LIPODYSTROPHIES

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Endo-ERN
European Reference Network on Rare Endocrine Conditions

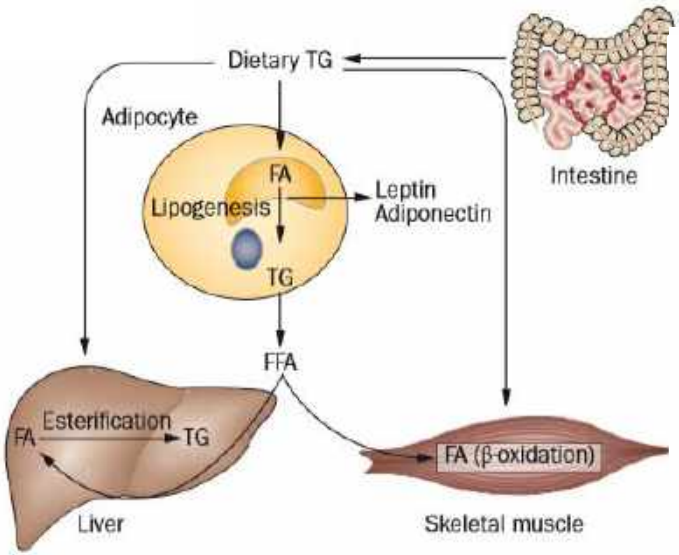
European Consortium of lipodystrophies

DEFINITION AND MECHANISMS

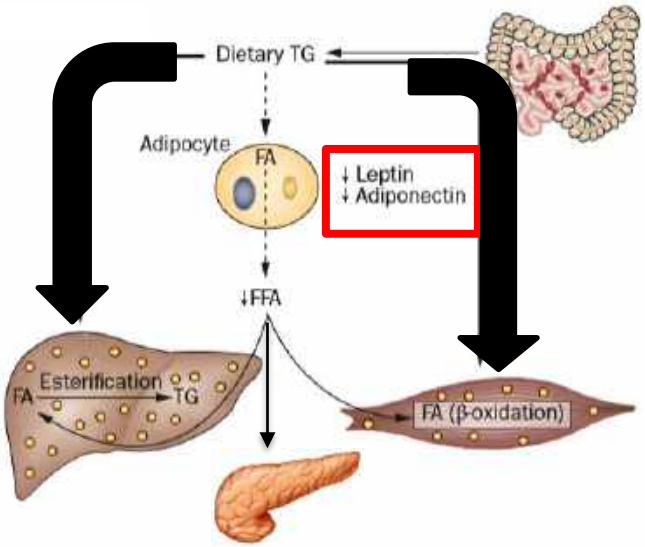
Lipodystrophies are heterogeneous disorders characterized by **complete or partial absence of adipose tissue** resulting in **defective metabolism of fat**, **reduced protective factors** (leptin) and **ectopic lipid storage**.

Prevalence: 3.07/1.000.000

NORMAL



LIPODYSTROPHY



Inadequate fat tissue storage capacity

Leptin deficiency Hyperphagia

Failure of buffering lipids

Ectopic storage of fat

Acquired and inherited lipodystrophies, Garg et al 2004

Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges; Chiquette et al 2017

Leptin deficiency and ectopic lipid storage

Loss of adipose tissue

Leptin deficiency and ectopic lipid storage

LEPTIN DEFICIENCY + **ECTOPIC LIPID STORAGE**

↑ **Food Intake**

Energy Expenditure (?)

