Lipodystrophy syndromes

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Meet the Expert Session
AACE meeting
May 16, 2015

- I have no financial disclosures

Patient #1

A 17 year old girl who recently relocated to the area is referred from the dermatologist with a yellow skin rash. The rash developed over the past week. She has occasional upper abdominal pain after meals but no nausea or vomiting.

Her mother reports that the patient was very thin as an infant. She also recalls that "it was hard for her to gain weight despite eating a lot". At age 14, diabetes with ketosis was diagnosed and resulted in hospitalization. She was placed initially on insulin but later switched to metformin by a pediatric endocrinologist whom she has not seen in over a year.

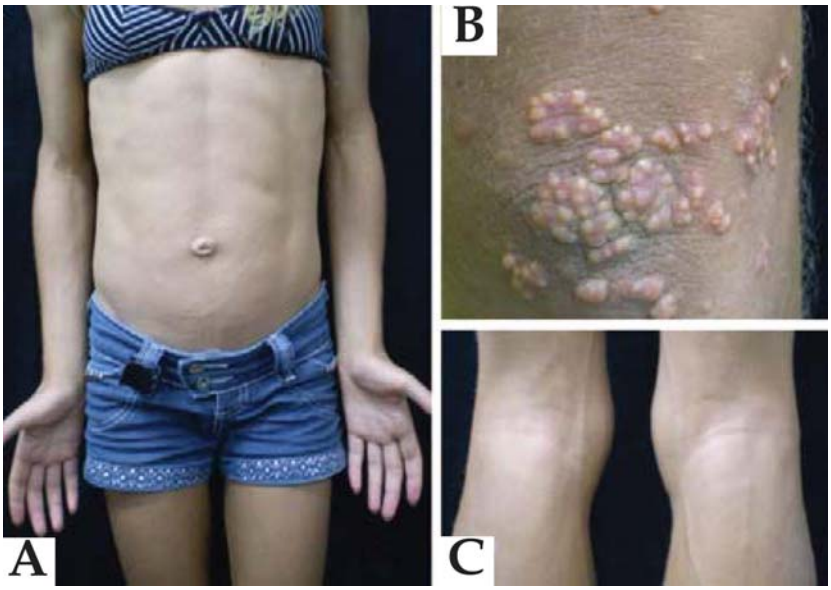
Patient #1

- She is currently on metformin 1000 mg twice daily. She does not check her blood sugars regularly.
- Menarche at age 9; menses are regular
- She is home schooled (since age 12) due to "issues at school".

Patient #1

Physical examination

- Weight 135 lbs, Height 5’9”
- Acromegaloid facies; axillary acanthosis nigricans
- Pale yellow papules with erythematous border on elbows
- No subcutaneous fat all over body
- Protuberant abdomen, hepatomegaly
- Prominent muscles and veins in arms and legs



Machado P 2013

Patient #1

Differential diagnosis?

- Normal lean
- Anorexia nervosa
- Cachexia of ? etiology
- Starvation
- Familial chylomicronemia syndrome due to LPL deficiency

Patient #1 – more history

- No h/o eating disorders
- She is an only child
- Mother and father are related

Patient #1

Differential diagnosis?

- ~~Normal lean~~
- ~~Anorexia nervosa~~
- ~~Cachexia of ? etiology~~
- ~~Starvation~~
- ~~Familial chylomicronemia syndrome due to LPL deficiency~~

Patient #1

- Fasting glucose 298 mg/dL
- HbA1c 12%

- Total cholesterol 579 mg/dL
- Triglycerides 3290 mg/dL

- AST 92 U/L
- ALT 130 U/L
- Albumin 4.2 mg/dL

Diagnosis

- Congenital generalized lipodystrophy : Berardinelli-Siep syndrome
- Very rare
- Autosomal recessive

Lipodystrophy syndromes

Heterogeneous group of disorders characterized by selective loss of adipose tissue

Classification of lipodystrophy

- **Etiology**
  - **Inherited/congenital**
  - **Acquired**
- **Based on body fat distribution**
  - **Generalized**
  - **Partial**

