Uncommon Dyslipidemias with Common Presentations

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Disclosures

• Consultant: Aegerion Pharmaceuticals, Amarin, Amgen, AstraZeneca, Eli Lilly & Co., Genzyme, Sanofi, Alexion, Synageva, Recombine

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• Speakers bureau: Amgen, Genzyme, Aegerion, Regeneron, AstraZeneca, Merck & Co., Inc., Alexion/Synageva
Outline

• Case Study
• Lysosomal Acid Lipase Deficiency (LAL-D)
• Familial Chylomicronemia Syndrome (FCS)
• FCHL
• Lipodystrophy
The eye cannot see what the mind does not know.

--Anonymous
Case Study

- 40-year-old male with history of overweight, BMI 26 and mild dyslipidemia. Treated with atorvastatin 20 mg daily, and aggressive diet and lifestyle interventions.
- Total chol 210 mg/dL, HDLc 38 mg/dL, TG 200 mg/dL, LDLc 132 mg/dL
- Mild fatty liver on abdominal sono, ALT 47, AST 52
- Lost to follow-up for 7 years. Returns at age 47. Off statin (told to stop due to increasing liver function tests).
- Total chol 250 mg/dL, HDLc 25 mg/dL, TG 180 mg/dL, LDLc 189 mg/dL
- Repeat AST 110, ALT 100, GGT 280, Bilirubin normal
- BMI 27, repeat sono shows progressive fatty liver with hepato-splenomegaly
- Liver biopsy, mixed macro and microvesicular pattern with some steatohepatitis
Common Causes of Hypertriglyceridemia

- High-carbohydrate diet
- Excessive alcohol consumption, especially when combined with high saturated fat diet
- Hypothyroidism
- Renal disease
- Poorly controlled insulinopenic T2DM
- Physical inactivity, sedentary lifestyle
- Pregnancy
- Polycystic ovary syndrome
- Excess visceral fat, abdominal adiposity
- Hepatic steatosis or steatohepatitis
- Autoimmune diseases (eg, SLE with anti-LPL antibodies)
- Genetic defects involving apo AV, apo CII, LPL, GPIHBP1, and others
- Familial combined hyperlipidemia (FCHL): apo B excess (VLDL and LDL excess), polygeneic
- Familial hypertriglyceridemia (FHTG): VLDL excess, polygenic
- Type III dyslipidemia or dysbetalipoproteinemia: excess VLDL and IDL remnants, apo E ε2/ε2 genotype

Apo, apolipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase; T2DM, type 2 diabetes mellitus; SLE, systemic lupus erythematosus; VLDL, very-low-density lipoprotein.
# Drugs Associated with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Beta blockers without alpha antagonist activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Retinoic acid drugs</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Oral estrogens (not transcutaneous)</td>
</tr>
<tr>
<td>λ-Asparaginase</td>
<td>α-Interferon</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td></td>
</tr>
</tbody>
</table>

Lysosomal Acid Lipase Deficiency (LAL-D)

- Historical terms to describe the disease
  - “Wolman disease”
    - 1956 by Dr. Moshe Wolman
    - Described an infant who died at the age of 3 months: poor weight gain, GI symptoms, hepatosplenomegaly, and adrenal calcifications
  - “Cholesteryl Ester Storage Disease or CESD”
    - 1963 by Dr. Donald S. Fredrickson
    - Described 12-year-old with hypercholesterolemia + hepatomegaly
- Underlying cause is the same\(^1\)-\(^4\)
  - Autosomal recessive disease affecting lipid metabolism
  - Results in lysosomal accumulation of lipids (cholesteryl esters and triglycerides) and multi-organ system damage (liver, GI tract, and blood vessel walls)

LAL-D Presentation in Children and Adults

- Common presenting abnormalities\(^1\)\(^-\)\(^3\)
  - Unexplained persistent elevated ALT/AST
  - High/very high LDL-c and low HDL-c

- Diagnosis requires high index of clinical suspicion\(^1\)
  - Many patients diagnosed in childhood
  - Others present with symptoms but are not diagnosed until adulthood

- High potential for mis- or delayed diagnosis; many patients remain undiagnosed\(^3\)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-c: high-density lipoprotein cholesterol

