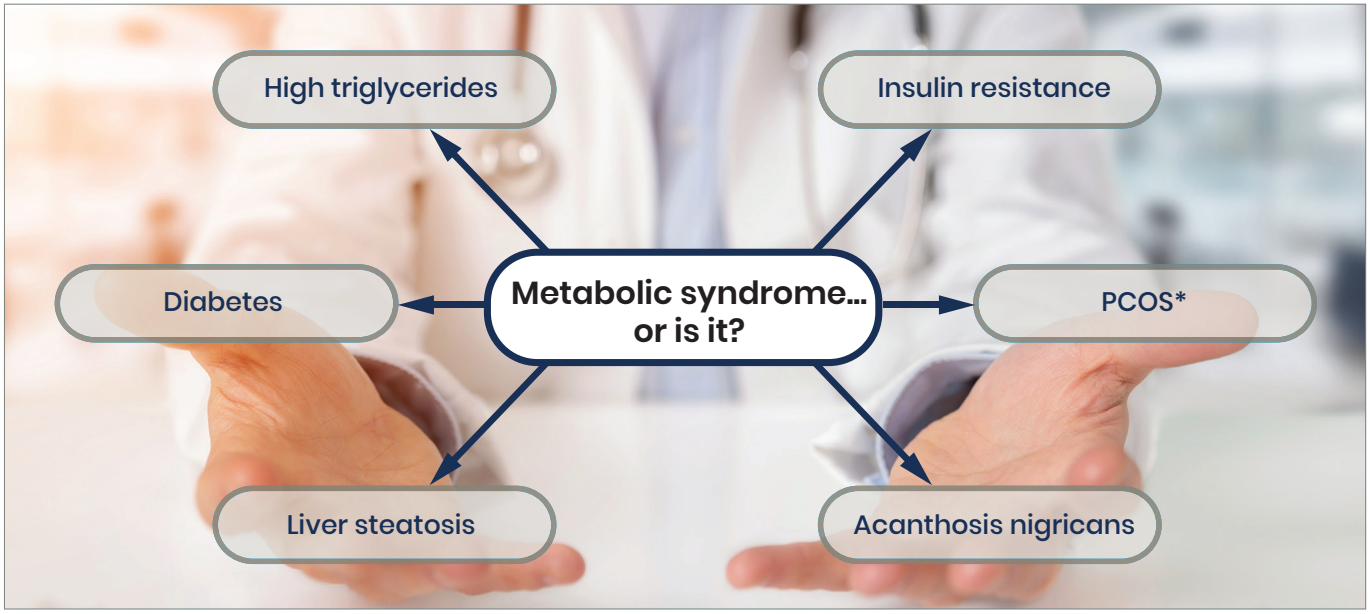
A CLEAR CASE OF METABOLIC SYNDROME OR COULD IT BE LIPODYSTROPHY?

Report on an Amryt-sponsored symposium at e-ECE 2020: the 22nd European Congress of Endocrinology



PCOS: Polycystic ovary syndrome

Lipodystrophy is a heterogeneous group of rare metabolic disorders characterised by the loss of adipose tissue without evidence of nutritional deprivation or a catabolic state.[1] Although lipodystrophy may share some of the signs of metabolic syndrome, such as high blood glucose, insulin resistance, raised triglycerides and increased abdominal girth, the disease driver is very different.[2] In lipodystrophy, the lack of subcutaneous fat leads to leptin deficiency which, when combined with decreased adipose storage capacity, results in ectopic storage of fat, especially in the liver, and severe metabolic complications.[2]

