



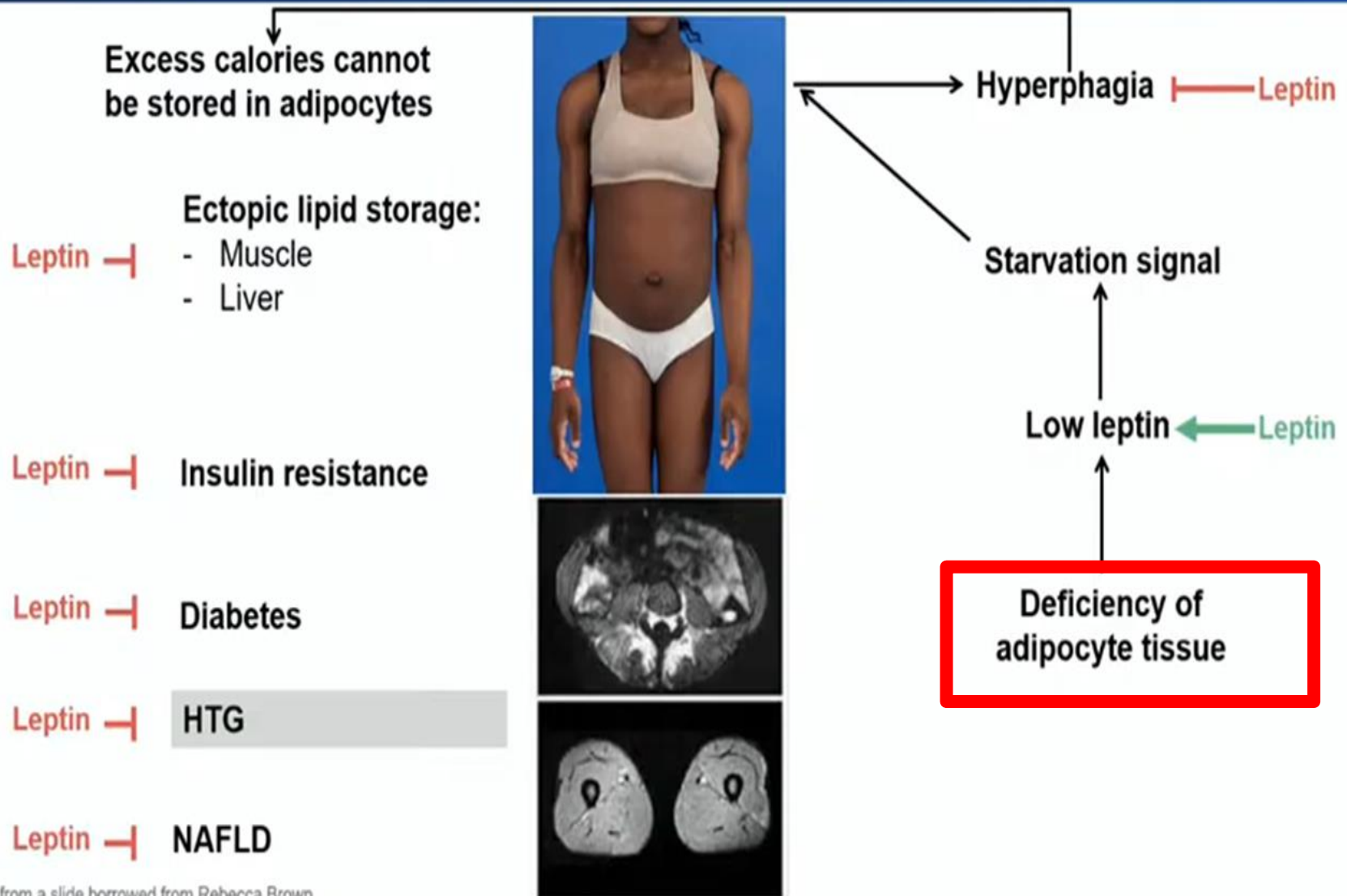
Juvenile Dermatomyositis and AGL

Lipodystrophic syndromes

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Pathophysiology of Generalized Lipodystrophy and Leptin



Loss of sc fat

- Primary event
- Ectopic storage of fat

Severe hypertriglyceridemia

- Acute pancreatitis

Heart disease

- Atherogenic lipid profile
- Atherosclerosis
- Cardiomyopathy
- Arrhythmias

Liver disease

- Increased *de novo* lipogenesis
- MAFLD
- MASH
- Cirrhosis

Neuromuscular disease

- Bone cysts
- Myopathy

High mortality

- Cardiovascular disease
- Sepsis
- Liver disease
- Kidney disease



Leptin deficiency

- Hyperphagia
- Core pathophysiology leading to metabolic abnormalities

Severe insulin resistance

- Poorly controlled diabetes
- Complications of diabetes

Kidney disease

- Proteinuria
- End stage renal disease

Reproductive abnormalities in females

- Failure in puberty progression
- Hyperandrogenism
- Polycystic ovaries
- Infertility

Autoimmunity in acquired cases

- Autoimmune hepatitis
- Glomerulonephritis

Poor quality of life

- Low self esteem
- High rates of depression and anxiety
- Attention deficit problems
- Fatigue
- Pain

WHY IS IT IMPORTANT TO DIAGNOSE LIPODYSTROPHY ?

- UNDERSTAND THE REAL PREVALENCE OF THE DISEASE (REGISTRY)
- LIPODYSTROPHIES MAY BE CONFUSED WITH OTHER ENDOCRINE DISORDERS:
ACROMEGALY, CUSHING, ANOREXIA, PCOS
- IS POSSIBLE A GENETIC DIAGNOSIS
- METABOLIC COMPLICATIONS ARE MORE DIFFICULT TO BE TREATED AND
PREVENTIVE STRATEGIES SHOULD BE ADOPTED
- PATIENTS MAY FIND A UNIFYING ANSWER TO THEIR MULTIPLE SYMPTOMS
- HIGH SOCIAL COSTS (INCLUDING STIGMATISATION) RELATED TO THE DISEASE
- PATIENTS NEED A DEDICATED MULTIDISCIPLINARY SUPPORT TEAM
- SPECIFIC THERAPIES ARE NOW AVAILABLE

Lipodystrophy associated comorbidities

Key metabolic features

- Severely elevated triglycerides
- Severe insulin resistance
- Ectopic lipid deposition
- Progression to poorly controlled diabetes, complications of diabetes

- Hyperphagia

Liver

- Hepatic steatosis
- Hepatomegaly
- Steatohepatitis
- Cirrhosis

Kidney

- Proteinuric renal disease
- Glomerulonephritis

Other general

- Chronic pain
- Mood disturbances

Heart

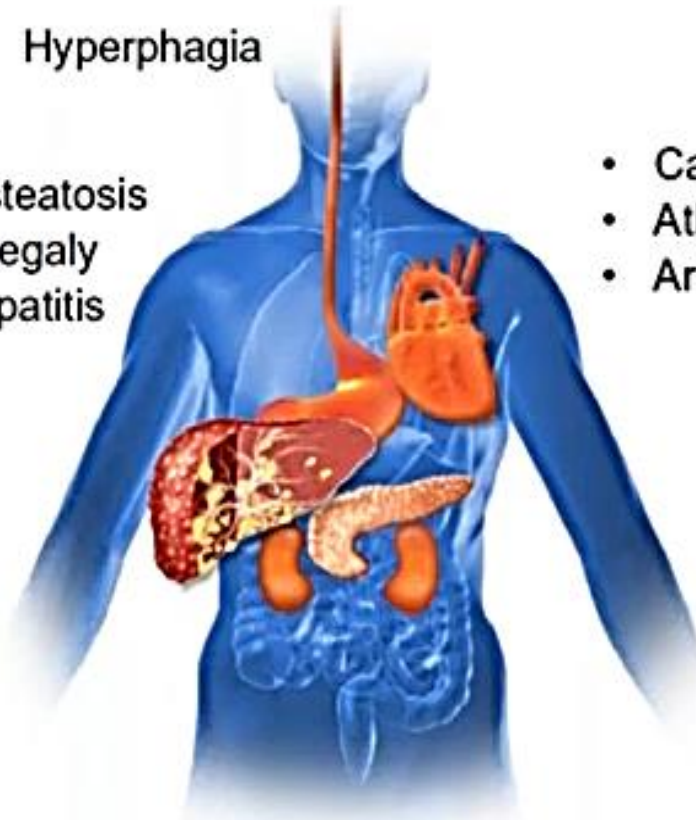
- Cardiomyopathy
- Atherosclerosis
- Arrhythmias

Pancreas

- Episodes of pancreatitis

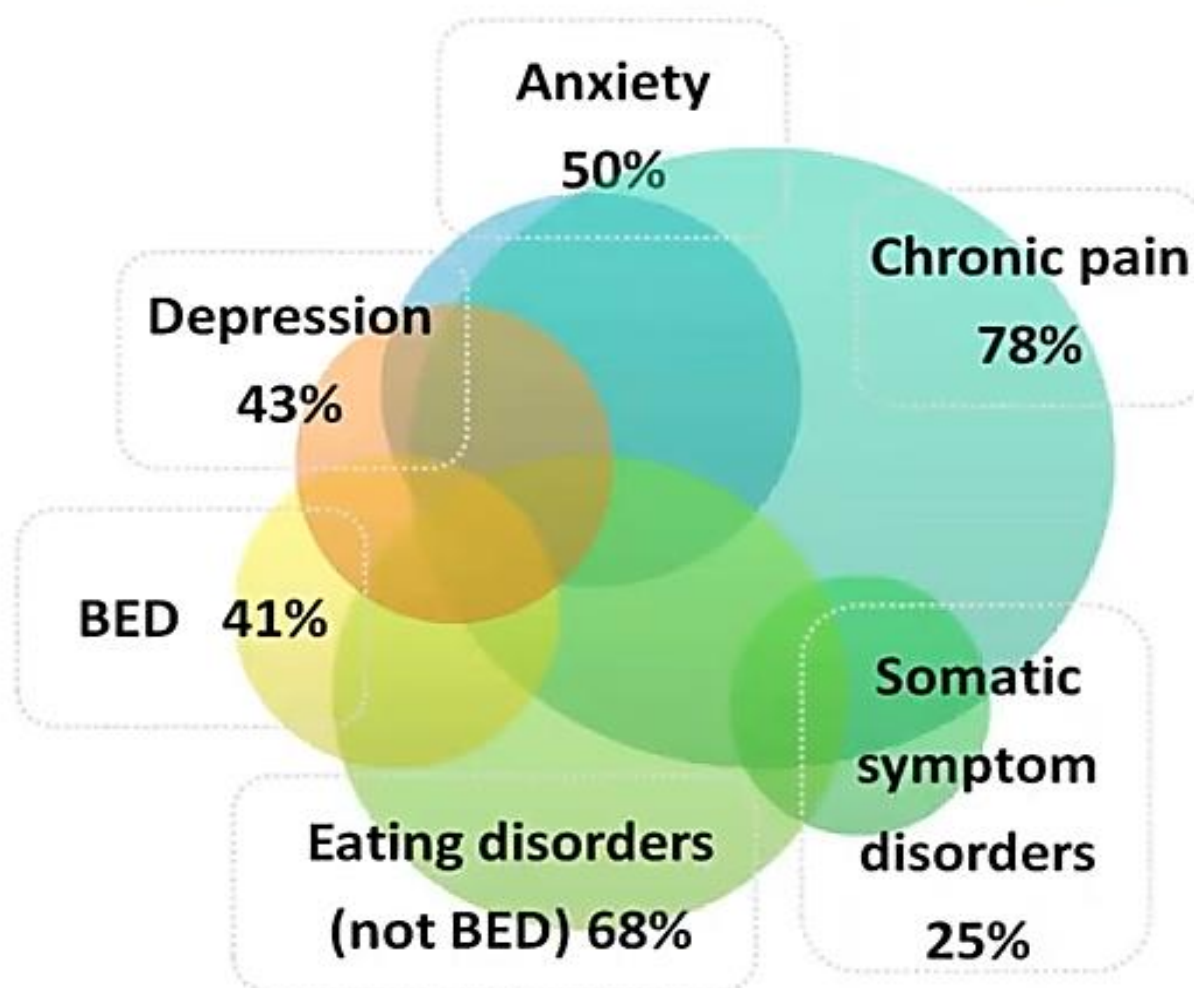
Reproductive

- Infertility
- Hyperandrogenism
- Polycystic ovaries



Psychopathological and psychiatric evaluation of patients affected by lipodystrophy