Metabolic Effects

- ↓ Insulin-sensitivity, β cell disf.
- ↓ Glucose uptake
- ↑ Hepatic glucose production
- ↑ Liver Trigl. Synthesis

Reproductive effect

Hypogonadotropic hypogonadism, loss of LH-pulsatility, amenorrhea

Immunological defects

↓

INSULIN RESISTANCE/DIABETES

HYPERTRIGLYCERIDEMIA

HEPATIC STEATOSIS

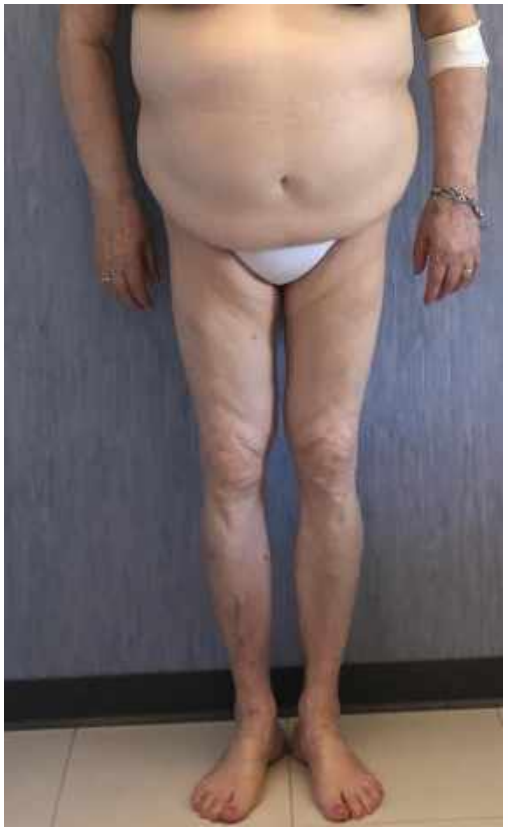
PCOS/INFERTILITY

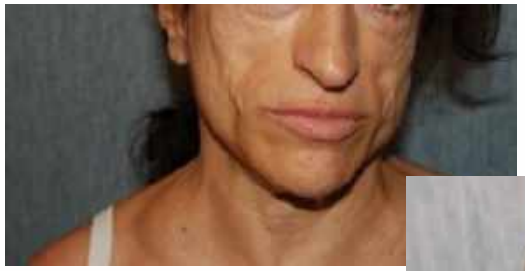
Modified from: Farooqi et al, J Endocrinol 2014; Moon et al, Endocrine Reviews 2013

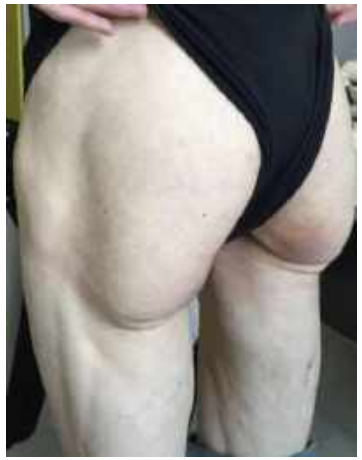
Clinical Characteristics That Raise Suspicion for Lipodystrophy

Core clinical characteristic for lipodystrophy:

Loss of subcutaneous body fat in a partial or generalized fashion







Clinical Characteristics That Raise Suspicion for Lipodystrophy

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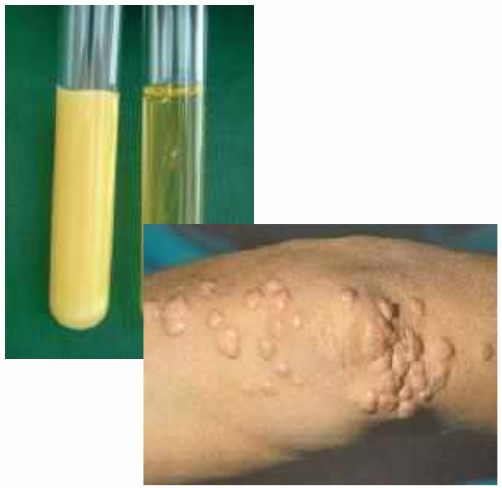
Supportive clinical characteristics for lipodystrophy

- Prominent muscularity and phlebomegaly (enlarged veins) in the extremities, umbilical hernia
- Pseudo-acromegaloid appearance, Progeroid appearance, Cushingoid appearance
- Diabetes with evidence of severe insulin resistance (high doses of insulin, Acanthosis nigricans, PCOS or PCOS-like symptoms)
- Presence of hypertriglyceridemia
- Evidence of hepatic steatosis or steatohepatitis



