EA, Chan JL. Rationale for leptin-replacement therapy for severe lipodystrophy. Endocr Pract. 2010 Mar-Apr;16(2):324-33. doi: 10.4158/EP09155.RA. PMID: 20061299. https://pubmed.ncbi.nlm.nih.gov/20061299/

This research explores the potential of replacing leptin in lipodystrophy patients, observing **positive outcomes in blood sugar control and insulin sensitivity**. Though not officially approved, special arrangements allow access to the hormone, suggesting a promising approach to improve health in severe lipodystrophy cases.

G. Araújo-Vilar D, Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest. 2019 Jan;42(1):61-73. Epub 2018 Apr 27. PMID: 29704234; PMCID: PMC6304182. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6304182/

This study aims to help doctors identify and treat lipodystrophy more effectively and quickly. A therapy called leptin replacement has shown promise in improving the health of people with lipodystrophy. **The study hopes to improve the recognition and treatment of this rare condition, providing a framework for physicians to determine whether their patient has lipodystrophy and includes specific signs for each type**.

H. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother KI, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. J Clin Endocrinol Metab. 2016 Dec;101(12):4500-4511. doi: 10.1210/jc.2016-2466. Epub 2016 Oct 6. PMID: 27710244; PMCID: PMC5155679. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5155679/

Lipodystrophy syndromes are diverse and diagnosed by appearance and, sometimes, genetic testing. **Patients should get regular checkups for diabetes, high cholesterol, and other health issues.** A proper diet is crucial for managing these problems.

Metreleptin therapy works well for some patients with low leptin levels and certain types of lipodystrophy. **Other general treatments like metformin for diabetes and statins or fibrates for high cholesterol may also help.** Avoid using oral estrogens in these cases. Regular monitoring and a healthy lifestyle are essential for managing lipodystrophy.

I. Meral R, Ryan BJ, Malandrino N, Jalal A, Neidert AH, Muniyappa R, Akıncı B, Horowitz JF, Brown RJ, Oral EA. "Fat Shadows" From DXA for the Qualitative Assessment of Lipodystrophy: When a Picture Is Worth a Thousand Numbers. Diabetes Care. 2018 Oct;41(10):2255-2258. doi: 10.2337/dc18-0978. PMID: 30237235; PMCID: PMC6150431. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/30237235/

The study introduces a **diagnostic method called "fat shadows" derived from DXA scans to identify lipodystrophy syndromes**, which are disorders characterized by the selective absence of fat. This method uses color-coded representations to highlight fat tissue distribution in the body. In a retrospective validation study, fat shadows **successfully differentiated patients with generalized lipodystrophy (GL) from nonobese control subjects with 100% sensitivity and specificity**. Additionally, familial partial lipodystrophy (FPLD) was distinguished from control subjects with 85% sensitivity and 96% specificity. The fat shadow method **provides a qualitative tool for inferring clinical phenotype and supporting the diagnosis of lipodystrophy syndromes**, offering potential benefits in therapeutic decisions and clinical settings.

J. Pahuja I, De P, Sharma N, Kulshreshtha B. Polycystic ovarian syndrome in patients with lipodystrophy: Report of 2 cases with review of literature. Indian J Endocrinol Metab. 2012 Nov;16(6):1022-5. doi: 10.4103/2230-8210.103031. PMID: 23226657; PMCID: PMC3510931. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3510931/

The presented cases describe two females with partial lipodystrophy exhibiting features of polycystic ovarian syndrome (PCOS). Lipodystrophy involves abnormal fat distribution, and in these cases, it led to hyperinsulinemia, insulin resistance, and glucose homeostasis abnormalities. PCOS, characterized by hyperandrogenism and oligoanovulation, is influenced by hyperinsulinemia. The patients displayed varying PCOS phenotypes, with one presenting hyperandrogenism and hirsutism, while the other lacked hirsutism. Despite the lean phenotype, both individuals had elevated insulin levels and impaired glucose tolerance. **Ultrasound examinations revealed polycystic ovaries**. These cases suggest that hyperinsulinemia plays a primary role in the development of polycystic ovaries in lipodystrophy patients, with hyperandrogenism arising as a secondary manifestation. **The study underscores the complexity of metabolic and endocrine interactions in lipodystrophy, contributing to conditions like PCOS**.

More on Metreleptin and Leptin

A. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010 Jan 19;152(2):93-100. doi: 10.7326/0003-4819-152-2-201001190-00008. PMID: 20083828; PMCID: PMC2829242. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2829242/

The introduction begins by highlighting leptin's initial promise as an obesity treatment, which later shifted focus to its role in energy deficiency states. The subsequent sections explore **leptin's biology, functions, and its potential therapeutic applications in specific leptin-deficient conditions, providing a comprehensive overview of its clinical relevance**.

