Lipodystrophy: Metabolic and Clinical Aspects

Resource Room Slide Series
Lipodystrophy Diagnosis and Clinical Presentation

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Disclosures

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- Current research support from GI Dynamics
Objectives

• Describe key characteristics of lipodystrophy syndromes to translate commonly used classification schemes
• Explain clinical problems in lipodystrophy to identify the need for treatment
• Review common expected complications, comorbidities, and mortality to educate patients and their families
• Recognize lessons from misdiagnosed or undiagnosed cases to distinguish common pitfalls of clinical care
Lipoatrophic Diabetes,* Lipoatrophy,* Lipodystrophy*

• Paucity of adipose tissue
• Insulin resistance
• Hypertriglycerideridemia

*Terms are used interchangeably in the literature and can be considered synonymous.
Lipodystrophy Syndromes

• Fatty infiltration of liver and other tissues
• Deficiency of adipocyte hormones (eg, leptin)
Spectrum of Fat Loss

- Variable degree of fat loss
- Correlation between the spectrum of fat loss and metabolic consequences
Classification of Lipodystrophies

- Etiology
  - Genetic (congenital)
  - Autoimmune (acquired)
  - Other
Seip-Berardinelli Syndrome

- Autosomal recessive
- Heterogeneous: multiple genes
  - e.g., AGPAT-2, seipin, caveolin 1 (Garg A. J Clin Endocrinol Metab. 2011;96:3313-3325.
- Generalized fat loss
- Congenital onset of lipoatrophy
  - Early-onset insulin-resistant diabetes
  - Early-onset hypertriglyceridemia
- Associated features
  - Recurrent pancreatitis
  - Steatohepatitis with risk of cirrhosis
Seip-Berardinelli Syndrome, cont.
Kobberling-Dunnigan Syndrome

- Partial lipodystrophy
  - Decreased fat in limbs and trunk
  - Sparing head and neck (? compensatory hypertrophy)
- Onset around puberty
  - ? Greater severity in females
- Autosomal dominant inheritance
  - Mutation in the lamin A gene (LMNA) is most common. (Cao H, Hegele RA. *Hum Mol Genet*. 2000;9:109-112.)
  - Other unknown genes also exist.
- Hypertriglyceridemia and mixed hypercholesterolemia
Kobberling-Dunnigan Syndrome, cont.
Classification of Lipodystrophies

- Etiology
  - Genetic
  - Autoimmune
  - Other
Lawrence Syndrome

- Generalized lipodystrophy
- Autoimmune etiology (?)
  - Associated with other autoimmune diseases
- Acquired within first decade of life
- Variable presentation, probably heterogeneous
- Metabolic consequences (severe)
  - Diabetes (~5 years after fat loss)
  - Severe hypertriglycerideridemia
Acquired Generalized Lipodystrophy (AGL)
Other Acquired Lipodystrophies

- Partial lipodystrophy: variable patterns of fat loss, heterogeneous
- Typically acquired within second or third decades
- Female preponderance
- Autoimmune etiology
  - Other autoimmune diseases, especially juvenile dermatomyositis
  - Complement component 3 (C3) protein deficiency, presence of C3 nephritic factor (C3NeF), and/or glomerulonephritis
  - Low complement component 4 (C4) and multiple autoimmune diseases (type 1 diabetes, chronic achive hepatitis, and Hashimoto’s)
- Metabolic consequences less severe
Barraquer-Simmons Syndrome: Acquired Partial Lipodystrophia (APL)
Lipodystrophy Is Rare in JDM and Adult Dermatomyositis

- 8.6% in JDM (28/324)
- <1% in adult dermatomyositis
- None in polymyositis or overlap myositis (juvenile or adult)

Juvenile Dermatomyositis (JDM)-Associated Lipodystrophy
Generalized Lipodystrophy in JDM
JDM-Associated Partial Lipodystrophy
JDM-Associated Focal Lipodystrophy
Classification of Lipodystrophies

• Etiology
  – Genetic
  – Autoimmune
  – Other
Other Etiologies for Lipodystrophy

- Specific drugs (e.g., antiretroviral drugs)
- Viral illness (molecular mimicry?)
- Local injections (typically only focal fat loss)
Spectrum of Fat Loss

- Variable degree of fat loss
- Correlation between the spectrum of fat loss and metabolic consequences

Very important take-home point!
Objectives

• Describe key characteristics of lipodystrophy syndromes to translate commonly used classification schemes
• **Explain clinical problems in lipodystrophy to identify the need for treatment**
• Review common expected complications, comorbidities, and mortality to educate patients and their families
• Recognize lessons from misdiagnosed or undiagnosed cases to distinguish common pitfalls of clinical care
Typical Physical Findings

