Challenges in the diagnosis and management of lipodystrophy

An expert panel discussion

Code: LD/UK/076
Date of preparation: March 2022

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Online activity details

This resource has been downloaded from a touchROUNDTABLE.

The full activity, which includes video resources, can be accessed at:

www.touchendocrinologytmc.com/challenges-in-diagnosis-and-management-of-lipodystrophy/

This content is for healthcare professionals only.

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Learning objectives

The touchROUNDTABLE activity aims to:

- ✓ Improve awareness among endocrinologists of the presentation of lipodystrophies and the burden of the patient
- ✓ Support early diagnosis and referral to specialist centres
- ✓ Provide guidance on the optimum management to prevent long term complications
- ✓ In a heterogenous partial lipodystrophy population, provide guidance on appropriate patient selection for leptin replacement therapy, dose escalation and stopping criteria

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Expert panel

Prof. Elif A. Oral

University of Michigan,
Ann Arbor, MI, USA

Prof. Barış Akıncı

University of Michigan,
Ann Arbor, MI, USA &
Dokuz Eylul University, Turkey

Prof. Ferruccio Santini

University Hospital of Pisa,
Pisa, Italy

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Disclosures

- **Prof. Elif A. Oral**
  - Prof. Oral has received consultancy fees from Amryt Pharma DAC, the current owner of metreleptin
  - She is an inventor of the method of use patent for “metreleptin in the treatment of lipoatrophy, lipodystrophy, lipoatrophic diabetes and related conditions”
  - She serves as a consultant to Akcea Therapeutics, Ionis Pharmaceuticals, Rhythm Pharmaceuticals and Regeneron Pharmaceuticals through payments made to the University of Michigan and is receiving grant support from all
  - She received grant support from Gemphire Therapeutics in the past 2 years
  - She has ongoing grant support from GI Dynamics, and Novo Nordisk

- **Prof. Barış Akıncı** has received consultancy fees from Amryt Pharma DAC

- **Prof. Ferruccio Santini** has received consultancy fees from Amryt Pharma DAC

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Agenda

Introduction to lipodystrophy and diagnosis
Prof. Elif A. Oral

Management of generalised lipodystrophy (GL) patients
Prof. Barış Akıncı

Optimum management of partial lipodystrophy (PL) patients
Prof. Ferruccio Santini

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Introduction to lipodystrophy and diagnosis

Prof. Elif A. Oral

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Objectives for discussion today

Improve awareness among endocrinologists of the presentation of lipodystrophy syndromes and the burden of the patient

Support early diagnosis and referral to specialist centres

Provide guidance on the optimum management to prevent long term complications

In a heterogenous lipodystrophy population, provide guidance on appropriate patient selection for leptin replacement therapy, dose escalation and stopping criteria

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https://emedicine.medscape.com/article/128355-overview

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Lipodystrophy syndromes

- Paucity of adipose tissue without caloric deficit
- Insulin resistance
- Hypertriglyceridemia
- Fatty infiltration of liver and other tissues

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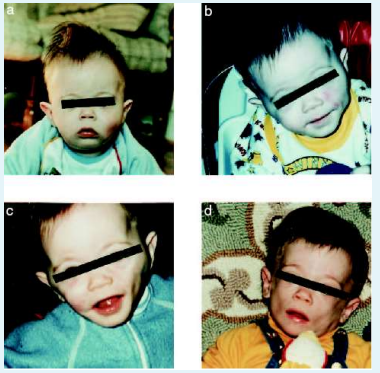
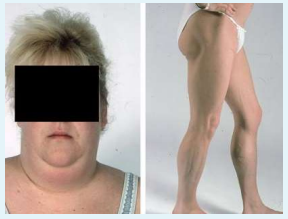
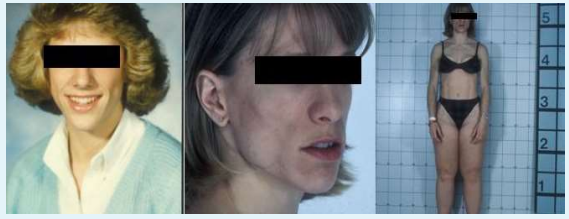
https://emedicine.medscape.com/article/128355-overview

Classification of lipodystrophy syndromes

>30 different conditions

Prevalence estimated to be 3/1M looking at EMR data only

Population based genetic study in the PA valley in the US: 1/20K

	Inherited Caused by genetic mutations (known and unknown)	**Acquired*** Often associated with autoimmune diseases (also idiopathic, other etiologies*)
Generalised		
Partial		

EMR = Electonic Medical Record
*Chiquette E et al Diabetes Metab Syndr Obes.2017
**Gonzaga-Jauregui C et al Diabetes 2020
Garg. N Engl J Med. 2004;350:1220-34; Chan et al. Endocr Pract. 2010;16:310-23; Garg. Am J Med. 2000;108:143-52:143-52

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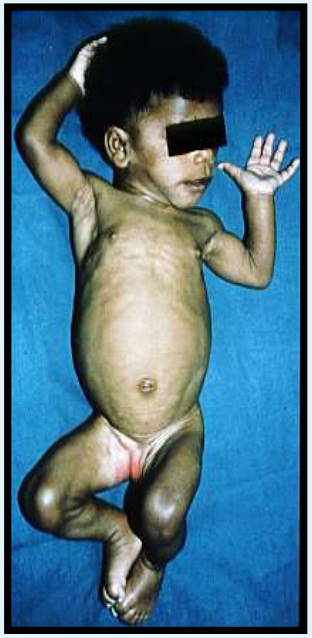
Congenital generalised lipodystrophy

Lipodystrophy syndromes



Subtype	Gene
• CGL1	*AGPAT2*
• CGL2	*BSCL2*
• CGL3	*CAV1*
• CGL4	*PTRF*

New genetic markers:
PYCT1-A, LMNA, PPARG, etc.

- Fat loss apparent at birth, typically Autosomal Recessive
- Metabolic manifestations early

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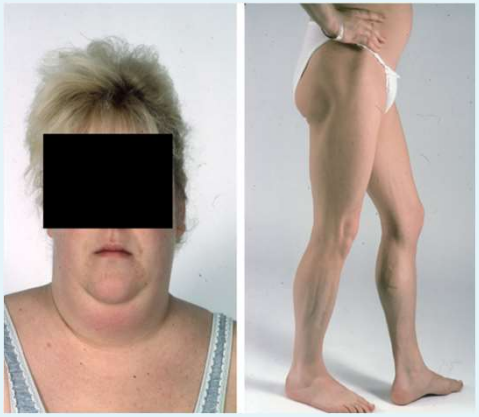
Familial partial lipodystrophy



Subtype	Gene
FPL1	Unknown or polygenic
FPL2	*LMNA*
FPL3	*PPARG*
FPL4	*PLIN1*
FPL5	*CIDEC*
FPL6	*LIPE*

Newer genes: AKT, ADR2A, Mitofusin 2, OPA1 etc.

