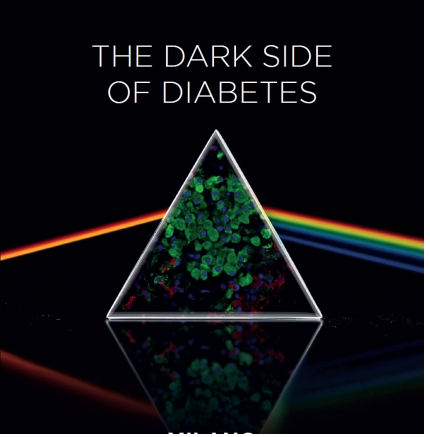


Lipodistrofie: inquadramento clinico

Caterina Pelosini (Pisa)

Terapia delle lipodistrofie

Flavia Prodam (Novara)

La gestione in ambulatorio

Giulia Rodari (Milano)

SCDU Endocrinologia

Dipartimento di Scienze della Salute

Università del Piemonte Orientale

DISCLOSURES

La D.ssa FLAVIA PRODAM dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Amryt/Chiesi; Abiogen; Caelus Health; Difass International; Novo Nordisk; Novartis; Menarini, Probiotical; Sanofi, Therascience

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

MOLECULAR PATHWAYS OF LIPODYSTROPHY

Mancanza/perdita di tessuto adiposo con conseguente deficit di leptina e:

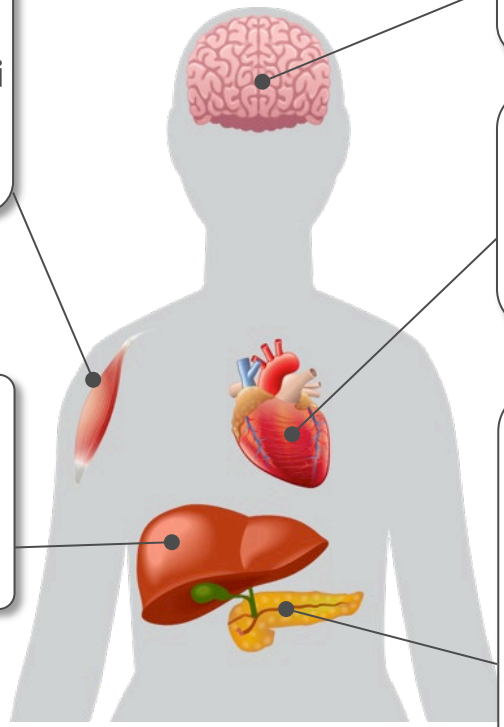
- Steatosi ectopica
- Lipotossicità
- Lipoapoptosi

Muscolo

- Ridotto utilizzo di glucosio
- Ridotta ossidazione degli acidi grassi

Fegato

- Aumento liposintesi
- Aumento neoglucogenesi



SNC

- Aumento sensazione di fame
- Aumento introito calorico

Cuore

- Aumento FFAs circolanti
- Possibile cardiomiopatia lipotossica

Pancreas

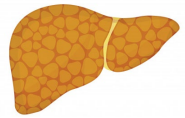
- Aumentop produzione e secrezione di insulina
- Progressiva disfunzione beta-cellulare

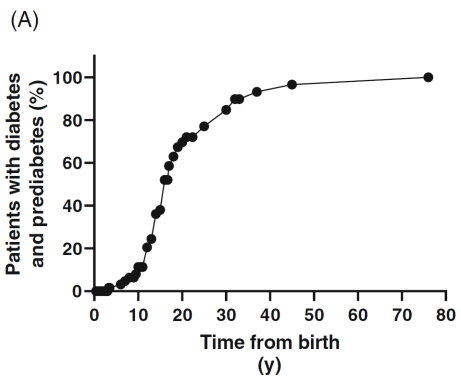
Iperinsulinemia con:

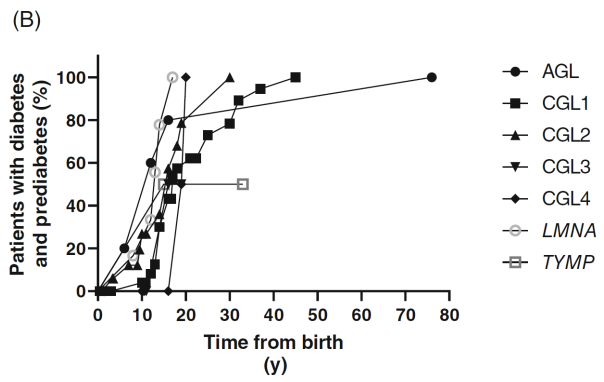
- Sindrome dell'ovaio policistico (PCOS)
- Acantosi nigricans
- Aspetto acromegaloide

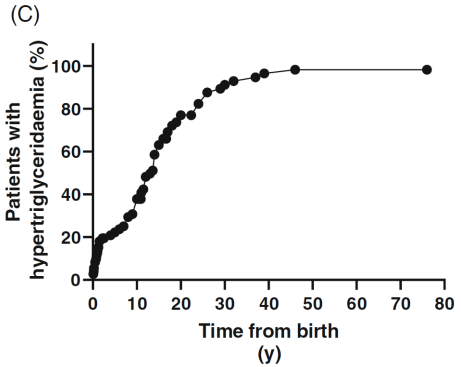
Park Metabolism 2015.
Moon Endocr Rev. 2013
Garg J Clin Endocrinol Metab 2011