Biology of Lysosomal Acid Lipase

Hepatocyte

LDL particle

lysosome

Free cholesterol and free fatty acids

nucleus

LAL
Pathophysiology of LAL-D

Low HDL-C in LAL Deficiency Is Mechanistically Linked to ABCA1

- Recent data indicates that cholesterol flux out of lysosomes is a key regulator of ABCA1 expression (Bowden KL et al, 2011)
- Fibroblasts from LAL deficient patients
  - Decreased basal and LDL stimulated ABCA1 and ABCG1 expression
  - Decreased apoA-I mediated efflux of phosphatidylcholine, sphingomyelin and unesterified cholesterol (UC)
  - LXR agonists correct ABCA1 expression but not efflux
  - Decreased generation endogenous oxysterols including 27 hydrocholesterol

# LAL Deficiency: Genetic Epidemiology

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Carriers of E8SJM/ Sample Size</th>
<th>Estimated Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muntoni et al</td>
<td>Arterioscler Thromb Vasc Biol; 2007;27:1866-8.</td>
<td>10/2023 (German population)</td>
<td>1:43,000 to 1:78,000</td>
</tr>
<tr>
<td>Grabowski et al</td>
<td>Scriver’s OMMBID; 2012</td>
<td>9/7011 (European Americans)</td>
<td>1:159,000 to 1:294,000</td>
</tr>
<tr>
<td>Scott et al</td>
<td>Hepatology; 2013;58:958-65.</td>
<td>14/4569 (Caucasian + Hispanic)</td>
<td>1:111,000 to 1:204,000</td>
</tr>
<tr>
<td>Stitziel et al</td>
<td>Arterioscler Thromb Vasc Biol; 2013;33:2909-14.</td>
<td>88/27,472 (European ancestry)</td>
<td>1:102,000 to 1:189,000</td>
</tr>
</tbody>
</table>

*Range based upon assumption of the “common” E8SJM representing 51 to 69% of all disease causing mutations*
Elevated LDL-C Is Common in Patients with Documented LAL Deficiency

ADD Reference here.
Combined Hyperlipidemia Is a Common Feature of LAL Deficiency

ADD Reference here.
Low HDL-C Is a Characteristic Feature of LAL Deficiency

ADD Reference here.
Effects of Lysosomal Acid Lipase Deficiency on Hepatic and Plasma Lipid Metabolism and Effects of Sebelipase Alfa Infusion

Severe Hypertriglyceridemia and Chylomicronemia
Case Study: Severe Hypertriglyceridemia with Multifactorial Etiology

**Abbreviations:** SLE, systemic lupus erythematosus; Tx, treatment; OM3FA, omega-3 fatty acids; TG, triglycerides; LMF-1, Lipase Maturation Factor-1.


**Case Summary**
- **Patient with recurrent pancreatitis despite treatment**
- **Genotyping revealed a novel heterozygous missense mutation of LMF-1**
- **Indicated primary cause of symptoms as severe hypertriglyceridemia**
- **Current status after treatment with multiple TG-lowering therapies:**
  - Stabilized TG levels (<150mg/dL) for the last six months
  - Stable SLE
  - Patient is doing well
Triglyceride-rich Lipoprotein Metabolism

Brahm & Hegele. Nat. Rev. Endocrinol. advance online publication 3 March 2015; doi:10.1038/nrendo.2015.26
Etiology of Severe Hypertriglyceridemia (Important to make a diagnosis)

- Primary Causes (monogenetic)
- Secondary Causes
- Primary (Less severe phenotype) + Secondary Insult
## Primary Chylomicronemia: Monogenic and Polygenic Forms