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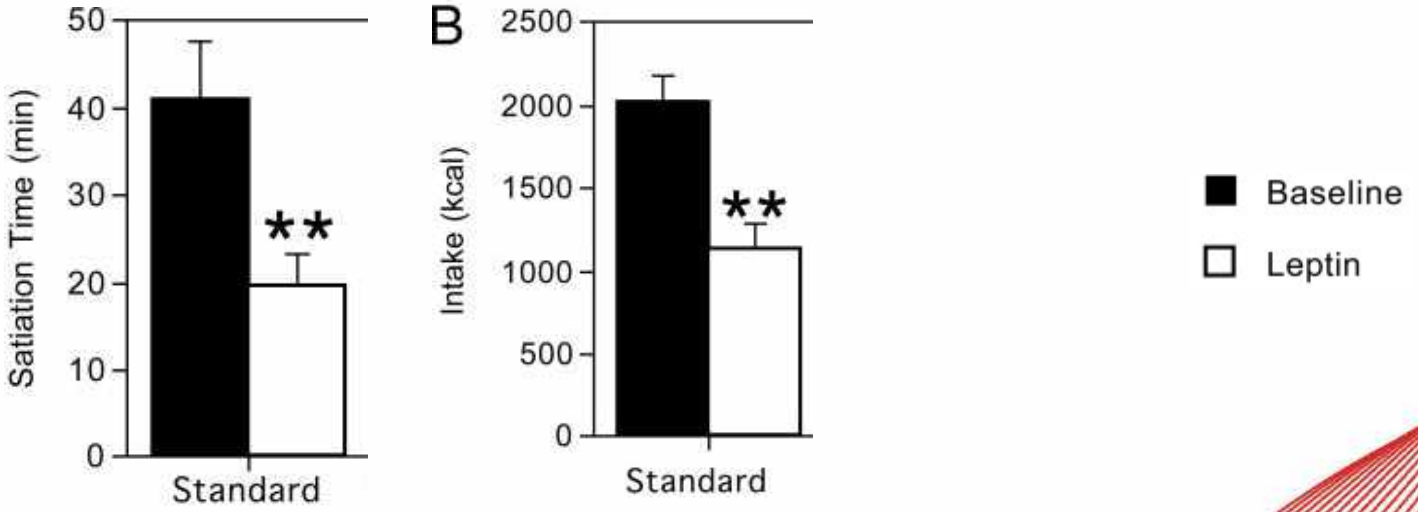
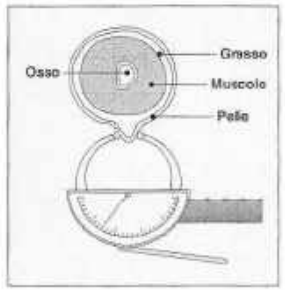
- **Disproportionate hyperphagia (cannot stop eating, waking up to eat, fighting for food)**