Calabrò, Ceccarini, Calderone, Lippi, Piaggi, Ferrari, Magno, Pedrinelli, Santini
Eating and Weight Disorders -2019



LIPODYSTROPHY

(LIPODYSTROPHY = LIPOATROPHY)

A CONDITION RESULTING IN FAT TISSUE LOSS WITHOUT EVIDENCE OF NUTRITIONAL DEPRIVATION OR CATABOLISM

MAY BE ASSOCIATED WITH “METABOLIC SYNDROME”

LIPODYSTROPHY IS NOT A UNIQUE DISEASE

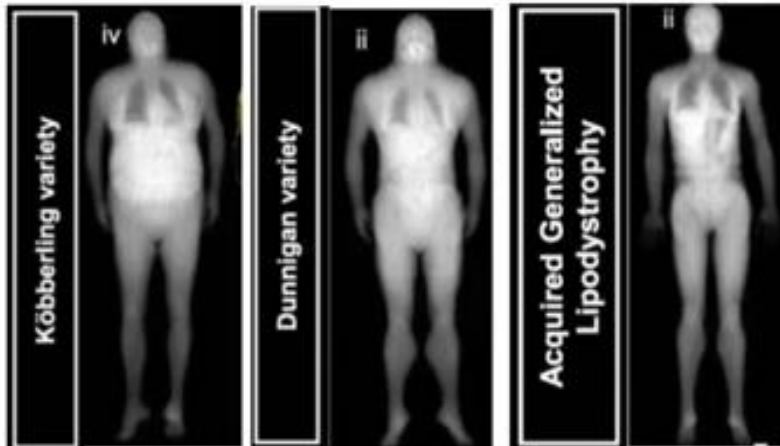
EXISTIMATED PREVALENCE: 3 CASES/1.000.000



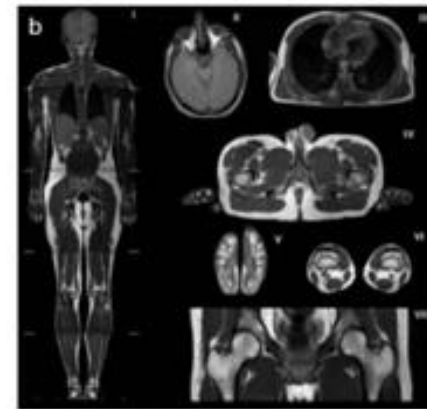
HOW TO EVALUATE PATIENTS? PLICOMETRY, DEXA, MRI, APPS



PLICOMETRY



**DUAL ENERGY
X-RAY
ABSORPTIOMETRY**



MRI



**LIPODDX MOBILE
APPLICATION**

Physical Appearance Classification

Lipodystrophic syndromes
→ heterogeneous group of:

1. Congenital
2. Acquired disorders

Characterized by lack of
adipose tissue (lipoatrophy):

1. Complete
2. Partial

In some accumulation of fat
in other regions of body

CONGENITAL OR FAMILIAR

Generalized



Partial

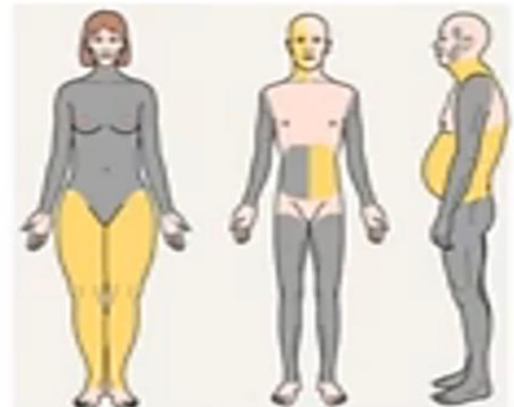


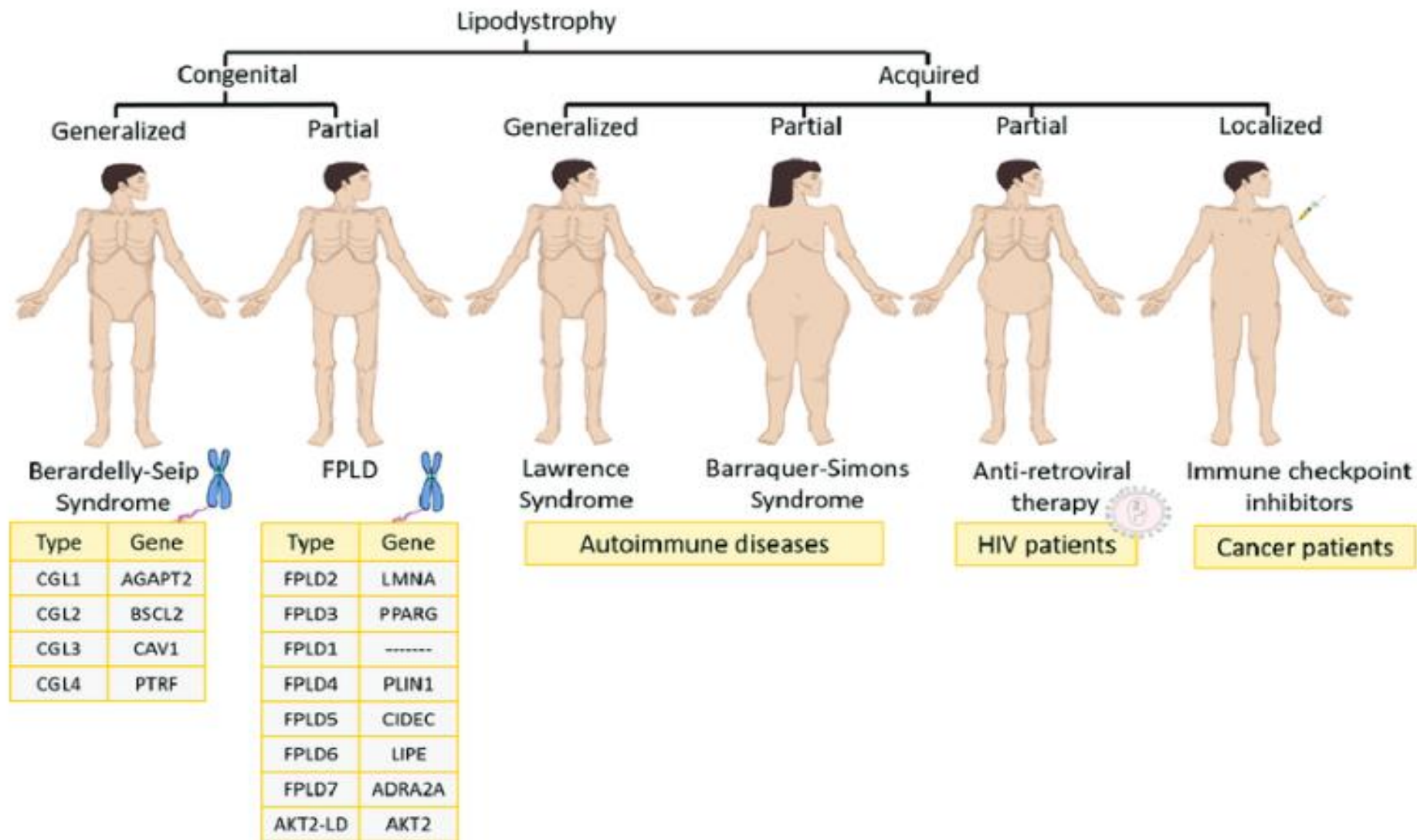
ACQUIRED

Generalized



Partial





Lipodystrophy syndromes classification. FPLD, familial partial lipodystrophy.



Inherited Lipodystrophies

Type	Salient features	Mode of inheritance	Genetic defects
Congenital generalized lipodystrophy	Generalized deficiency of subcutaneous fat from birth	Autosomal recessive	AGPAT2, BSCL2, CAV1, PTRF, FBN1, BANF1
Familial partial lipodystrophy	Loss of subcutaneous fat from extremities with variable loss/excess of fat from trunk and face	Autosomal dominant (usually)	LMNA, PPARG, AKT2, PLIN1, CIDEA*
Lipodystrophy in association with other rare syndromes	Variable degree of fat loss in association with features of other syndromes such as MAD, SHORT, progeria and autoinflammatory syndromes	Both autosomal recessive and autosomal dominant	LMNA, ZMPSTE24, PSMB8, PIK3R1

Acquired Lipodystrophies

Acquired generalized lipodystrophy	Development of generalized loss of subcutaneous fat, with normal fat distribution at birth
Acquired partial lipodystrophy	Loss of subcutaneous fat from face, upper extremities and trunk, but not from lower extremities
HIV-associated lipodystrophy	Loss of fat from face and limbs with variable loss/excess from trunk and associated with antiretroviral therapy
Localized lipodystrophy	Patchy loss of subcutaneous fat usually following trauma or injections

Abbreviations in the table: MAD, mandibuloacral dysplasia; SHORT, short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay.

*CIDEA reported in a single patient with autosomal recessive inheritance.

When to Think of Lipodystrophy?



Essential Feature

Generalized or regional
absence of body fat



Physical Features

- Failure to thrive (infants and children)
- Prominent muscles
- Prominent veins (phlebomegaly)
- Severe acanthosis nigricans
- Eruptive xanthomata
- Cushingoid appearance
- Acromegaloid appearance
- Progeroid (premature aging) appearance

Think early about LD!

- Generalized absence of fat
- Muscular appearance with failure to thrive in infancy
- Insulin-resistant diabetes or acanthosis in lean child or adolescent
- NAFLD in lean child or adolescent
- PCOS in lean adolescent/young women
- Severe HTG or its complications
- Metabolic disease out of proportion to adiposity in patients with partial lipodystrophy



Clinical features of patients with lipodystrophic disorders

Lipodystrophy

Acanthosis nigricans (associated with severe hyperinsulinemia)

Muscle hypertrophy, prominent veins

Hepatomegaly

Fatty liver

Cirrhosis

Hypertrichosis, hirsutism (occasionally)

Cardiomegaly due to hypertrophic cardiomyopathy (occasionally)

Mental retardation (occasionally)

Metabolic abnormalities

Hyperglycemia, but no ketosis

Insulin resistance

Hypertriglyceridemia

Increased metabolic rate

TYPE 2 DIABETES WITH SEVERE INSULIN RESISTANCE

**HIGH INSULIN REQUIREMENTS
MANY ANTI-DIABETIC DRUGS
ACANTHOSIS NIGRICANS
PCOS OR PCOS-LIKE SYMPTOMS**



HYPERTRIGLYCERIDEMIA



SEVERE HYPERTRIGLYCERIDEMIA

TRIGLYCERIDE LEVELS THAT ARE NON-RESPONSIVE
TO THERAPY AND/OR MODIFICATIONS TO DIET

HYSTORY OF PANCREATITIS ASSOCIATED WITH
HYPERTRIGLYCERIDEMIA

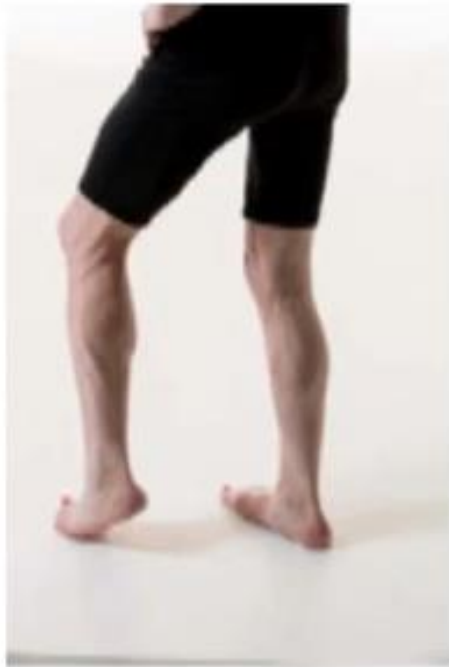
XANTHOMATA



HEPATOMEGALY AND/OR ELEVATED TRANSAMINASES IN THE ABSENCE OF A KNOWN CAUSE OF LIVER DISEASE



PROMINENT MUSCULARITY AND PHLEBOMEGALY (ENLARGED VEINS)



LIPOATROPHY: LOOK AT PHYSICAL APPEARANCE

ACROMEGALOID FACE



MANDIBULAR HYPOPLASIA



PROGEROID FACE



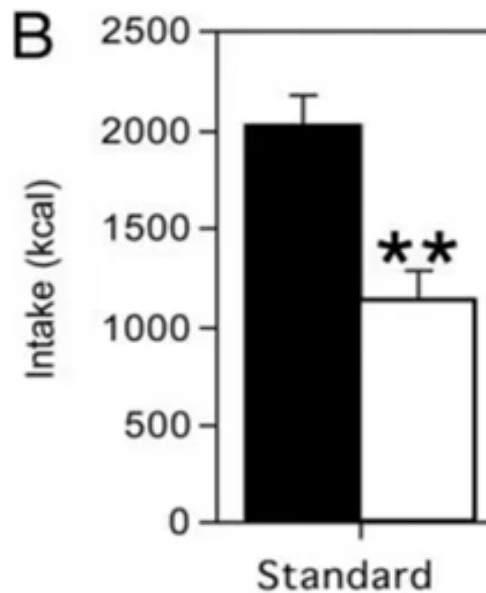
CUSHINGOID FACE



LIPOATROPHIC FACE



HYPERPHAGIA (THINKING TO FOOD, CANNOT STOP EATING)



Lipodystrophic patients eat on average 30% more daily calories than the predicted

Extent of fat loss correlates with severity of metabolic abnormalities

- Clinically, severe lipodystrophy have:
 - Severe insulin resistance
 - Severe hyperlipidemia
 - Progressive liver disease
 - Increased metabolic rate

Severity of Comorbidities?