- Typically autosomal dominant
- Normal fat distribution at birth or subtle loss from lower extremities
- Changes around puberty
- Selective absence from extremities
- Hypertrophy of residual depots especially upon weight gain or positive caloric balance

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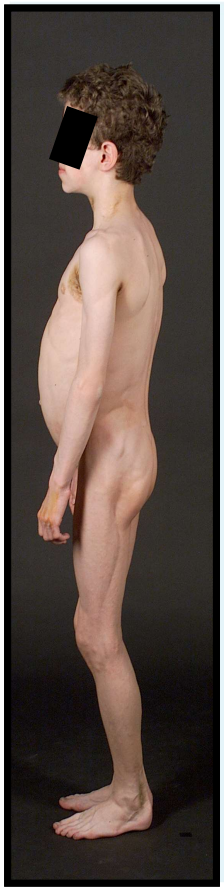
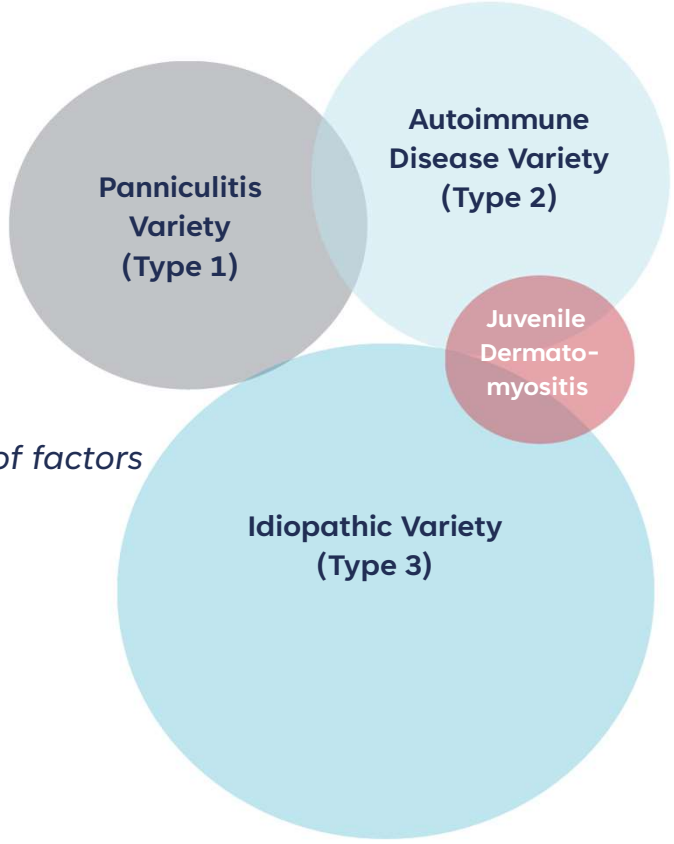
Acquired generalised lipodystrophy



- Very rare
- Onset in childhood or adolescence
- Female-to-male ratio: 3:1



Predominant T-cell mediated disease, check point genes?

Oligogenic?
Combination of factors

LMNA p.T10I
Other nuclear envelope proteins?
Progeroid flavour

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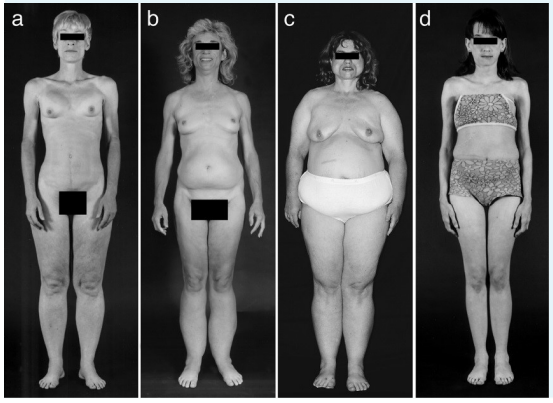
Misra and Garg. Medicine 2003;82:129-46.

Acquired partial lipodystrophy

Age of Onset	~10 yr.
Female to Male Ratio	4:1
Low Serum C3	72%
C3NeF Positive	83%
Autoimmune Diseases	11%
MPGN	19%



Caphalocaudal Variety (Barraquer Simmons type)

Autoimmune Disease Variety

Juvenile Dermato-myositis

Idiopathic Variety

Post childhood cancer: due to XRT or CTx

HIV related LD not shown.

Misra et al. Medicine 2004;83:18-34.

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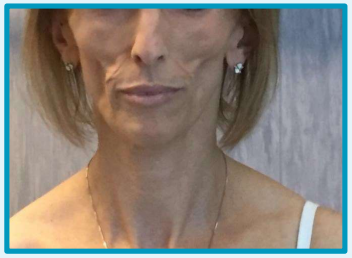
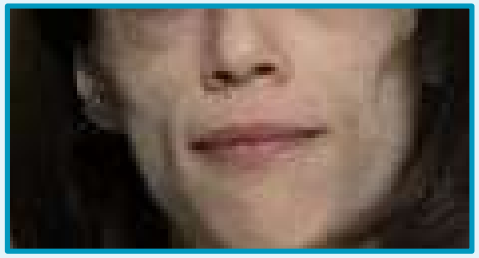
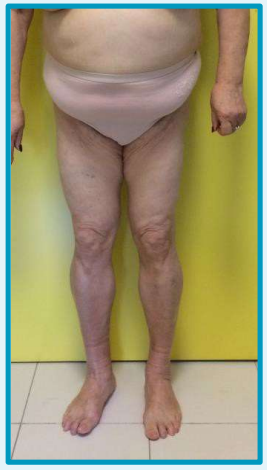
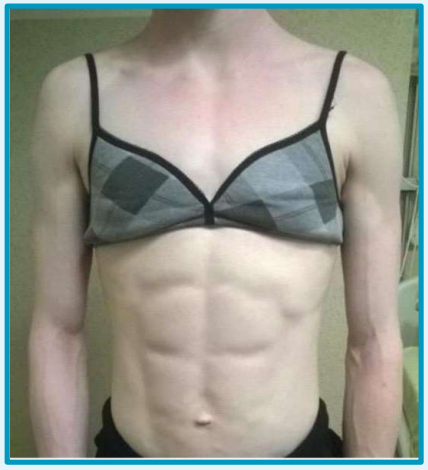
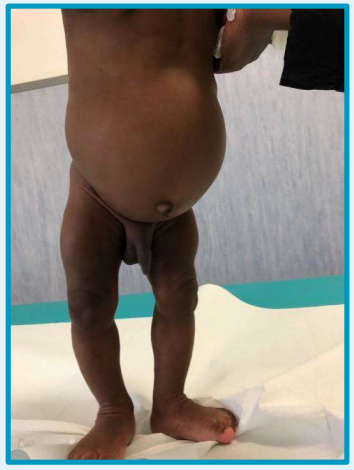
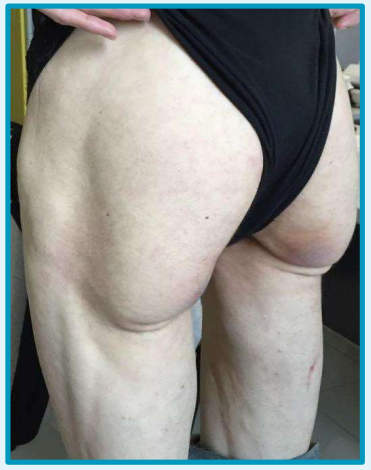
Core clinical characteristics for lipodystrophy