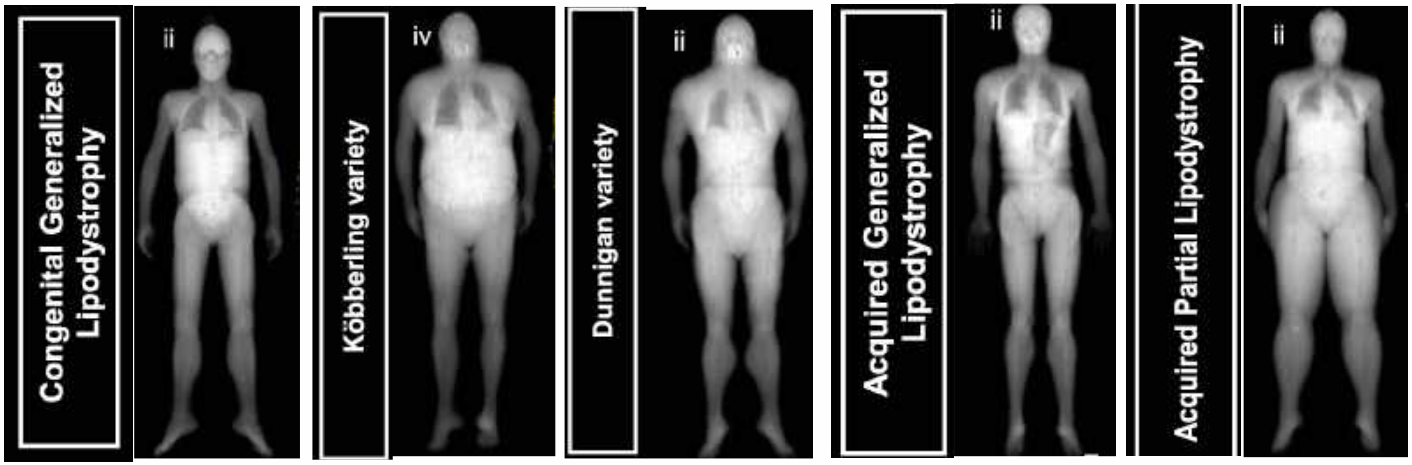


McDuffie J Clin Endocrinol Metab 2004

How to measure? Plicometry and DEXA



Plicometry

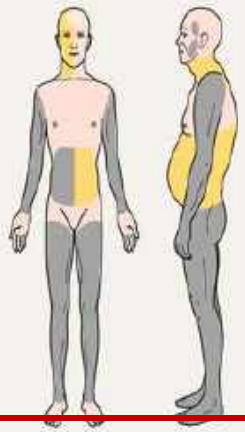
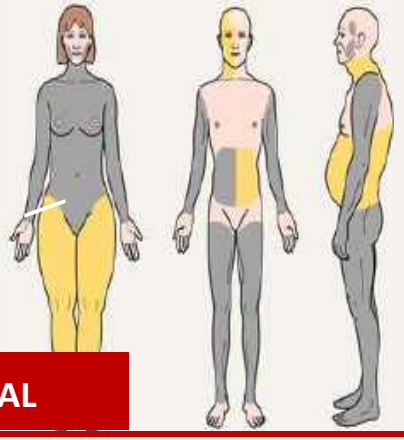


Dual energy X-ray absorptiometry

Trunk fat / Lower limbs fat	Cut-Off	Sensitivity	Specificity
Subscapular/calf skinfolds (Kob index)	3.477	89 %	84 %
Trunk fat mass / Lower limbs fat mass (Kg)	2.153	89 %	78 %
Trunk fat mass / Lower limbs fat mass (%)	1.282	81 %	87 %