Lipodystrophy is divided into several subtypes based on aetiology, namely whether the condition is congenital or acquired, and whether the loss of adipose tissue affects the whole body, as is the case in generalised lipodystrophy, or whether the loss of adipose tissue is partial or localised to certain areas of the body.[1] This gives rise to four major categories of lipodystrophy: congenital generalised lipodystrophy (Berardinelli–Seip syndrome), familial partial lipodystrophy, acquired generalised lipodystrophy (Lawrence syndrome) and acquired partial lipodystrophy (Barraquer–Simons syndrome).[1] Generalised lipodystrophies are less frequent than partial subtypes, occurring in 0.2–1 per million and 1.7–2.8 persons per million, respectively.[3]

For all subtypes of lipodystrophy, a diagnosis is made based on a clinical examination of the patient's body composition and clinical history, with genetic markers providing support for the diagnosis.[1] However, as there is a high degree of phenotypic heterogeneity between and within subtypes of lipodystrophy, diagnosis of this rare condition can be challenging. General physical signs that may lead to a suspicion of lipodystrophy include a lack of subcutaneous adipose tissue, failure to thrive in both infants and children, pseudohypertrophy of muscles, prominent veins, pronounced acanthosis nigricans, disproportionate hyperphagia and eruptive xanthomas.[4] Other supporting findings include high insulin demand (≥200 U/day, ≥2 U/kg/day or insulin U-500), diabetes mellitus, hypertriglyceridaemia (≥500 mg/dL or ≥250 mg/dL with therapy and/or dietary modification), a history of pancreatitis, hepatic steatosis, and in females, polycystic ovary syndrome.[4] In certain subtypes, genetic testing can help confirm a suspected diagnosis, in addition to assessing the risk of lipodystrophy in family members. There are no leptin cut-off values, which confirm or exclude a diagnosis of lipodystrophy.[1]

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The identification of specific characteristics and time of disease onset can also assist with determining subtypes of lipodystrophy. Congenital generalised lipodystrophy is an autosomal recessive condition, characterised by a generalised loss of adipose tissue from birth or infancy, in addition to other typical features of lipodystrophy.[1] Umbilicus and abdominal prominence, along with acrochordon in the neck and acromegalic features from around adolescence, are also present in some patients.[5]

In acquired generalised lipodystrophy, patients demonstrate selective loss of adipose tissue affecting the large corporal regions, usually starting during childhood or adolescence.[1] Disease progression can be prolonged, with the facial adipose tissue, in some cases, being preserved for years, and in some patients, a loss of adipose tissue in the palms and soles can be characteristic. Some cases also have a history of subcutaneous nodular swelling or associated autoimmune disease.[1]

The many types of familial partial lipodystrophy are defined by the involvement of specific gene mutations. The classical phenotype of the disease is characterised by a lack of adipose tissue in the limbs and hip/buttocks, in addition to fat accumulation in the face, neck, axillae, upper back and labia, and in some patients, the development of lipomas.[1,6] The onset in females is usually around puberty, and during adulthood in males. Women typically demonstrate wide shoulders and narrow hips; however, in men, this lipodystrophy phenotype is frequently not obvious and is often diagnosed based on a confirmed diagnosis in related family members. In patients with the *LMNA* mutation, reduced skinfold thickness and increased fasting triglyceride levels can be an early indicator of familial partial lipodystrophy, even before puberty.[7]

In acquired partial lipodystrophy, adipose tissue loss is typically restricted to the area above the upper part of the trunk, with a cephalo-caudal progression from childhood or adolescence, and is four-times more common in females.[1] By contrast, fat accumulation can occur in the hip, buttocks and legs in some patients. Other suggestive features include the presence of autoimmune disease, low C3 complement, increased C3 nephritic factor and tendency for membrano-proliferative glomerulonephritis. Unlike the other three main subtypes of lipodystrophy, metabolic disturbances are uncommon.