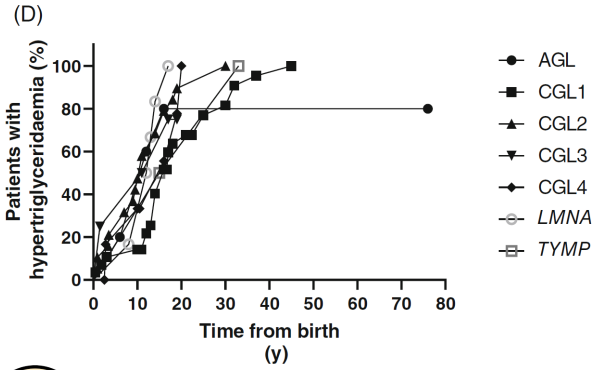
COMORBIDITIES' PROGRESSION

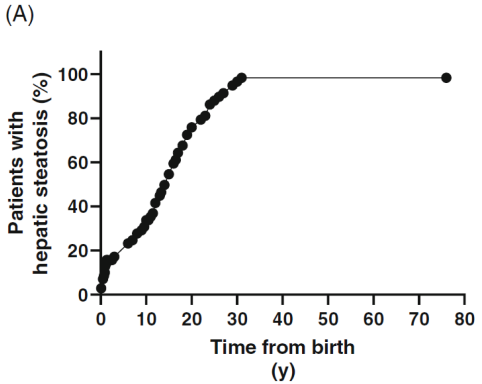


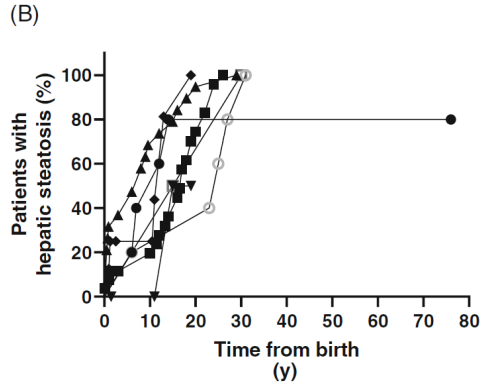


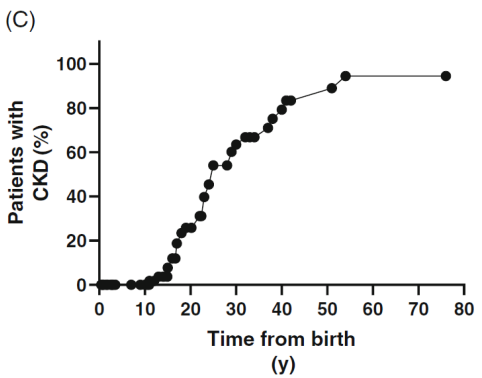


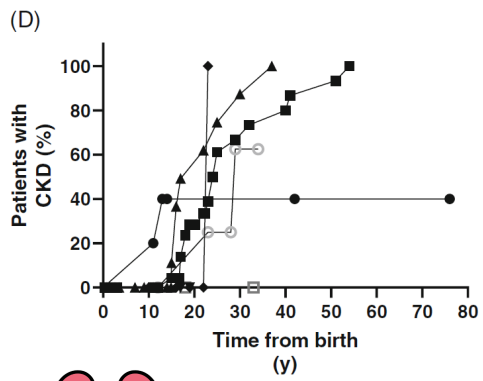












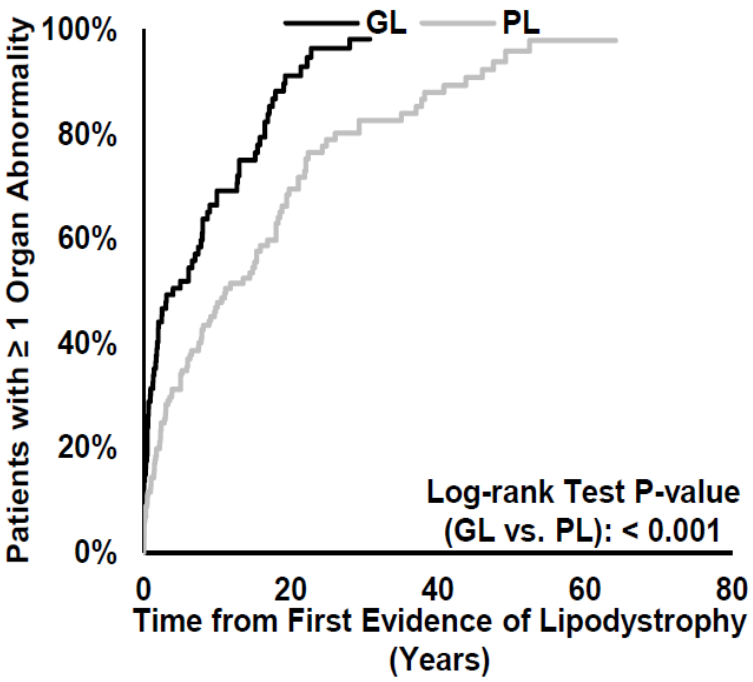
F>M

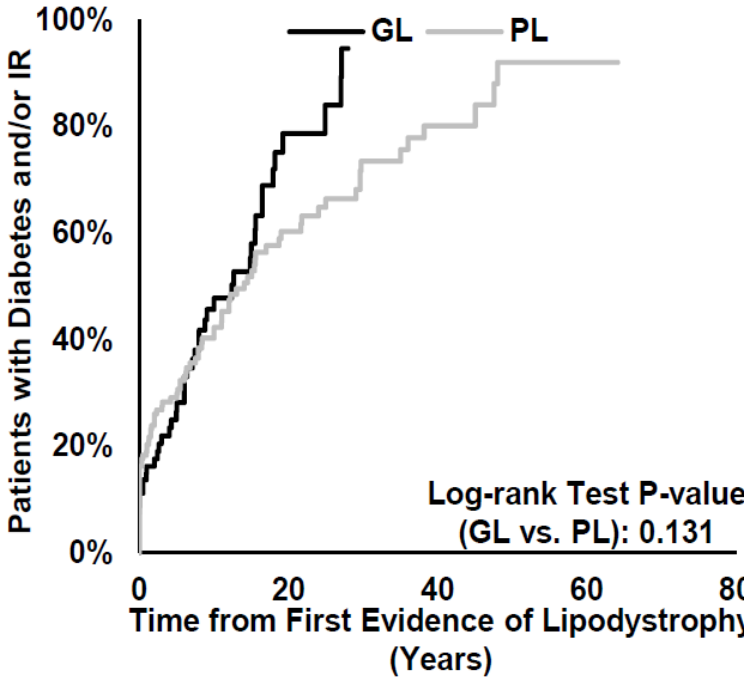
Simsir IY et al Diab Obes Metab 2023

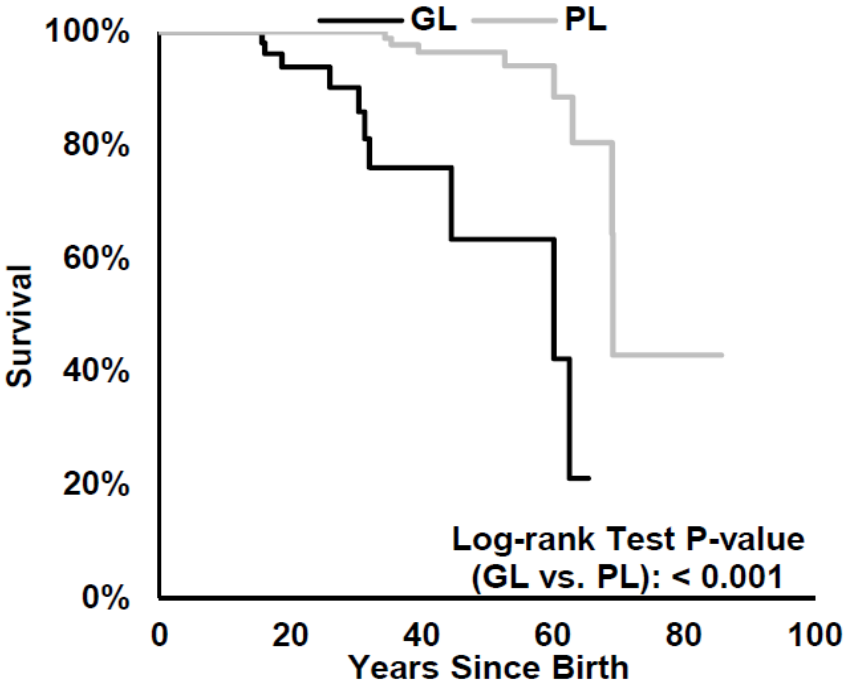
Kushchayeva YS et al JCEM 2020

COMORBIDITIES' PROGRESSION

230 subjects



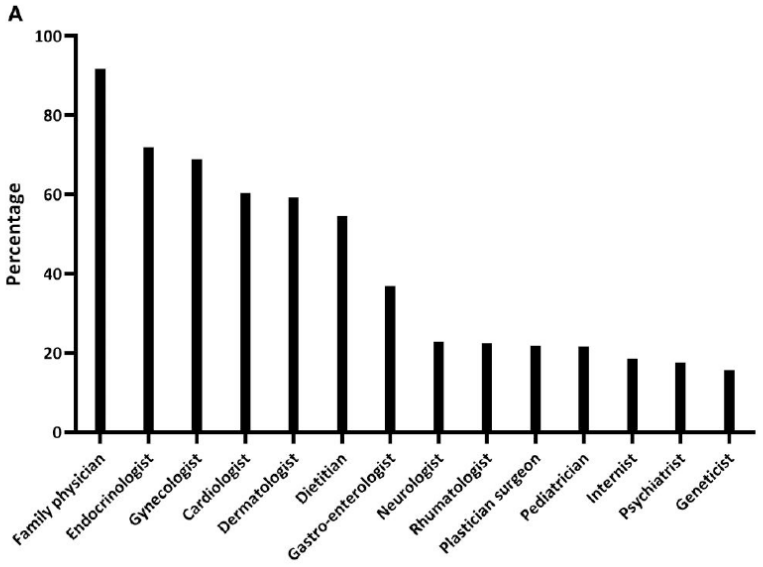


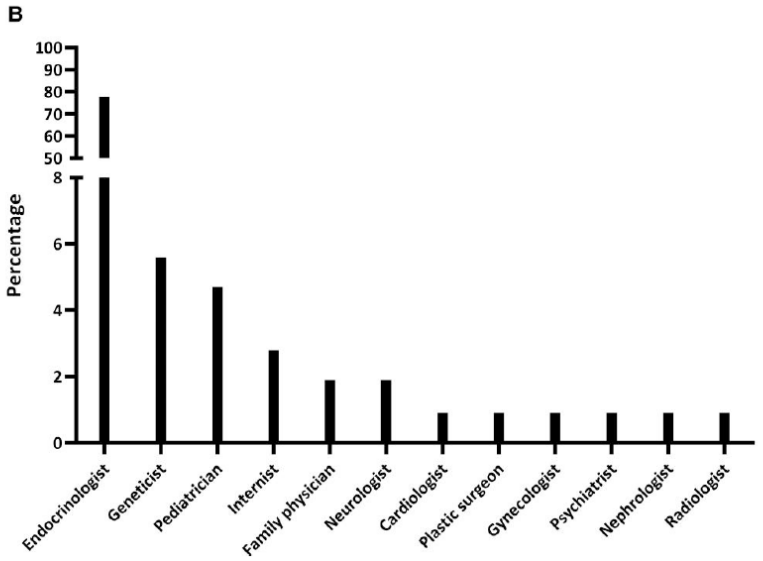


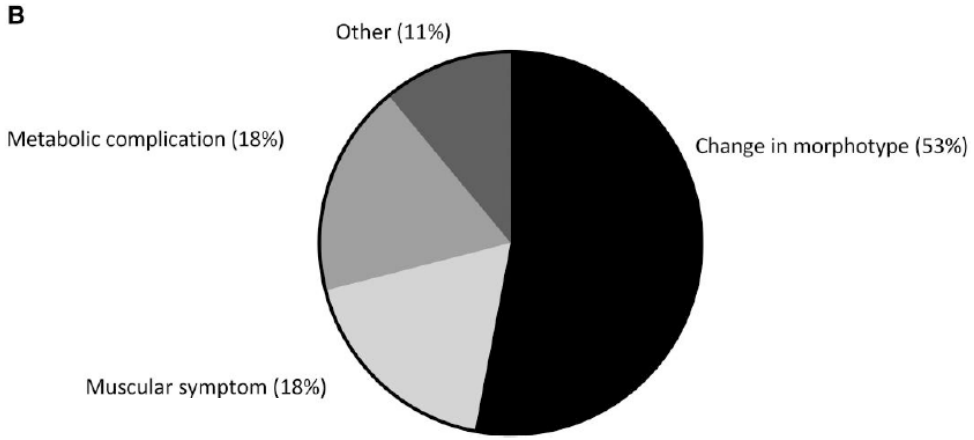
F>M

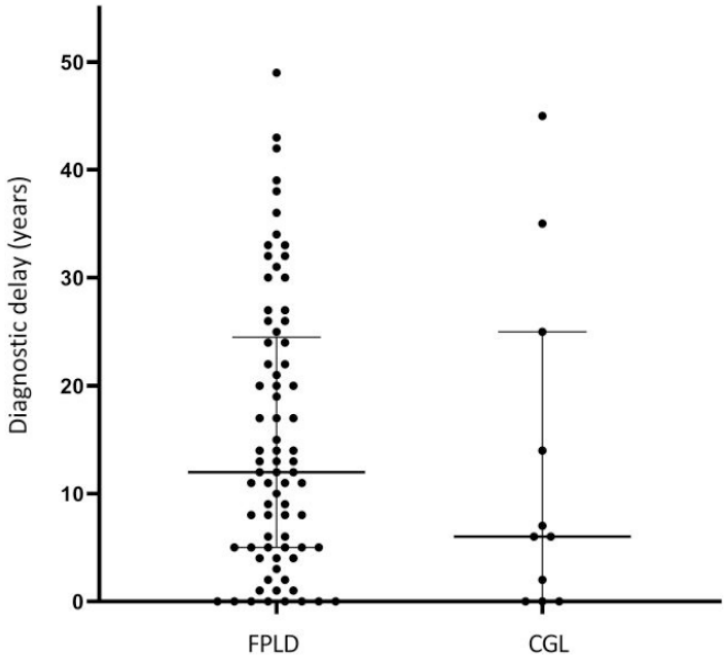
Akinci B et al JCEM 2019

DIAGNOSIS DELAY









FIRST SYMPTOMS CGL

Mosbah E et al. EJE 2024

TREATMENT LIPODYSTROPHY

Diet

- Most patients should follow diets with balanced macronutrient composition. (Class IIa, Level C)
- Energy-restricted diets improve metabolic abnormalities and may be appropriate in adults. (Class I, Level C)
- Very-low-fat diets should be used in chylomicronemia-induced acute pancreatitis. (Class I, Level C)
- A dietician should be consulted for specialized dietary needs, especially in infants and young children.Overfeeding should be avoided. (Class IIa, Level C)
- Medium-chain triglyceride oil formulas can provide energy and reduce triglycerides in infants. (Class IIa, Level C)

