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# Lipodystrophy – How to Recognise it and What to Do

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# Disclosures

- I have received honoraria from Novo Nordisk, Eli Lilly and Amryt for delivering CPD talks on lipodystrophy and severe insulin resistance at sponsored meetings
- I have acted as Consultant and am UK PI for a Clinical Trial in Segmental Overgrowth (not endocrine) for Novartis

# **Clinical Features of Severe IR**

## **Acanthosis Nigricans**



Semple R et al Endocr Rev. 2011 Aug;32(4):498-514

## **Ovaries and Severe Insulin Resistance**



Semple *et al Endocr Rev.* 2011 Aug;32(4):498-514

#### Ovarian Hyperandrogenism and Response to Gonadotropin-releasing Hormone Analogues in Primary Severe Insulin Resistance

Isabel Huang-Doran,<sup>1,2</sup> Alexandra B. Kinzer,<sup>3</sup> Mercedes Jimenez-Linan,<sup>4</sup> Kerrie Thackray,<sup>1,2</sup> Julie Harris,<sup>1,2</sup> Claire L. Adams,<sup>1,2</sup> Marc de Kerdanet,<sup>5</sup> Anna Stears,<sup>6</sup> Stephen O'Rahilly,<sup>1,2</sup> David B. Savage,<sup>1,2</sup> Phillip Gorden,<sup>3</sup> Rebecca J. Brown,<sup>3,\*</sup> and Robert K. Semple<sup>7,1,\*</sup>



#### The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 8, 2367–2383

# Pseudoacromegaly or Prepubertal overgrowth



Parker, Semple Eur J Endocrinol. 2013;169(4):R71-80.



Srinivasan S *et al Arch Dis Child*. 2003 Apr;88(4):332-4

# Hypoglycaemia

### Glucose



### Insulin



# Severe insulin resistance in disguise: A familial case of reactive hypoglycemia associated with a novel heterozygous *INSR* mutation



Innaurato et al, Pediatric Diabetes. 2018;19:670-674

# Severe Insulin Resistance in Paediatrics

	Presenting prepubertally	Presenting postpubertally
Lipodystrophic	<ul> <li>Congenital generalised LD</li> <li>Acquired LD</li> <li>(Familial partial LD)</li> </ul>	<ul> <li>Familial partial LD</li> <li>Acquired LD</li> <li>(Congenital generalised LD)</li> </ul>
Non lipodystrophic	<ul> <li>Donohue syndrome</li> <li>Rabson Mendenhall syndrome</li> <li>SHORT syndrome</li> <li>Dyslipidaemic IR (mostly idiopathic)</li> <li>(Acquired)</li> </ul>	<ul> <li>Generalised or "Type A" IR</li> <li>Acquired or "Type B" IR</li> <li>Dyslipidaemic IR (mostly idiopathic)</li> </ul>
Complex/ syndromic	<ul> <li>Alström Syn</li> <li>Werner Syn</li> <li>Bloom Syn</li> <li>MOPDII</li> <li>MDP Syn.</li> <li>Mandibuloacral dysplasia</li> <li>Other</li> </ul>	• Formes frustes?

Lipodystrophy

# Definition of Lipodystrophy

- Diagnosis remains largely clinical/subjective, although collateral support from MRI, DXA, clinical anthropometry may be garnered
- Conventionally denotes regional or global lack of adipose tissue despite adequate nutrition
- Conceptually linked to obesity with metabolic complications by the ideas of adipose tissue expandability and "adipose failure"



# **Clinical Presentation of Lipodystrophy**

- <u>Regional</u> or <u>global</u> lack of adipose tissue, especially femorogluteal
- Muscular appearance
- Severe hypertriglyceridaemia
- Previous episodes of pancreatitis
- Severe fatty liver with or without inflammation/fibrosis
- Features of severe insulin resistance (acanthosis nigricans, DM, severe PCOS)

# **Generalised Lipodystrophy**





Khandpur et al Net Case 2011:77:3;402-402





Araújo-Vilar & Santini J. Endo. Inv. 42, 61–73 (2019)

Brown et al JCEM 2016 Dec;101(12):4500-4511

Patni & Garg Curr Diabetes Reports 22, 461–470 (2022)

## Dunnigan Köbberling Lipodystrophy (Familial Partial Lipodystrophy Type 2; FPLD2) Autosomal dominant; LMNA





Parker & Semple *Eur J Endocrinol.* 2013;169(4):R71-80.