Genetic Lipodystrophies

Comorbid Conditions

- Diabetes mellitus with high insulin requirements
 - ≥ 200 U/d or ≥ 2 U/kg/d or requiring U-500 insulin
- Severe HTG
 - ≥ 500 mg/dL with or without therapy
 - History of acute pancreatitis secondary to HTG
- MASH in an individual without obesity
- Early-onset cardiomyopathy
- PCOS

Hirsutism, acanthosis nigricans

Progeroid facies

Severity of Comorbidities?

Acquired Lipodystrophies

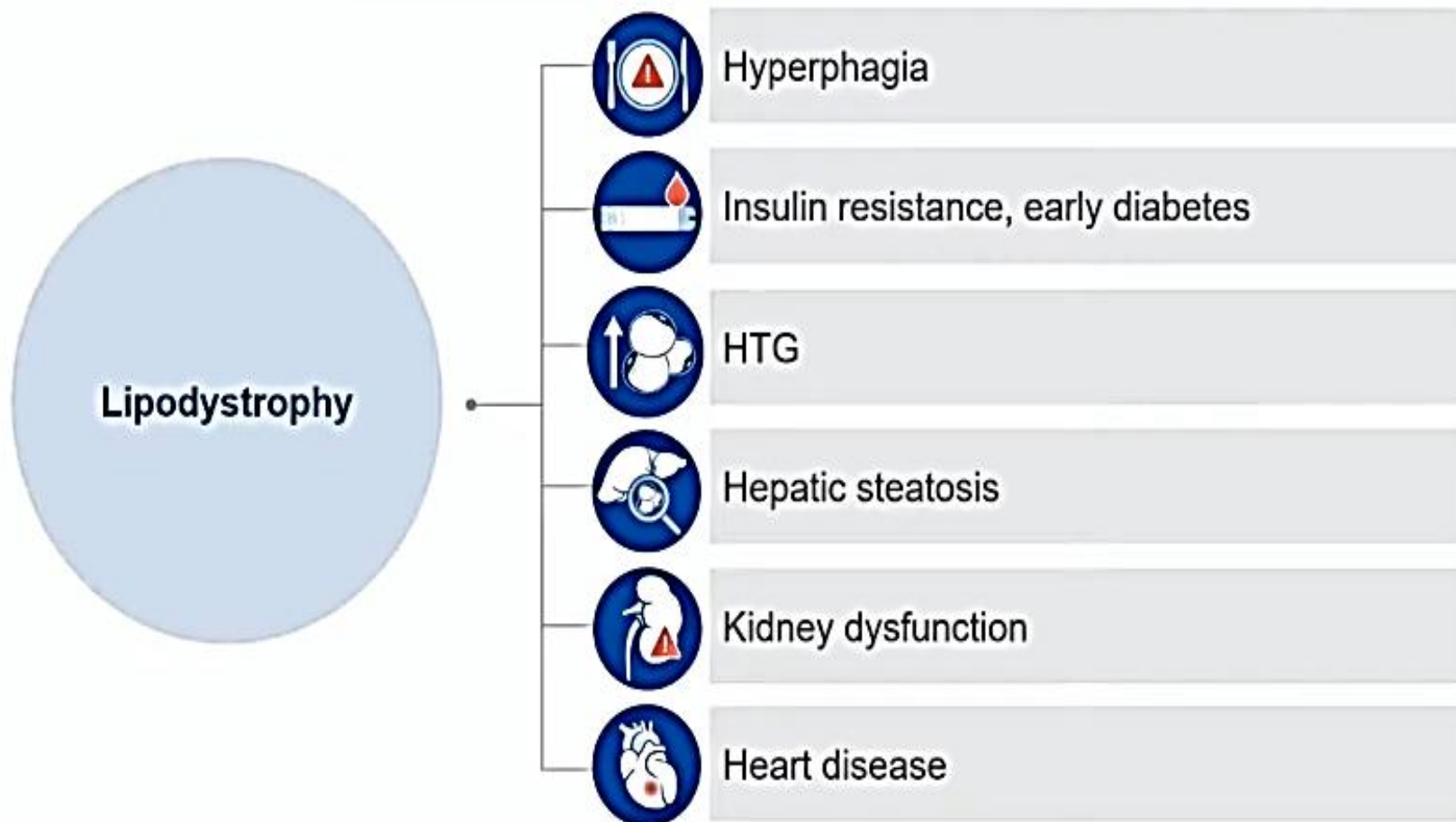
Comorbid Conditions

- Diabetes mellitus with high insulin requirements
- Severe HTG
- Acanthosis nigricans
- MASH in an individual without obesity
- MPGN
- Drusen retinopathy

Associated autoimmune diseases (JDM, SLE, etc)

Panniculitis, generalized lymphadenopathy

Recognize Comorbidities Early



Acquired and congenital lipodystrophies may also be associated with:

- Proteinuric kidney diseases
- Renal biopsy in nephrotic range proteinuria has revealed :
 1. Focal segmental glomerulosclerosis or
 2. Membranoproliferative glomerulonephritis

Etiology



- There is increasing understanding of **molecular basis** for these disorders, but it is likely that multiple molecular defects are responsible

Differentiation of adipocytes, demonstrating gene activation and signaling pathways, in relation to acquired lipodystrophies: lipodystrophy genes and their associated protein products are **bolded**.

Mesenchymal stem cells have pluripotent ability to differentiate into osteocytes, myocytes, chondrocytes, stromal cells, or adipocytes.

Wnt signal transduction pathways and other transcription factors lead to development of a committed pre-adipocyte.

Subsequently, **adipogenic stimuli, such as insulin, glucocorticoids, IGF-1, and prostaglandins**, initiate cell changes to differentiate into adipocyte.

Current data suggests that **BSCL-2** gene, coding for seipin, and **AKT-2** play a role in adipocyte differentiation, and their mutations are involved in congenital generalized lipodystrophy (**CGL**) 2 and familial partial lipodystrophy (**FPLD**) 4, respectively.

CCAAT-enhancer-binding proteins (**C-EBP**) **b/d** transcription factors stimulate factors PPAR γ , C-EBP α , and sterol regulatory element-binding protein (SREBP)1c, which are upregulated in this process;

PPAR γ mutations are associated with **FPLD3**.

Intracellular lipid accumulation in an adipocyte is dependent on substrate availability.

In response to a variety of lipogenic signals, an adipocyte matures as size of lipid droplets are increased. Fatty acid synthase (FAS), acetyl coenzyme A carboxylase, and diacylglycerol acyltransferase (DGAT) expression is upregulated, necessary for biosynthesis of phospholipids and triglycerides.

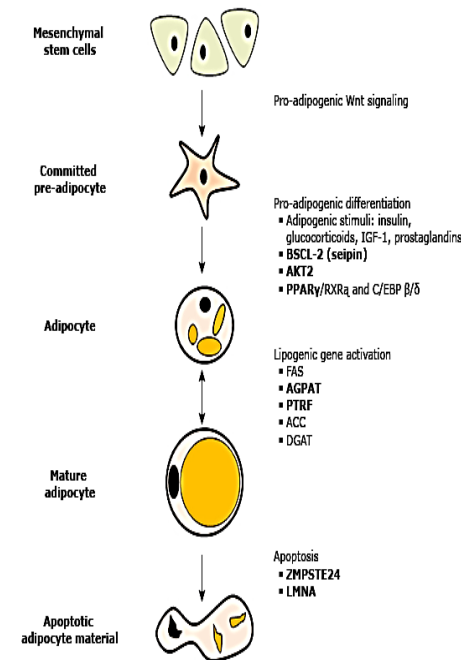
AGPAT is responsible for acylating phosphatidic acid to synthesize triglycerides and phospholipids, and its mutation is involved in **CGL1**.

PTRF regulates caveolae intracellularly and its functional loss results in **CGL4**.

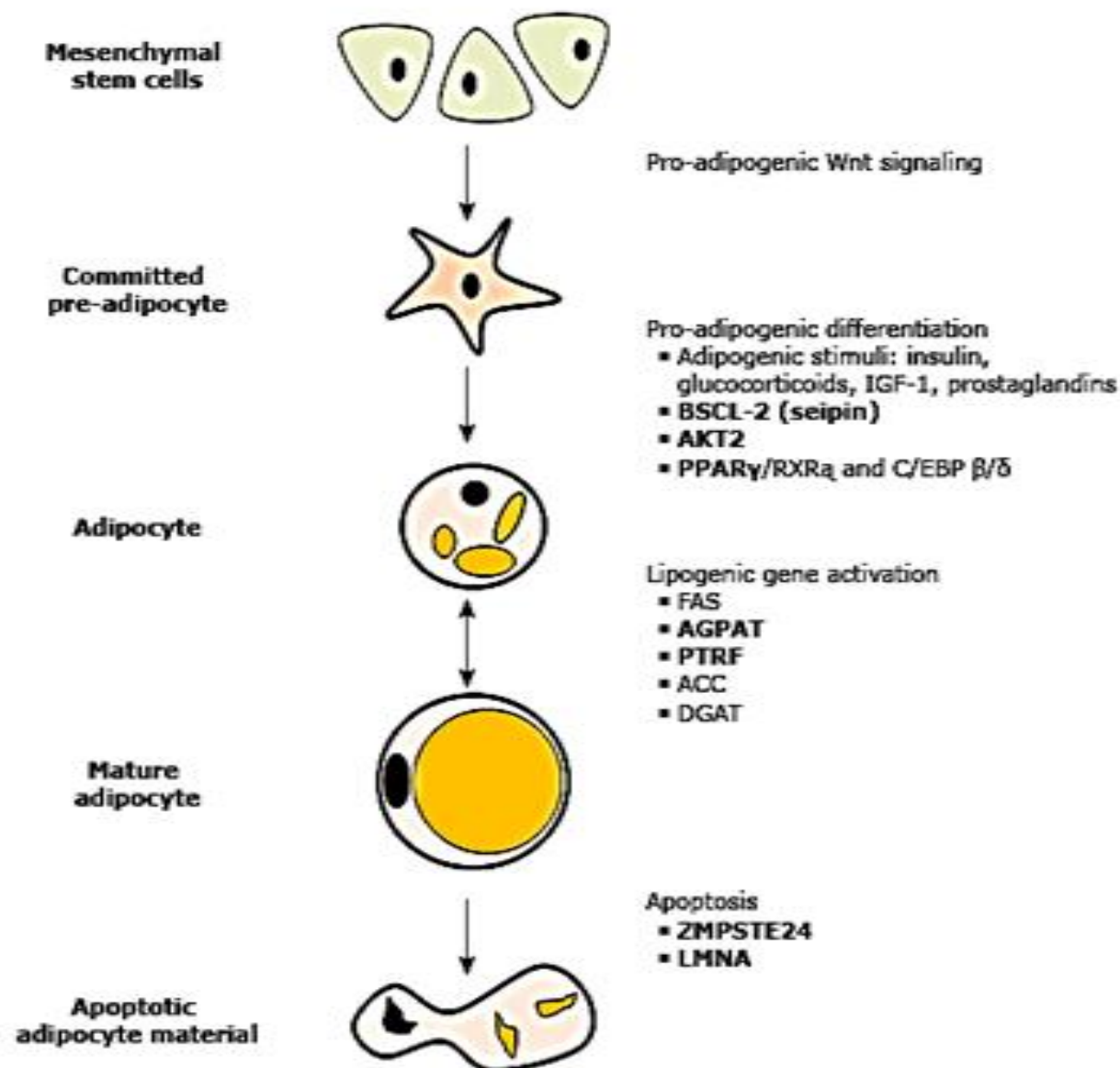
Apoptosis of adipocytes is influenced by **LMNA**, encoding for nuclear lamina proteins, and **ZMPSTE24** required for post-translational lamina processing.