Timely diagnosis and management of lipodystrophy is key in limiting the risk of morbidity and mortality. Based on the results of a retrospective chart review study, the most common complications of untreated lipodystrophy are reported to be liver disease (72%), diabetes and insulin resistance (58%), kidney abnormalities (40%), heart problems (30%) and acute pancreatitis (13%).[8] These complications tend to occur earlier in patients with generalised compared with partial lipodystrophy,[9,10] with time to diagnosis of diabetes and/or insulin resistance 12.7 and 19.1 years, and time to organ abnormality 7.7 and 16.1 years, respectively.[8] However, the mean age at diagnosis is 12.3 years for patients with generalised lipodystrophy and 33.7 years for partial lipodystrophy.[8] Similarly, patients with generalised versus partial lipodystrophy also have a shorter time to death (51.2 versus 66.6 years, respectively).[8]

There is no cure for lipodystrophy, meaning lost adipose tissue is never recovered.[1] Consequently, current treatment focuses on managing the metabolic aspects of disease and comorbidities.[1] The only currently approved treatment for lipodystrophy is metreleptin, which is indicated as an adjunct to dietary control as replacement therapy for the treatment of leptin deficiency in patients:

- ≥2 years of age with congenital generalised lipodystrophy or acquired generalised lipodystrophy;
- ≥12 years of age with confirmed familial or acquired partial lipodystrophy who have failed to achieve adequate metabolic control with standard treatments.[11]

Recent studies examining metreleptin treatment of generalised and partial lipodystrophy have confirmed that it improves glycaemic control, hypertriglyceridaemia and fatty liver disease.[12–14] A non-randomised crossover study demonstrated that metreleptin treatment improves insulin sensitivity independent of food intake in metreleptin naïve patients (n=14), whereas metreleptin withdrawal (n=8) was associated with a 41% decrease in insulin sensitivity.[12] An open-label study of metreleptin in 11 patients found that insulin sensitivity correlates with *de novo* lipogenesis, with increased insulin sensitivity decreasing *de novo* lipogenesis, hepatic steatosis and dyslipidaemia.[15] In both generalised and partial lipodystrophy patients, the long-term efficacy and safety of metreleptin is good, with decreased levels of glycated haemoglobin, fasting plasma glucose, fasting triglycerides and liver volume following 12 months of treatment.[13,14] Finally, improvements in quality of life and mortality have been reported in association with metreleptin.[16,17]

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In summary, the heterogeneous phenotype of lipodystrophy can often make the identification and diagnosis of the disease challenging. Increased recognition of the typical symptoms of lipodystrophy and more specific symptoms of disease subtypes may facilitate earlier patient diagnosis and treatment initiation. Metreleptin has been demonstrated to be effective at treating the metabolic symptoms of patients with generalised lipodystrophy and patients with partial lipodystrophy who have failed to achieve adequate control on standard therapy.

This report provides key highlights from a symposium sponsored by Amryt Pharmaceuticals DAC, held at e-ECE 2020 in September 2020. To view the full touchSYMPOSIUM HIGHLIGHTS activity, please visit: https://touchendocrinologytmc.com/general-endocrinology/learning-zone/general-endocrinology-learning-zone-diagnosis-burden-and-management-of-lipodystrophy/

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Prescribing Information - Myalepta® ▼ (metreleptin) 3 mg, 5.8 mg and 11.3 mg powder for solution for injection

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See below for how to report adverse reactions

Legal Category: POM

Indications: Adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with:

- confirmed congenital generalised LD (*Berardinelli-Seip syndrome*) or acquired generalised LD (*Lawrence syndrome*) in adults and children 2 years of age and above
- confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

Dosage: *See SmPC for full details and guidelines on dose calculation and dose adjustments.*

Treatment should only be initiated and monitored by a professional experienced in diagnosis and management of metabolic disorders. To avoid medication errors and overdose the dose calculation and dose adjustment guidelines must be followed. A review of the patient's self administration technique is recommended every 6 months whilst using Myalepta.