Gambineri *et al*, *Eur J Endocrinol*. 2008;59:347-3553. Araújo-Vilar & Santini J. Endo. Inv. 42, 61–73 (2019)

## PPARgamma Ligand Resistance Syndrome (PPARG mutations; FPLD3) Autosomal Dominant



# Mitofusin 2-related Lipodystrophy



Rocha et al, eLife, 2017







Hum Mol Genet. 2015;24:5109-14.



Capel et al, J Clin Lipidol. 2018

# Lipodystrophy after childhood cancer treatment



- "Metabolic syndrome" increased in cancer survivors
- In some cases IR and dyslipidaemia extreme; metabolic phenocopy of lipodystrophy
- Centripetal adiposity common; frank lipodystrophy rare
- Risk greatest with whole body irradiation

Modelled in mice (Poglio et al, Am J Path 2009):

- Female ob/ob mice exposed to 8 Gy TBI plus BMT
- No appetite change but reduced adipose accumulation
- More severe IR and hepatic steatosis
- Fewer small adipocytes in irradiated animals

Mayson et al, Endoc. Prac. 2013

# Example of Chemotherapy-induced Lipodystrophy

- 18-year-old female survivor of neuroblastoma, treated by partial resection, focal irradiation, chemotherapy, TBI, and autologous BMT at 3-4 years old.
- Slipped femoral epiphyses, bilateral cataracts, short stature, and secondary oligomenorrhea.
- T2DM at age 12; poor control (HbA1c > 11%) despite increasing insulin. Triglyceride levels severely elevated with hepatic steatosis.
- Acute pancreatitis developed when serum triglycerides 52 mmol/l.
- Height 147 cm, BMI 20.5 kg/m<sup>2</sup>. Adipose deposition pronounced centripetally. Flexural acanthosis nigricans, multiple acrochordons. Eruptive xanthomata on dorsal surface of forearms, upper arms, liver palpably enlarged at 18 cm in the mid-axillary line.
- Despite low fat diet, fenofibrate and insulin hyperglycaemia and hypertriglyceridaemia persisted, requiring U500 insulin.
- At 24-months after pancreatitis pioglitazone was begun, with good effect

## **Published Cases**

Lorini R, Cortona L, Scaramuzza A, et al. Hyperinsulinemia in children and adolescents after bone marrow transplantation. *Bone Marrow Transplant* 1995; 15: 873–77.

EARLY REPORTS

#### Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood

Mervi Taskinen, Ulla M Saarinen-Pihkala, Liisa Hovi, Marita Lipsanen-Nyman

Lancet 2000; 356: 993-97

Adverse metabolic and cardiovascular risk following treatment of acute lymphoblastic leukaemia in childhood; two case reports and a literature review

P. Amin, S. Shah, D. Walker\* and S. R. Page

# Consequences of Lipodystrophy

## Generic SIR complications

- Acanthosis nigricans
- Hyperandrogenism
- Female subfertility
- Precocious puberty
- Diabetes mellitus
- Soft tissue overgrowth
- Lipotoxic complications
  - Severe dyslipidaemia
  - NAFLD, cirrhosis, HCC
  - Premature atherosclerosis
- Specific to LD
  - Cosmetic distress
  - "Mechanical" problems













# Principles of Management of Lipodystrophy

### Lipodystrophy = "Adipose Failure"

### 1. Offload adipose tissue

- "obesity therapies", guided by rationale and clinical experience
- Low fat, hypocaloric diet, orlistat, GLP1 agonists, SGLT2 inhibitors are all used off licence
- Bariatric surgery described
- Leptin licensed in a subset of patients