<table>
<thead>
<tr>
<th>Features</th>
<th>Monogenic chylomicronaemia</th>
<th>Polygenic chylomicronaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former designations</td>
<td>Familial chylomicronaemia</td>
<td>Mixed dyslipidaemia</td>
</tr>
<tr>
<td></td>
<td>Type 1 hyperlipoproteinaemia (WHO)</td>
<td>Type 5 hyperlipoproteinaemia (WHO)</td>
</tr>
<tr>
<td>Main lipoprotein disturbances</td>
<td>Increased number of chylomicron particles only</td>
<td>Transient increase in levels of triglyceride-rich</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipoproteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased number of chylomicron particles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased levels of VLDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased number of chylomicron remnants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased number of VLDL remnants</td>
</tr>
<tr>
<td>Associated lipoprotein</td>
<td>Reduced levels of VLDL, LDL and HDL</td>
<td>Usually reduced levels of HDL, sometimes reduced</td>
</tr>
<tr>
<td>disturbances</td>
<td></td>
<td>levels of LDL</td>
</tr>
<tr>
<td>Typical onset</td>
<td>Paediatric or adolescent</td>
<td>Adulthood</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Failure to thrive</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Vomiting</td>
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<tr>
<td></td>
<td>Vomiting</td>
<td>Eruptive xanthomas (rare)</td>
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<tr>
<td></td>
<td>Eruptive xanthomas (rare)</td>
<td>Lipaemia retinalis (rare)</td>
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<tr>
<td></td>
<td>Lipaemia retinalis</td>
<td>Pancreatitis (~1% risk per year)</td>
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<tr>
<td></td>
<td>Pancreatitis</td>
<td></td>
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<td></td>
<td>Hepatosplenomegaly</td>
<td></td>
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<tr>
<td>Association with CVD</td>
<td>Minimal</td>
<td>Some evidence of increased risk</td>
</tr>
<tr>
<td>Prevalence</td>
<td>~1:100,000 to ~1:1,000,000</td>
<td>~1:600</td>
</tr>
<tr>
<td>Contribution of secondary</td>
<td>Minimal</td>
<td>Major</td>
</tr>
<tr>
<td>factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inheritance pattern</td>
<td>Autosomal recessive</td>
<td>Familial clustering, but no discrete classical</td>
</tr>
<tr>
<td>Genetic causes</td>
<td>Mutations in (LPL^4), (APOC2^4), (APOA5^43),</td>
<td>Genetic pool of affected individuals has increased</td>
</tr>
<tr>
<td></td>
<td>(GPIHBP1^{51}) and (LMF1^{55})</td>
<td>prevalence of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Heterozygous rare variants in (LPL), (APOC2),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(APOB), (GCKR), (APOA5), (LMF1), (GPIHBP1) and (CREBH) with large effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Common variants (SNP) with small effects in ~40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>genes identified in genome-wide association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>studies</td>
</tr>
<tr>
<td>Current treatment</td>
<td>Dietary control: restriction of fat intake ±</td>
<td>Dietary control: reduced intake of calories, fats,</td>
</tr>
<tr>
<td></td>
<td>increased consumption of MCTG</td>
<td>simple sugars and alcohol</td>
</tr>
<tr>
<td></td>
<td>Pharmacologic control: minimal effect of</td>
<td>Control of secondary factors</td>
</tr>
<tr>
<td></td>
<td>fibrates, niacin, (\omega-3) fatty acids and</td>
<td>Pharmacologic control: (\omega-3) fatty acids</td>
</tr>
<tr>
<td></td>
<td>statins</td>
<td>and niacin (both have variable efficacy)</td>
</tr>
</tbody>
</table>

## Genetic Causes of Primary Monogenic Chylomicronemia

<table>
<thead>
<tr>
<th>Gene (gene product)</th>
<th>Homozygote prevalence</th>
<th>Gene product function</th>
<th>Clinical features</th>
<th>Molecular features</th>
<th>% of monogenic mutations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL (LPL)</td>
<td>~1 per million individuals&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Hydrolysis of triglycerides and peripheral uptake of FFA</td>
<td>Severe chylomicronaemia in infancy or childhood</td>
<td>Severely reduced or absent LPL enzyme activity</td>
<td>95.0</td>
<td>4,28,32,36</td>
</tr>
<tr>
<td>APOC2 (apoC-II)</td>
<td>10 families reported</td>
<td>Required cofactor of LPL</td>
<td>Severe chylomicronaemia in childhood or adolescence</td>
<td>Absent or non-functional apoC-II</td>
<td>2.0</td>
<td>4,37</td>
</tr>
<tr>
<td>GPIHBP1 (GPI-HBP1)</td>
<td>10 families reported</td>
<td>Stabilizes binding of chylomicrons near LPL; Supports lipolysis</td>
<td>Chylomicronaemia in late adulthood</td>
<td>Absent or defective GPI-HBP1</td>
<td>2.0</td>
<td>47,51</td>
</tr>
<tr>
<td>APOA5 (apoA-V)</td>
<td>Three families reported</td>
<td>Enhancer of LPL activity</td>
<td>Chylomicronaemia in late adulthood</td>
<td>Absent or defective apoA-V</td>
<td>0.6</td>
<td>40,41</td>
</tr>
<tr>
<td>LMF1 (LMF1)</td>
<td>Two families reported</td>
<td>Chaperone molecule required for proper LPL folding and/or expression</td>
<td>Chylomicronaemia in late adulthood</td>
<td>Absent or defective LMF1</td>
<td>0.4</td>
<td>55</td>
</tr>
</tbody>
</table>

Abbreviations: apoA-V, apolipoprotein A-V; apoC-II, apolipoprotein C-II; FFA, free fatty acid; GPI-HBP1, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase.