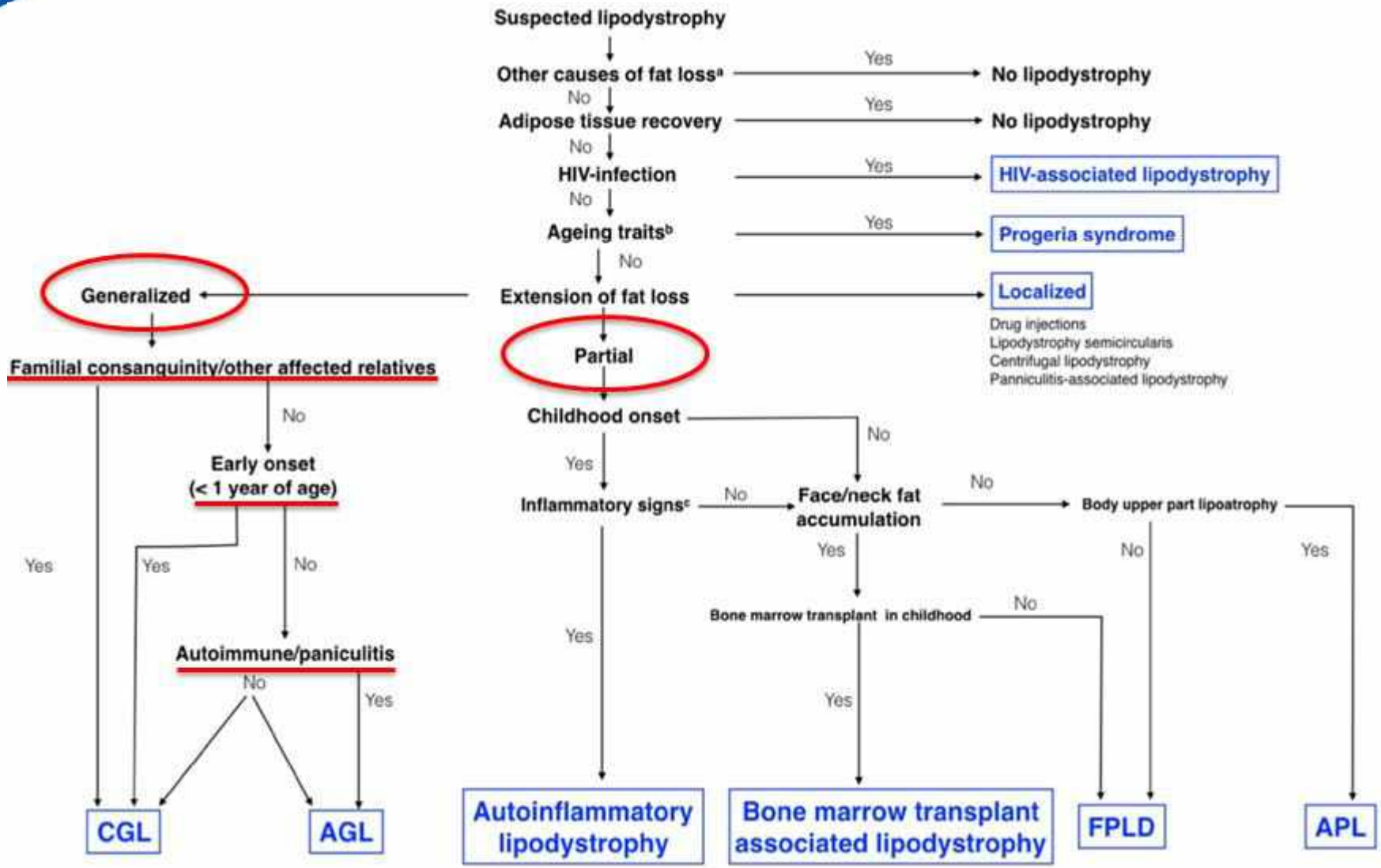
Meral et al, Diabetes Care 2018 – Guillin Amarelle et al, Endocrine 2016

CLASSIFICATION

	GENETIC	ACQUIRED
GENERALIZED	 AGPAT2, BSCL2, PTRF, CAV1, PIK3R1, POLD1,KCNJ6, BANF1,ZMPSTE24, SPRTN, ERCC6,ERCC8, LMNA	 ACQUIRED GENERALIZED LD (LAWRENCE SYNDROME)
PARTIAL	 LMNA, PPARG, PLIN1, CIDEC, LIPE, AKT2, CAV1, FBN1,WRN/RECQL2, PCYT1A, RECQL3, POLR3A, PSMB8	 -HIV-ASSOCIATED LIPODYSTROPHY -ACQUIRED PARTIAL LD (BARRAQUER-SIMONS SYNDROME) -LD ASSOCIATED WITH TOTAL BODY IRRADIATION AND HEMATOPOIETIC STEM CELL TRANSPLANT -LOCALIZED LD (DRUG INJECTIONS, PANNICULITIS)

Modified from diagnosis and treatment of lipodystrophy: a step by step approach. Araujo-Vilar D and Santini F. JEI 2018

LIPODYSTROPHY DIAGNOSIS



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CONGENITAL GENERALIZED LIPODYSTROPHY

	n	years
AGE AT SYMTOMS ONSET (YEARS)	64	19 (15.6-22-3)
AGE AT DIAGNOSIS (YEARS)	64	37.4 (33-41.6)
DELAY IN DIAGNOSIS (YEARS)	62	17.8 (14-21.7)

