Congenital and Acquired Disorders of Insulin Action: How to Spot Them and What to Do

CalSoc, Dunkeld, November 2014

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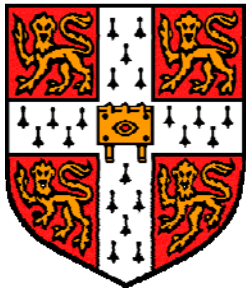


UNIVERSITY OF CAMBRIDGE

Metabolic Research Laboratories,

Institute of Metabolic Science

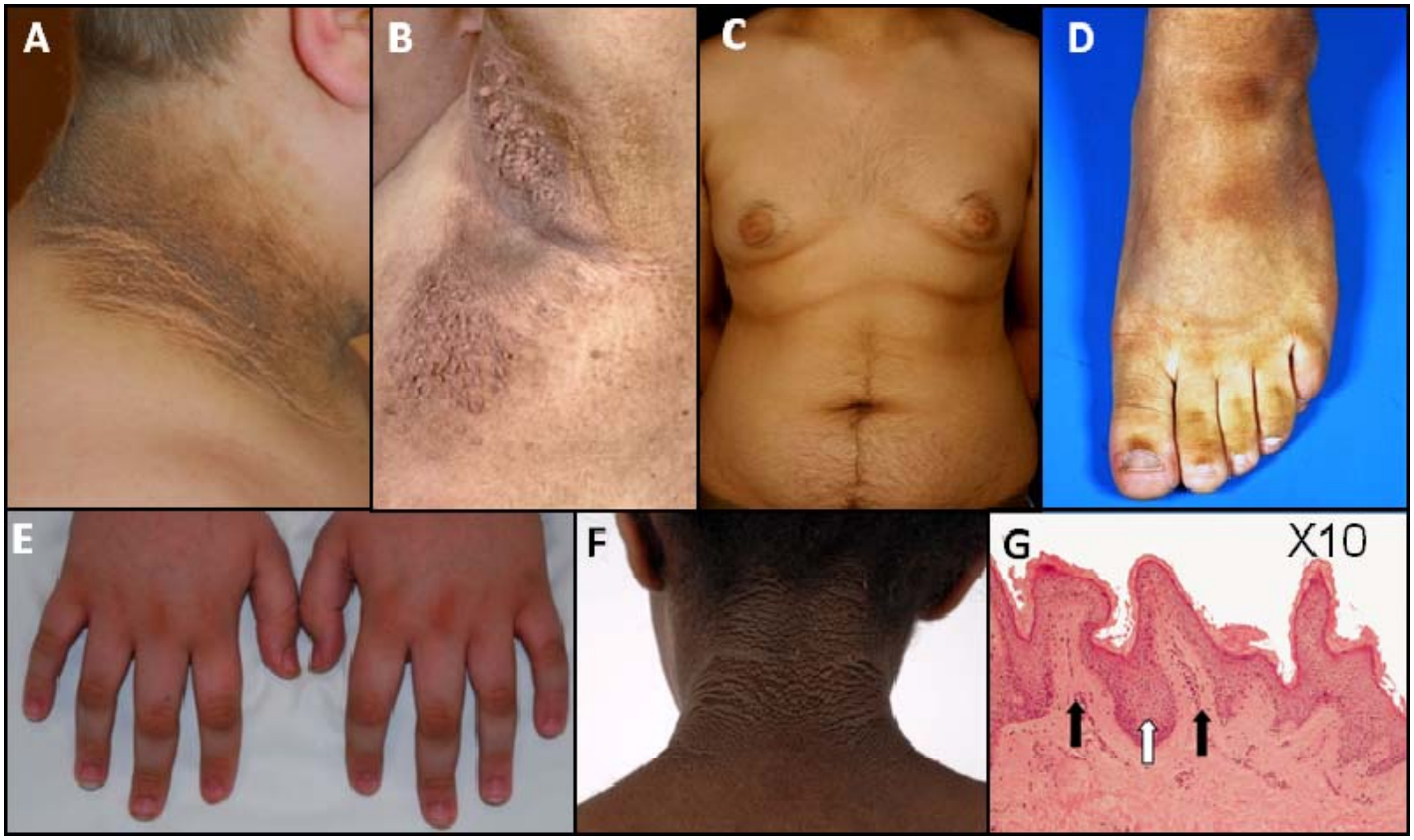
IMS MRL

Severe Insulin Resistance

- Insulin Resistance ≠ Diabetes
- Severe monogenic forms as likely to present to endocrinologists, gynaecologists, dermatologists, hepatologists, lipidologist, acute surgical take as to a diabetes clinic
- Hormones rarely measured
- Obesity creates major “background to noise” problem
- *Probably* significantly rarer than MODY
- All this creates a major role for the astute clinician