Loss or absence of subcutaneous body fat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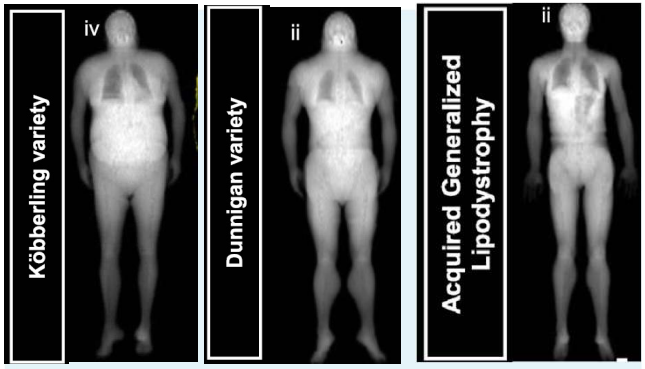
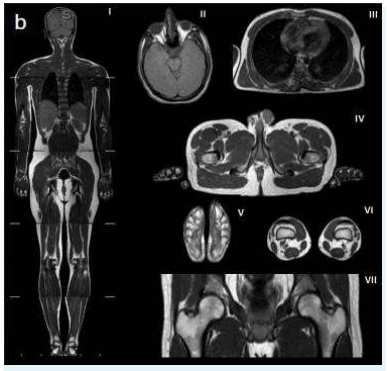
How to diagnose lipodystrophy

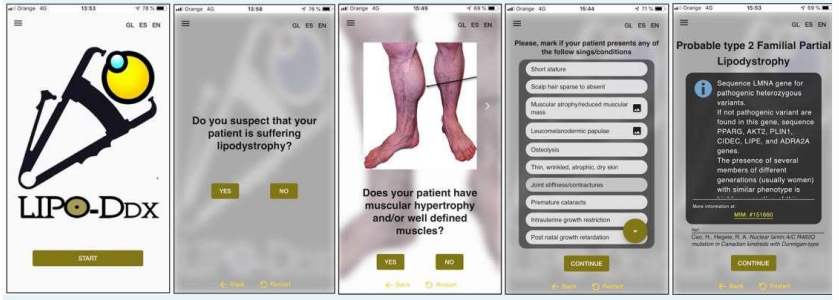
Anthropometry



Dual X-ray Absorbtiometry: Fat shadows



MRI



LipoDDx Mobile App

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Altay C Diagn Interv Radiol 2017 – Meral et al Diabetes Care 2018- Araújo-Vilar et al OJRD 2020

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Metabolic alterations in different lipodystrophy syndromes and associated comorbidities

Key metabolic features

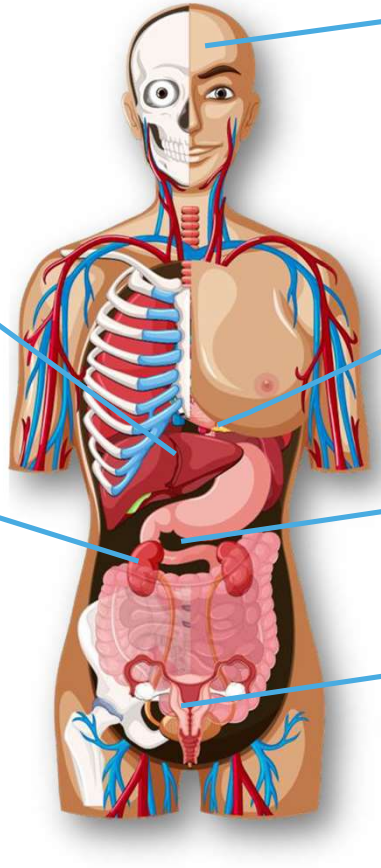
- Severe elevated triglycerides
- Ectopic lipid deposition
- Progression to poorly controlled diabetes, complications of diabetes
- Hyperphagia

Liver

- Hepatic steatosis
- Hepatomegaly
- Steatohepatitis
- Cirrhosis

Kidney

- Proteinuric renal disease
- Glomerulonephritis



Other

- Chronic pain
- Mood disturbances

Heart

- Cardiomyopathy
- Atherosclerosis
- Arrhythmias

Pancreas

- Episodes of pancreatitis

Reproductive

- Infertility
- Hyperandrogenism
- Polycystic ovaries

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Akinci B, et al. Curr Diab Rep 2018;18:143

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Key clinical points for lipodystrophy syndromes

Lipodystrophy syndromes are heterogeneous; but there are some common themes in pathophysiology. While it is important to recognise the common issues, it is also important to recognise the differences for management decisions

Diagnosis of lipodystrophy syndromes may be challenging and can only be accomplished with physicians who can recognise the pattern. Failure to recognise the pattern leads to a delay in diagnosis

Lipodystrophy syndromes are multi-system disorders and affect not only metabolism but the entire body

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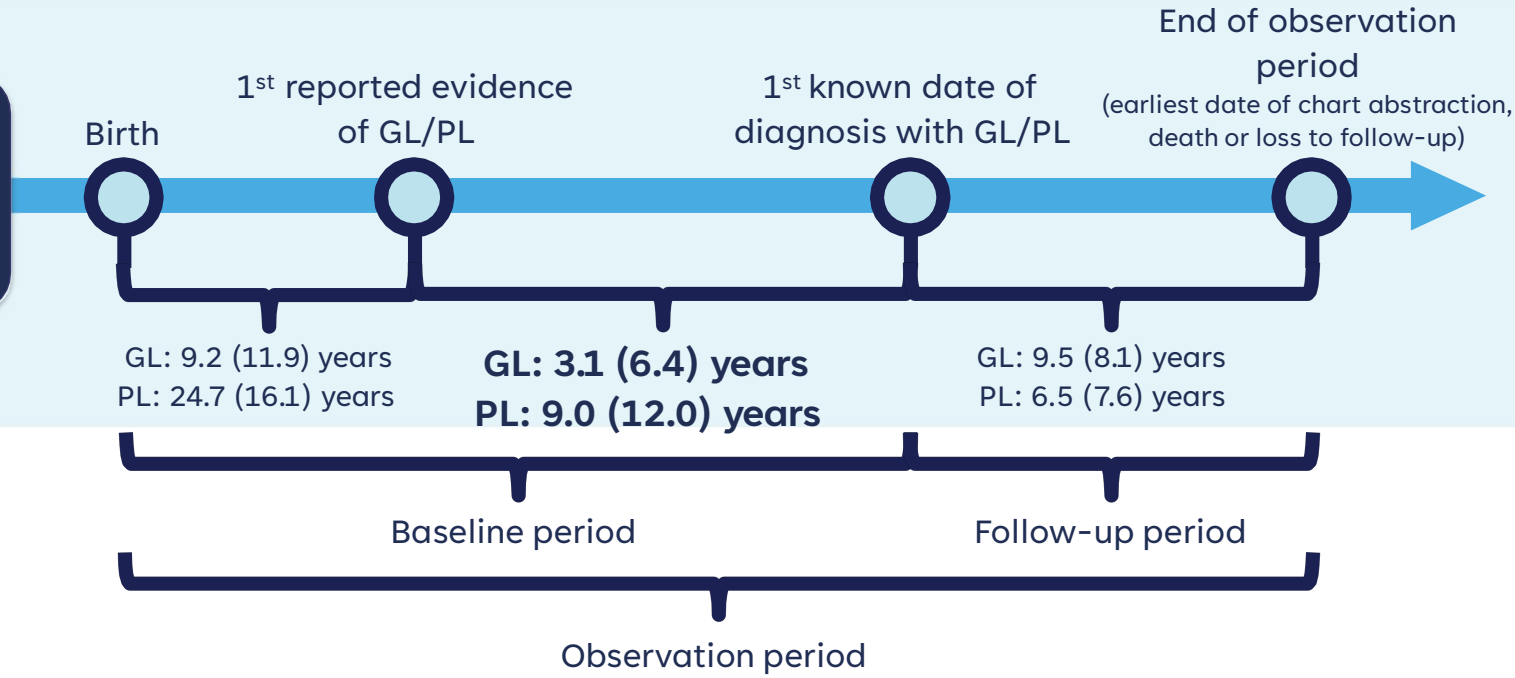
Disease identification and progression –