Dose calculation: In order to ensure patients and carers understand the correct dose to be injected, the prescriber should prescribe the appropriate dose in milligrams and volume in millilitres. The recommended daily dose is based on actual body weight as shown:

Metreleptin recommended dose

Baseline weight	Starting daily dose (injection volume)	Dose adjustments (injection volume)	Maximum daily dose (injection volume)
Males and females ≤40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males > 40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females > 40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

Dose adjustments: *See SmPC for full details of recommended dose adjustments.*

Adjustments are recommended based on clinical response (as defined in SmPC), or other consideration e.g. tolerability issues, excessive weight loss especially in paediatric patients. Increases should not be made more than once every four weeks; decreases can occur weekly based on weight loss.

Administration: Subcutaneous use. *See SmPC for full details on reconstitution and correct injection technique.*

It is the responsibility of the prescribing physician to provide appropriate training to the patient/carer who will administer the treatment and that the first dose should be administered under the supervision of a qualified healthcare professional as per section 4.2 of the SPC.

Special populations: The safety and efficacy of metreleptin in children aged 0-2 years with generalised LD and aged 0-12 years with partial LD has not been established. Very limited data are available for children, especially less than 6 years, with generalised LD. No dose recommendation can be made in patients with renal or hepatic impairment. In elderly patients (≥ 65 years), dose selection and modification should be cautious.

See Summary of Product Characteristics (SmPC) before prescribing.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions: *HIV related LD:* Data do not support treatment.

Hypersensitivity reactions: Generalized hypersensitivity (e.g. anaphylaxis, urticaria or generalised rash) reactions may occur immediately after administration of Myalepta. If an anaphylactic reaction or other serious allergic reaction occurs, administration should be permanently discontinued immediately and appropriate therapy initiated.

Non-compliance with, or abrupt discontinuation of Myalepta may result in worsening hypertriglyceridaemia and associated pancreatitis particularly in patients with risk factors for pancreatitis: If a patient develops pancreatitis whilst being treated with metreleptin, it is advised that metreleptin be continued uninterrupted, as stopping treatment abruptly may exacerbate the condition. If metreleptin must be stopped for any reason, tapering of the dose over a two week period is recommended in conjunction with a low fat diet, see section 4.2 of the SmPC. During tapering, monitor triglyceride levels and consider initiating or adjusting the dose of lipid lowering medicinal products as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.

Hypoglycaemia with concomitant insulin and other anti-diabetics: There is a risk of hypoglycaemia in patients treated with Myalepta who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues (e.g. sulphonylureas). Large dose reductions of 50 % or more of baseline insulin requirements may be needed in the first 2 weeks of treatment. Once insulin requirements have stabilised, dose adjustments of other anti-diabetics may also be needed in some patients to minimise the risk of hypoglycaemia. Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogues and combination

treatment. Patients and carers should be advised to be aware of the signs and symptoms of hypoglycaemia. In clinical studies, hypoglycaemia has been managed with food/drink intake and by modifying the dose of anti-diabetic medicinal product. In case of hypoglycaemic events of a non-severe nature, food intake management may be considered as an alternative to dose adjustment of anti-diabetics according to the treating physician's opinion. Rotation of injection sites is recommended in patients co administering insulin (or other subcutaneous medicinal products) and Myalepta.

T-cell lymphoma: Cases of T-cell lymphoma have been reported while using Myalepta. A causal relationship between Myalepta and the development and/or progression of lymphoma has not been established. Evaluate benefits and risks before using Myalepta in patients with acquired generalised LD and/or in patients with significant haematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).

Immunogenicity: Antidrug antibodies (ADA) to metreleptin were reported to occur very commonly (88%) in clinical trials. If a patient develops a serious and severe infection, an association with the development of blocking activity against metreleptin cannot be excluded. In patients with serious and severe infections, continuation of Myalepta should be at the discretion of the prescriber. Neutralising antibodies could theoretically also affect the activity of endogenous leptin, although this was not confirmed in clinical trials.