Classification of lipodystrophy

Inherited lipodystrophies

Type	Subtypes	Genetic defect	Clinical features
Congenital generalized lipodystrophy (CGL)	CGL1	AGPAT2	Severe IR, dyslipidemia, fatty liver, PCOS, pseudoacromegaly
	CGL2	BSCL2	
	CGL3	CAV1	
	CGL4	PTRF	

Adapted from Garg A, JCEM 2011

Classification of lipodystrophy

Inherited lipodystrophies

Type	Subtypes	Genetic defect	Clinical features
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	CGL2	BSCL2	
	CGL3	CAV1	
	CGL4	PTRF	
Familial partial lipodystrophy (FPLD)	**FPLD1 – Köbberling**	**unknown**	**Fat loss from extremities**
	FPLD2 – Dunnigan	**LMNA**	**Fat loss from extremities and trunk**
	FPLD3	**PPARG**	**Fat loss from extremities**
	FPLD4	**AKT2**	
	FPLD5	**CIDEC**	

Adapted from Garg A, JCEM 2011

Classification of lipodystrophy

Acquired lipodystrophies

TYPE	SUBTYPE	FEATURES
Acquired generalized lipodystrophy	**•Autoimmune •Idiopathic**	**Severe IR, dyslipidemia, fatty liver, PCOS, pseudoacromegaly**
Acquired partial lipodystrophy	**•Autoimmune •MPGN •Idiopathic**	**Other autoimmune diseases**

Adapted from Garg A, JCEM 2011

Classification of lipodystrophy

Acquired lipodystrophies

TYPE	SUBTYPE	FEATURES
Acquired generalized lipodystrophy	•Autoimmune •Idiopathic	Severe IR, dyslipidemia, fatty liver, PCOS, pseudoacromegaly
Acquired partial lipodystrophy	•Autoimmune •MPGN •Idiopathic	Other autoimmune diseases
HIV associated lipodystrophy	•Protease inhibitors •NRTI	Loss of sc fat from face, extremities; fat deposition in neck and abdomen
Localized lipodystrophy	•Drug induced •Pressure induced •Idiopathic	Loss of sc fat from localized areas

Adapted from Garg A, JCEM 2011

Endocr Pract. Author manuscript; available in PMC 2014 Jul 23.
Published in final edited form as:
Endocr Pract. 2013 Jan-Feb; 19(1): 107–116.

PMCID: PMC4108221
NIHMSID: NIHMS614356

THE CLINICAL APPROACH TO THE DETECTION OF LIPODYSTROPHY – AN AACE CONSENSUS STATEMENT

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Back to patient #1

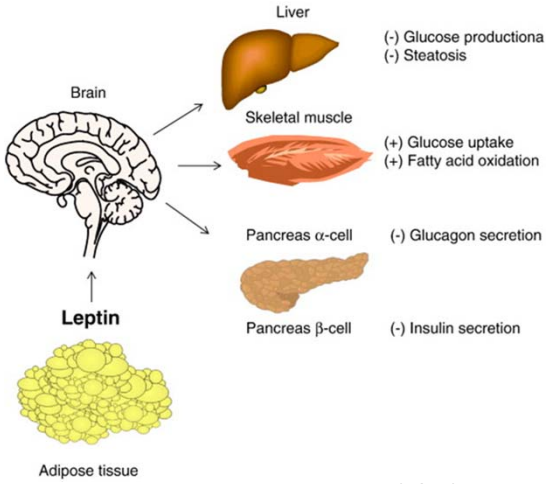
- Lean phenotype
- Absence of body fat
- Type 2 diabetes, poorly controlled
- Severe hypertriglyceridemia

How do you treat patient #1?

- Challenging!