• Lack of fat depots
• Hypertrophic muscles and veins
• Acanthosis nigricans
• Hirsutism and virilization in females
• Enlarged liver
• Enlarged ovaries in females
• Heat production and sweating
Acanthosis Nigricans

Hyperpigmentation and coarsening of the skin
Hyperandrogenism
Typical Laboratory Findings

- Insulin resistance and hyperinsulinemia
- Diabetes or impaired glucose tolerance test
- Triglyceride and free fatty acid (FFA) levels ↑↑↑
- HDL cholesterol levels ↓
- LDL cholesterol ↑ (variable)
- Androgen levels in females ↑

<table>
<thead>
<tr>
<th></th>
<th>Generalized Lipodystrophy</th>
<th>Partial Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>3/9</td>
<td>2/21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>2-27</td>
<td>26-65</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>9.9±3.5</td>
<td>7.2±0.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>2,015±1,463</td>
<td>426±164</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>7.7±2.6</td>
<td>23.8±2.5</td>
</tr>
</tbody>
</table>

Data from NIH case series in 1999, unpublished data.
Insulin Action: Control Versus Lipodystrophy

Muscle Glucose Uptake

mg/(kg LBM-min)

Control

Lipodystrophic

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lipodystrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/(kg LBM-min)</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

Suppression of Glucose Production (%)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lipodystrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>100</td>
<td>75</td>
</tr>
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</table>

Mechanisms of Insulin Resistance in Lipodystrophy

- Elevated FFA levels in circulation
- Increased lipid deposition in liver and muscle
- Abnormal levels of adipocyte hormones
Data from NIH case series in 1999, unpublished data.
Metabolic Effects of FFAs

- Decreased carbohydrate oxidation
  - Inhibition of pyruvate dehydrogenase (Randle hypothesis)
- Inhibition of glucose transport/phosphorylation
- Activation of protein kinase C
  - ? Protein kinase C-θ
  - Inhibition of molecules in insulin signaling pathway

Increased Rate of Lipolysis

• Whole-body glycerol turnover is elevated nine-fold in lipoatrophic patients compared to normal patients.

• Unanswered questions:
  – Source: Liver?
  – Which lipase?
Mechanisms of Insulin Resistance in Lipoatrophic Diabetes, cont.

- Elevated FFA levels in circulation
- Increased lipid deposition in liver and muscle
- Abnormal levels of adipocyte hormones
Tissue Deposition of Triglycerides

Generalized Lipoatrophy
Severe Insulin Resistance

Normal Adiposity
Normal Insulin Sensitivity

Generalized Obesity
Severe Insulin Resistance
Accumulation of Triglycerides Outside Adipose Tissue: Possible Cause of Insulin Resistance

- Intramyocellular triglyceride
  - Correlated with degree of insulin resistance

- Obesity
  - Exceed capacity of adipose tissue
  - Overflow of triglyceride into other tissues (eg, skeletal muscle and liver)

- Lipoatrophy
  - Absence of adipose tissue
  - “Ectopic” storage of triglyceride in other tissues (eg, skeletal muscle and liver)

Mechanisms of Insulin Resistance in Lipoatrophic Diabetes, cont.

- Elevated FFA levels in circulation
- Increased lipid deposition in liver and muscle
- Abnormal levels of adipocyte hormones
Adipose Tissue: An Endocrine Organ

TNF-α, tumor necrosis factor-α; IL-6, interleukin-6
Leptin Levels in Lipodystrophy

$r = 0.86, P < 0.001$
Lipodystrophy Syndromes

- Loss of adipose tissue
- Altered pattern of adipocyte hormones

- Ectopic fat deposition in liver and muscle
- Impaired fat oxidation
- Insulin resistance

- Non-alcoholic fatty liver disease
- Diabetes
- Hypertriglyceridemia

- Diabetes complications:
  - Accelerated microvascular complications from uncontrolled diabetes
  - Acute pancreatitis

- Cardiovascular disease
- Renal disease
Objectives

• Describe key characteristics of lipodystrophy syndromes to translate commonly used classification schemes
• Explain clinical problems in lipodystrophy to identify the need for treatment
• Review common expected complications, comorbidities, and mortality to educate patients and their families
• Recognize lessons from misdiagnosed or undiagnosed cases to distinguish common pitfalls of clinical care
Other Clinical Manifestations in Lipodystrophy

• Related to insulin resistance:
  – Steatohepatitis
  – Reproductive phenotype
  – Cardiac manifestations
• Renal manifestations
• Other specific manifestations
Prevalence of Transaminitis

- All patients: 35%
  - Generalized lipodystrophy: 63%*
  - Partial lipodystrophy: 26%*