Mutations in these genes lead to **mandibuloacral dysplasia** via premature nucleus disruption.

Differentiation of adipocytes in relation to acquired and congenital lipodystrophies

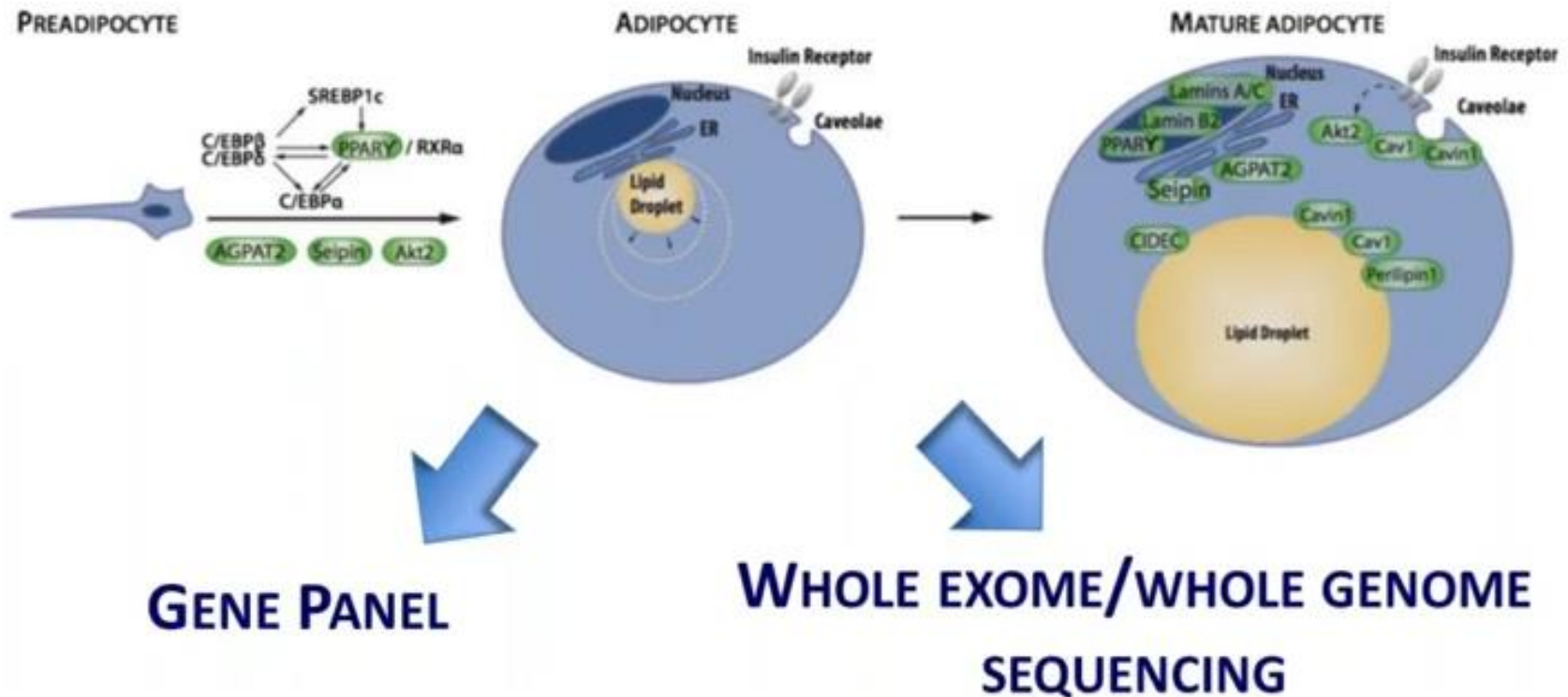


Differentiation of adipocytes in relation to acquired and congenital lipodystrophies

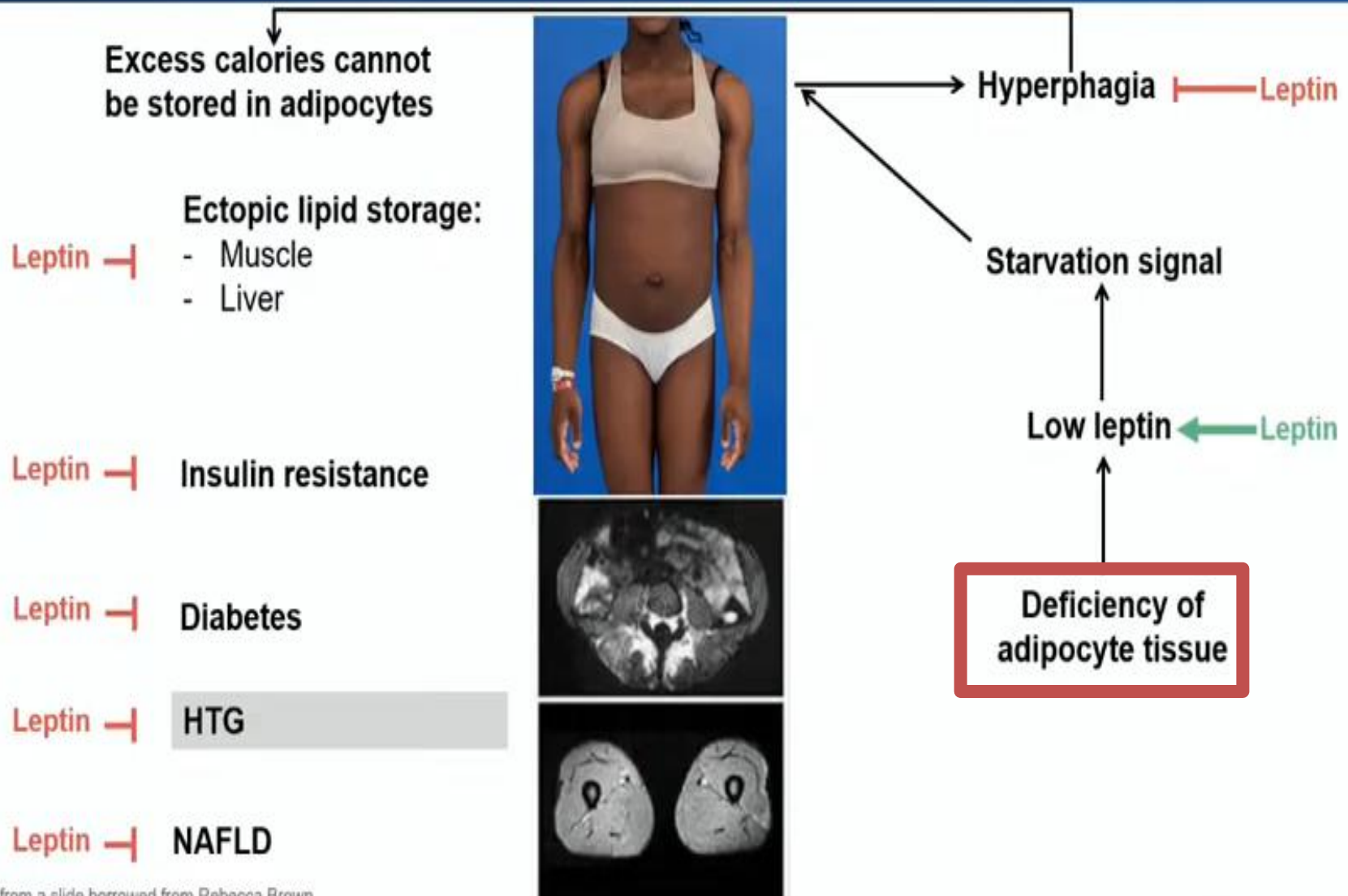


CONGENITAL OR FAMILIAL LIPODYSTROPHIES

TYPE	GENERALIZED	PARTIAL
GENES INVOLVED	AGPAT2, BSCL2, PTRF, CAV1, PIK3R1, POLD1, KCNJ6, BANF1, ZMPSTE24, SPRTN, ERCC6, ERCC8, LMNA	LMNA, PPAR γ , PLIN1, CIDEA, LIPE, AKT2, CAV1, FBN1, WRN/RECQL2, PCYT1A, RECQL3, POLR3A, PSMB8



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Heart disease

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- Cardiomyopathy
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Liver disease

- Increased *de novo* lipogenesis
- MAFLD
- MASH
- Cirrhosis

Neuromuscular disease

- Bone cysts
- Myopathy

High mortality

- Cardiovascular disease
- Sepsis
- Liver disease
- Kidney disease



Leptin deficiency

- Hyperphagia
- Core pathophysiology leading to metabolic abnormalities

Severe insulin resistance

- Poorly controlled diabetes
- Complications of diabetes

Kidney disease

- Proteinuria
- End stage renal disease

Reproductive abnormalities in females

- Failure in puberty progression
- Hyperandrogenism
- Polycystic ovaries
- Infertility

Autoimmunity in acquired cases

- Autoimmune hepatitis
- Glomerulonephritis

Poor quality of life

- Low self esteem
- High rates of depression and anxiety
- Attention deficit problems
- Fatigue
- Pain

Other disorders that need to be differentiated from lipodystrophies

Differential diagnosis of lipodystrophic disorders

SHORT syndrome - short stature, hyperextensibility of joints and/or hernia (inguinal), ocular depression, Reiger anomaly (ocular and dental), teething delay

Leprechaunism

Widemann-Rautenstrauch syndrome (neonatal progeroid syndrome)

Severe weight loss due to anorexia nervosa, starvation, malnutrition, uncontrolled diabetes, hyperthyroidism, adrenal insufficiency, cancer cachexia, severe chronic infections

Multiple symmetric lipomatosis



Current most prevalent form of lipodystrophy is:

HIV infection

- Is likely related to antiretroviral therapy

GENERALIZED LIPODYSTROPHY

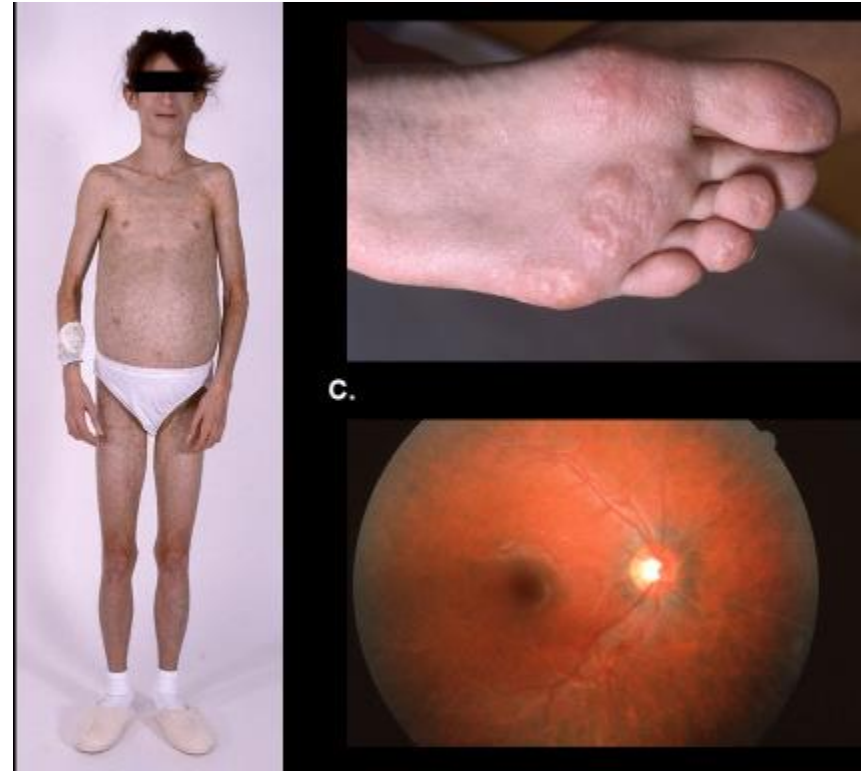
1-Congenital

(Seip-Berardinelli syndrome)

2-Acquired

(Lawrence syndrome)

Their prevalence → < 1 case per 1 million people



- Generalized lack of subcutaneous fat (6A), eruptive xanthomata (6B), and lipemia retinalis (6C) secondary to severe hypertriglyceridemia in a patient with heterozygous LMNA p.T10I pathogenic variant.