B. Brown RJ, Oral EA, Cochran E, Araújo-Vilar D, Savage DB, Long A, Fine G, Salinardi T, Gorden P. Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. Endocrine. 2018 Jun;60(3):479-489. doi: 10.1007/s12020-018-1589-1. Epub 2018 Apr 12. PMID: 29644599; PMCID: PMC5936645. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/29644599/

This study assesses the effectiveness and safety of metreleptin in 66 patients with congenital or acquired generalized lipodystrophy, presenting **significant reductions in glycated hemoglobin, fasting triglycerides, and fasting plasma glucose at 12 months** (all $p \leq 0.001$). Long-term treatment with metreleptin demonstrates **sustained improvements in hypertriglyceridemia, glycemic control, and liver volume, with 80% of patients achieving a 1% decrease in HbA1c or ≥30% decrease in fasting triglycerides at month 12**. Moreover, a considerable percentage discontinues insulin, oral antidiabetic medications, and lipid-lowering medications, emphasizing metreleptin's well-tolerated and beneficial outcomes in patients with generalized lipodystrophy.

C. Simha V, Subramanyam L, Szczepaniak L, Quittner C, Adams-Huet B, Snell P, Garg A. Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the Dunnigan variety. J Clin Endocrinol Metab. 2012 Mar;97(3):785-92. doi: 10.1210/jc.2011-2229. Epub 2011 Dec 14. PMID: 22170723; PMCID: PMC3319219. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22170723/

This study compares the efficacy of leptin replacement therapy in patients with familial partial lipodystrophy, Dunnigan variety (FPLD), distinguishing between severe hypoleptinemia (SH) and moderate hypoleptinemia (MH). The open-label, observational study involves 14 SH and 10 MH women with FPLD, receiving 0.08 mg/kg · d of metreleptin for 6 months. **Both groups show significant reductions in fasting serum triglycerides and hepatic triglyceride levels, with no significant difference between them**. Metreleptin replacement therapy is equally effective in reducing triglyceride levels in FPLD patients with SH and MH, but it does not improve hyperglycemia.

D. Cook K, Adamski K, Gomes A, Tuttle E, Kalden H, Cochran E, Brown RJ. Effects of Metreleptin on Patient Outcomes and Quality of Life in Generalized and Partial Lipodystrophy. J Endocr Soc. 2021 Feb 16;5(4):bvab019. doi: 10.1210/jendso/bvab019. PMID: 33817539; PMCID: PMC7993583. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33817539/

This study assessed the clinical and humanistic consequences of **generalized and partial** lipodystrophy, rare diseases characterized by the absence of subcutaneous adipose tissue. Using data from a cohort of 112 metreleptin-treated patients, the study revealed various lipodystrophy-related issues, such as metabolic impairment, liver abnormality, hyperphagia, and reproductive dysfunction, among others. **Following metreleptin treatment, improvements were observed in these attributes, leading to significant quality-adjusted life-year gains**, suggesting that metreleptin is associated with meaningful clinical and quality-of-life enhancements for individuals with both lipodystrophy.

E. Dessie G, Ayelign B, Akalu Y, Shibabaw T, Molla MD. Effect of Leptin on Chronic Inflammatory Disorders: Insights to Therapeutic Target to Prevent Further Cardiovascular Complication. Diabetes Metab Syndr Obes. 2021 Jul 17;14:3307-3322. doi: 10.2147/DMSO.S321311. PMID: 34305402; PMCID: PMC8296717. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8296717/

This review explores the **role of leptin in chronic inflammatory disorders** and its impact on **cardiovascular complications**. Leptin, released by adipose tissue in response to obesity, contributes to the pathogenesis of disorders like rheumatoid arthritis, lupus, and psoriasis by activating the secretion of pro-inflammatory cytokines. Elevated leptin levels in obesity-associated hypertension lead to increased aldosterone production, contributing to elevated blood pressure and promoting atherosclerosis, ultimately **highlighting leptin as a potential therapeutic target to prevent cardiovascular complications in chronic inflammatory disorders and metabolic syndrome**.