* P <0.01
## Lipodystrophy Syndromes

15 Patients with Abnormal Liver Function Tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>92</td>
<td>44-331</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>58</td>
<td>34-107</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>1.6</td>
<td>1.2-3.8</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>abnormal in 3/15 (20%)</td>
<td></td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>abnormal in 4/13 (31%)</td>
<td></td>
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Lipodystrophy Syndromes
15 patients with Liver Disease

- Two were mildly symptomatic
- Eight had hepatomegaly
- No other signs of liver disease
- Ultrasound in all patients:
  - Abnormal echogenicity in all but one patient, suggestive of fatty liver
  - None had splenomegaly
- Eleven underwent percutaneous liver biopsy

Data from NIH case series in 1999, unpublished data.
Lipodystrophy Syndromes
Liver Biopsy in 11 Patients

- All were compatible with nonalcoholic steatohepatitis
- All had steatosis (1+ to 4+)
- All had lobular inflammation and necrosis
- Fibrosis in eight (73%)
- Mallory bodies in six (54%)
- No cirrhosis in this series, although it is reported in case reports, autopsies, and transplant literature
Other Clinical Manifestations in Lipodystrophy, cont.

- Related to insulin resistance:
  - Steatohepatitis
  - Reproductive phenotype
  - Cardiac manifestations
- Renal manifestations
- Other specific manifestations
Reproductive Phenotypes in Lipodystrophy

- **Males:**
  - Premature balding
  - Impaired fertility

- **Females:**
  - Hyperandrogenism
  - Primary or secondary amenorrhea/oligomenorrhea
  - Infertility
Hyperandrogenism

Data from NIH case series in 1999, unpublished data. This earlier case series formed the basis of the later publication shown in the slide note.
### Amenorrhea/Oligomenorrhea

<table>
<thead>
<tr>
<th></th>
<th>Generalized Lipodystrophy</th>
<th>Partial Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>4/10</td>
<td>1/6</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>4/10</td>
<td>5/6</td>
</tr>
<tr>
<td>Leptin (ng/dL)</td>
<td>1.4±0.7</td>
<td>3.8±0.9</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>6/10</td>
<td>5/6</td>
</tr>
</tbody>
</table>

Data from NIH case series in 1999, unpublished data. This earlier case series formed the basis of the later publication shown in the slide note.
Infertility in Lipodystrophy

- Fertility is reduced in generalized lipodystrophy, but patients have rarely been known to conceive spontaneously.
- Most Dunnigan’s patients can bear children, but younger generations with more body fat seem to have a severe polycystic ovarian syndrome phenotype.
Ovaries in Congenital Generalized Lipodystrophy (CGL)
Reproductive Phenotype in Males with Lipodystrophy

- Lower testosterone in adulthood in CGL
- Premature hypothalamic-pituitary-gonadal axis and infertility*
- Familial partial LD patients have normal reproductive function, although erectile dysfunction has been noted in older males with diabetes.

* Only in patients with generalized lipodystrophy
Other Clinical Manifestations in Lipodystrophy, cont.

- Related to insulin resistance:
  - Steatohepatitis
  - Reproductive phenotype
  - **Cardiac manifestations**
- Renal manifestations
- Other specific manifestations
### Cardiac Findings in Lipodystrophy

<table>
<thead>
<tr>
<th>Type</th>
<th>Patients (n)</th>
<th>Cardiac Echo Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGL-1</td>
<td>19</td>
<td>10 with LVH, 4 with LVD, 1 with PDA</td>
</tr>
<tr>
<td>CGL-2</td>
<td>10</td>
<td>8 with LVH</td>
</tr>
<tr>
<td>FPLD-2</td>
<td>9</td>
<td>Moderate LVD</td>
</tr>
<tr>
<td>FPLD-?</td>
<td>2</td>
<td>Concentric remodeling</td>
</tr>
<tr>
<td>AGL</td>
<td>13</td>
<td>6 with LVH, 1 with LVD</td>
</tr>
</tbody>
</table>

Cardiac Findings in Lipodystrophy, cont.

- Cardiomyopathy (hypertrophic or dilated)
- Conduction system abnormalities in some
- Sudden cardiac death
- Premature coronary artery disease
Other Clinical Manifestations in Lipodystrophy, cont.