#### 2. Maximise insulin sensitivity

- Exercise
- Metformin, (pioglitazone) off licence
- 4. Treat dyslipidaemia, hypertension, hyperandrogenism
- 5. Address QoL, cosmetic issues, genetic counselling

# Gaining information - food diary

Search foods       Gub       Protein       Fat       Alkahal       Fat       Alkahal       Fat       Alkahal       Fat       Alkahal       Fat       Alkahal       Fat       Alkahal       Fat       Fat       Alkahal       Fat       Fat       Alkahal       Fat	<	Wednesday, 14 March 12 >						0		T	home food log exercise log body log dashboard resources	profile
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# Patient feedback

• What have they learnt from the food diary / changes made?

Nutrient	<b>Your intake</b> (average over 7 days)	Recommended intake		
Energy	2,100kcal	Aiming for 5% weight loss 1,600kcal		
Protein	15.5%	20%		
Fat	38.2%	20-30%		
Carbohydrate	46.3%	55-60%		

• Individualised plans based on this

# Leptin therapy

- Leptin is produced by adipocytes
- A low leptin concentration signals starvation and increases hunger
- Patients with lipodystrophy may have a low leptin concentration and increased appetite
- In well chosen patients s/c leptin therapy (metreleptin, od or bd) has marked benefits in terms of metabolic control and QoL
- Metreleptin is now licensed and approved by NICE for treating the complications of leptin deficiency in generalised lipodystrophy for people 2 years and over, and as an option in partial lipodystrophy for people 12 years and over, with poor metabolic control (HbA1c > 58 mmol/mol fasting Tg > 5.0 mM; SMC is currently considering
- <u>Metreleptin is a high cost treatment which should only be started in</u> <u>liaison with the National Severe IR service or equivalent</u>

## Leptin treatment in Generalised LD



Oral et al N Engl J Med. 2002 Feb 21;346(8):570-8.

# **Case History**

- 8 year old female
- Born at 37 weeks, birthweight 2.5kg
- Poor feeding, jaundice, admitted to PICU
- Diagnosis of generalised lipodystrophy at 12 months, mutation in BSCL2 gene
- Developed diabetes aged 5 years
- Poor control despite metformin 500mg bd
- Developmental delay, acanthosis nigricans, hepatomegaly, precocious puberty, HOCM
- 'Always hungry'



# Case History ctd

	15/03/2012	14/06/2012
HbA1c (%)	8.7	6.4
HbA1c (mmol/mol)	72	46
Glucose (mmol/l)	5.8	4.4
Insulin (0-60 pmol/l)	571	270
C Peptide (pmol/l)	3343	1916
Adiponectin (ug/ml)	2.9	3.2
Leptin (ug/L)	<0.1	48.4
Triglyceride (mmol/l)	3.2	1.9
Cholesterol (mmol/l)	4.4	3.6
Alk Phos (30- 135 U/L)	362	383
ALT (0-50 U/L)	64	64
Height (cm)	145.2	147.2
Weight (kg)	32.4	32.2
BMI (kg/m2)	15.4	14.9

# Other management issues

- Screening for complications (liver, cardiac)
- Treatment of hyperandrogenism
- Treatment of hypertension (*PPARG* patients)
- Genetic counselling
- Cosmetic appearance
- Mechanical symptoms

# A case of diencephalic syndrome presenting with isolated lipodystrophy

John H. McDermott<sup>a,c</sup>, Julie Harris<sup>e</sup>, Joanne Fédée<sup>h</sup>, Mars Skae<sup>b,d</sup>, Robert Semple<sup>f,g</sup> and Sofia Douzgou<sup>a,c</sup>

#### Clinical Dysmorphology 2018, 27:122-125

- Beware "Lipodystrophy" without biochemical "adipose failure"
- Consider CNS tumours