Exercise

- Patients with lipodystrophy should be encouraged to exercise in the absence of specific contraindications. (Class IIa, Level C)
- Patients with subtypes of lipodystrophy predisposed to cardiomyopathy should undergo cardiac evaluation before initiating an exercise regimen. (Class III, Level C)

Brown RJ et al JCEM 2016

TREATMENT LIPODYSTROPHY

Dyslipidemia

- Statins should be used concomitantly with lifestyle modification (after consideration of age, reproductive status, and tolerance). (Class 1, Level C)
- Fibrates and/or long-chain omega-3 fatty acids should be used for triglycerides >500 mg/dL and may be considered for triglycerides >200 mg/dL. (Class IIb, Level C)

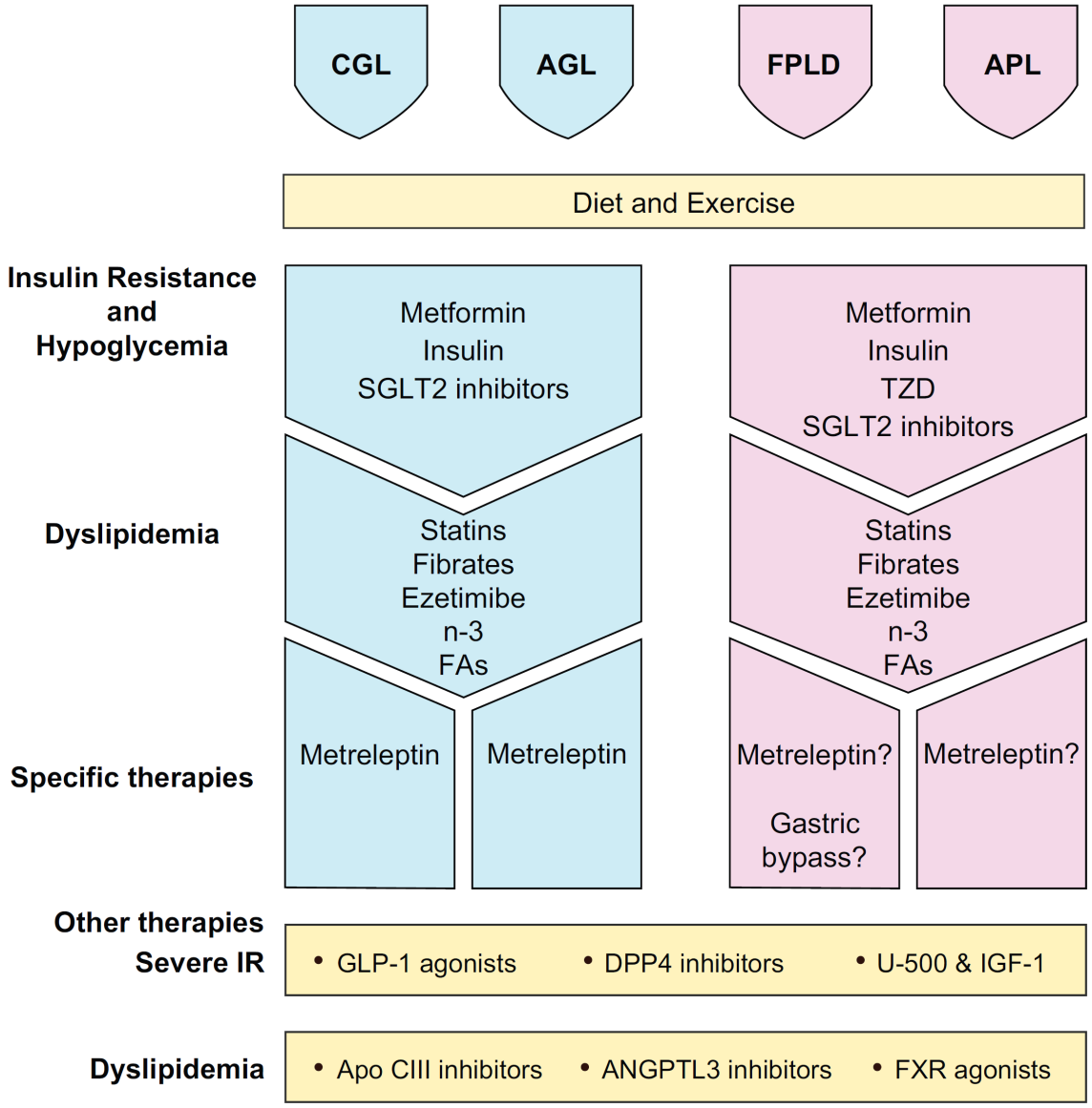
VOLANESORSEN (FPLD, BROADEN study, 40 patients)
EVINACUMAB (ongoing)

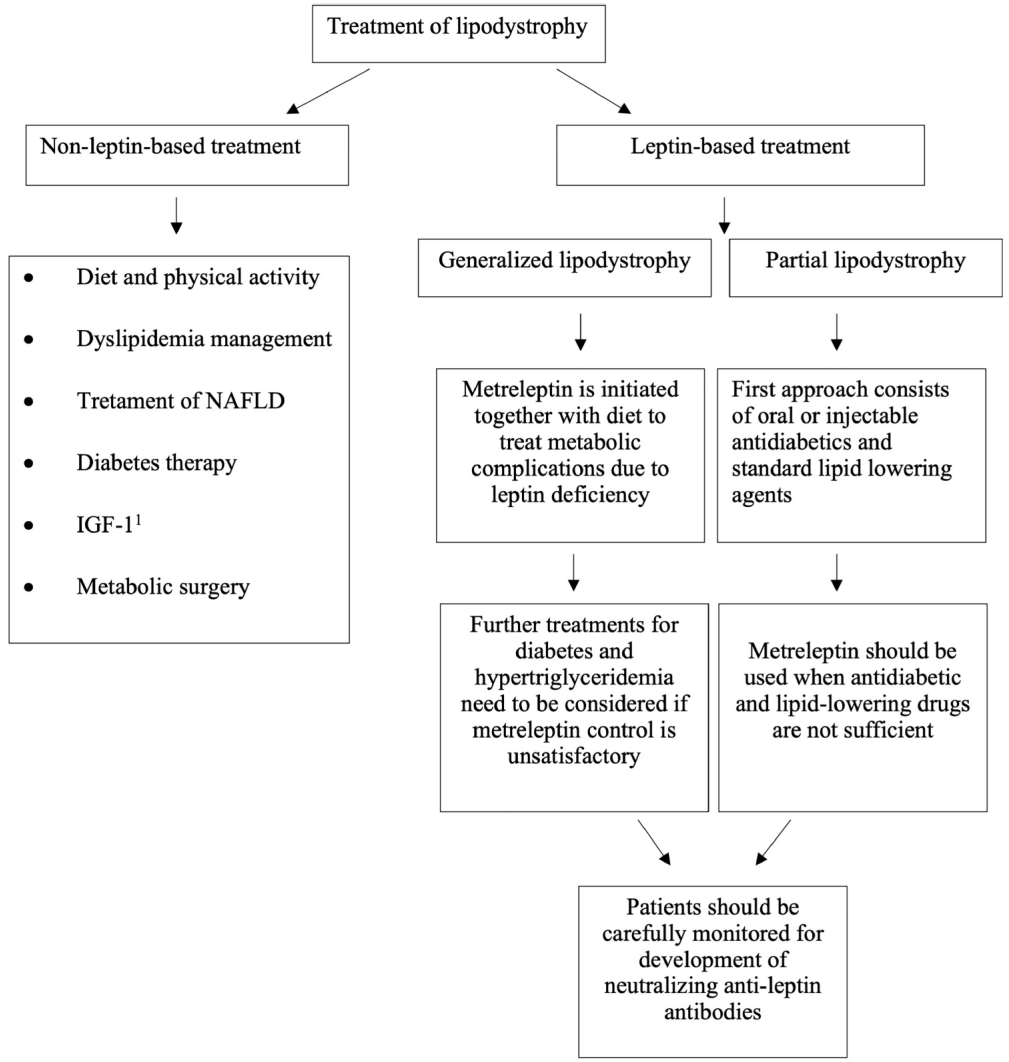
Diabetes

- Metformin is a first-line agent for diabetes and insulin resistance. (Class IIa, Level C)
- Insulin is effective for hyperglycemia. In some patients, concentrated preparations and high-doses may be required. (Class IIa, Level C)
- Thiazolidinediones may improve metabolic complications in partial lipodystrophy but should only be used with caution in generalized lipodystrophy. (Class IIb, Level B)

Brown RJ et al JCEM 2016

TREATMENT LIPODYSTROPHY





Mainieri F et al. Front Endocrinol 2022

Lim K et al. Physiol Rev 2021

TREATMENT

Hypertension

- Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes. (Class IIa, Level C)