**The Role of Lipase Maturation Factor-1 (LMF-1)**

- LMF-1 is a protein that spans the ER membrane
- Involved in post-translational folding, maturation, and therefore active expression of enzymatic lipases (LPL and HL)
- A conserved C-terminal domain (DUF1222) makes up about ~70% of the gene sequence
- Previously identified human LMF-1 mutations were **homozygous nonsense mutations**
  - Involved truncation of the C-terminal domain
- A greater level of truncation was associated with increased severity of pancreatitis

**LMF-1 in Lipase Assembly and Folding**

Abbreviations: NH$_2$, amino terminal; cld, combined lipase deficiency; COOH, carboxy terminal; ER, endoplasmic reticulum; LPL; lipoprotein lipase; HL, hepatic lipase.

Conclusions

• Our patient’s complex medical history and course point towards the complexity and multifactorial causes which lead to hypertriglyceridemia.

• Description of LMF-1 mutations in animal and human phenotypes has allowed for a more nuanced understanding of the shared pathway which promotes biochemical maturation of LPL, HL, and EL.

• Though the most commonly encountered mutations in primary hypertriglyceridemia remain related to LPL and ApoC-II, LMF-1 mutations are an important addition to the list of possible causes.

• Though we do not have post-heparin lipase activity levels from her presentation, we hypothesize that this novel mutation played an important role in her disease course.

Abbreviations: LMF-1, Lipase Maturation Factor-1, LPL; lipoprotein lipase; HL, hepatic lipase; EL, endothelial lipase; ApoC-II, apolipoprotein C2
Treatment of Hypertriglyceridemia Results in Fewer Hospital Admissions

• Treatment of familial hypertriglyceridemia may not decrease plasma triglyceride levels
• Additional treatment of the secondary causes of hypertriglyceridemia may be needed to further reduce plasma triglyceride levels

Comparison of plasma TG levels in patients with pancreatitis (index patients) before and after treatment of secondary causes of hypertriglyceridemia

Treatment of secondary causes of high TG levels reduces hospitalization rates due to pancreatitis

Before Treatment:
• 105 admissions per 100 patient years

After Treatment:
• 1.8 admissions per 100 patient years

Abbreviations: TG, triglycerides
Marked hypertriglyceridemia is possibly the result of an interaction between familial lipid disorders and secondary causes of hypertriglyceridemia.

**Familial Causes**
- Inherited lipid disorder that results in elevated triglycerides

**Secondary Causes**
- Untreated fasting hyperglycemia
- Lipoprotein lipase deficiency
- Estrogen therapy
- Nephrotic syndrome
- Alcohol intake

Abdominal Pain (Pancreatitis)

**Marked Hypertriglyceridemia**
- In the presence of chylomicronemia

Emerging Therapies for Chylomicronemia

<table>
<thead>
<tr>
<th>Drug class (example)</th>
<th>Mechanism of action</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTTP Inhibition</td>
<td>Prevents triglyceride</td>
<td>Small molecule that can be</td>
<td>Common gastrointestinal adverse</td>
<td>101, 104–107</td>
</tr>
</tbody>
</table>

Emerging Therapies for Hypertriglyceridemia

- Omega 3 Ethyl Ester
- DGAT 1 inhibitors
- ApoCIII Inhibitors
- Lomitapide
- Linkage Technology
Familial Combined HL

• First described in 1973 as a common familial disorder characterized by multiple lipoprotein phenotypes and increased risk of premature cardiovascular disease (CVD)

• Genetic basis for FCH and mode of inheritance remains controversial

• Characterized by several phenotypes, including increased total cholesterol (TC), increased triglycerides (TG), decreased HDL cholesterol (HDL-C), increased apolipoprotein B (apoB), and the presence of small, dense LDL

Circulation. 2004;109:2980-2985.)
FCHL

• Increased production of VLDL with or without impaired clearance of TG-rich lipoproteins in most patients that results in the generation of increased numbers of small, dense LDL particles

• ApoB increased out of proportion to LDLC
Pathways involved in the pathogenesis of FCHL