Autoimmune disorder progression: Autoimmune disorder progression/flares, including severe auto-immune hepatitis, have been observed in some patients treated with Myalepta but a causal relationship between Myalepta treatment and progression of autoimmune disease has not been established. Close monitoring for underlying autoimmune disorder flares (sudden and severe onset of symptoms) is recommended.

Pregnancy: Unplanned pregnancies may occur due to restored luteinizing hormone (LH) release.

Drug Interactions: Myalepta may reduce the exposure to substrates of CYP3A through enzyme induction, therefore it may reduce the efficacy of hormonal contraceptives and an additional non-hormonal contraceptive method should be considered during treatment. Because of the effects of metreleptin on CYP450 enzymes, in patients treated with CYP450 substrates with narrow therapeutic index, the dose may need to be individually adjusted and therapeutic monitoring of effect (e.g. warfarin) or of drug concentrations (e.g. cyclosporin or theophylline) should be performed.

Pregnancy and breastfeeding: Myalepta is not recommended during pregnancy and in women of childbearing potential not using contraception. Abortions, stillbirths and preterm deliveries have been reported in women exposed to metreleptin during pregnancy, though there is currently no evidence to suggest a causal relationship with the treatment.

A decision must be made whether to discontinue breast-feeding or to abstain from Myalepta therapy whilst breastfeeding.

Fertility: Data suggest metreleptin may increase fertility, due to effects on LH, with consequential potential for unplanned pregnancy. Animal studies showed no adverse effects on male or female fertility.

Effects on ability to drive and use machines: Myalepta has a minor influence on the ability to drive and use machines due to fatigue and dizziness.

Undesirable effects: Most commonly reported adverse drug reactions included: Very common (≥ 1/10) hypoglycaemia, weight decreased, common (≥ 1/100 to <1/10) decreased appetite, headache, abdominal pain, nausea, alopecia, menorrhagia, fatigue, injection site bruising, injection site erythema, injection site reaction, neutralising antibodies. Other adverse reactions reported in clinical trials or post-marketing with metreleptin, the frequency of which was not known, included: influenza, pneumonia, anaphylactic reaction, diabetes mellitus, hyperphagia, insulin resistance, tachycardia, deep vein thrombosis, cough, dyspnoea, pleural effusion, abdominal pain upper, diarrhoea, pancreatitis, vomiting, pruritus, rash, urticaria, arthralgia, myalgia, fat tissue increased, injection site haemorrhage, injection site pain, injection site pruritus, injection site swelling, malaise, peripheral swelling, blood glucose abnormal, blood triglycerides increased, drug specific antibody present, glycosylated haemoglobin increased, weight increased.

See section 4.8 of the SmPC for other reported adverse drug reactions (ADRs) for which the frequency is not known.

See section 6.4 and 6.6 of the SmPC for instructions on storage, handling and disposal.

Quantities and Marketing Authorisation numbers:

30 vials 3mg PLGB 50688/0009, EU/1/18/1276/004,

30 vials 5.8mg PLGB 50688/0010, EU/1/18/1276/006,

30 vials 11.3mg PLGB 50688/0008, EU/1/18/1276/002

Cost: NHS list price (excluding VAT)
30 vials x 3mg £17,512.50, 30 vials x 5.8mg £35,025.00, 30 vials x 11.3mg £70,050.00

Marketing Authorisation Holder:
Amryt Pharmaceuticals DAC,
45 Mespil Road, Dublin 4, Ireland.
For further information contact
medinfo@amrytpharma.com.

Date of first authorisation: 30/7/2018.
Date of revision: September 2021

REPORTING OF SUSPECTED ADVERSE REACTIONS:

Adverse events should be reported. Reporting forms and information can be found at:

UK: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Ireland: HPRA Pharmacovigilance, www.hpra.ie

Adverse events should also be reported to Amryt by email to medinfo@amrytpharma.com or by telephoning the freephone number 00800 4447 4447 or +44 1604 549 952.