Cosmetic treatment

- Patients should be assessed for distress related to lipodystrophy and referred as necessary to mental health professionals and/or plastic surgeons. (Class IIa, Level C)

Reproductive

Hyperandrogenemia, hirsutism

Oligomenorrhoea, subfertility

Polycystic ovarian syndrome

- Oral estrogens are contraindicated. (Class IIa, Level C)
- If contraception is needed, progestin-only or nonhormonal contraceptives should be considered. (Class IIa, Level C)
- If estrogen replacement is needed, transdermal estrogen should be used. (Class IIa, Level C)

Brown RJ et al JCEM 2016

Bagias C et al It Diab Met Synd Obes Targ Ther 2020

TREATMENT

TABLE 5 Causes of mortality in patients

Age at death (y)	Gender	Cause of death
37	Female	ESRD, sepsis after COVID
62	Female	Myocardial infarction
67	Male	ESRD, died after CABG
45	Male	ESRD, sepsis after CABG
62	Female	Stroke after CABG
29	Female	Angiosarcoma
26	Female	ESRD, sepsis after diabetic foot
11	Male	Liver complications
15	Female	Sepsis, multiorgan failure
16	Female	Sepsis because of recurrent intestinal perforations
12	Female	Dilated cardiomyopathy, heart failure

Clinical characteristics OR (95% CI)	Non-HIV-LD individuals vs matched controls from the all-adult cohort without HIV[a]
Metabolic comorbidities/complications	
Hypertension	3.58 (2.89–4.44)
Hyperlipidemia	3.32 (2.71–4.09)
Diabetes	4.72 (3.85–5.79)
MASLD/MASH	3.40 (2.13–5.39)
AMI	2.45 (1.27–4.57)
Liver fibrosis/cirrhosis	4.06 (1.66–9.95)
Acute pancreatitis	4.04 (1.41–11.6)
Autoimmune diseases	
Rheumatoid arthritis	2.86 (1.67–4.84)
Autoimmune thyroiditis	3.30 (1.45–7.37)
Lupus erythematosus	5.21 (1.72–16.53)
Cancer	
Any cancer[c]	2.20 (1.59–3.01)
Breast cancer	2.59 (1.52–4.33)
Prostate cancer	2.27 (1.08–4.58)
Lymphoma	1.09 (0.19–4.15)
Other	
Serious infections resulting in hospitalization[d]	3.00 (2.19–4.10)
Kidney disease[e]	2.78 (2.19–3.53)

TABLE 4 Medications used in leptin naïve patients with GL

	n	%
Antidiabetic agents	44	61.1%
Insulin	31	43.1%
Metformin	37	51.4%
DDP4i	2	2.8%
TZDs	9	12.5%
Lipid-lowering agents	46	63.9%
Statins	8	11.1%
Fibrates	39	54.2%
Fish oil	14	19.4%
ACEi/AT2 antagonists	18	25.0%
Beta blockers	10	13.9%
Calcium channel blockers	3	4.2%
Antiplatelet agents	8	11.1%

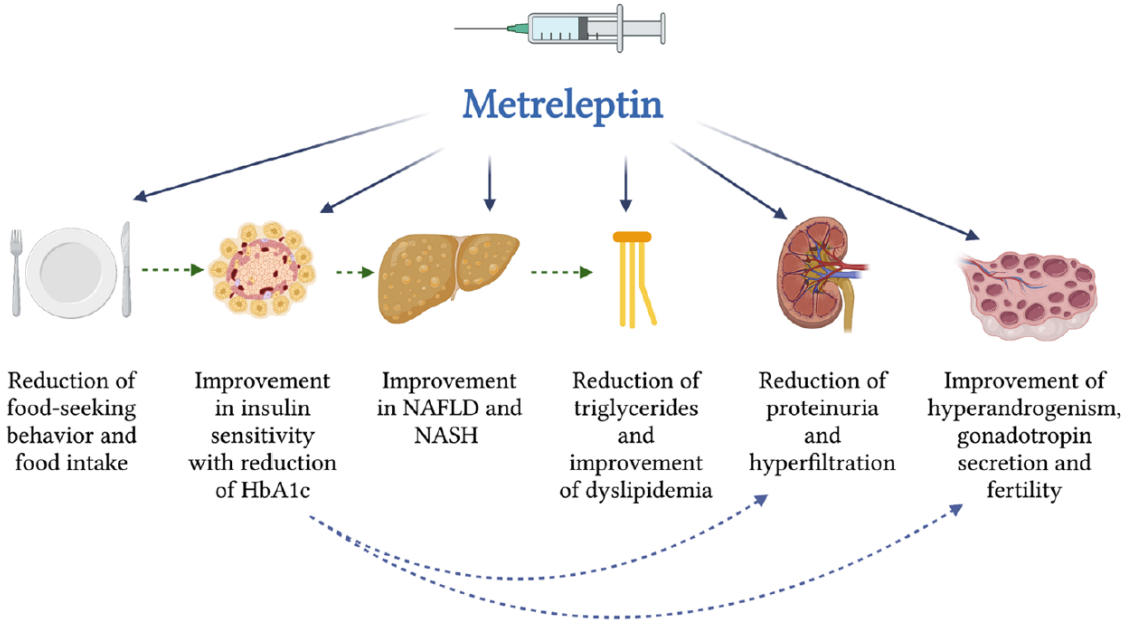
Yang S et al BMC Endocr Disord 2024

Simsir IY et al Diab Obes Metab 2023

TREATMENT

Metreleptin

- In generalized lipodystrophy, metreleptin (with diet) is a first-line treatment for metabolic and endocrine abnormalities (Class I, Level B) and may be considered for prevention of these comorbidities in children. (Class IIb, Level C)
- Metreleptin may be considered for hypoleptinemic (leptin <4 ng/mL) patients with partial lipodystrophy and severe metabolic derangements (HbA1c >8% and/or triglycerides >500 mg/dL). (Class IIb, Level B)



Brown RJ et al JCEM 2016
Calcaterra V et al. Pharmacol Res 2023

METRELEPTIN

JAPAN

March 2013 Metreleptin was approved as replacement therapy to treat the complications of leptin deficiency in patients with both generalized and partial lipodystrophy

FDA

February 2014 Metreleptin was approved as replacement therapy to treat the complications of leptin deficiency in patients with generalized lipodystrophy

EMA & AIFA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

July 2018 and March 2020 was approved as replacement therapy to treat:
-adults and children (>2 years) with generalized lipodystrophy (Berardinelli-Seip syndrome and Lawrence syndrome)
-adults and children (>12 years) with confirmed partial (localised) lipodystrophy (including Barraquer-Simons syndrome), when standard treatments have failed, with poor metabolic control under standard treatments

AIFA

Il trattamento con Myalepta deve essere avviato e monitorato da un operatore sanitario con esperienza nella diagnosi e nella gestione dei disturbi del metabolismo[6]

METRELEPTIN

Indicazioni proposte per l'accesso alla terapia con Metreleptin in pazienti con LD parziale congenita o acquisita, adulti e bambini di età pari o superiore a 12 anni

Hb glicata ≥ 8 % **E/O**

Trigliceridi a digiuno ≥ 500 mg/dl **E**

Almeno una delle seguenti condizioni patologiche aggiuntive:

- NASH/NAFLD/Epatomegalia
- ≥ 1 episodio di pancreatite
- Malattia cardiovascolare e/o cardiomiopatia
- Insufficienza renale (albuminuria e/o proteinuria)
- Insulinemia a digiuno ≥ 30 mcU/ml e/o 300 mcU/ml (durante OGTT)

E

Risposta non adeguata alla terapia convenzionale di supporto (anti-diabetica, ipolipemizzante, anti-ipertensiva, antidolorifica) al dosaggio massimo tollerato

METRELEPTIN

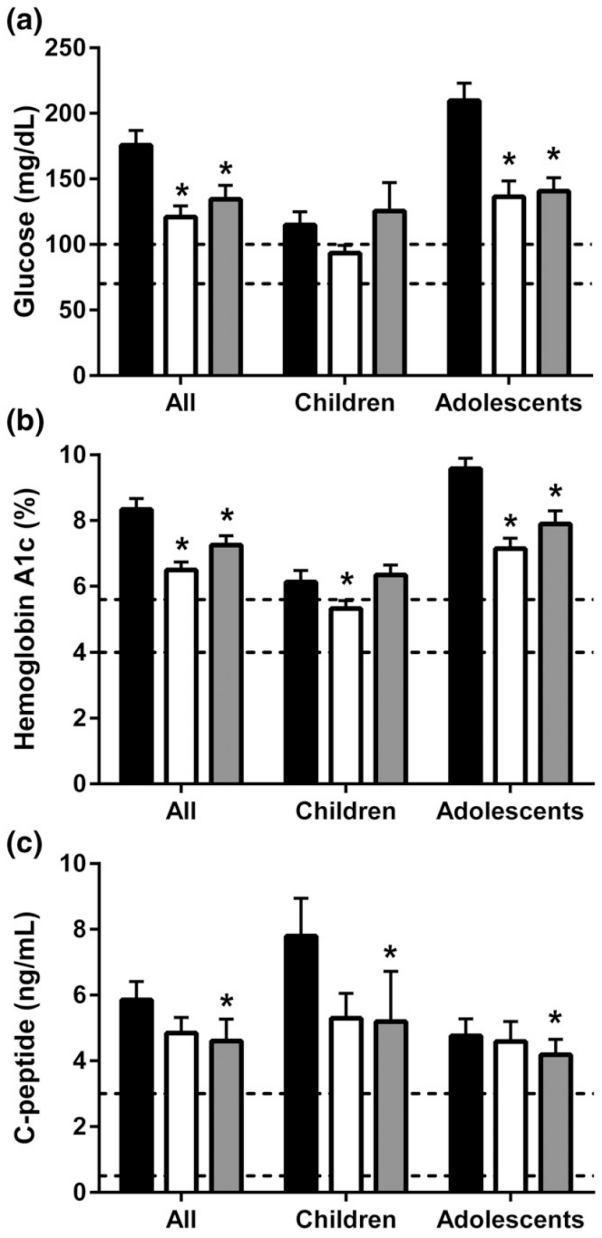
AIFA

Specificare se si tratta di:		
☐ Prima prescrizione (durata 6 mesi)		
☐ Prosecuzione di terapia	☐ durata 6 mesi	☐ durata 12 mesi
Il paziente ha ottenuto un miglioramento clinico, definito da una riduzione dell'HbA1c ≥1.0% e/o dei trigliceridi a digiuno ≥30%.	☐ Si	☐ No
La prosecuzione della terapia a carico SSN è consentita soltanto in caso di miglioramento clinico secondo la definizione sopra riportata.		