F. Elif Arioglu Oral, M.D., Vinaya Simha, M.D., Elaine Ruiz, N.P., Alexa Andewelt, B.S., Ahalya Premkumar, M.D., Peter Snell, Ph.D., Anthony J. Wagner, Ph.D., Alex M. DePaoli, M.D., Marc L. Reitman, M.D., Ph.D., Simeon I. Taylor, M.D., Ph.D., Phillip Gorden, M.D., and Abhimanyu Garg, M.D. Leptin-Replacement Therapy for Lipodystrophy, February 21, 2002 N Engl J Med 2002; 346:570-578 DOI: 10.1056/NEJMoa012437 https://www.nejm.org/doi/full/10.1056/NEJMoa012437

This study investigated the impact of recombinant methionyl human leptin (recombinant leptin) therapy on individuals with lipodystrophy and leptin deficiency. Administered subcutaneously over four months at escalating doses, **recombinant leptin significantly increased serum leptin levels, leading to a substantial decrease in glycosylated hemoglobin and triglyceride levels**. Additionally, liver volume decreased, resulting in

improved glycemic control, reduced reliance on antidiabetes therapy, and decreased caloric intake and resting metabolic rate. The findings highlight the **therapeutic potential of leptin replacement in addressing insulin resistance and metabolic abnormalities associated with severe lipodystrophy.**

G. Ebihara K, Nakao K. Translational Research of Leptin in Lipodystrophy and Its Related Diseases. In: Nakao K, Minato N, Uemoto S, editors. Innovative Medicine: Basic Research and Development [Internet]. Tokyo: Springer; 2015. doi: 10.1007/978-4-431-55651-0_14 https://www.ncbi.nlm.nih.gov/books/NBK500338/

Research using leptin transgenic mice demonstrated its pleiotropic effects, including the regulation of insulin sensitivity and lipid metabolism. The study also highlighted the significance of leptin replacement therapy in treating lipodystrophy, a condition characterized by a lack of adipose tissue, showcasing its potential as a therapeutic option for various metabolic disorders such as diabetes, hyperlipidemia, and fatty liver.

New Patient Resources

A. NTSAD, "First Steps After Getting a Rare Disease Diagnosis: Practical Action Items to Start Managing a Rare Disease," https://ntsad.org/support-for-families/navigating-a-rare-disease-diagnosis/

When faced with a rare disease diagnosis, it's common to feel overwhelmed; **taking time to process the news and seeking support** from family, friends, and neighbors can be beneficial. To navigate the complexities of managing a rare disease, steps such as **gathering key information, exploring government resources for coverage, assembling a healthcare team, understanding insurance policies, creating a personalized care plan, and ensuring clear communication with healthcare providers** are recommended.

B. Rare Advocacy Movement, "Support Beyond Therapeutic Products, The Holistic Toll Levied Upon Rare Disease Patients, Caregivers, and Families," 2018 https://www.rareadvocacymovement.com/_files/ugd/e4b885_10f99b2a7294450d8747282bdcf7312d.pdf

The report delves into the often **overlooked challenges and dynamics faced by individuals and families affected by rare diseases**, emphasizing the significant emotional, social, and psychological tolls that accompany such conditions. It highlights the sacrifices made by caregivers and family members to accommodate the limitations imposed by rare diseases, shedding light on the intricate web of daily tasks and emotional strains experienced within rare disease households. Additionally, the report underscores the **need for genuine collaboration between stakeholders, including patient advocacy leaders**, to address unmet needs, foster understanding, and drive progress in research, care delivery, and policy development within the rare disease community.

C. Global Genes, "Women with Rare Disease: The Reproductive Years," https://globalgenes.org/wp-content/uploads/2016/03/GG_toolkit_women-genetics-1.pdf

This toolkit serves as a valuable resource for women with rare disorders, offering guidance and resources to navigate the **complex decision of pregnancy, addressing considerations around genetic risks and maternal health**, while also acknowledging the challenges of caring for both children and aging parents with similar conditions, thereby assisting individuals in planning for pregnancy and adapting to the dual role of motherhood and caregiver within the context of their rare condition.

D. Global Genes, "The Circle Of Care Guidebook For Caregivers Of Children With Rare And/Or Serious Illnesses," https://globalgenes.org/wp-content/uploads/Rare-Caregivers-Guidebook.pdf

The Circle of Care Guidebook is a comprehensive resource designed to support caregivers of children with rare diseases, offering **insights, strategies, and resources to navigate the complex challenges they face**. Acknowledging the profound impact of caregiving on individuals' lives, the guide addresses various aspects of care, from diagnosis to treatment, advocacy, and support services. With nearly 100 topics covered, it provides a wealth of information and **resources to assist caregivers in their journey**, emphasizing the importance of community support and collaboration. Developed in collaboration with caregivers, experts, and organizations, **the guidebook serves as a valuable tool for addressing the unique needs and pressures faced by those caring for children with rare and serious illnesses**, offering guidance and empowerment in navigating the caregiving journey.