- Lower triglycerides to decrease acute pancreatitis risk
- Manage diabetes/severe insulin resistance
- Counsel parents – important to allay psychosocial stress
- Cosmetic treatment
- Specific treatment - leptin

Leptin



Maintains energy homeostasis

Promotes satiety

Park & Ahima, Metabolism. 2015 Jan;64(1):24-34

Treatment of lipodystrophy

Leptin replacement

Metreleptin

- **Increases insulin sensitivity**
- **Decreases TGs and liver fat**
- **Curbs appetite**
- **Normalizes menses**
- **Improves fertility**
- **Decreases hyperfiltration and protein loss through kidneys**

Leptin in lipodystrophy

Picture courtesy of Dr. R. Brown NIH

Leptin (metreleptin or Myalept) in lipodystrophy

- **Approved only for generalized lipodystrophy (congenital or acquired)**
- **Not approved for partial lipodystrophy, irrespective of metabolic disease**
- **Not approved in HIV lipodystrophy**

Patient #2

- A 42 year old non-smoking woman is referred for history of markedly elevated triglycerides. She has no history of pancreatitis. While in college, she was found to have triglycerides (TG) ~800 mg/dL.
- Two years ago she was placed on gemfibrozil by an endocrinologist for TGs of 754 mg/dL. She has treated hypothyroidism and pre-diabetes (A1c 6%).

Patient #2

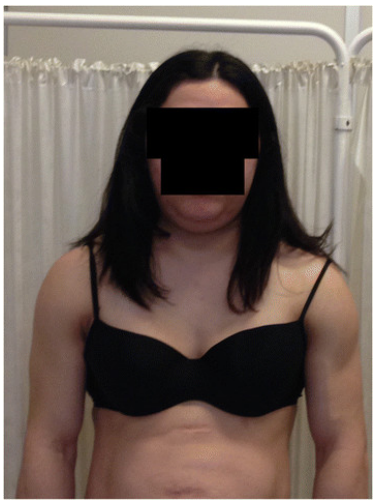
- She had breast augmentation surgery about 12 years ago. She also revealed that she is contemplating gluteal implants.
- Her father and brother also have elevated TGs (but no pancreatitis) and are on treatment. Her father had MI at age 77. There is no family h/o premature CAD.
- She exercises 6x a week. She has 3-5 drinks a week.
- She has irregular menses. She is single and has no children

Patient #2

Physical examination

- Weight 156 lbs; BMI 27; BP 131/87mmHg
- Face -prominent cheeks and thick neck with no buffalo hump or acanthosis
- Normal skin thickness, no striae or bruising
- Dark terminal hair on chin and below umbilicus
- Muscular arms and legs with prominent veins, no subcutaneous fat on extremities or abdomen
- No gluteal shelf
- Large labia

Patient #2



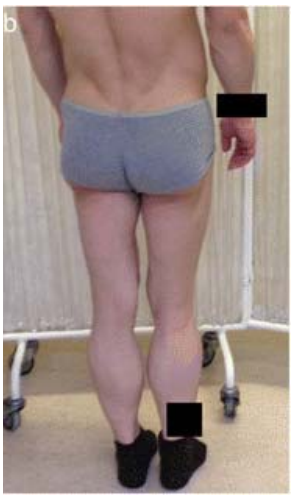


Photo source: Belo S et al. BMC Research notes 2015, 8: 140

Patient #2

Laboratory test	Value
TOTAL CHOLESTEROL	207 mg/dL
TRIGLYCERIDE *	315 mg/dL
HDL	39
LDL	105
A1c	6.0%
TSH	2.515mIU/mL

** On gemfibrozil*

Differential?

- ✓ Normal
- ✓ Non-classical CAH
- ✓ Polycystic ovary syndrome
- ✓ Lipodystrophy
- ✓ Something else?

More labs

- Total testosterone 0.4 ng/mL
- Free testosterone 1.4 pg/mL
- 17 hydroxyl progesterone 132 ng/dL
- 24 hr urinary cortisol - normal

Differential?

- ~~✓Normal~~
- ~~✓Non-classical CAH~~
- ~~✓Polycystic ovary syndrome~~
- ✓**Lipodystrophy**
- ✓**Something else?**

How do you distinguish normal lean from lipodystrophy?

- **Lean muscular phenotype could be normal in an athletic individual**

<u>Red flags:</u>

- **Metabolic disease in a lean individual**
  - **Acanthosis**
  - **Diabetes**
  - **Hypertriglyceridemia**
  - **Fatty liver/NASH**

Diagnosis

- **What kind of lipodystrophy does she have?**
  - ***Familial partial lipodystrophy 2 (Dunnigan variety)***
- **Genetic testing?**
  - **LMNA gene mutation**
- **How do you treat it?**
  - **Leptin?**

Patient #3

- A 51 y/o woman is referred for management of elevated triglycerides and poorly controlled diabetes. She has had Type 2 diabetes 19 years with erratic control. She is currently on U-500 insulin 40 units twice daily. She has treated hypertension.
- She had seen an endocrinologist 2 years ago who reported performed “some hormone tests”. She has since abandoned follow up.