METRELEPTIN

Table 1. Baseline Characteristics

Parameter	Children (≤12 Years Old; n = 19)	Adolescents (>12 and <18 Years Old; n = 34)	All Pediatric Patients <18 Years Old (N = 53)
Demographics			
Female sex, n (%)	13 (68)	28 (82)	41 (77)
Age, y	8.0 ± 3.5	15.5 ± 1.8	12.8 ± 4.4
Lipodystrophy type, n (%):			
Acquired generalized lipodystrophy	5 (26)	3 (9)	8 (15)
Congenital generalized lipodystrophy	10 (53)	22 (65)	32 (60)
Familial partial lipodystrophy	1 (5)	7 (21)	8 (15)
Atypical progeria	3 (16)	2 (6)	5 (9)

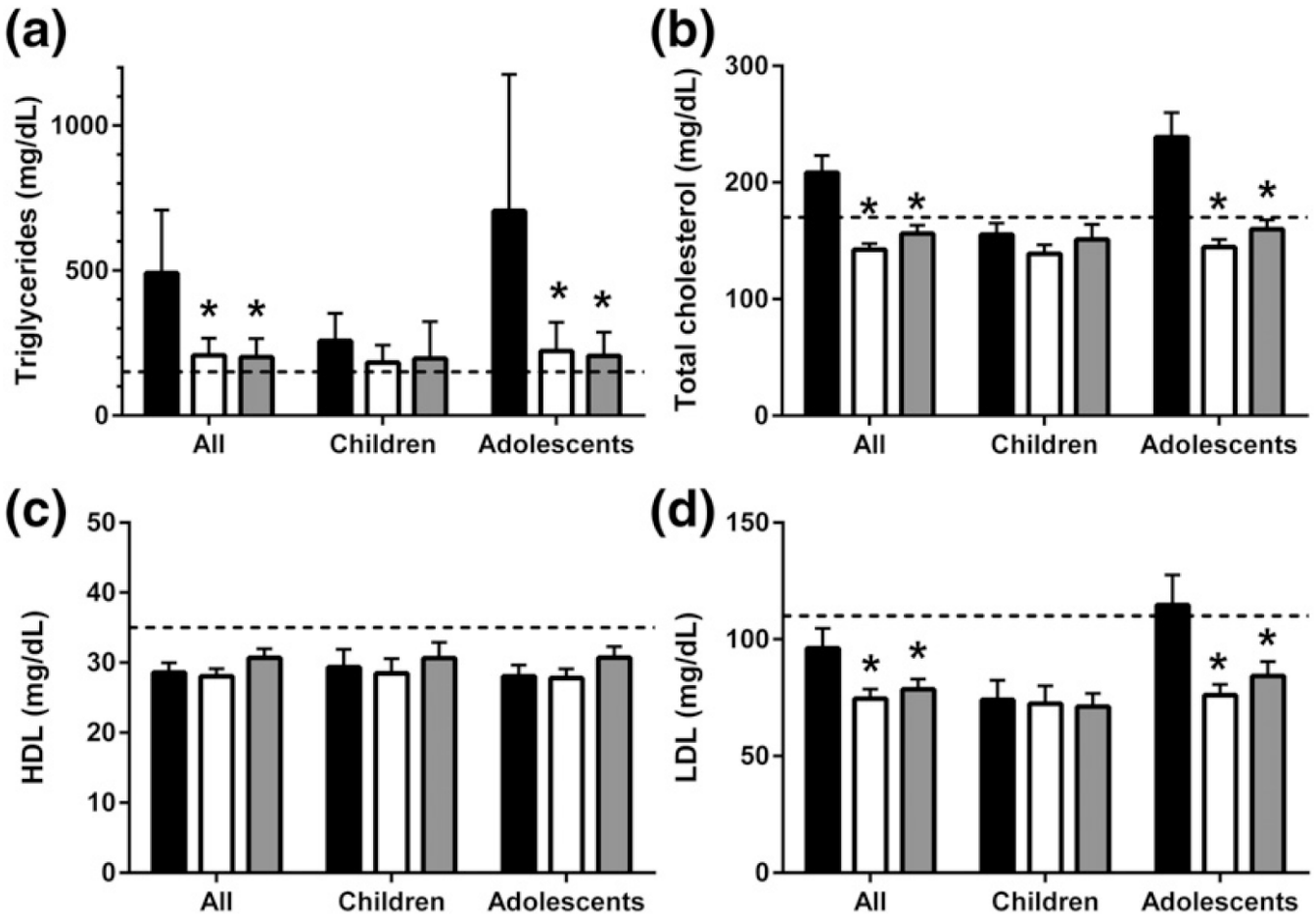


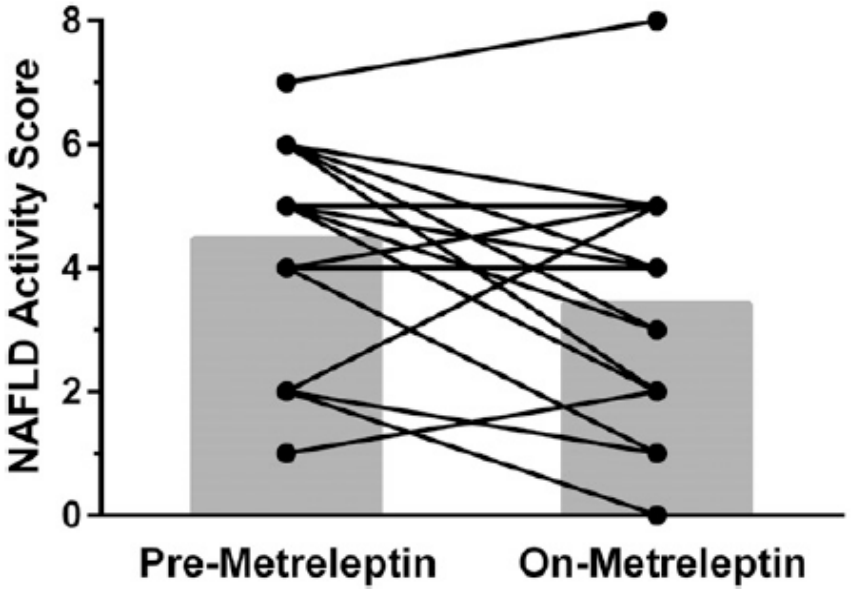
Brown RJ et al JCEM 2017

NO ALTERATION IN GROWTH AND PUBERTY DURING THE TREATMENT

1-5 years of treatment

METRELEPTIN



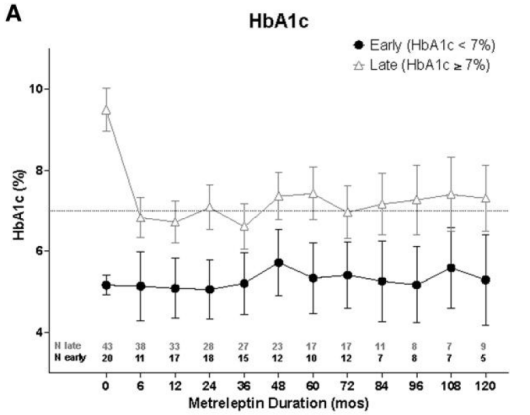


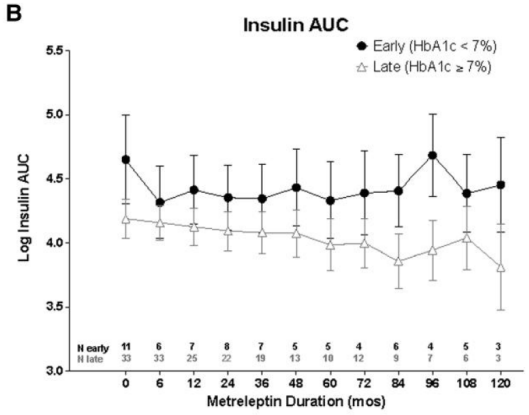
Brown RJ et al JCEM 2017

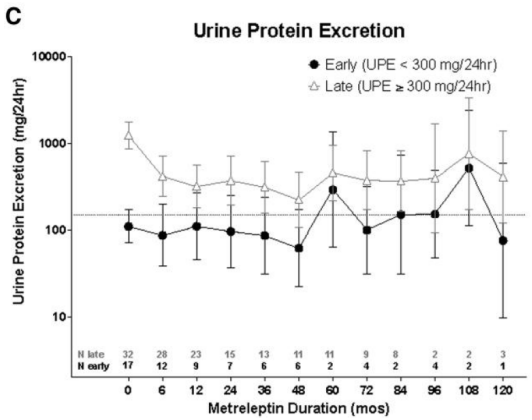
METRELEPTIN

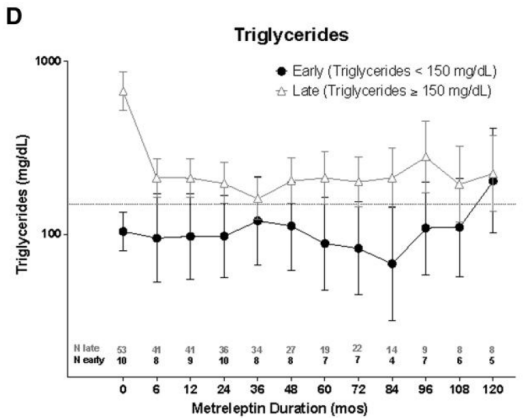
Effects of Metreleptin in Patients With Generalized Lipodystrophy Before vs After the Onset of Severe Metabolic Disease

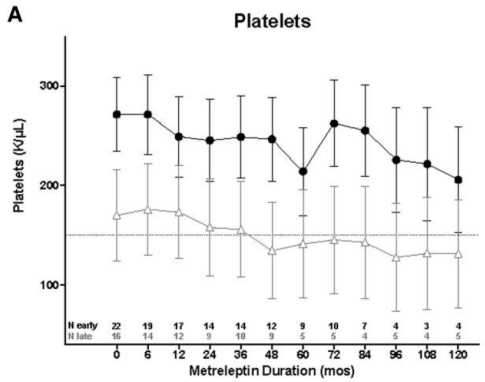
Conclusion: Patients with GLD who initiated metreleptin before the onset of severe metabolic complications had better long-term control of diabetes, proteinuria, and hypertriglyceridemia. Early treatment may also result is less severe progression of liver fibrosis, but further histological studies are needed to determine the effects of metreleptin therapy on liver disease.