Congenital generalized lipodystrophy

Congenital generalized lipodystrophy

- CGL → AR
- At least four molecularly distinct forms
- Mutations of **AGPAT2** and **BSCL2** in 95 % of CGLs

Congenital Generalized Lipodystrophy

Type 1 (*AGPAT2*) Type 2 (*BSCL2*) Type 4 (*PTRF*)



Clinical features CGL

In first two years of life, often at or soon after birth

-Adipose tissue is almost completely absent from abdomen, thorax, and bone marrow,

-But normal in orbits, mouth and tongue, palms and soles, scalp, perineum, and periarticular regions

During childhood have :

- Voracious appetite
- Accelerate linear growth
- metabolic rate↑
- Advanced BA

Final height is usually normal

Other abnormalities:

- AN
- Protuberant abdomen

due to hepatomegaly from fatty infiltration of liver can lead to cirrhosis

-Prominent musculature

-Precocious puberty may occur

-some intellectual impairment

woman and man with CGL types 1 and 2

Type 1 → mutation in **AGPAT2** gene

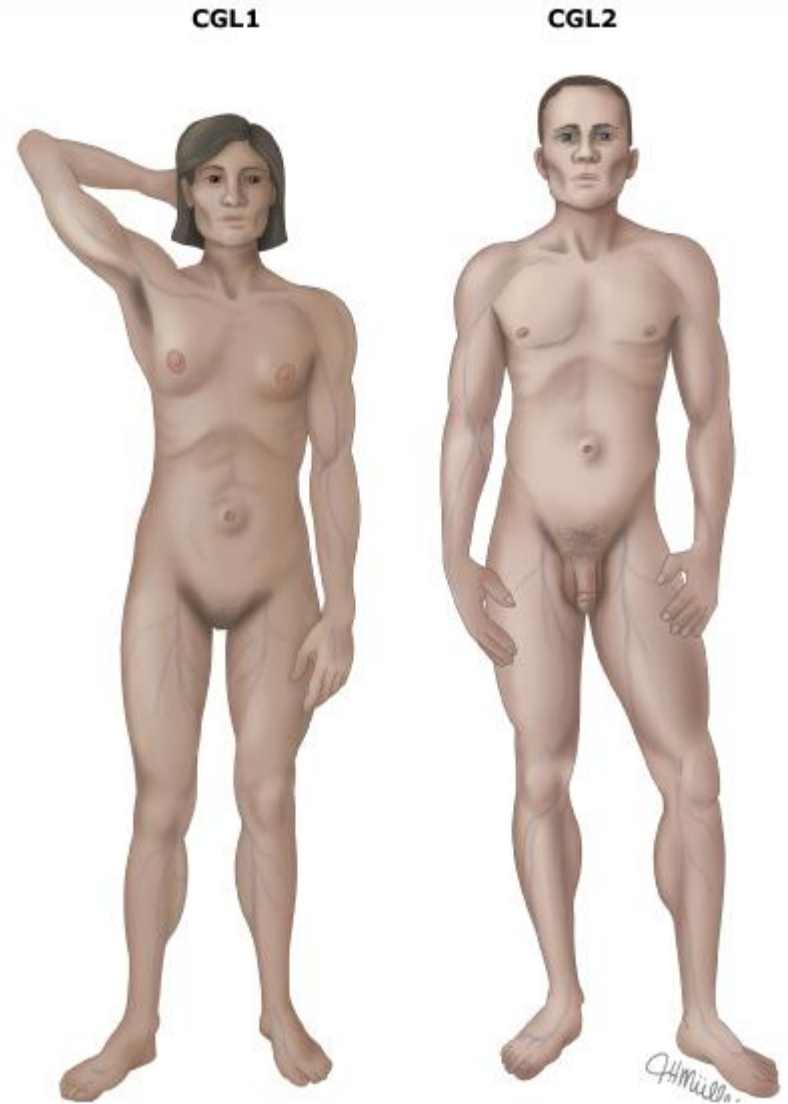
Type 2 → mutation in **seipin** gene

Both types are characterized by :

- Generalized lack of fat
- Extreme muscularity
- AN in groin and axillae
- Acromegaloid features

CGL2 → higher prevalence of intellectual impairment and cardiomyopathy

Patients with congenital generalized lipodystrophies



Type 1 CGL (CGL1) → **AGPAT2 gene mutations** on chromosomes 9q34. It encodes enzyme acyltransferase 1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2), which catalyzes acylation of lysophosphatidic acid to form phosphatidic acid, a key intermediate in biosynthesis of TG and glycerophospholipids. AGPAT2 mutations are found predominantly in patients of African ancestry.

Type 2 CGL (CGL2) → **BSCL2 gene** mutations on 11q13 and encodes 398-amino-acid protein called seipin. cells lacking BSCL2 failed to induce expression of key lipogenic transcription factors, including peroxisome-proliferator activated receptor gamma (PPARG), CCAAT/enhancer binding protein-alpha (C/EBP-alpha), as well as enzymes AGPAT2, DGAT2, and lipin1

Type 3 CGL (CGL3) → homozygous nonsense **mutation of CAV1**, probably as a result of a consanguineous union. CAV1 is located on 7q31. Its end product, caveolin-1, is a highly conserved 22-KDa protein and a major fatty acid binder on plasma membranes as well as a crucial component of plasma membrane microdomains known as caveolae. These plasma membrane domains have important roles in regulating signaling pathways and processes such as cell migration, polarization, and proliferation. Mutated function of CAV1 may lead to lipodystrophy by interfering with lipid handling, lipid droplet formation, and adipocyte differentiation.

Type 4 CGL (CGL4) → **mutations in PTRF gene**. PTRF, also known as cavin, is a polymerase I and transcript release factor involved in biogenesis of caveolae, regulating caveolin 1 and 3 expression. To date, 21 patients with PTRF mutations have been reported in the literature.

Of note, there are several patients with CGL who do not have any of four known gene mutations, possibly leading to future identification of novel CGL genes.

Type 1 CGL (CGL1) →

- Normal intelligence
- Mechanical fat preserve (orbital, palms, soles, and joints).

Type 2 CGL (CGL2) →

- More severe than CGL1
- Higher incidence of premature death
- More pronounced absence of body fat
- Loss of metabolically active fat (SC, intermuscular, bone marrow, intraabdominal and intrathoracic regions)
- Lack of mechanical fat
- Higher prevalence of intellectual impairment and cardiomyopathy than CGL1

Type 3 CGL (CGL3) →

- clinical features intermediate between these two
- normal intelligence
- their mechanical fat is preserved

Type 4 CGL (CGL4)

- moderate lipodystrophy
- Congenital myopathy
- Esophageal dysfunction
- Pyloric stenosis
- Atlantoaxial instability
- QT interval prolongation
- exercise-induced VT
- sudden death

Metabolic abnormalities

- ↓Serum leptin due to near total absence of body fat
- Insulin resistance noted at an early age
- Diabetes mellitus usually:
 1. In early teens
 2. ketosis is rare
 3. usually refractory to insulin therapy.
- Hypertriglyceridemia with:
 1. ↑ both VLDL and chylomicrons is common
 2. May acute pancreatitis
 3. Fatty liver

CONGENITAL GENERALIZED LIPODYSTROPHY

(BERARDINELLI SEIP TYPE 1-AGPAT2 GENE-RECESSIVE)



NO COMPLICATIONS



**INSULIN RESISTANCE
HEPATOMEGALY**

**SEVERE INSULIN RESISTANCE
HEPATOMEGALY
HYPERTRIGLYCERIDEMIA**



**TYPE 2 DIABETES + COMPLICATIONS
HEPATIC STEATOSIS
HYPERTRIGLYCERIDEMIA**

Differential Diagnosis for Generalized Lipodystrophy



Conditions presenting with severe weight loss

- Malnutrition
- Anorexia nervosa
- Uncontrolled diabetes mellitus
- Thyrotoxicosis
- Adrenocortical insufficiency
- Cancer cachexia
- HIV-associated wasting
- Chronic infections



Insulin receptor mutations: Rabson-Mendenhall syndrome and Donohue syndrome

Acquired generalized lipodystrophy

ACQUIRED GENERALIZED LIPODYSTROPHY (LAWRENCE SYNDROME)



- MORE FREQUENT IN F > M (3 :1)
 - ONSET CHILDHOOD OR ADOLESCENCE
 - ONSET WITH PANNCULITIS IN 1/3 PATIENTS
 - GENERALIZED FAT LOSS (30-50% PALMS AND SOLES)
-
- PRESERVED RETRO-ORBITAL AND BONE MARROW FAT
 - PROGRESSION: WEEKS, MONTHS, YEARS
 - MEAN AGE AT ONSET OF TYPE 2 DM 16 YRS
 - INCREASED RISK OF LIMPHOMA (PREVALENCE 7 %)
 - ANTI-PERILIPIN 1 IgG AUTOANTIBODIES

Acquired generalized lipodystrophy

- Characteristics of AGL similar to congenital
- Except in **previously healthy child** or adult over a period of days to weeks

Acquired Generalized Lipodystrophy Clinical Features

- Female to male ratio: 3:1
- Usually before adolescence with progressive loss of fat affecting the whole body, including palms and soles
- Some fat accumulation can appear in the face, neck, or axillae
- Frequent and severe metabolic complications



Pathogenesis

- A **previous infection** linked to this syndrome with **panniculitis** in histologic analysis of SC tissue
- **Antibodies against adipocyte-membrane antigens** detected in a few patients (PLIN1= perilipin 1 pr)
- **May coexist with other autoimmune diseases**(Hashimoto's thyroiditis, rheumatoid arthritis, hemolytic anemia, chronic active hepatitis)

Acquired Generalized Lipodystrophy (cont)



Prevalence of anti-PLIN1 autoantibodies in AGL is 37% to 50%



Useful diagnostic biomarker for autoimmune and panniculitis subtypes of AGL



Patients with anti-PLIN1 autoantibodies exhibited earlier onset of LD and more extensive loss of adipose tissue



Autoantibody titers showed a strong association with worse glycemic and lipid control and higher transaminase levels

- “Panniculitis” term for inflammation in layer of fat beneath skin
- Painful lumps (nodules) form
- Look like small bruises
- Most common on lower legs



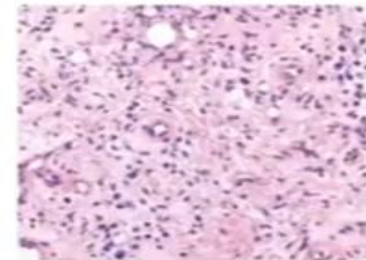
ACQUIRED LIPODYSTROPHY: PANNICULITIS



CD8 + LYMPHOCYTES



MONOCYTES RIMMING ADIPOCYTE



ADIPOCYTE DROP OUT WITH COMPENSATORY FIBROSIS OF THE FAT LOBULE



Metabolic abnormalities

- Patients have :
 - Severe insulin resistance
 - Hyperinsulinemia
 - Diabetes
 - HyperTG
 - Low HDL
 - Often high metabolic rate
 - High serum free fatty acid, and excessive lipolysis
- Most patients **do not become ketotic**, but DKA has been reported

CONGENITAL PARTIAL LIPODYSTROPHY

CONGENITAL PARTIAL LIPODYSTROPHY

- Several syndromes of **regional** lipoatrophy
- Simultaneous **hypertrophy of adipose tissue** in nonatrophic areas

Familial partial lipodystrophy

- FPLD syndromes are rare
- Variable loss of adipose tissue during childhood, puberty, or young adulthood

DISEASE	GEN PROTEIN FUNCTION	PHENOTYPE
FPLD1 ^{41, 42} (Köbberling)	UNKNOWN	Childhood onset. Worsens in menopause. Lower limb subcutaneous lipodystrophy, variable in the upper limbs. Fat accumulation in the abdomen (subcutaneous and intra-abdominal), cervico-thoracic, face. Insulin resistance and metabolic syndrome.
FPLD2 ^{14, 17-39} (Dunnigan)	<i>LMNA</i> (heterozygous) Lamin A/C Nuclear lamina (see text)	Pubertal onset. Subcutaneous fat loss in the lower limbs, upper limbs and abdomen. Fat excess in the face, neck, axillae, labia majora, intra-abdominal region. Insulin resistance and metabolic syndrome. Cardiac abnormalities may be present.
FPLD3 ^{43, 46}	<i>PPARG</i> (heterozygous) Peroxisome Proliferator Activated Receptor ϵ Adipogenesis	Adult onset. Less severe fat loss. No fat accumulation in the face and neck. Severe metabolic complications. Severe hypertension.
FPLD4 ^{47, 48}	<i>PLIN1</i> (heterozygous) Perilipin 1 Lipid droplet	Childhood onset. Limb lipodystrophy. Facial / neck fat accumulation may be present or absent. Insulin resistance and metabolic syndrome.
FPLD5 ⁵⁰	<i>CIDEA</i> (homozygous) Cell Death Inducing DFFA Like Effector C Preadipocyte differentiation, lipid droplet	Childhood onset. Limb and abdominal subcutaneous lipodystrophy, no abnormal fat depots. Marked hypermuscular appearance. Ketotic diabetes, albuminuria.
FPLD6 ^{49, 51}	<i>LIPE</i> (homozygous) Hormono sensitive lipase Regulation of lipolysis	Adult onset. Limb lipodystrophy. Fat accumulation in a "Cushing" fashion including back. Insulin resistance and metabolic syndrome. Muscular dystrophy with high CPK levels.
LCCNS ⁵³	<i>CAVI</i> (heterozygous) Caveolin 1 Caveolae formation	28 yr old woman. Atypical lipodystrophy of the upper body. Severe hyperlipemia, recurrent pancreatitis. Congenital cataracts. Neurodegeneration syndrome.
FPLD ⁵²	<i>AKT2</i> (heterozygous) AKT Serine/Threonine Kinase 2 Insulin signalling pathways	Adulthood onset. Partial lipodystrophy. Marked hyperinsulinemia, diabetes around 30 years of age.