Patient #3

- She reports that she has had elevated TGs “for as long as she can remember”. She has no current h/o abdominal pain but recalls an episode of pancreatitis 10 years ago when she discontinued all her diabetes medications. She has had trouble with her weight for years, and is at her maximum weight of 320 lbs. One year ago she lost 100 lbs and was able to decrease her insulin dose. However her weight has increased and much of it is in her abdomen. Her husband has observed a hump on the back of her neck.
- She does not smoke or drink. She has 2 adult children. Her daughter, aged 26 is also heavy.

Patient #3

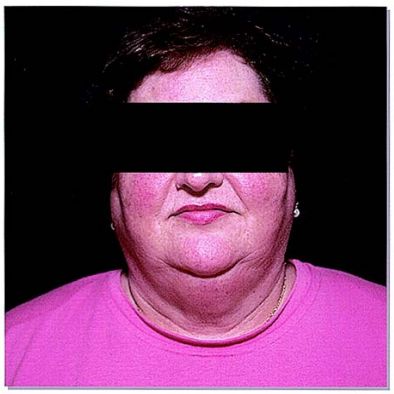
- On physical exam:
- Weight 320lbs, BMI 54.9; BP 116/62mmHg
- Cushingoid face, buffalo hump, supraclavicular fat pad
- Acanthosis around neck
- Pendulous, obese abdomen,

no hepatomegaly

- Normal skin thickness,

no violaceous striae (only white)

- Phlebomegaly in forearms and legs



Patient #3

Laboratory studies:

- Total cholesterol 389 mg/dL
- Triglycerides 940 mg/dL
- HDL 26 mg/dL
- HbA1c 11.2%

Differential?

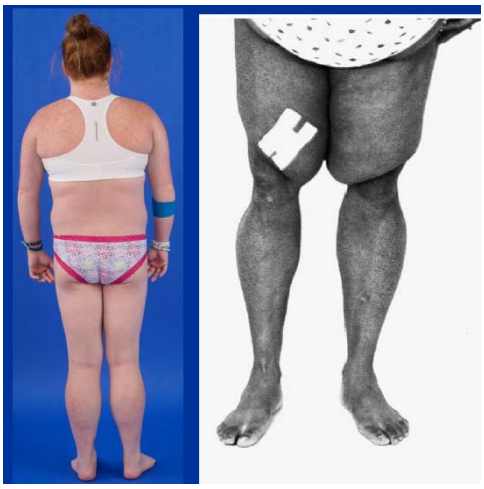
- **Normal obesity**
- **Cushing syndrome**
- **Lipodystrophy**

How do you distinguish an obese individual from a lipodystrophic individual?

- Obesity is extremely common!

Think outside the box when:

- Fat distribution is unusual
- Metabolic disease is out-of-proportion to obesity
- Positive family history

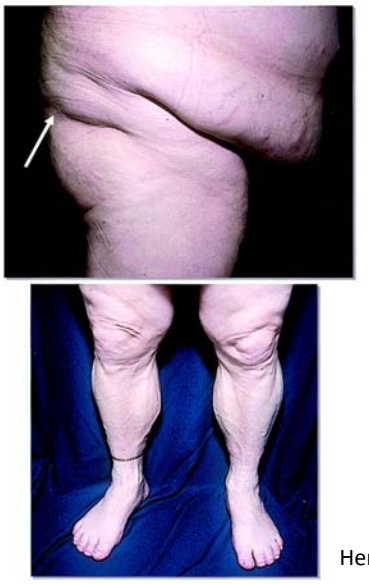


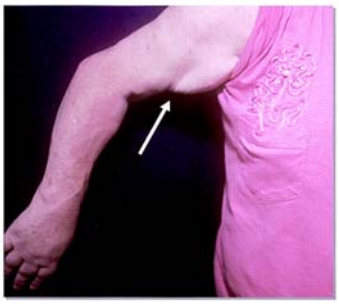
Picture courtesy of Dr. R. Brown NIH

Patient #3

- Underwent work up for Cushing syndrome
- Overnight 1mg dexamethasone suppression test:
  - Cortisol 0.7ug/dL
- 24h urine cortisol 43.6ug/24h (10-80)
  - Urine volume 1650mL
  - No urine creatinine was performed

Patient #3





Herbst K et al. Diabetes Care. 2003 Jun;26(6):1819-24.