E. University of Cambridge, Claire Adams, Specialist Nurse & Senior Research Nurse, "The Impact of Non-metabolic Multi-system Manifestations," https://docs.google.com/presentation/d/1DUzRZj3pUOF8qlUanELH4orXgEtUyurc/edit?usp=sharing&ouid=117732520439588777473&rtpof=true&sd=true

Body image isn't solely physical; it affects psychology too. Social acceptance is tough with body image concerns. Workshops addressing body image could help, covering coping strategies, handling unwanted attention, breathing techniques, clothing advice to avoid drawing attention, with facilitators promoting open discussions for community bonding. Mood disorders are prevalent; 40% of Severe Insulin Resistance Service attendees with lipodystrophy were prescribed antidepressants. It's crucial to further understand the mental health requirements of the lipodystrophy community.

Other Relevant Research Research

A. Wakabayashi N, Yagishita Y, Joshi T, Kensler TW. Forced Hepatic Expression of NRF2 or NQO1 Impedes Hepatocyte Lipid Accumulation in a Lipodystrophy Mouse Model. Int

J Mol Sci. 2023 Aug 28;24(17):13345. doi: 10.3390/ijms241713345. PMID: 37686150; PMCID: PMC10487640. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/37686150/

This study examines how enhancing **NRF2 signaling in the liver can alleviate fatty liver disease**, a common complication of lipodystrophy, a disorder where fat accumulates in organs due to impaired fat tissue production. Using mouse models, researchers found that **increasing NRF2 expression in the liver significantly reduced hepatic damage and triglyceride levels associated with lipodystrophy**. Specifically, injecting vectors containing a dominant-active form of NRF2 or its target gene Nqo1 into the liver led to notable improvements in liver health, suggesting **potential therapeutic avenues** for managing lipodystrophy-related metabolic abnormalities.

Lipodystrophy in the News

A. NewsWise, "A unique patient case inspiring research," Tessa Roy, Jan. 22, 2024, https://www.newswise.com/articles/a-unique-patient-case-inspiring-research?fbclid=IwAR12dajrBTcf5haGirplteQZu0xgAZ9dDFhWdN3ISuf2WpsMgFirUXXXMCM

Mallory Mattison, a film student, stands as the inspiration behind crucial medical research aimed at supporting patients with Familial Partial Lipodystrophy (FPL). Her journey, which began at age 11, involved significant health challenges, including recurrent hospitalizations due to pancreatic episodes. **Through collaborative efforts led by Dr. Elif A. Oral and researchers like Maria Foss-Freitas, Mattison became a pivotal figure in testing novel therapies**, resulting in transformative outcomes and pioneering advancements in FPL treatment, showcasing the power of patient-centered research and collaborative healthcare initiatives.

B. Global Genes, "Health Canada Approves Chiesi's Myalept for Lipodystrophy," Feb. 5, 2024, https://globalgenes.org/raredaily/health-canada-approves-chiesis-myalepta-for-lipodystrophy/

Health Canada has approved Chiesi Global Rare Diseases' Myalepta as an adjunct to diet for treating complications of leptin deficiency in lipodystrophy. **The approval covers patients with congenital or acquired generalized lipodystrophy and familial partial lipodystrophy who haven't responded to standard treatments**. Myalepta, developed by Amryt Pharma and acquired by Chiesi Group, showed significant efficacy in reducing metabolic abnormalities in both generalized and partial lipodystrophy patients, with common adverse reactions including weight loss, hypoglycemia, and fatigue.

C. Fred Hutch Cancer Center: Science Spotlight, "Using a mouse model to combat the effects of lipodystrophy," L Brady, Oct. 16, 2023, https://www.fredhutch.org/en/news/spotlight/2023/10/phs-kensler-ijms.html

Dr. Nobunao Wakabayashi and his team at Fred Hutchinson Cancer Center are investigating the **molecular mechanisms underlying lipodystrophy**, a condition characterized by the loss of adipose tissue leading to metabolic disturbances and potential cancer development. Through mouse models, they discovered that **enhancing NRF2 expression, a transcription factor regulating various cellular pathways including oxidative stress response, in the liver can protect against lipodystrophy-induced hepatic damage.** Their research, recently published in the International Journal of Molecular Sciences, demonstrates that liver-directed NRF2 targeting could offer therapeutic opportunities to mitigate the effects of lipodystrophy, potentially preventing fatty liver disease and other metabolic complications associated with the condition.

Additional Resources

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government website.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website:
https://rarediseases.org/living-with-a-rare-disease/find-clinical-trials/

For information about clinical trials sponsored by private sources, in the main, contact:
www.centerwatch.com
For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

Contact for additional information about congenital generalized lipodystrophy:
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Please go to https://globalgenes.org/resources/?s=#/types/toolkit to look at a long list of toolkits that might be right for your specific needs