An international chart review to assess the natural history of patients with GL and PL

Multi-national perspective on how patients with lipodystrophy progress through life and the impact of disease on end-organ function

230 patients with confirmed GL (81 patients; 35.2%) and 149 (64.8%) with PL at five treatment centers who never received leptin



Results

- Diabetes/insulin resistance 58.3%
- Liver abnormalities 71.7%
- Kidney abnormalities 40.4%
- Heart problems 30.4%
- Pancreatitis 13.0%

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Akinci B, et al. J Clin Endocrinol Metab 2019;104:5120-5135

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Recommendations from guidelines –
Current therapeutic options

- **Diet:**
  - Balanced composition of macronutrients, energy-restricted diets if practicable
  - A dietitian should be consulted, especially in infants and young children
- **Exercise:**
  - In the absence of contraindications (caution needed if there is cardiomyopathy risk)
- **Diabetes medications:**
  - E.g., metformin (first-line), insulin for hyperglycemia; use thiazolidinediones with caution
- **Lipid-lowering medications:**
  - Statins (first-line); fibrates and/or long-chain omega-3 fatty acids if triglycerides high
- **Anti-hypertensive treatment**

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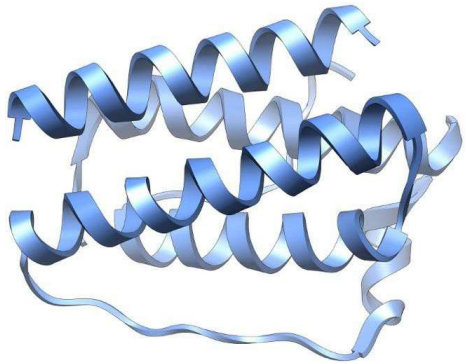
Brown RJ, et al. 2016 J Clin Endocrinol Metab;101:4500-4511
Medications must be appropriate for the age of the patient

Recommendations from guidelines –
Current therapeutic options (2)

- **Metreleptin:**
  - In generalised lipodystrophy, metreleptin (with diet) is a first-line treatment for metabolic and endocrine abnormalities (Class I, Level B)
  - May be considered for prevention of these comorbidities in children (Class IIb, Level C)
- **Metreleptin is approved in:**
  - US
    - Generalised lipodystrophy
  - EEA
    - Generalised lipodystrophy in patients >2 years
    - Partial lipodystrophy in patients >12 years



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Brown RJ, et al. J Clin Endocrinol Metab 2016;101:4500-4511 Foss-Freitas MC, et al. Expert Rev Endocrinol Metab 2020;15:95-114
Metreleptin https://www.clinicaltrialsarena.com/projects/myalepta-metreleptin/

Management of generalised lipodystrophy (GL) patients

Prof. Barış Akıncı

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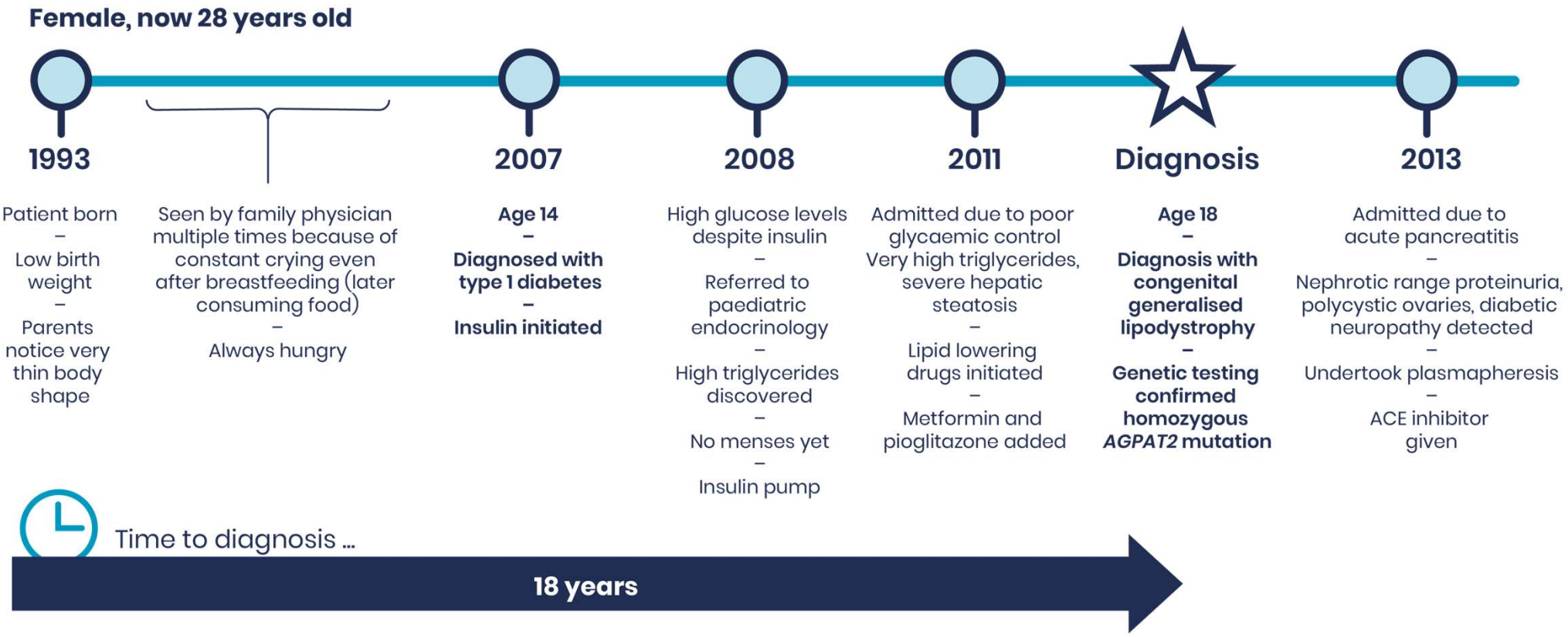
A case with congenital generalised lipodystrophy



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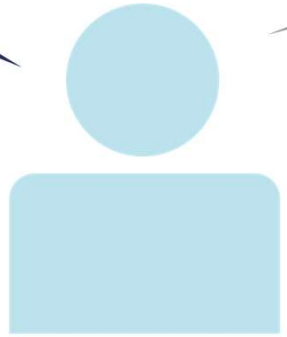
ACE, angiotensin converting enzyme

Some quotes: patient's perspective

"My sugars were very high. I had to follow a strict diet, but it was impossible because I was hungry all the time. All I was thinking was water, food, and sleep because I was so tired."