NATURAL HISTORY STUDY OF LIPODYSTROPHY: DIAGNOSTIC DELAY

Eldin AJ et al, Poster, Endocrine Society Meeting 2019

NOVEMBER 2018

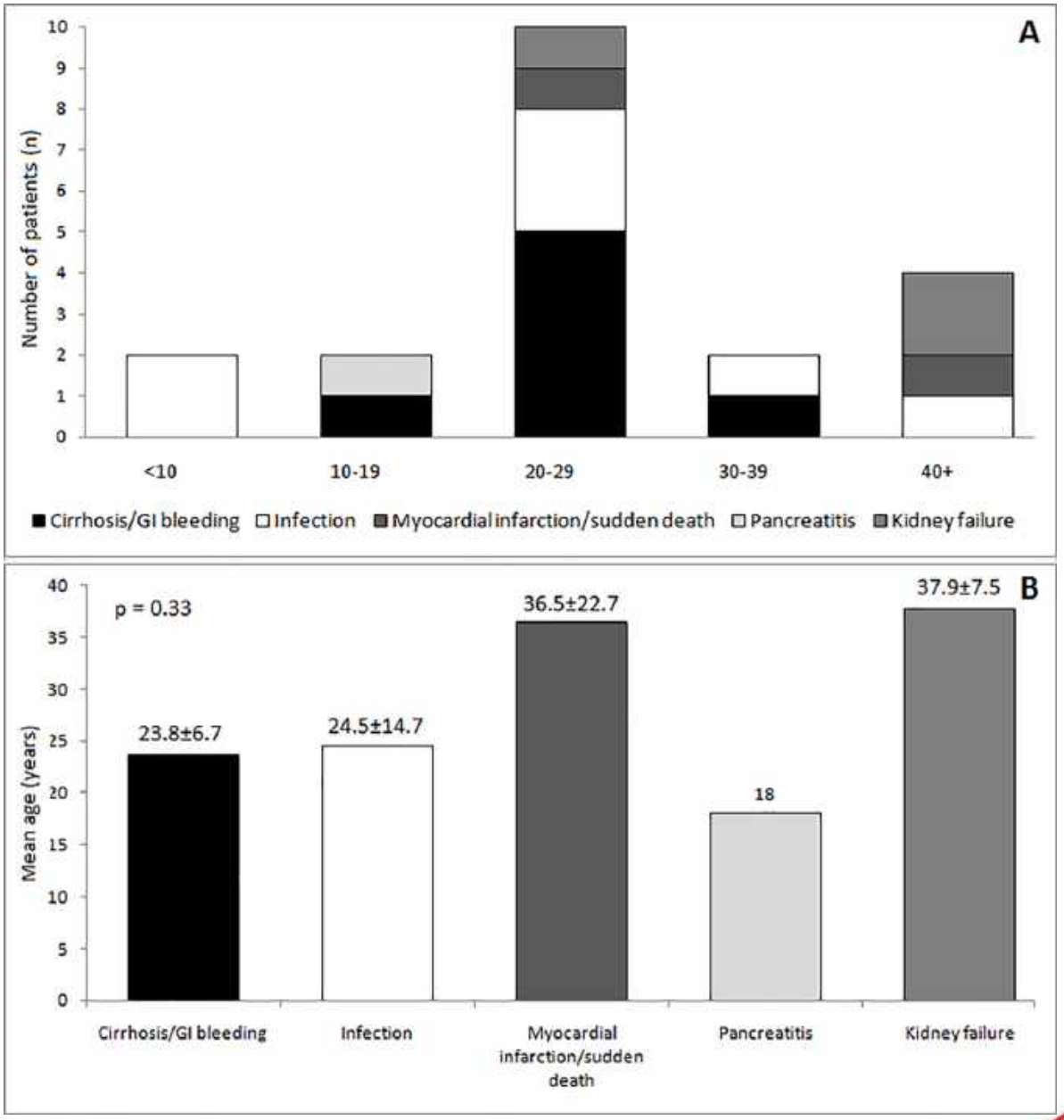
DIAGNOSIS OF CGL (R159C) WITH HEPATIC STEATOSIS, DM2 WITH DIABETIC RETINOPATHY AND NEPHROPATHY, HYPERTENSION AND HYPERTENSIVE HEART DISEASE, HYPERTRIGLYCERIDEMIA AND BONE CYSTS