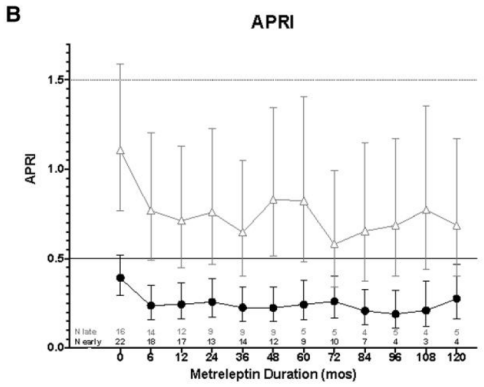


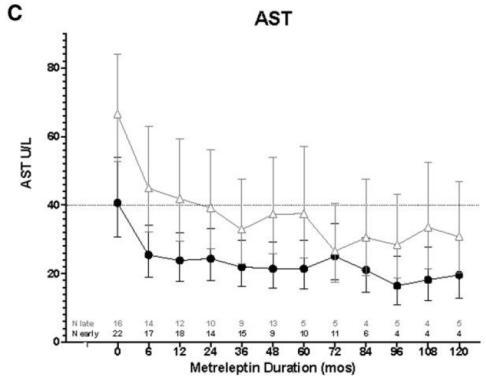


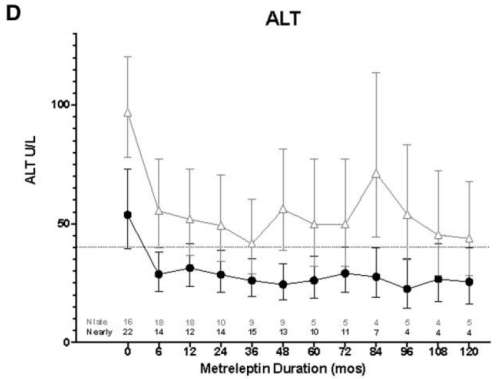












Early (Fibrosis score < 3) Late (Fibrosis score ≥ 3)

Brush M et al. JCEM 2024

Metreleptin for the treatment of progressive encephalopathy with/without lipodystrophy (PELD) in a child with progressive myoclonic epilepsy: a case report

Table 1 Fasting lipid profile before and after starting treatment with metreleptin 0.06 mg/kg/day

Lipid levels (mg/dL)	Age 4 years (no metreleptin)		Age 5 years (baseline before starting metreleptin)	Age 5 years (2 months after starting metreleptin)
	Pre-diet	Post- diet		
Cholesterol				
Total	212	117	129	102
HDL	33	30	29	39
LDL	100	74	74	51
Triglycerides	396	102	121	60

HDL high-density lipoprotein, *LDL* low-density lipoprotein

Improvement liver steatosis
Reduction epileptic seizure

CGL-2

Pedicelli S It J Ped 2020

SAFETY

AE

hypoglycaemia (1:10)
weight loss (17%)
infrequent injection site reactions (erythema, urticaria)
neutralizing antibody activity to leptin
hypophagia
headache
abdominal pain
nausea
alopecia
menorrhagia
weakness

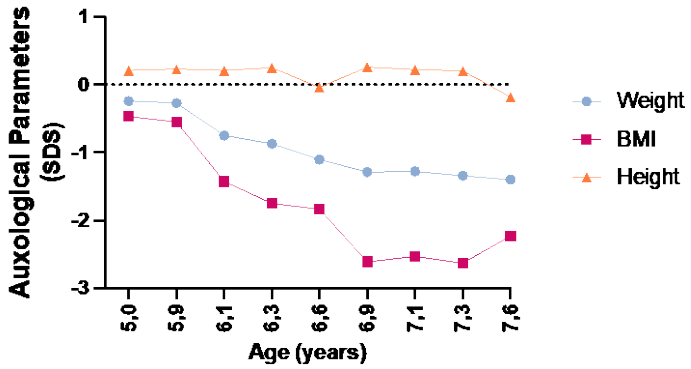
Informazioni cliniche e terapeutiche per la riduzione del rischio nei pazienti

La lipodistrofia è causa di importanti disfunzioni metaboliche e neuroendocrine[4] che portano a iperlipidemia,[1] diabete di difficile controllo,[1] riduzione della risposta immunologica[7] e disfunzione ormonale,[1] tutte condizioni originate da una riduzione della secrezione di leptina.[4,8] Alcuni dei potenziali rischi associati all'uso di Myalepta (o alla sua sospensione nel caso di pancreatite acuta, come indicato più avanti) riguardano le seguenti aree:

- Ipersensibilità
- Pancreatite acuta
- Linfoma
- Ipoglicemia con uso concomitante di insulina e secretagoghi dell'insulina
- Gravidanze non programmate in donne in età fertile
- Perdita di efficacia, possibilmente dovuta alla presenza di anticorpi neutralizzanti, e infezioni serie e gravi secondarie alla presenza di anticorpi neutralizzanti
- Infezioni serie e gravi secondarie alla presenza di anticorpi neutralizzanti e perdita di efficacia, potenzialmente dovuta alla presenza di anticorpi neutralizzanti
- Errori nella somministrazione del medicinale

Questo opuscolo contiene ulteriori indicazioni su questi rischi, inclusi interventi volti, laddove possibile, a minimizzarli e a facilitare il colloquio con il paziente.