"I started studying for the university entry exams, but I was even not sure if I would be alive next year."



"I was very thin, but my liver got bigger and bigger, so I started wearing lousy clothes because people were thinking that I was pregnant."

"I was hopeless. Hospitals, doctors, drugs, serums, blood tubes, urine cups, ultrasounds, MRIs, alternative medicines, alarms that I set to catch my medicine time, pain, cramps, medical articles ... from the day I was born, I was a mystery that nobody could solve."

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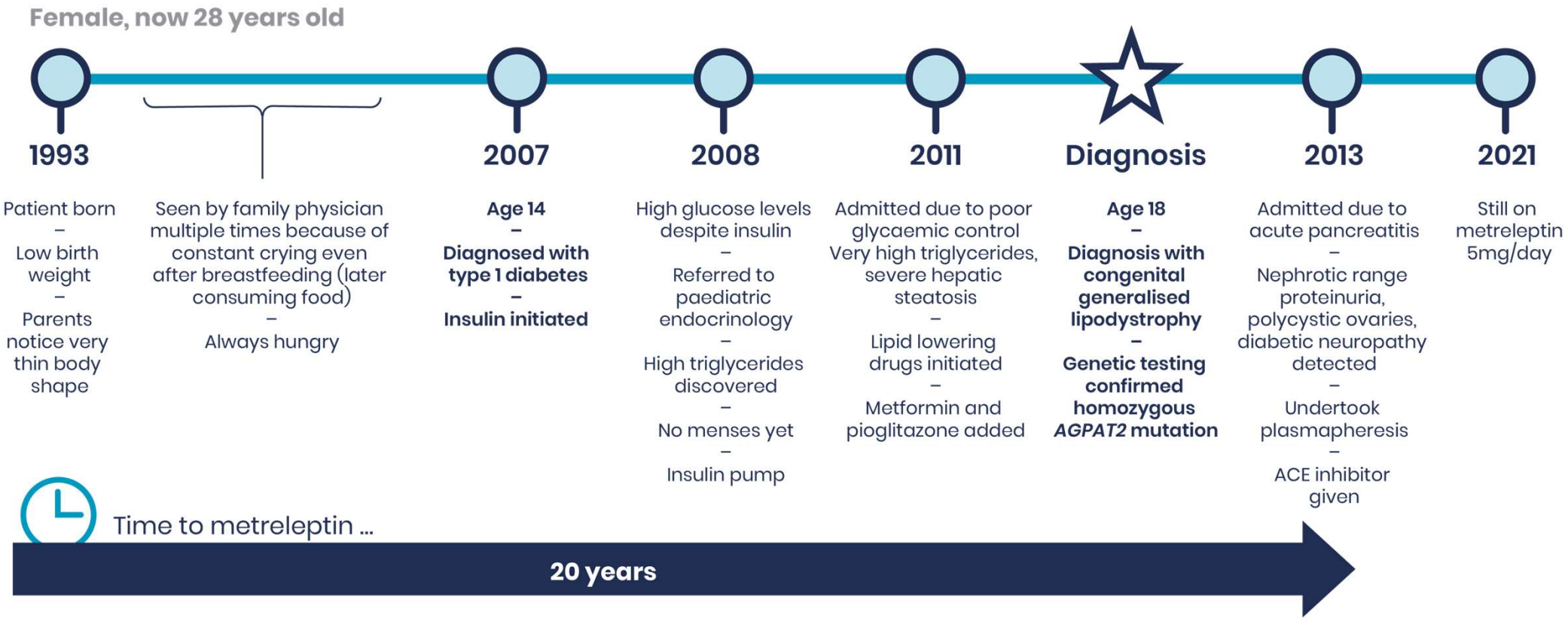
A case with congenital generalised lipodystrophy



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ACE, angiotensin converting enzyme

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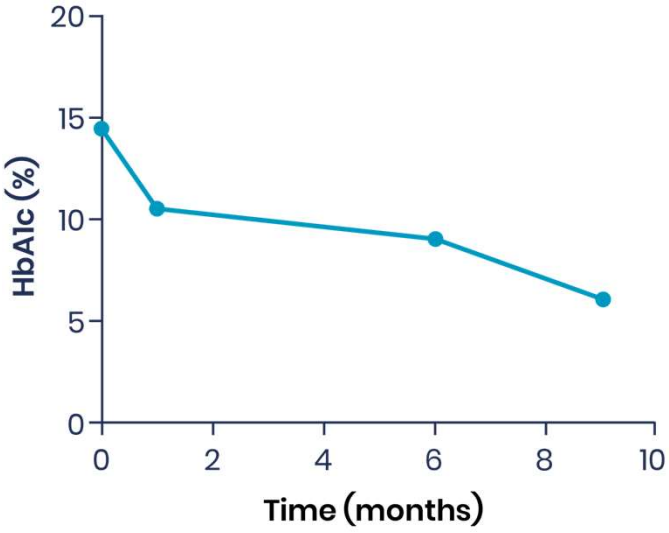
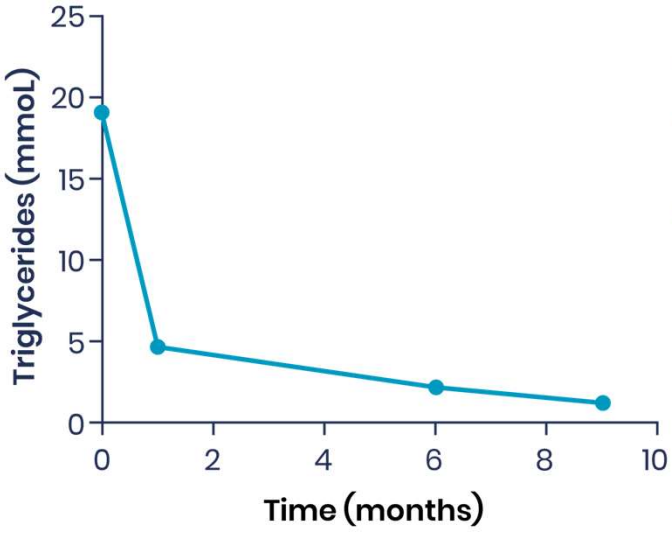
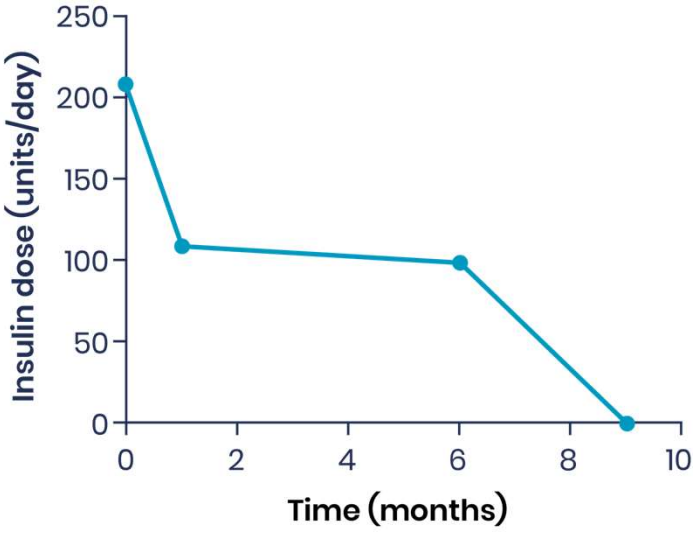
Patient case: metabolic effects of metreleptin