MARCH 2019

MASSIVE MYOCARDIAL INFARCTION AND ACUTE HEART FAILURE; DESPITE TRANSCUTANEOUS REVASCULARIZATION SHE DEVELOPED PROGRESSIVE CARDIAC INSUFFICIENCY AND KIDNEY FAILURE AND DIED IN THE INTENSIVE CARE UNIT

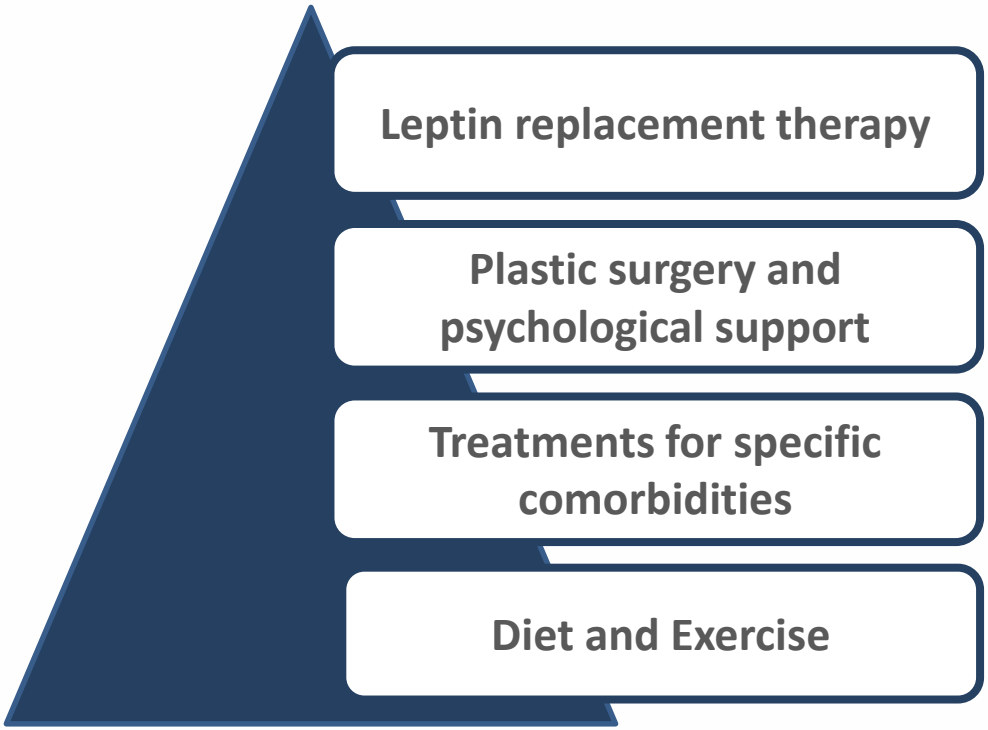
CAUSES OF DEATH IN PATIENTS WITH CGL

20 patients
(12 female and 8 male)



Causes of death in patients with Berardinelli-Seip congenital generalized lipodystrophy, Lima et al Plos One 2018

Treatment of Lipodystrophy Syndromes



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In Febraury 2014 Metreleptin was approved by **FDA** in patients with generalized LD

In July 2018 Metreleptin was approved by **EMA** for**:**

- CGL and AGL (> 2 yrs)
- FPLD2, APL (>12 yrs), who have failed to achieve adequate metabolic control with standard treatment

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AILIP
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GRAZIE PER L'ATTENZIONE