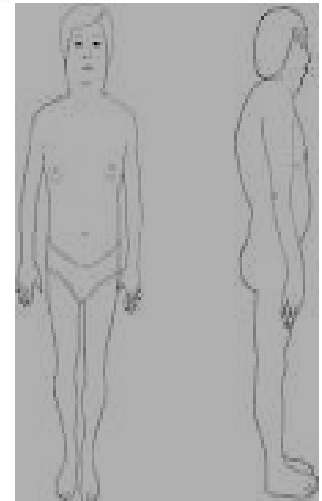
FPLD type 1 (Kobberling lipodystrophy)

- Loss of adipose tissue in extremities
- Normal adipose tissue elsewhere
- May excessive amounts of SC truncal fat
- Age of onset, mode of inheritance, and Genetic defect are **not well defined**, due to small number of cases described



- FPLD 2 (Dunnigan lipodystrophy)
- ✓ Fat loss from extremities, abdomen, and thorax
- ✓ Excess SC fat in chin and supraclavicular area
- a. Usually onset of puberty
- b. Excess supraclavicular fat and round facies
- Increased muscularity
- X-linked dominant,
- AD in some family

Clinical Features of FPLD2



FAMILIAR PARTIAL LIPODYSTROPHY TYPE 2 (DUNNIGAN SYNDROME)-LMNA MUTATIONS (DOMINANT)





FPLD type 2

- Missense mutation
LMNA gene that
encodes lamins A and C

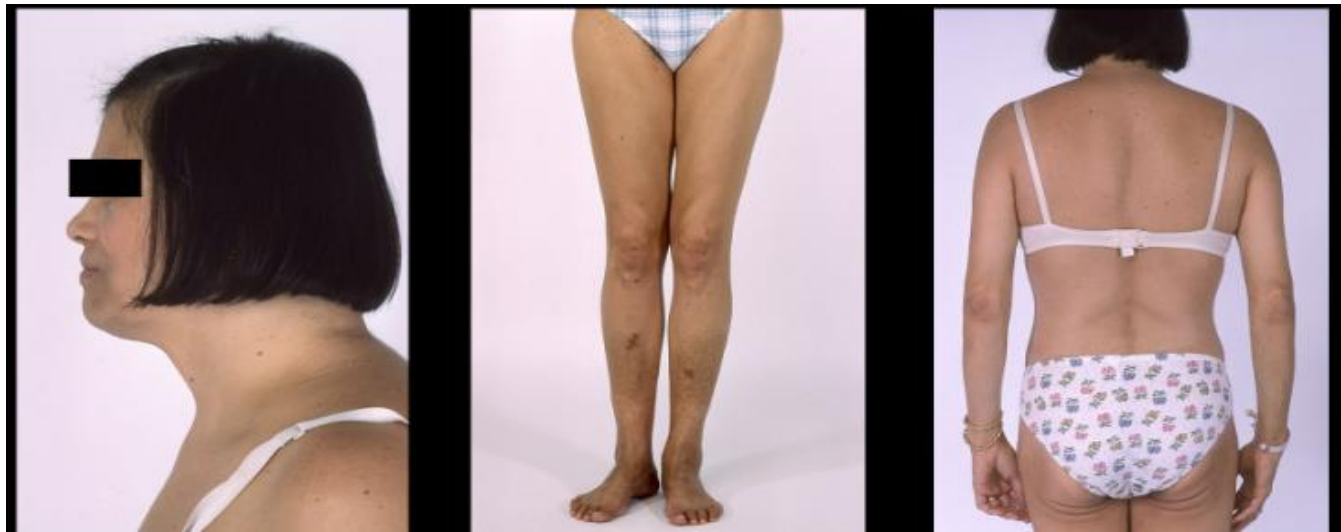
familial partial lipodystrophy type 2

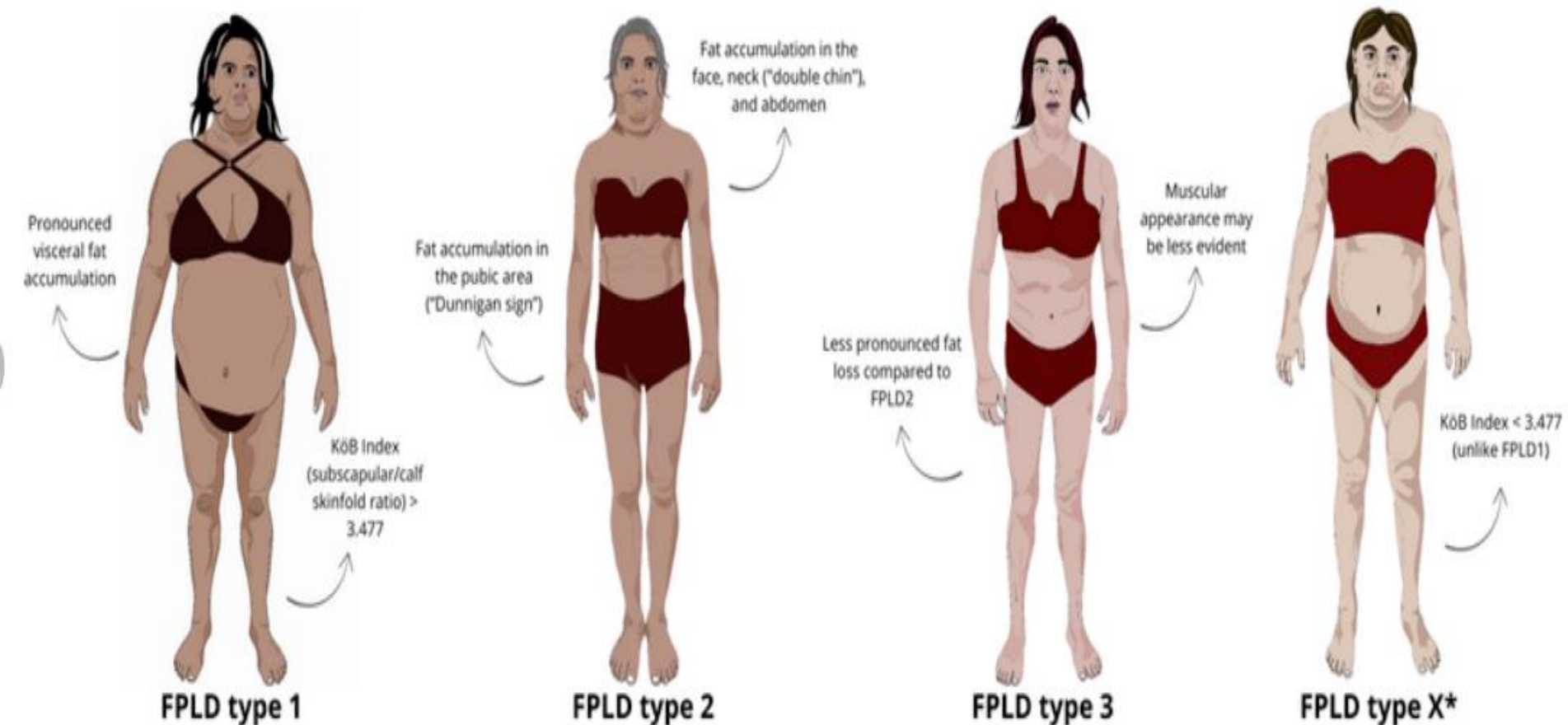
FPLD type 2



FPLD type 3

FPLD 3 with heterozygous PPARG gene mutations
Similar to Dunnigan's variety, exception fat
accumulation in head and neck may be spared
FPLD3 have more severe metabolic abnormalities
than FPLD2





Visual spectrum of familial partial lipodystrophy (FPLD) phenotypes and their specific hallmarks. *FPLD type X includes patients with lipodystrophic features, no identified pathogenic variant, and a KöB index < 3.477, differentiating it from FPLD1

FPLD type 4

- Mutation PLIN1 gene coding for perilipin 1, required component of **lipid droplet membranes** and **essential for lipolysis and lipid storage**
- Phenotypically by loss of SC fat from extremities

FPLD type 5

- AR mutation in CIDEA gene → encodes CIDEA pr
→ expressed in lipid droplets → leading to lack of ability of
lipid droplets to store fat
 - Partial lipodystrophy
 - Severe insulin resistance
 - Fatty liver
 - AN
 - Diabetes
 - Muscular hypertrophy but no accumulation of adipose
tissue
 - Ketotic diabetes
 - Albuminuria

FPLD type 6

- Mutation in LIPE (lipase E) gene
- Abnormal SC fat distribution
- May have:
 - ↑↑visceral fat
 - Impaired lipolysis
 - Dyslipidemia
 - Hepatic steatosis
 - Insulin resistance, and diabetes
 - Some patients manifest muscular dystrophy and elevated CPK
 - Cushing fasion

FPLD can due to mutation of AKT2

- AKT2 mutations :
 1. Reduced adipocyte differentiation and
 2. Dysfunctional post-receptor insulin signaling
- PL
- Marked hyperinsulinism
- Diabetes around 30 yrs

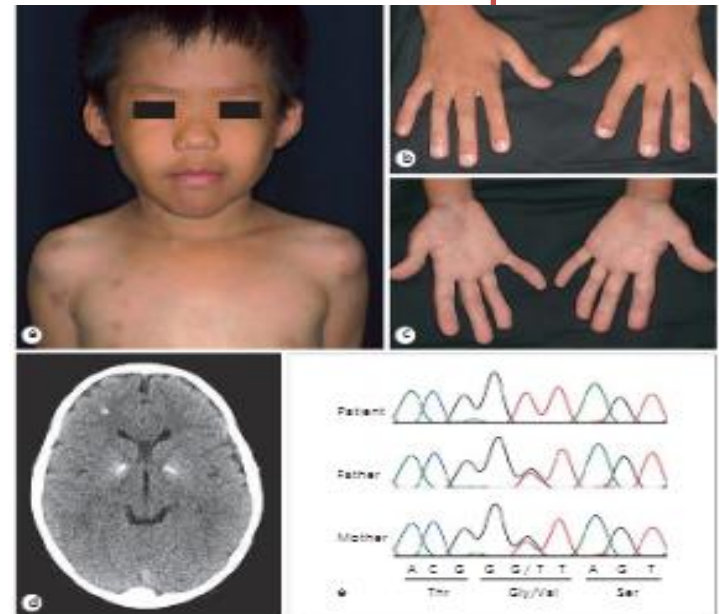
PLD due to CAV1 mutation

- A mutation in CAV1 → rare cause of PL
- Two cases been reported:
 - SC fat loss in face and upper body
 - Micrognathia
 - Congenital cataracts
 - One case with abnormal neurologic findings
 - Diabetes, hyperTG, and recurrent pancreatitis