Diagnosis?

- **FPLD type 1 : Köbberling's lipodystrophy**
  - Truncal and neck adiposity with no fat in extremities
- Severe insulin resistance
  - High insulin requirements - >1000 units/day
  - Insulin sensitizers- Metformin, pioglitazone
  - GLP-1 agonists
- Severe hypertriglyceridemia
  - Diet – avoid alcohol
  - Fibrate
  - Statin
- Cardiovascular risk management – CAD, cardiomyopathy, conduction abnormalities
- Cosmetic management - liposuction

Photo source: Endocr Pract. 2013 Jan-Feb; 19(1):107-116

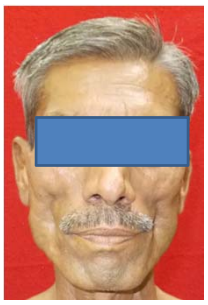
Patient #4

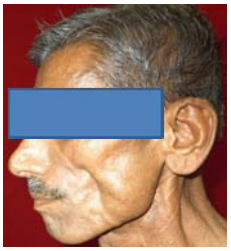
- A 51 year old non-smoking male presents for management of moderate hypertriglyceridemia. He has known HIV treated with HAART. His viral load is undetectable with excellent CD4 counts. He endorses change in his facial appearance with thinning of his face and increased abdominal obesity over the past 5 years. He also has well controlled T2DM, treated with metformin. His weight has been stable and he does not consume alcohol.
- He takes HAART –zidovudine and tenofovir, lopinavir/ritnovir, atorvastatin 10mg.

Patient #4

On examination,

- Weight 152 lbs, BMI 26, BP 128/70
- Loss of subcutaneous fat in cheeks, no subcutaneous fat in arms and legs
- Dorso-cervical fat pad
- Obese, protuberant abdomen





Patient #4

- Laboratories:
- Total cholesterol 220mg/dL
- Triglycerides 620mg/dL
- HDL 36
- LDL not calculated

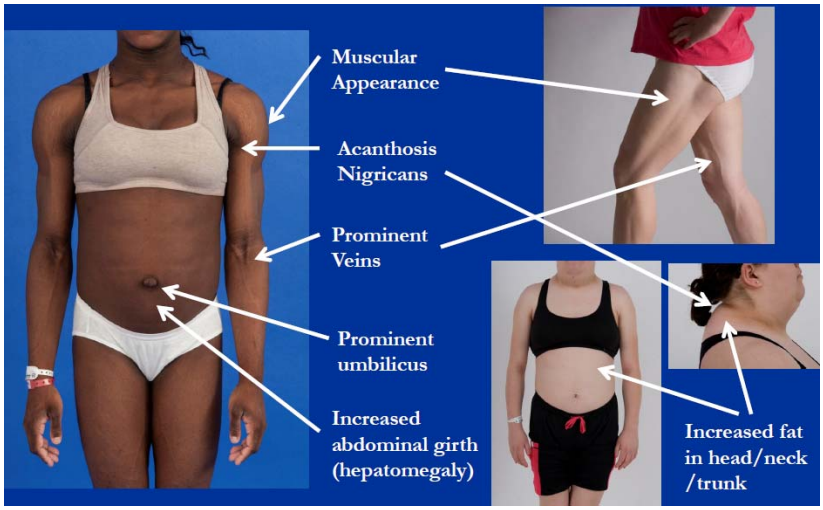
- HbA1c 7.2%

HIV lipodystrophy

- What do you do for this man?

- Switch to more modern HAART regimen
- Treat dyslipidemia
- Cosmetic treatment

Summary: Recognizing lipodystrophy



Adapted from Dr. Rebecca Brown, NIH

Localized lipodystrophy