- Related to insulin resistance:
  - Steatohepatitis
  - Reproductive phenotype
  - Cardiac manifestations
- Renal manifestations
- Other specific manifestations
Renal Findings in Lipodystrophy

- Hyperfiltration and proteinuria (AGL, CGL)
- Pathology of diabetic nephropathy rare
- Focal segmental glomerulosclerosis (AGL, CGL, and mandibuloacral dysplasia (MAD)-associated lipodystrophy)
- Membranoproliferative glomerulonephritis (even in familial partial lipodystrophy [FPL]), may be associated with low C3 and C3NeF
- May progress to end-stage renal disease
Baseline Albumin Excretions (a) and Creatinine Clearances (b) of All Patients Who Had Generalized Lipodystrophy and Were Evaluated

Dashed lines correspond to abnormal thresholds.

Spectrum of Glomerular Diseases in Patients with Insulin-Resistant Diabetes and Lipodystrophies

Other Clinical Manifestations in Lipodystrophy, cont.

- Related to insulin resistance:
  - Steatohepatitis
  - Reproductive phenotype
  - Cardiac manifestations
- Renal manifestations
- Other specific manifestations
Other Specific Manifestations

- Increased appetite and hyperphagia in generalized lipodystrophy (due to low leptin)
- Skeletal system: lytic bone lesions in CGL
- Muscles: myopathic features in FPL
- Skin: neutrophic dermatosis, panniculitis, etc.
- Manifestations of specific syndromes
- Manifestations of associated autoimmune diseases
- Lymphomas in AGL (late-onset) or APL
- Potential for malignancy: breast, endometrial
Diabetes Complications in Lipodystrophy

- Diabetic retinopathy; especially in patients with heroic doses of insulin
- Diabetic nephropathy: not common despite presence of other types of renal disease
- Macrovascular disease
- Neuropathy:
  - Severe pain syndrome in some
  - Mixed myopathy and neuropathy
  - Neuropathy associated with high triglycerides (?)
Other Potential Causes of Mortality and Morbidity

High triglycerides:
- Acute pancreatitis
- Eruptive xanthomata
Clinical Approach: First Steps

- History: presentation, family history, consanguinity
- Careful physical examination
  - “You will know it when you see one!”
- Body fat quantification: skin folds, DEXA, MRI T1 weighted images, CT
- Genetic testing: commercially available or research labs:
  - LMNA, AGPAT2, BSCL2, ZMPSTE24, PPAR-γ
- Screen for diabetes or insulin resistance and lipids
Diagnosis of Fat Loss

- Face (sunken cheeks, temple hollowness, sunken eyes, prominent zygomatic arch)
- Arms (skinny, prominent veins, muscularity and bones)
- Legs (skinny, symmetrical, prominent non-varicose veins, muscularity and bones)
- Buttocks (loose skin folds, prominent muscles, loss of contour/fat, hollowing)
- Trunk (loss of fat, prominent veins, muscularity and bones)

Clinical criteria alone are sufficient. Clinician must perform a full physical exam. This diagnosis cannot be established without an exam.
Measurement of Lipodystrophy: Some Tools Used in HIV-Related LD

Carr et al.:  
• Self-assessment  
• Physician assessment  
• Fasting triglycerides  
• Fasting C-peptide and insulin  
• DEXA

Others:  
• Masked photography  
• Single-cut MRI  
• Anthropometry

Can potentially be adopted for all forms of lipodystrophy

Clinical Approach: Next Steps

- Think about liver, heart, kidney involvement
  - Liver tests, imaging, biopsy
  - Heart: consider stress test, echo, ECG, and Holter as indicated
  - Reproductive phenotype: hyperandrogenism and fertility issues

- Specific:
  - Skeletal survey for MAD or CGL
  - Acquired, or skin findings: skin biopsy
  - Autoimmune disease considerations, C3 and C4 levels
  - Question hyperphagia and food-seeking behavior
Differential Diagnosis

- Generalized:
  - Cachexia
  - Anorexia nervosa
  - Starvation
- Partial
  - Cushing’s syndrome
  - Truncal obesity
  - Multiple symmetric lipomatosi
  - Other regional lipomatosi syndromes
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Challenging Diagnoses: A Few Clinical Pearls
Partial Lipodystrophy Due to PPAR-γ Mutations

Case was followed as a type A insulin-resistant patient for years
Teenager with Atypical Partial Lipodystrophy: Initial Diagnosis of Pediatric Cushing’s Syndrome

Lots of body fat, but leptin undetectable
Importance of Full Physical Exam
If there is a proband, look at all relatives with a FULL physical exam!
Conclusions

• A paucity of fat (regionally or generally), in association with severe insulin resistance and dyslipidemia, is a hallmark of clinical diagnosis.
• Metabolic and reproductive abnormalities constitute the majority of clinical problems.
• Lipodystrophy diagnosis is associated with significant morbidity and an increased risk of early mortality.
• There may be significant variation in clinical presentation. Diagnosis may be difficult to establish without a full physical exam.