Results

- We observed a gradual improvement in her glycaemic control, along with a decrease in the amount of insulin that she used
- On her next visit after 6 months, we observed that HbA1c remained at target levels
- Triglyceride levels dropped progressively, starting from the the first weeks of treatment







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Simsir IY, et al. Diabetes Obes Metab 2017;19:299-301

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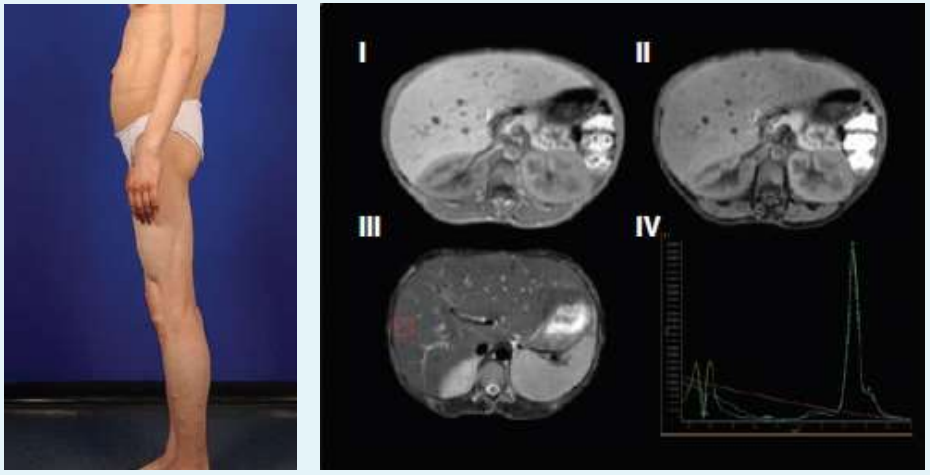
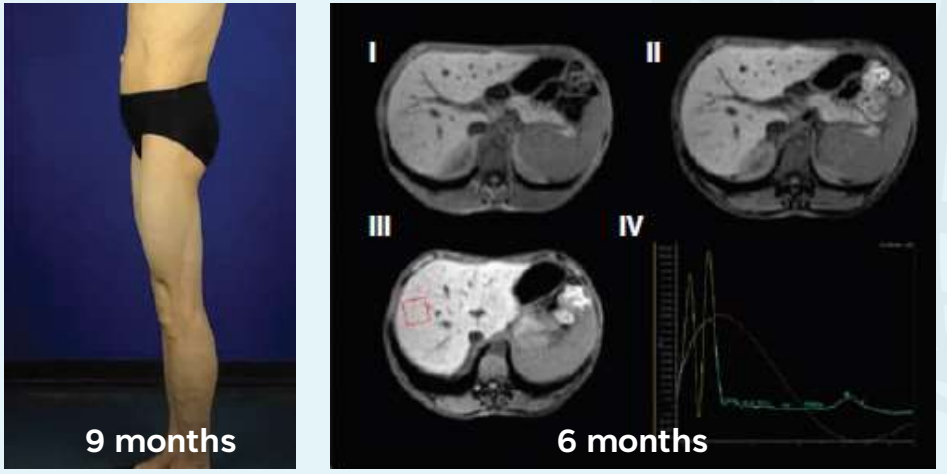
Patient case: the effect of metreleptin on the liver

- Hepatic steatosis improved significantly
- The regression in abdominal protrusion caused by hepatomegaly was remarkable on physical examination

Before metreleptin



After metreleptin



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Simsir IY, et al. Diabetes Obes Metab 2017;19:299-301

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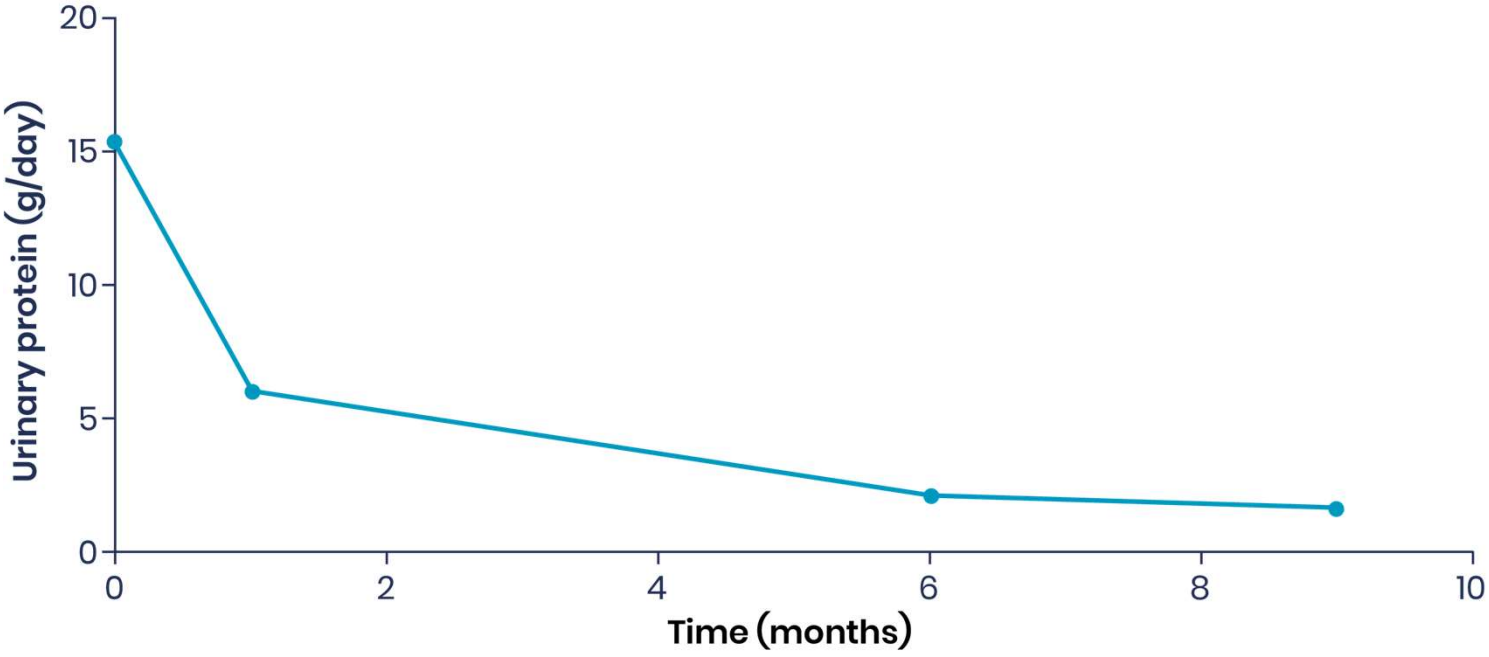
Patient case: the effect of metreleptin on proteinuria



We observed a significant decrease in proteinuria, which was at extreme levels before treatment

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Simsir IY, et al. Diabetes Obes Metab 2017;19:299-301

Patient reported outcomes

- Regular menses
- Excessive sweating disappeared
- Her pain and muscle stiffness/cramps improved
- Psychoemotional health improved*

In this patient, no treatment-related side effects were observed.