# **Primary Insulin Signalling Defects**

# Genetic Insulin Receptoropathies



- Donohue Syndrome
- Rabson-Mendenhall Syndrome
- Type A Insulin Resistance
- HAIR-AN
- Risk of Milder Insulin Resistance

# Donohue Syndrome

(formerly Leprechaunism; AR; Little/no INSR function)

- IUGR, severe failure to thrive
- $\downarrow$ adipose tissue, muscle, Frequent infections
- Large, low-set ears, Wide nostrils, Thick lips, Gingival hyperplasia
- Breast hyperplasia, Prominent nipples, Enlarged external genitalia, Cystic ovaries
- Abdominal distention, Cholestasis, Hepatic fibrosis, rectal prolapse
- Large hands/feet, Acanthosis, Hypertrichosis
- Nephromegaly, nephrocalcinosis
- LVH
- Extreme hyperinsulinaemia, Islet hyperplasia, Postprandial hyperglycemia, Fasting hypoglycemia





De Bock *et al, J Clin Endocrinol Metab*, 2012, 97(5):1416–1417

## Rabson Mendenhall Syndrome (AR; 5-10% INSR function?)



C.T. Thiel et al. Molecular Genetics and Metabolism 94 (2008) 356-362

# **Type A Insulin Resistance**

- Presentation usually peri-puberty
- Precocious puberty
- Oligomenorrhoea/amenorrhoea
- Hyperandrogenism
- Cystic ovaries
- Acanthosis nigricans
- Severe hyperinsulinaemia
- Hypoglycaemia
- Insulin-resistant diabetes

Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. N Engl J Med. 1976, 294(14):739-45

# SHORT syndrome and Severe IR: PIK3R1





Huang-Doran et al, JCI Insight, JCI Insight;1(17):e88766.

# **IR in Complex Syndromes**



POC1A (SOFT syndrome) Chen et al, J. Mol Endo 55(2):147-58.



*PCNT (MOPDII)* Rauch *et al, Science* 2008 319, 816-819 Huang Doran *et al, Diabetes* 60:925–935, 2011

ALMS1 (Alstrom syndrome) Hearn J Mol Med (Berl). 2019 97(1):1-17



Raffan et al, Front Endo 2011 29;2:8



**POLD1** Weedon *et al, Nat Gen* 2013 45(8):947-50.



**NSMCE2** Payne et al, J Clin Invest. 2014124(9):4028-38.

# Werner Syndrome, 1904

- Mutations in the *WRN* gene, encoding a DNA helicase
- Features include
  - Premature ageing (hair, skin)
  - Short stature, Subfertility
  - Sclerodermatous skin changes
  - Loss of subcutaneous fat
  - Insulin resistance, diabetes, dyslipidaemia
  - Malleolar ulceration
  - Cataracts
  - Premature arteriosclerosis
  - <u>Cancer</u>
  - Osteoporosis
  - Sarcopenia







Raffan *et al*, Frontiers in Endocrinology 2011



Atallah *et al*, J Clin Lipidol 2022

# The dangers of "feeding up" in lipodystrophy

- Children with lipodystrophy may never be able to gain adipose tissue
- Supplementing caloric intake to try to achieve this may cause harm
- Atypical body composition and energy expenditure may complicate calculations of requirements



Logan et al, Am J Hum Genet 2018 Dec 6;103(6):1038-1044.

# Practical Summary: Lipodystrophy in Scotland

- Generalised lipodystrophy may be acquired or congenital easy to identify in girls, less so in boys
- Clues are fatty liver, high Tg, low HDL-chol, episodes of pancreatitis, often with acanthosis, and PCOS from end of the first decade
- Partial lipodystrophy may be much more subtle. Important to assess in underwear. The above metabolic abnormalities should trigger consideration even if LD not clinically obvious
- When "fat failure" is recognized, OFFLOAD fat with "obesity therapies. Beware attempt to correct FTT nutritionally
- If LD generalized or extensive, then check serum leptin and refer subcutaneous metreleptin has striking benefit and should hopefully be available soon in Scotland.