In FCHL, it is anticipated that there is a dys-balance between de-novo lipogenesis and β-oxidation, in favour of the former resulting in hepatic fat accumulation and VLDL overproduction.
Genetics of FCHL

FCHL Diagnosis

Clinical Investigation and Reports

Nomogram to Diagnose Familial Combined Hyperlipidemia on the Basis of Results of a 5-Year Follow-Up Study

Mario J. Veerkamp, MD; Jacqueline de Graaf, MD, PhD; Jan C.M. Hendriks, PhD; Pierre N.M. Demacker, PhD; Anton F.H. Stalenhof, MD, PhD

ApoB
By Stefan Verweij
Open iTunes to buy and download apps.

Description
Accurate diagnosis is essential for the best care of patients with lipid disorders but until recently this was not possible in routine clinical care. Now, using the apoB diagnostic algorithm, which is based on total cholesterol, triglycerides and apoB, all physicians can easily make the correct diagnosis, even in complex cases. The apoB...
Potential role of statins + PCSK9i in FCHL

Lipodystrophy: Congenital, Acquired, General & Partial

- Lipodystrophy is an uncommon heterogeneous group of syndromes characterized by the complete or partial loss or absence of subcutaneous adipose tissue.
- Often seen with metabolic derangements, including insulin resistance, diabetes mellitus, hepatic steatosis or steatohepatitis, and dyslipidemia.
- Can lead to acute pancreatitis (due to severe hypertriglyceridemia), hepatic cirrhosis, and premature cardiovascular disease.
- Additional manifestations include polycystic ovarian syndrome (PCOS), acanthosis nigricans (due to severe insulin resistance), and eruptive xanthomas, NAFLD, and progressive liver disease.

Endocrine Abnormalities

- The key characteristic of lipodystrophy is the selective absence of adipose tissue (primarily subcutaneous), the levels of adipocytokine hormones can be altered
  - Reduced leptin levels
  - Reduced adiponectin levels
## Congenital Lipodystrophy: General & Partial

<table>
<thead>
<tr>
<th>Gene/protein</th>
<th>Specific clinical features</th>
<th>Main role of the affected protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital generalized lipodystrophies&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGPAT2/AGPAT2</td>
<td>Bone lesions</td>
<td>Acylation of lysophosphatic acid to form phosphatidic acid in TG and phospholipid biosynthetic pathway</td>
</tr>
<tr>
<td>BSCL2/sepin</td>
<td>Extreme lack of body fat, mild mental retardation, cardiomyopathy</td>
<td>Required for lipid droplet formation and for adipogenesis</td>
</tr>
<tr>
<td>CAV1/caveolin 1</td>
<td>Short stature, vitamin D deficiency (single case)</td>
<td>Integral protein of caveolae which binds fatty acids and translocates them to lipid droplets</td>
</tr>
<tr>
<td>PTRF/cavin 1</td>
<td>Muscular dystrophy, pyloric stenosis</td>
<td>Integral protein of caveolae which regulates the expression of caveolin 1 and caveolin 3</td>
</tr>
<tr>
<td>FOS/c-FOS</td>
<td>Growth retardation, hypercholesterolemia (single case)</td>
<td>Transcription factor involved in adipocyte differentiation</td>
</tr>
<tr>
<td>Partial lipodystrophies&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMNA/lamin A/C</td>
<td>Dunnigan syndrome—preserved or excess facial and neck fat at puberty</td>
<td>Protein of the nuclear envelope</td>
</tr>
<tr>
<td>PPARG/PPARγ</td>
<td>Preserved abdominal fat, hypertension</td>
<td>Transcription factor for adipocyte differentiation</td>
</tr>
<tr>
<td>PLIN1/perilipin 1</td>
<td>Small white adipocytes and increased fibrosis</td>
<td>Integral component of the adipocyte lipid droplet involved in lipid storage and lipolysis regulation</td>
</tr>
<tr>
<td>CIDEC/CIDECE</td>
<td>White adipocytes with multilocular lipid droplets (single case)</td>
<td>Regulation of lipid droplet size, thereby favoring lipid storage and inhibiting lipolysis</td>
</tr>
<tr>
<td>AKT2/AKT2</td>
<td>Single family</td>
<td>Serine/threonine kinase involved in insulin receptor signaling and adipocyte differentiation</td>
</tr>
</tbody>
</table>