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Personal observations; *Per psychologist and standard questionnaires used to evaluate QoL, depression level, and anxiety

Questions on generalised lipodystrophy

- How does generalised lipodystrophy present?
- The diagnostic journey of patients and time lag to diagnosis?
- What are the clues to diagnosis?
- How can we expedite the diagnosis?
- What goes into the decision of treatment initiation with metreleptin?
- How do you monitor the patients?
- Role for stopping or pausing treatment?
- Care models; how can we optimise?
- Patient advocacy and empowerment: how can we enable this?

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Optimum management of partial lipodystrophy (PL) patients

Prof. Ferruccio Santini

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Clinical history B.S.

1971

Normal distribution of adipose tissue

2002

2003

Pregnancy complicated by preeclampsia and gestational diabetes

2004

Loss of SC scadipose tissue at lower limbs level

Diabetes
Hypertriglyceridemia
Proteinuria

2016

- Insulin (66 UI/day)
- Linagliptin 5 mg/day
- Ezetimibe 10 mg/day
- Statin 20 mg/day
- Fenofibrate 145 mg/day
- Omega3 1000 mgx3/day
- Losartan 50 mg/day
- ACE inhibitor 10 mg/day
- Angiotensin receptor blocker 50 mg/day

2018

Metreleptin

First evaluation

Blood Tests:

- Glycemic profile: glucose 154 mg/dL; HbA1c 59 mmol/mol
- Lipid profile: Triglycerides 270 mg/dl, total cholesterol 203 mg/dl, HDL 38 mg/dl, LDL 111 mg/dl
- Liver profile: GOT 24 U/L, GPT 27 U/L, gGT 21 U/L
- Proteinuria 3,500 g/24h
- Serum leptin: 14.2 ng/ml

Abdominal ultrasound:
Hepatic steatosis and hepatomegaly

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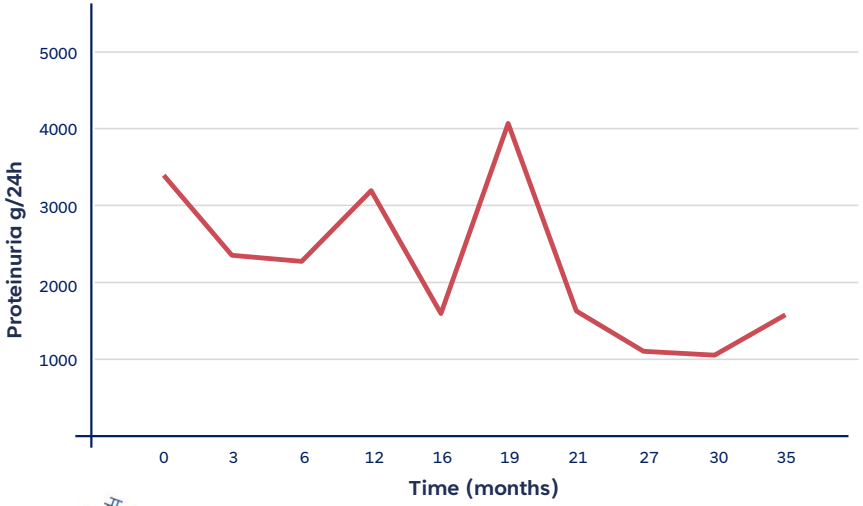
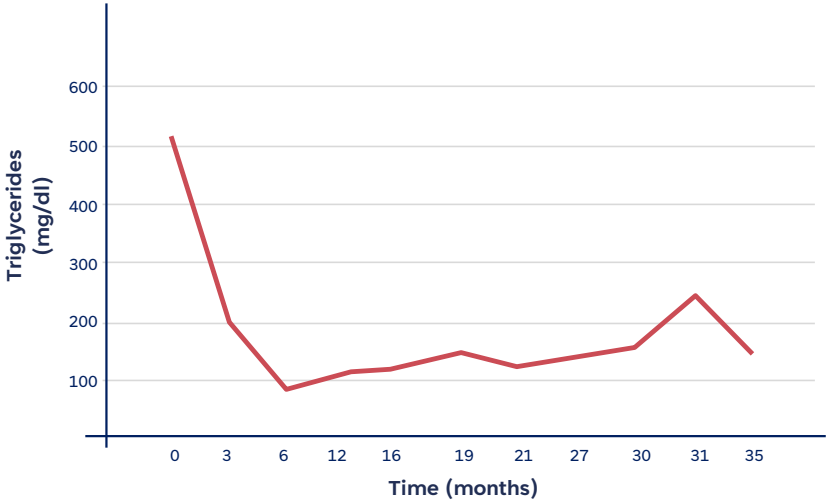
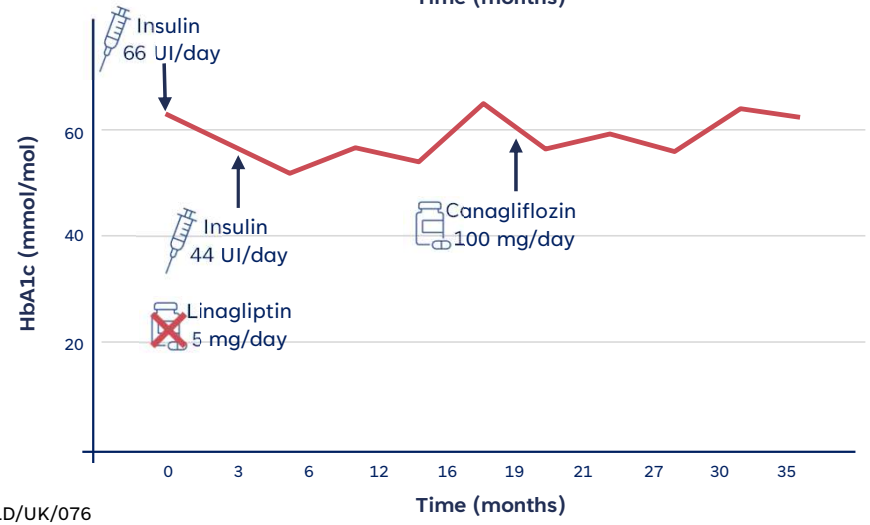
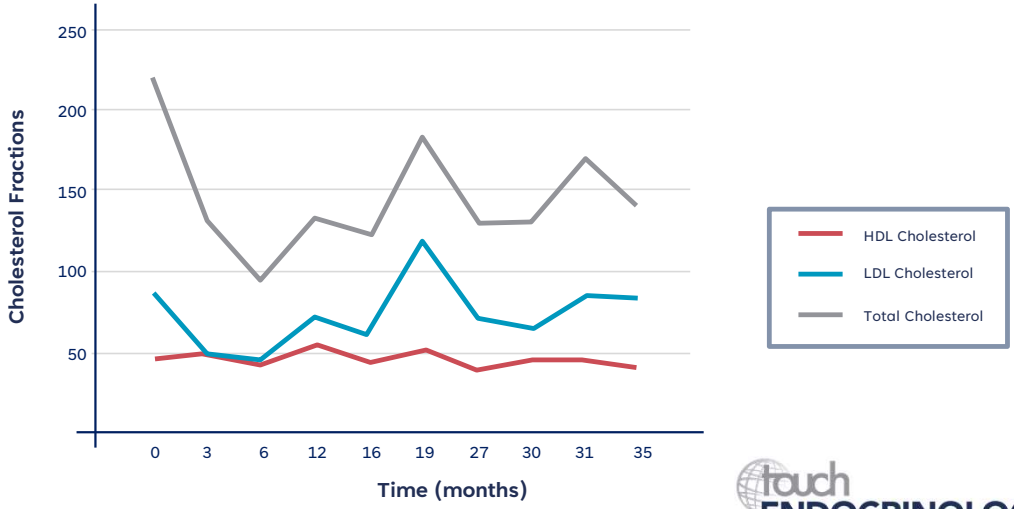
Metabolic profile