Autoinflammatory syndromes

Autoinflammatory syndromes

- **JMP** (j*oint* contractures, **m**uscle atrophy, **m**icrocytic anemia, **p**anniculitis-induced lipodystrophy) Syndrome
- AR
- Report 3 case from Japan and 2 family from Mexico and Portugal
- Hepatosplenomegaly
- Intermittent fever
- Calcification of basal ganglia
- Hypergammaglobulinemia
- loss-of-function mutation of (PSMB)-8 gene on chromosome 6



Autoinflammatory syndromes

- **CANDLE** (Chronic Atypical Neutrophilic Dermatositis with Lipodystrophy and Elevated temperature) syndrome causing partial lipodystrophy
- six patients, AR
 - Recurrent fevers
 - Annular violaceous plaques
 - Loss of adipose tissue from upper limbs and face
 - Hepatosplenomegaly
 - Anemia
 - Eyelid swelling
 - Calcifications of basal ganglia
- Molecular mechanism is unknown



Other syndromes with a
component of lipodystrophy

Hutchinson-Gilford progeria syndrome (HGPS)

- Progressive and generalized fat loss
 - Restrictive dermopathy
 - Progeria-associated arthropathy
- De novo LMNA mutations



Werner syndrome

- Short stature
- Birdlike appearance of face
- Early onset of aging processes

	PROGERIA (HUTCHINSON- GILFORD PROGERIA SYNDROME)	WERNER SYNDROME
Age of Onset	 Early childhood, typically around 1-2 years.	 In early twenties In late Thirties Adolescence or early adulthood, around 20s or 30s.
Genetic Cause	Mutation in the LMNA gene (Chromosome 1) , leading to the production of PROGERIN , a defective form of lamin A .	Mutation in the WRN gene (Chromosome 8) , which codes for the WERNER protein, involved in DNA repair and maintenance.
Primary Symptoms	Growth delay, loss of body fat and hair, aged-looking skin, stiffness of joints.	Premature aging symptoms :Greying of hair, wrinkled skin, ALSO more pronounced onset of age-related diseases like cataracts, type 2 diabetes, and osteoporosis.
Disease progression	Rapid	Gradual
Average life expectancy	Early twenties	Forties or fifties

@VijayPatho

Mandibuloacral dysplasia

- MAD is rare , AR, premature aging (progeroid) syn
- ~40 case
- Two distinctive phenotypes:
 - **Type A** → mutations of LMNA gene and loss of SC fat from arms and legs but normal or ↑ fat in face and neck
 - **Type B** → more generalized loss of SC fat
- Compound heterozygous mutations in gene (ZMPSTE24), on 1q34



Mandibuloacral dysplasia Clinical features

- Lipoatrophy in childhood or early adolescence
- More in females

Postnatal growth retardation

Craniofacial and skeletal abnormalities :

1. Mandibular and clavicular hypoplasia
2. Delayed closure of cranial sutures
3. Acro-osteolysis
4. Joint contractures
5. Bird-like face
6. Dental abnormalities

Cutaneous changes :

1. Restrictive dermatopathy
2. Skin atrophy
3. Alopecia
4. Mottled cutaneous)
5. Progeroid features

Normal intelligence



Mandibuloacral dysplasia Metabolic abnormalities :

- Hyperinsulinemia, insulin resistance, DM
- Hyperlipidemia reported in some patients
- Serum leptin can be low or normal
- Focal segmental glomerulosclerosis

A) Two years old patient, there is not evidence of Cockayne 's syndrome. B) Actual phenotype of patient. Note cachectic habitus, sunken eyes, lack of SC facial fat and others characteristics of the Cockayne's syndrome.

- Cockayne syndrome :

- Short stature
- Photosensitivity
- Hearing loss
- Premature aging



Carbohydrate-deficient glycoprotein syndrome

- Cerebellar hypoplasia
→ Nonprogressive ataxia
- Mental retardation
- Peripheral neuropathy
- Strabismus
- LD



Figure 1 Ichthyosis, hypotonia, and strabismus in a patient with SRD5A3-CDG. Courtesy of NIH, Lynne Wolfe, CRNP, Donna

SHORT syndrome :

- S-short stature
- H-hyperextensibility of joints
± inguinal hernia
- O-ocular depression
- R-Rieger anomaly
- T-teething delay



AREDYLD syndrome

- **A**cral **R**enal **E**ctodermal **D**ysplasia **L**ipoatrophic **D**iabetes
- Generalized lipodystrophy
- Ectodermal dysplasia



ACQUIRED PARTIAL LIPODYSTROPHY

Acquired partial lipodystrophy (Barraquer-Simons syndrome)

- ~ 250 patients report
 - Partial acquired **cephalothoracic lipodystrophy**
- Loss of adipose tissue from face and upper trunk
- With sparing or ↑adiposity in rest of body

Acquired partial
lipodystrophy



Barraquer-Simons syndrome

Pathogenesis

- Complement activation
- Serum immunoglobulin G, called C3 nephritic factor
- Renal disease —20 %MPGN, in average 8 to 10 yrs after diagnosis.

ACQUIRED PARTIAL LIPODYSTROPHY (BARRAQUER-SIMONS)



- MORE FREQUENT IN F > M 4 : 1
- CEPHALOCAUDAL PATTERN OF SC FAT LOSS
- ONSET CHILDHOOD OR ADOLESCENCE (MEAN AGE 7-8 YRS)
- INFECTIOUS ILLNESSES HAVE BEEN REPORTED TO PRECEDE THE ONSET OF APL

- LOWER PREVALENCE OF TYPE 2 DM (35 %) COMPARED TO AGL
- 50-70 % SHOW C3 AND PRESENCE OF IgG «NEFRITIC FACTOR», 30 % MP GLOMERULONEPHRITIS
- ASSOCIATED AUTOIMMUNE DISEASES 10-30%
- THE HLA ALLELE DRB1*11 WAS PRESENT IN 54% PATIENTS ¹

Lipodystrophy associated with HIV therapy

- HIV infection with antiretroviral therapy especially **HIV-1 protease inhibitors**

HIV therapy-associated lipodystrophy



Localized lipodystrophies

- Loss of SC fat from small areas of body but **not insulin resistance or other metabolic abnormalities**
- **Drug-induced lipodystrophy** at site of injection
 1. Insulin
 2. Glucocorticoids
 3. Antibiotics
- **Repeated pressure against any body part**

Lipodystrophia centrifugalis abdominalis infantilis syndrome

- lipoatrophy
- Centrifugal loss of adipose tissue in abdomen
- Erythematous and scaly changes at periphery
- Usually occurs before 3 yrs
- >50% recover spontaneously



(A) Lipodystrophy in **HIV** who antiretroviral therapy containing a protease inhibitor for six years.

Note loss of fat from face, arms, legs; ↑abdominal fat; buffalo hump

(B) **Acquired partial lipodystrophy** in **Barraquer-Simons' syndrome**.

loss of SC fat from face, neck, arms, thorax, upper abdomen began in adolescence.

Note excess SC fat in legs

(C) **Acquired generalized lipodystrophy**

generalized loss of SC adipose tissue began in adolescence.

Complications→severe insulin resistance, hyperinsulinemia, hyperTG, and low HDL

Patients with acquired lipodystrophies

HIV therapy-associated lipodystrophy



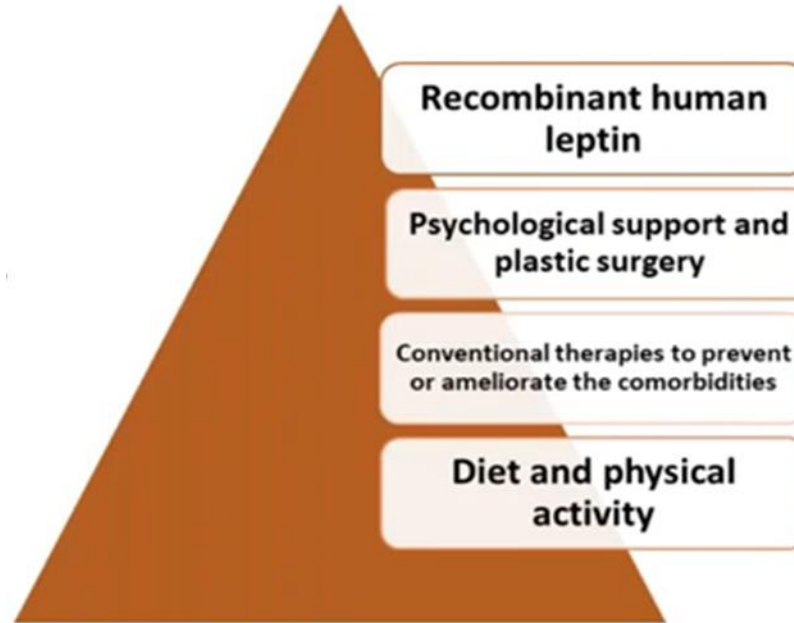
Acquired partial lipodystrophy



Acquired generalized lipodystrophy



TREATMENT OF LIPODYSTROPHY



General approach

- Initial treatment of metabolic disturbances (diabetes, hyperTG) same as without lipodystrophy
- **Lifestyle modification** (appropriate diet and exercise), metformin, and statins (and/or fibrates)
- **Insulin or other antidiabetics** (**thiazolidinediones**)
- If metabolic disturbances persist, could administer **metreleptin** in acquired or congenital generalized lipodystrophy, as part of a Risk Evaluation and Mitigation Strategy (REMS) program

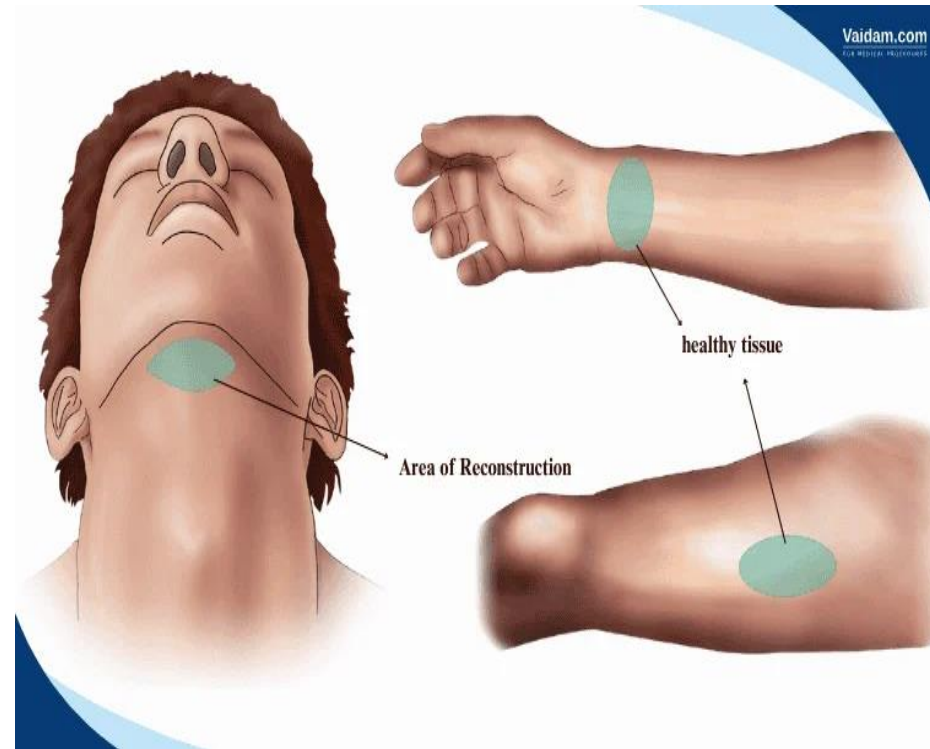
REMS program



- Metreleptin is available in United States only through an REMS program
1. Pharmacies must also be certified
 2. Patients with information about medication
 3. Health care professionals should consider benefits and risks of treatment

Cosmetic treatment

- **Facial reconstruction** with free flaps and silicone or other implants for "replace" adipose tissue.
- **Liposuction or lipectomy** for removal of excess fat.