<sup>a</sup> Prieur et al. *Curr Atheroscler Rep.* 2014;16:437
# Classification, Clinical Features, and Pathogenetic Basis of Acquired Lipodystrophies

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>Clinical features</th>
<th>Pathogenetic basis/other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy in HIV-infected patients</td>
<td>PI-induced</td>
<td>Loss of sc fat from the face and extremities and excess fat deposition in the neck and abdomen</td>
<td>PI may inhibit ZMPSTE24 and/or cause dysregulation of transcription factors involved in adipogenesis. NRTI may inhibit mitochondrial polymerase-γ and cause mitochondrial toxicity.</td>
</tr>
<tr>
<td></td>
<td>NRTI-induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired partial lipodystrophy</td>
<td>Autoimmune</td>
<td>Loss of sc fat from the face, neck, upper limbs, and trunk, sparing the lower abdomen and lower limbs</td>
<td>Low serum complement 3 levels and presence of an autoantibody, complement 3 nephritic factor, in most of the patients suggest autoimmune-mediated loss of adipose tissue.</td>
</tr>
<tr>
<td></td>
<td>MPGN-associated</td>
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<td></td>
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<tr>
<td></td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired generalized lipodystrophy</td>
<td>Autoimmune</td>
<td>Generalized loss of fat associated with tender sc nodules, autoimmune or other diseases</td>
<td>Panniculitis preceding the loss of sc fat and association of autoimmune diseases suggest immune-mediated loss of adipose tissue. Other mechanisms may also be involved.</td>
</tr>
<tr>
<td></td>
<td>Panniculitis-associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized lipodystrophy</td>
<td>Drug-induced</td>
<td>Loss of sc fat from small areas of the body</td>
<td>Multiple mechanisms including local drug-induced, immune-mediated, or pressure-induced atrophy of adipose tissue. Other unknown mechanisms may also be involved.</td>
</tr>
<tr>
<td></td>
<td>Panniculitis-induced</td>
<td></td>
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<tr>
<td></td>
<td>Pressure-induced</td>
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<td>Centrifugal</td>
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<td>Idiopathic</td>
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Metabolic Impact of Lipodystrophy

Lipodystrophy Treatment Issues & Options

• Reduce Triglycerides and Cardiovascular Risk
• Insulin Resistance/Diabetes
• Fatty Liver and Progression to Liver Disease
• Treatment
  – TLC: Restriction of total fat intake to between 20 and 30% of total dietary energy
  – N-3 Fatty Acids
  – Fibrates
  – Statins
  – Insulin Sensitizers: metformin and thiazolidinediones
  – Recombinant Leptin Replacement Therapy (Generalized Lipodystrophy): metreleptin

Curr Atheroscler Rep (2014) 16:437
Clinical Action of Metreleptin Treatment in Adipose-deficient Lipodystrophic Patients

Clinical effects of long-term metreleptin treatment in patients with lipodystrophy

Jean L. Chan, MD¹; Karen Lutz, PhD¹; Elaine Cochran, MSN, CRNP²; Wenying Huang, PhD¹; Yvette Peters, PhD¹; Christian Weyer, MD¹; Phillip Gorden, MD²

Evaluate the long-term clinical effect of treatment with metreleptin (an analogue of human leptin) on glycemic and lipid abnormalities and markers of hepatic steatosis in patients with inherited or acquired lipodystrophy:

• Fifty-five patients (36 with generalized lipodystrophy and 19 with partial lipodystrophy)

• Metreleptin treatment substantially reduced glycemic variables, triglycerides, and liver enzymes (ALT and AST) and demonstrated durability of response throughout a 3-year treatment period.
Metreleptin

- Approved for treatment of complications related to leptin deficiency in patients with general or acquired generalized lipodystrophy
- No established data for partial lipodystrophy, HIV-associated lipodystrophy, liver disease
- Not to be used for diabetes, hypertriglyceridemia without generalized lipodystrophy
- Safety issues: possibility of anti-drug and anti-neutralizing antibodies and risk of lymphoma
Summary/Take Away Messages

• The presentation of elevated triglycerides with or without pancreatitis, fatty liver, and other cardiometabolic risk factors is a common presentation in clinical practice.
• Patients can have underlying inherited disorders not with atypical clinical phenotypes.
• Secondary causes can often exacerbate less severe genetic abnormalities, whether monogenic or polygenic.
• Several less common disorders with common presentation can now be treated with new therapeutic interventions. Awareness leads to diagnosis and better management.