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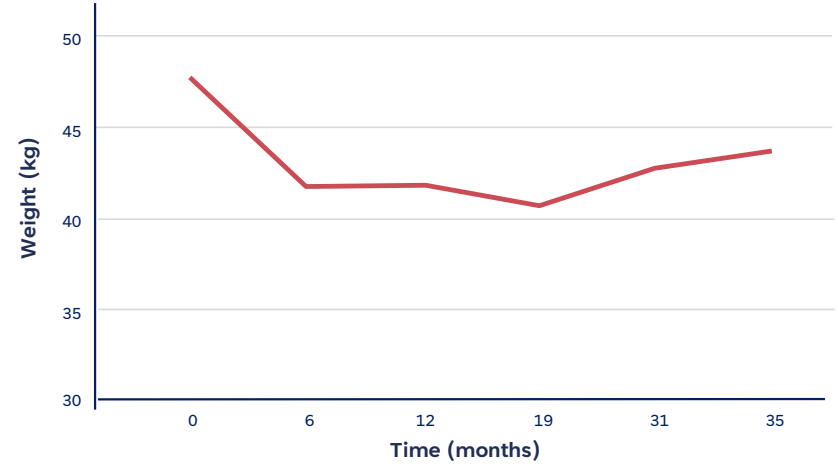
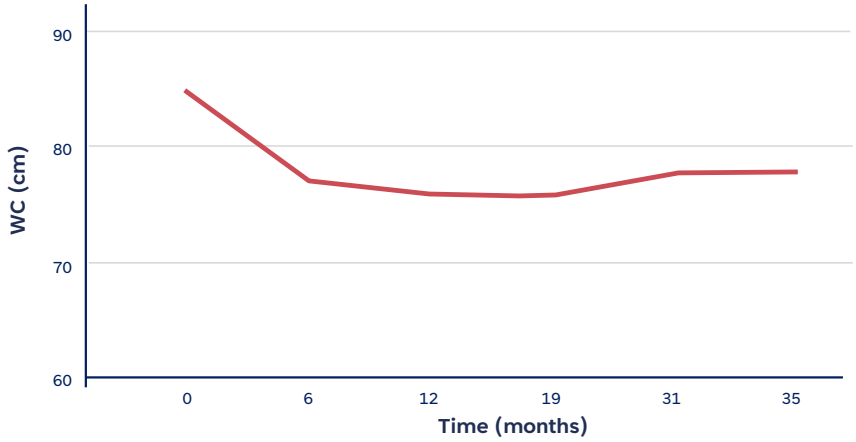
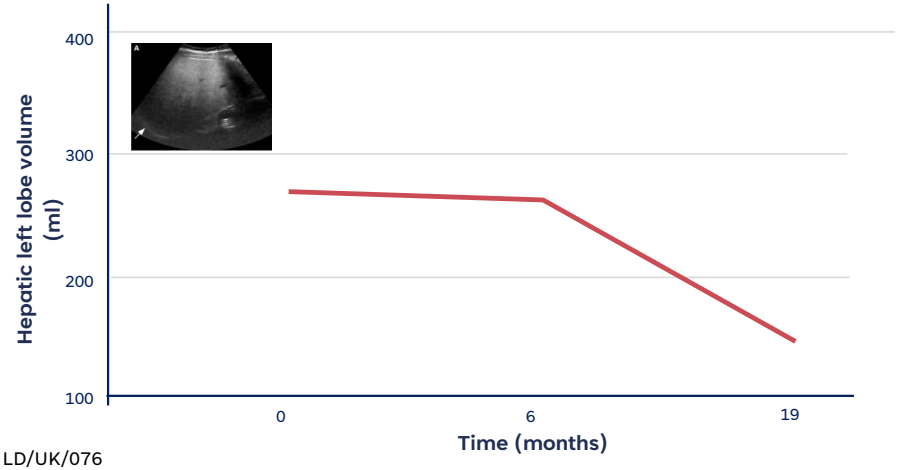
Anthropometric parameters







January 2020

- Metreleptin 5 mg/day
- Insulin (56 UI/day)
- Canagliflozin 100 mg/day
- Ezetimibe 10 mg/day
- Statin 10 mg/day
- Omega3 1000 mg x3/day
- Losartan 50 mg/day
- ACE inhibitor 10 mg/day

WC = waist circumference

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Questions on partial lipodystrophy

- How does partial lipodystrophy present?
- The diagnostic journey of patients and time lag to diagnosis?
- What are the clues to diagnosis?
- How can we expedite the diagnosis?
- What goes into the decision of treatment initiation with metreleptin?
- How do you monitor the patients?
- Role for stopping or pausing treatment?
- Care models; how can we optimize?
- Patient advocacy and empowerment: how to enable?
- Are there any additional considerations?

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Conclusions

Lipodystrophy syndromes are heterogenous, but the common denominator is fat loss. The adipocyte hormone leptin is low in patients with generalised lipodystrophy and in some forms of partial lipodystrophy, and may mediate the metabolic complications

Patients with lipodystrophy are at serious risk of morbidity and mortality from their metabolic problems

Patients also suffer from not only metabolic problems but also from other multi-system disorders and reduced quality of life, mood disorders and increased appetite that affect them adversely

Current treatment of lipodystrophy focuses on metabolic aspects of the disease and management of comorbidities

Timely management of lipodystrophy is important to slow down the progression of comorbidities and improve survival and can help with improvement in quality of life

Metreleptin is the first and currently only approved treatment for metabolic complications for non-HIV lipodystrophy

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