- There is **no diet** that reverses lipodystrophy, but **low fat diet is recommended**
- When hyperTG prominent, balanced **low fat, low carbohydrate** diet
- ↑physical activity and monitoring carbohydrate intake

Drugs



Initial treatment

- Initial treatment of (hyperglycemia, hyperTG) is same as other patients
- Metformin and statins and/or fibrates
- Thiazolidinediones or other PPAR γ modulators, which increase adiponectin, may be beneficial.
- Insulin, very high doses or concentrated insulins, U-500
- IGF-1 $\rightarrow$ improve glycemic control and insulin resistance
- A fibrate or combination of fibrate and statin for hyperTG, $\downarrow$ risk of pancreatitis

Persistent metabolic disturbances

- In 2014, FDA approved metreleptin **for congenital or acquired generalized lipodystrophy +** persistent metabolic disturbances
- **Not approved for :**
 - HIV-related lipodystrophy
 - DM and hyperTG
 - Partial lipodystrophy
 - Obesity

Table 1. Metreleptin dosing per the US Package Insert.⁴

	INITIAL 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)	1.25–2.5 mg (0.25–0.5 mL)	10 mg (2 mL)
Females >40 kg	5 mg (1 mL)	1.25–2.5 mg (0.25–0.5 mL)	10 mg (2 mL)

Other Effects of Leptin Therapy in Patients with LD



- Improvement in food intake and perception of hunger
- Improvement in liver health and NASH histopathology
- Improvement in proteinuria and hyperfiltration
- Improvement in cardiac parameters: LV remodeling
 - Not much data on atherosclerotic heart disease
- Improvement in QoL and psychoemotional health
- Improvement in neuroendocrine regulation
- Improvement in reproductive function
- Improvement in immune regulation
- Improvement in physical appearance
- Effects on body composition and bone health

> 60 papers

Metreleptin→analog of human leptin made by **recombinant DNA** technology
r leptin → SC one or twice daily **up to 12 months** to significant clinical improvement

- Studies showed ↓A1C, FBS , TG
- Improved peripheral glu disposal and ↓ hepatic glu output and hepatic steatosis

1. **Satiation** (time to voluntary cessation of eating) and
2. **Satiety** (inter-meal interval) also improved

Adverse Events Associated With Metreleptin



Metreleptin [product information], 2020

2 Black Box Warnings

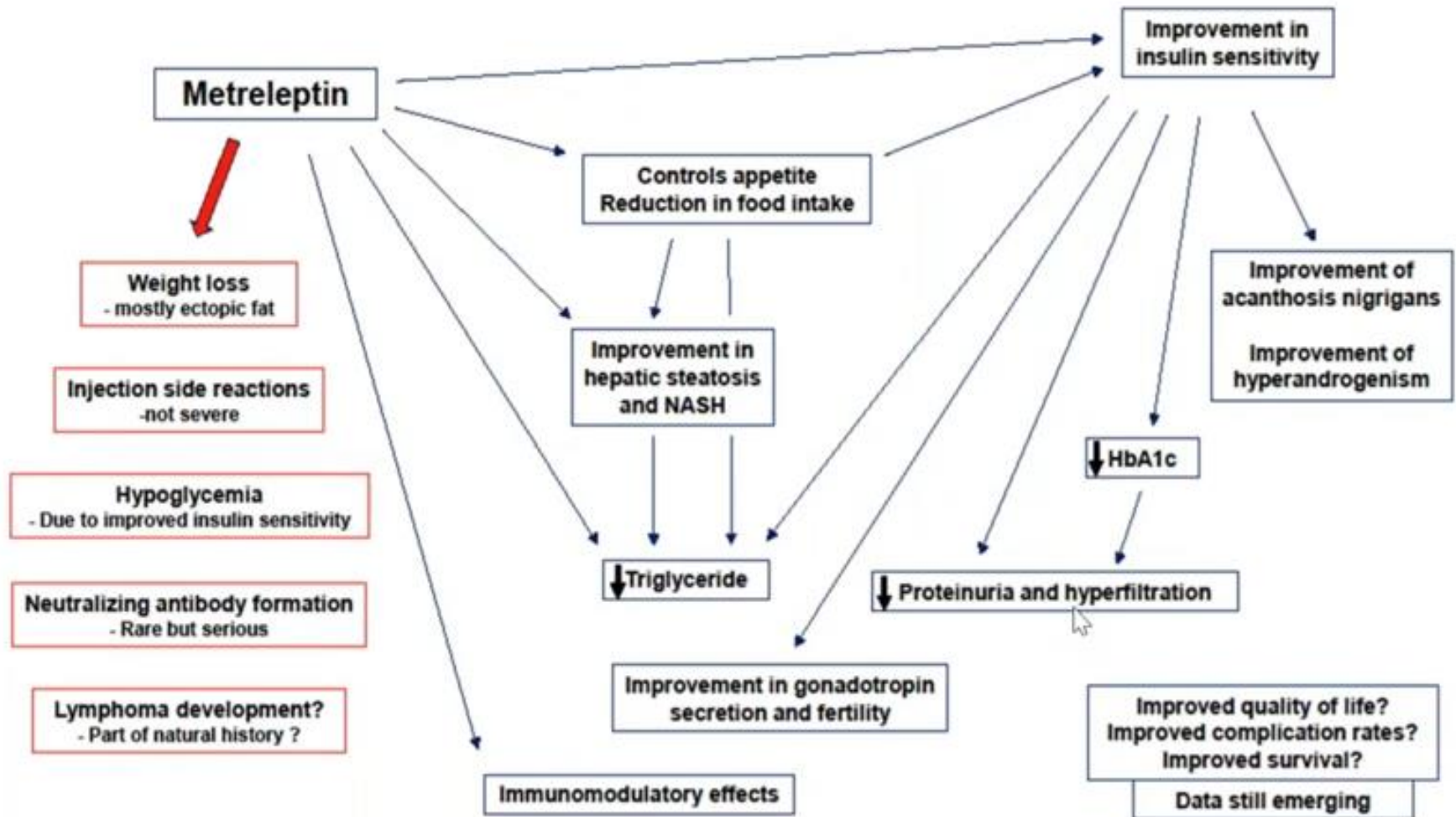
- Development of neutralizing antibodies
 - Concern for immune dysfunction and infections
 - Loss of efficacy of drug
- Development of T-cell lymphoma in a small number of individuals with AGL

Other Adverse Events

- Loss of appetite
- Weight loss
- Hypoglycemia (mostly in individuals with heroic doses of insulin)
- Acute pancreatitis (usually associated with missed doses or withdrawal of therapy)
- Progression of liver and kidney disease

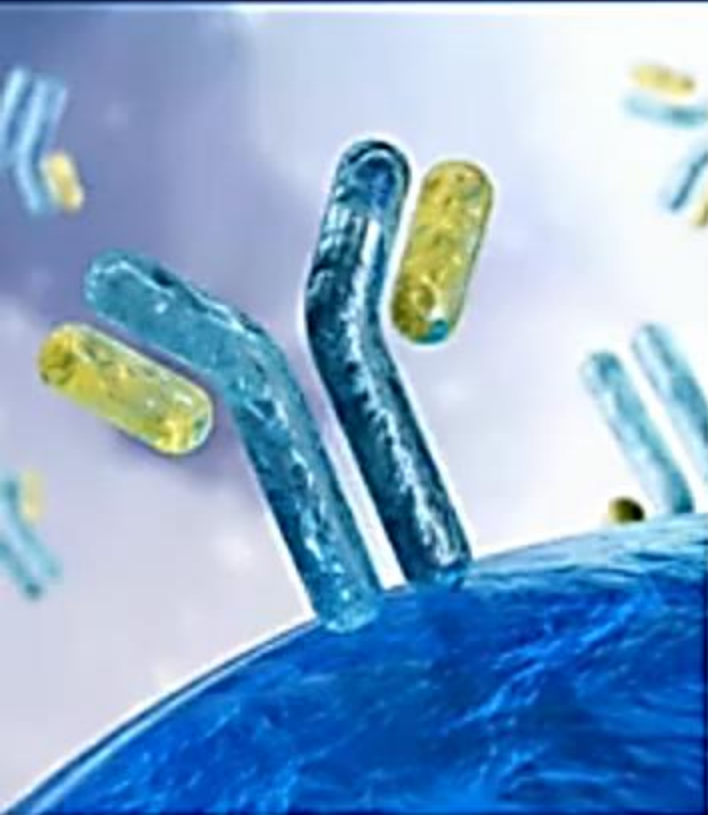
- Most common side effects of metreleptin :
 - Fatigue
 - Headache
 - Abdominal pain

Effect and Side Effects of Leptin



Mibavademab

Agonist Antibody to the Leptin Receptor



Fully human monoclonal antibody that binds and activates the human leptin receptor

Reverses the body weight and metabolic imbalances in preclinical models of monogenic obesity and GL

In clinical development for LD and obesity

Moving Beyond Leptin Pathway in PL



| Apo-CIII inhibition

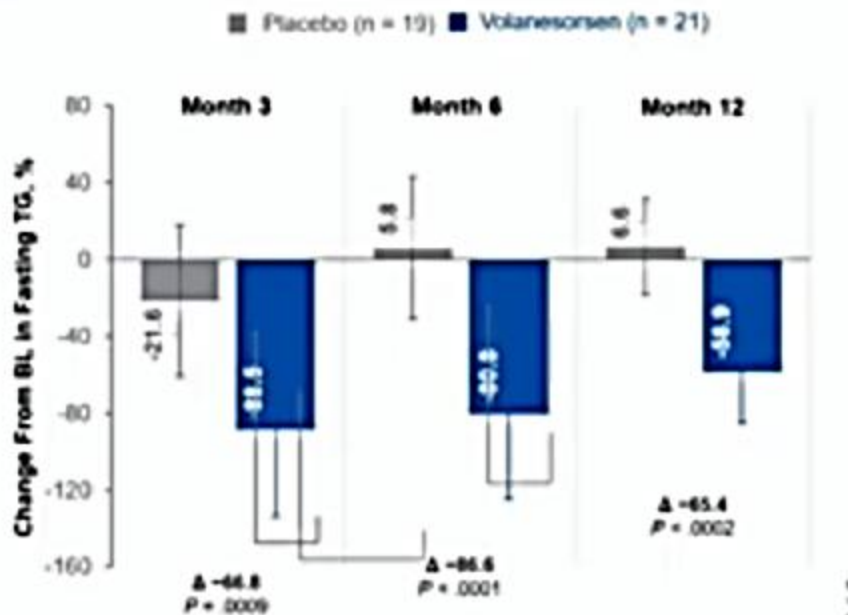
| ANGPTL3 inhibition

Volanesorsen bind to ApoC-III mRNA, leading to its degradation and reduce TG

BROADEN Study

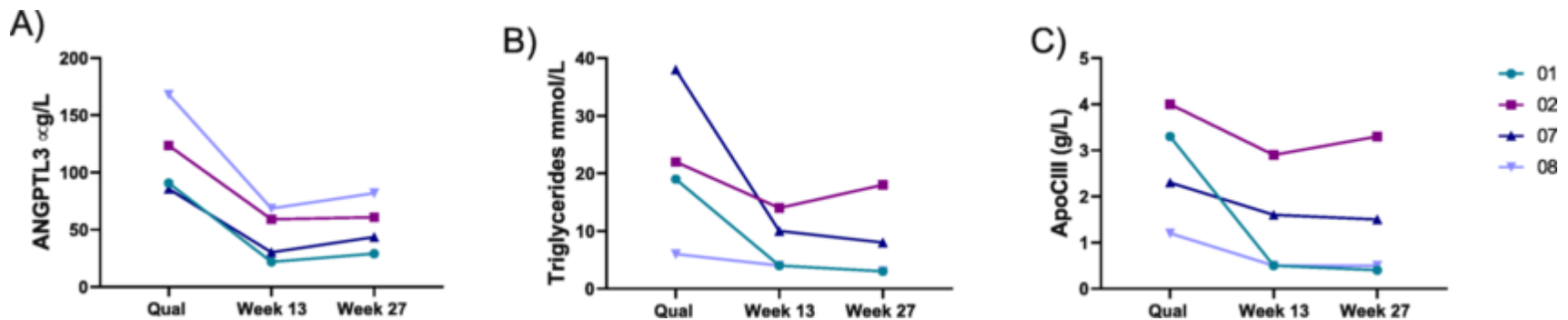
Effect of Volanesorsen, an Apo-CIII Inhibitor in FPLD

Volanesorsen significantly and sustainably reduced plasma TG levels in patients with FPLD



Vupanorsen, hepatic (Angiopoietin-Like Protein 3) Inhibitors. ANGPTL3 (inhibit lipoprotein lipase (LPL) and endothelial lipase (EL) in tissues) , significantly reduced non-HDL-C and triglycerides

Selective Targeting of ANGPTL3 With Vupanorsen for the Treatment of Patients With FPLD



Our Latest News in Therapy

Metabolic Improvements With Tirzepatide in LD



اللَّهُمَّ عَجِّلْ لَوْلِيِّكَ