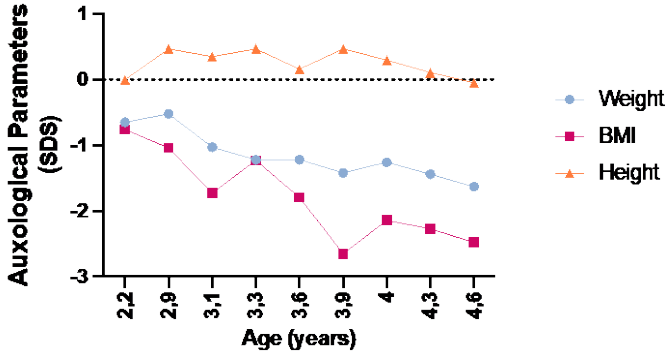
METRELEPTIN



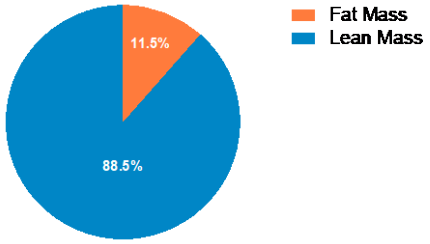
♀

Iperfagia

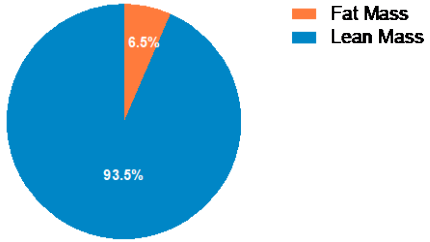
♂



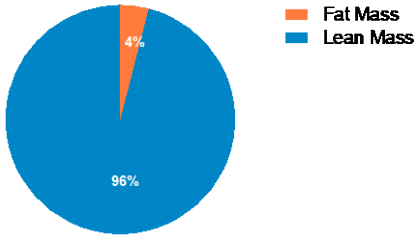
Body Composition V2 BIA



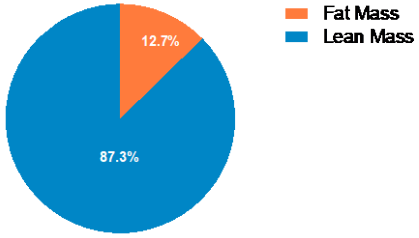
Body Composition V4 BIA



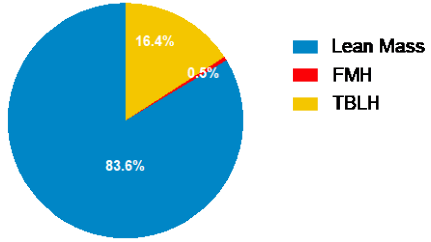
Body Composition V3 BIA



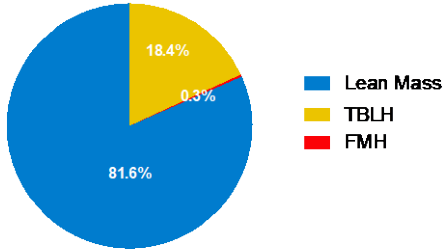
Body Composition V6 BIA



Body Composition V7 DXA



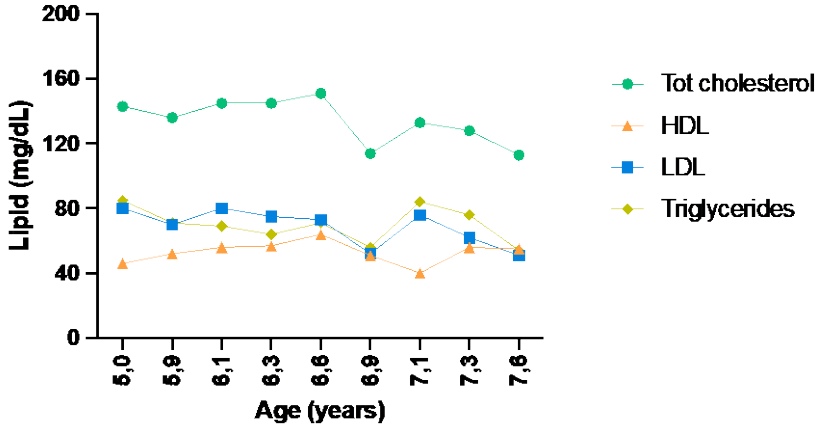
Body Composition V7 DXA



Manuscript in preparation

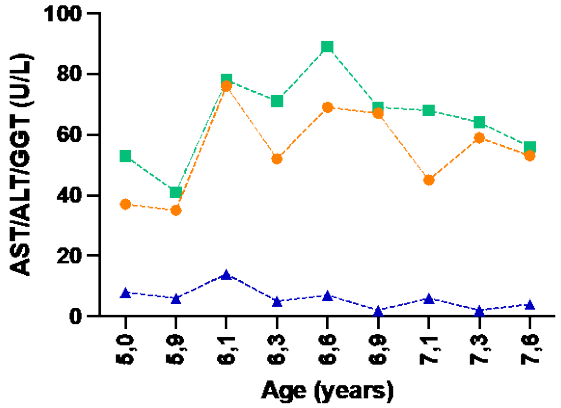
METRELEPTIN

♀



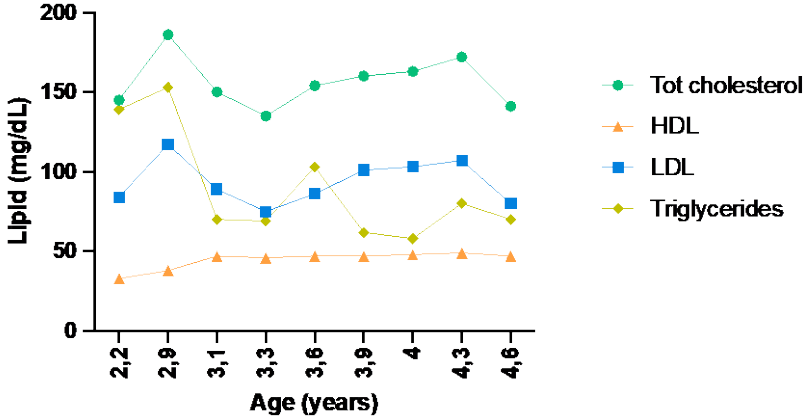
TG ↓

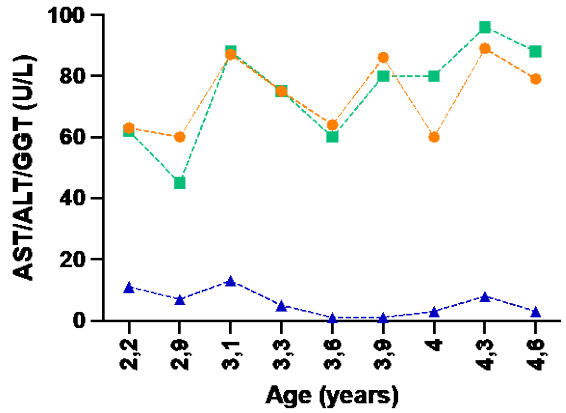
HDL ↑



Iniziale fibrosi al fibroscan (E 5.2 kPa).

♂



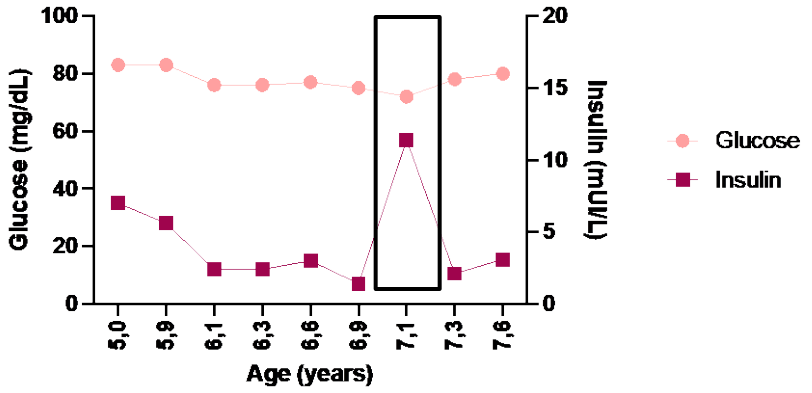


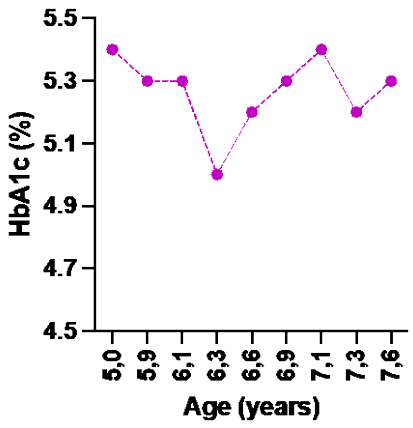
Quadro fibrosi stabile.

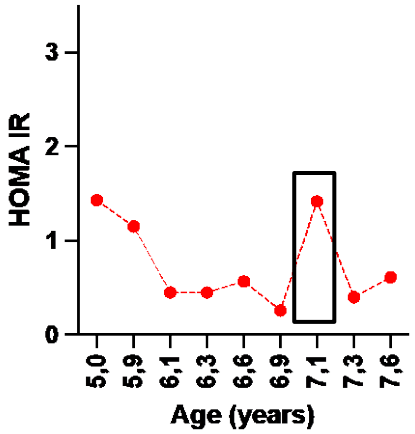
Manuscript in preparation

METRELEPTIN

♀

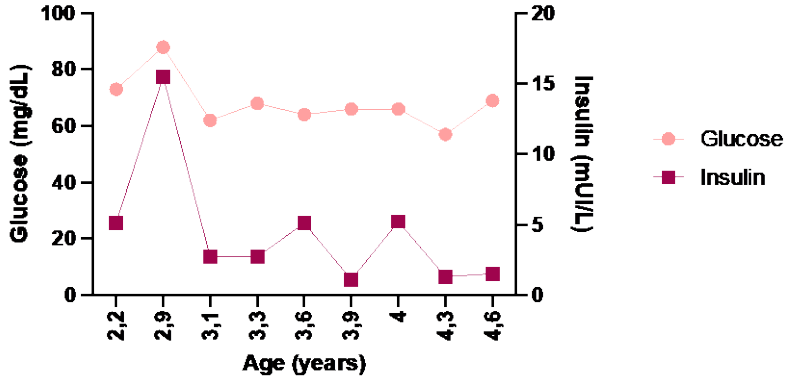


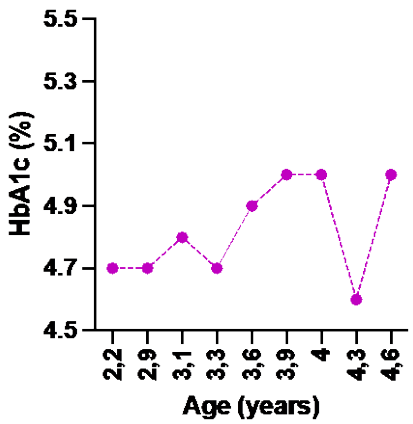


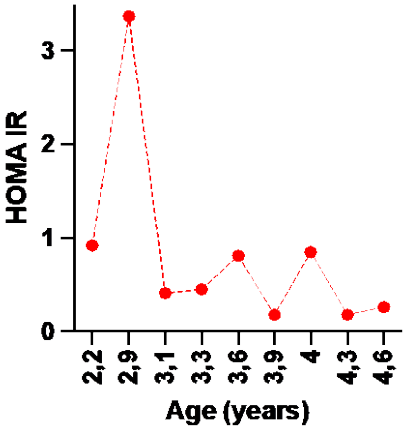


IR

♂



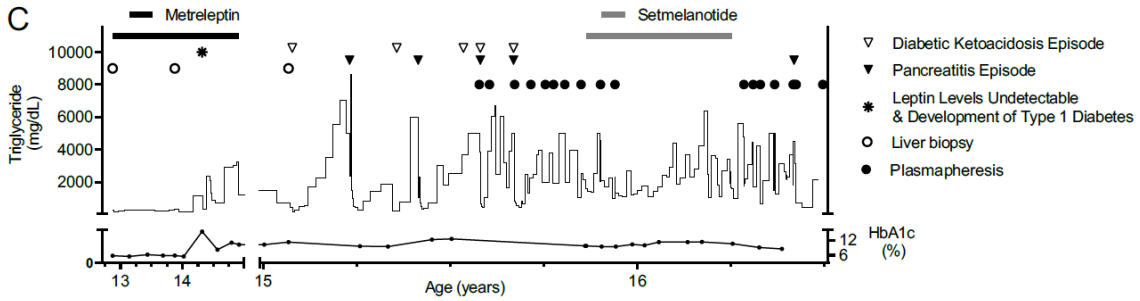




Manuscript in preparation

OTHER TREATMENTS?

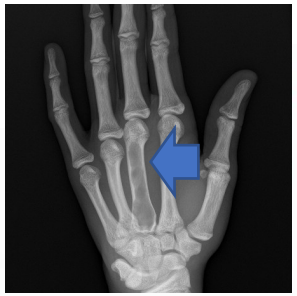
The complicated clinical course in a case of atypical lipodystrophy after development of neutralizing antibody to metreleptin: treatment with setmelanotide



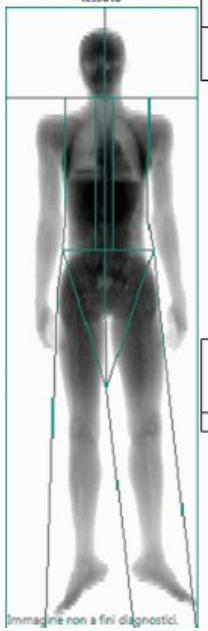
Learning points:

- A patient with atypical lipodystrophy with an initial benefit with metreleptin therapy developed neutralizing antibodies to metreleptin (Nab-leptin), which led to substantial worsening in metabolic control. The neutralizing activity in her serum persisted for longer than 3 years.
- Whether the worsening in her metabolic state was truly caused by the development of Nab-leptin cannot be fully ascertained, but there was a temporal relationship. The experience noted in our patient at least raises the possibility for concern for substantial metabolic worsening upon emergence and persistence of Nab-leptin. Further studies of cases where Nab-leptin is detected and better assay systems to detect and characterize Nab-leptin are needed.

Akinci B et al Endocr Diab Metab Case Rep 2020



Corpo intero Quantificazione del tessuto

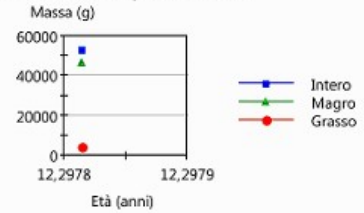


Composizione (Analisi potenziata)

Regione	Tessuto (% grasso)	Centile	Massa totale (kg)	Grasso (g)	Magro (g)	BMC (g)
Gambe	10,4	-	19,25	1.870	16.187	1.188,7
Tronco	5,5	-	26,45	1.406	24.149	892,7
Intero	9,0	-	57,25	4.909	49.404	2.940,5

Italia Diagramma di riferimento: mancano dati di riferimento per la regione Corpo intero [TBLH]. Italia della popolazione di riferimento non supporta Composizione per Pediatrico Corpo intero.

Tendenza della composizione: TBLH



Italia Tendenza: TBLH (Analisi potenziata)

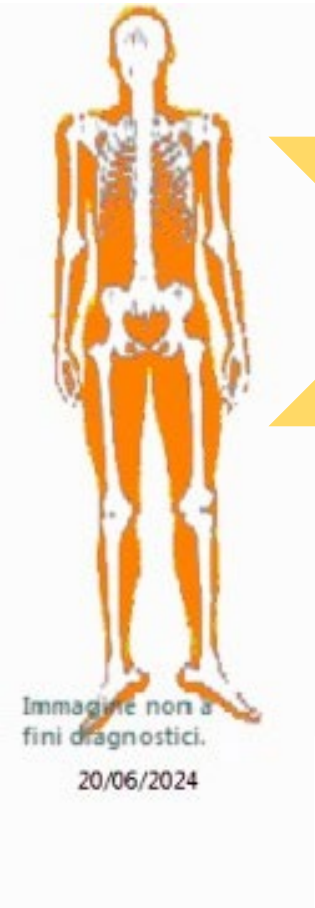
Data di misurazione	Età (anni)	Tessuto (% grasso)	Centile	Massa totale (kg)	Tessuto (g)	Grasso (g)	Magro (g)	BMC (g)	Senza grasso (g)
20/06/2024	12,2	8,2	-	53,25	50.699	4.158	46.541	2.546,4	49.088

LEPTINA < 0.2 µg/l
ADIPONECTINA 0.2 µg/ml

Variante patogenetica c.589-2A>G in omozigosi nel gene *AGPAT2* (CGL1)
Variante patogenetica c.424G>A (p.Val142Ile) nel gene *TTR*
Variante probabilmente patogenetica c.202G>A (p.Val68Met) nel gene *G6PD*
Variante emoglobinica *HbC*

Unpublished data

METRELEPTIN 3 mg/die (1/2 dose)



FGM
INS basal bolus
(1.7 UI/Kg/die)

GLC 800 mg/dl
HbA1c: 14.5%
Chetoni: 0.5 mmol/L
C-pept: 1.8 ng/ml
autoAb negativi

TG 300 mg/dl (>95°)

FGM
Stop INS ai pasti
⬇ INS basale
(in 3 die per IPOGLC)
⬇ METF

GLC 73 mg/dl
HbA1c: 6.5%
INS: 48.9 mcUI/ml
C-pept: 3.41 ng/ml
TIR 63%

TG 161 mg/dl (>95°)

Stop FGM
Stop METF

GLC 89 mg/dl
HbA1c: 5.4%
INS: 14.2 mcUI/ml
C-pept: 2.19 ng/ml
TIR 100%

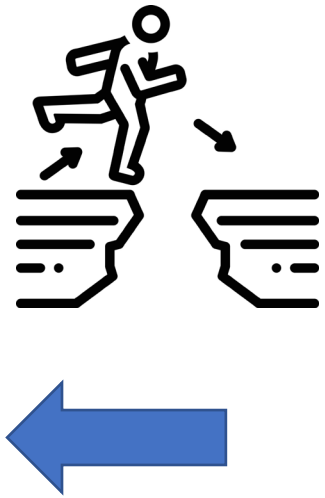
TG 80 mg/dl (50-75°)

MENARCA

Unpublished data

CHALLANGES

	Diet and exercise	Glucose-lowering medications	Lipid-lowering and CV medications	LD-specific therapy	Other
Treatment type	• Well-balanced, low-fat, low-calorie diet • Exercise is encouraged in the absence of specific contraindications	• Metformin • Insulin • Thiazolidinediones • GLP-1 receptor agonists • SGLT2i	• Statins • Fibrates • Omega-3 fatty acids • ACE inhibitors • ARBs • Beta-blockers	• Metreleptin	• Cosmetic surgery • Counselling
Objectives	• Cornerstone of LD treatment • To help manage weight gain and control calorie and fat intake	• Glycemic control	• Long-term cardiovascular risk reduction	• Only currently approved specific treatment for LD (to treat complications of leptin deficiency adjunct to diet) • In PL, often used only once SOC therapies are considered no longer effective	• May help patients feel better about their physical appearance and may offer an improved QoL
Challenges and considerations	• Considered burdensome for patients. Restrictive long-term diets are not easy to maintain • Dietary restriction challenging in hyperphagic patients	• Patient adherence to therapy • High need for careful monitoring especially patients requiring high-doses of insulin • Challenges with administering in patients with GL due to lack of subcutaneous fat	• Patient adherence to therapy	• Often used only once SOC therapies are considered no longer effective • Challenges with administering in patients with GL due to lack of subcutaneous fat • Restricted access in some regions (e.g., REMS program)	• Cosmetic surgery rarely mentioned by participants as a treatment option.



Patni N et al Orphanet J Rare Dis 2024

TAKE HOME MESSAGES

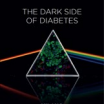
Treatment with metreleptin has been approved for generalized (< 2 years) and partial lipodystrophy (< 12 years).

Substitutive treatment with metreleptin improves metabolic alteration, reduces disease progression and the mortality risk.

Many efforts are needed to understand the best diet regimens and treatments of comorbidities when metreleptin cannot be prescribed.

Complex and tailored treatment regimens are needed for patients.

A multidisciplinary approach is needed to improve QoL and long-term care.



MINISTERO DELL' ISTRUZIONE, DELL'UNIVERSITÀ E DELLA RICERCA

EuroTransBio

Fondazione CARIPLO

Divisione di Pediatria,
Dipartimento di Scienze della Salute
UPO, Novara

Simonetta Bellone
Ivana Rabbone

Alice Monzani
Cristina Partenope
Silvia Savastio

Valentina Antoniotti

Valentina Mancioppi

Dipartimento di Medicina Traslazionale
Università del Piemonte Orientale
Novara

Nicoletta Filigheddu

Simone Reano
Tommaso Raiteri

Marcello Manfredi

Laboratorio di Genetica,
Dipartimento di Scienze della Salute
UPO, Novara

Mara Giordano
Simona Mellone

Chimica degli Alimenti
Dipartimento di Scienze del Farmaco
UPO, Novara

Marco Arlorio
Jean Daniel Coisson
Monica Locatelli

Microbiologia,
DISAFA
Università di Torino

Luca Simone Cocolin
Ilario Ferrocino

DISIT, DISSTE
UPO, Alessandria e Vercelli

Elisa Bona
Maria Cavaletto

Immunologia
Patologia Generale
Dipartimento di Scienze della Salute
Università del Piemonte Orientale
Novara

Annalisa Chiocchetti
Giuseppe Cappellano
Umberto Dianzani
Davide Raineri
Alessia Provera
Salvatore Sutti

NUTRICIA RESEARCH FOUNDATION

Endocrinologia,
nto di Medicina Traslazionale
UPO, Novara

Gianluca Aimaretti

Marina Caput0
Tommaso Daffara
Alice Ferrero
Paolo Marzullo
Grazia Mauri
Maria Teresa Samà
Marco Zavattaro

Martina Borrini
Leonardo Bighetti
Beatrice Cavigiolo
Carola Ciamparini
Samuele Costelli
Luisa Costantini
TGiulia Marsan
Edoardo M. Mollero
Chiara Mele
Rosa Pitino
Francesca Pizzolitto
Martina Romanisio
Sara Sturnia
Davide Vimercati

Alessandro Antonioli
Jessica Baima
Daniele Spadaccini
Sabrina Tini

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani
NODES
mipaaf Ministero delle politiche agricole alimentari e forestali
REGIONE PIEMONTE
PSR

UPO UNIVERSITÀ DEL PIEMONTE ORIENTALE