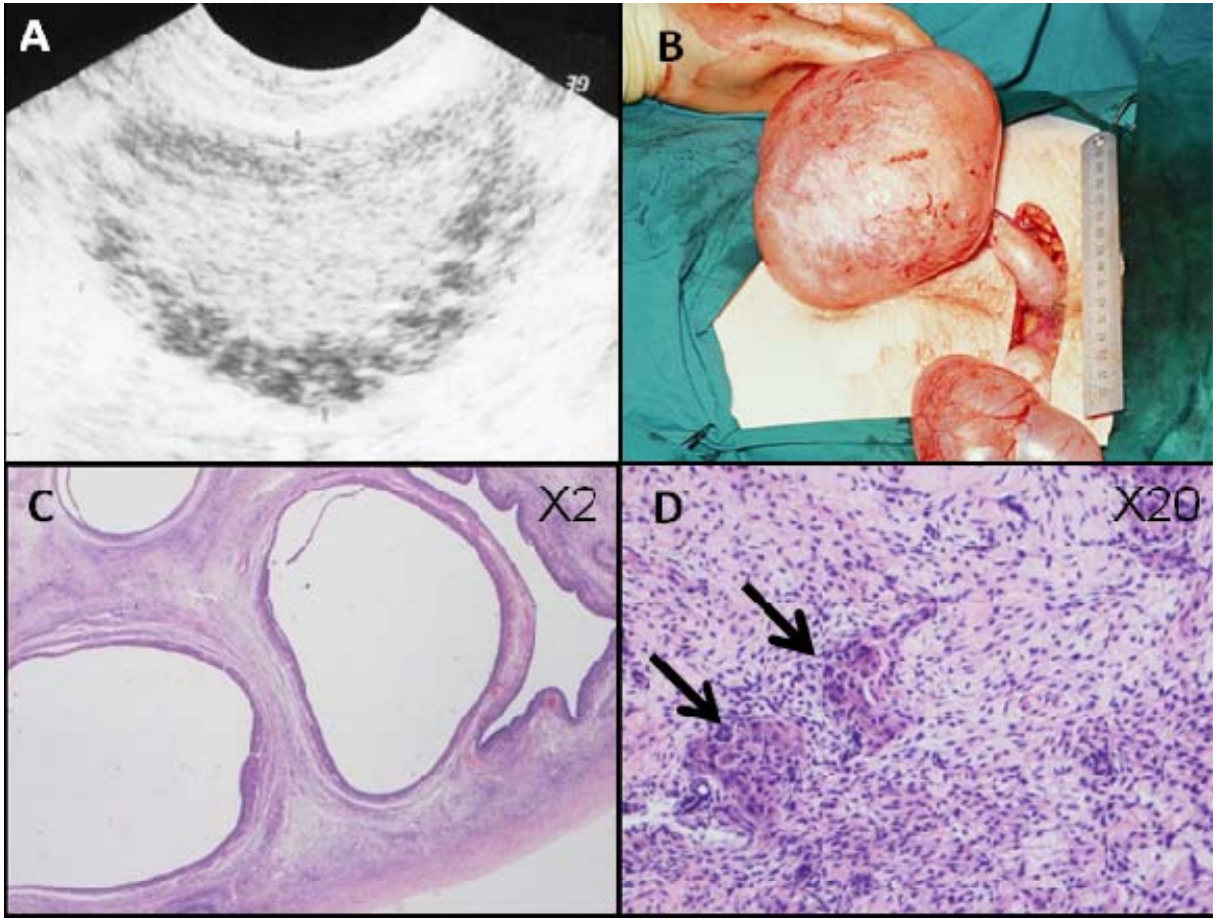
Clinical Features of Severe IR

Acanthosis Nigricans



Semple *et al*, Endocrine Reviews 2011

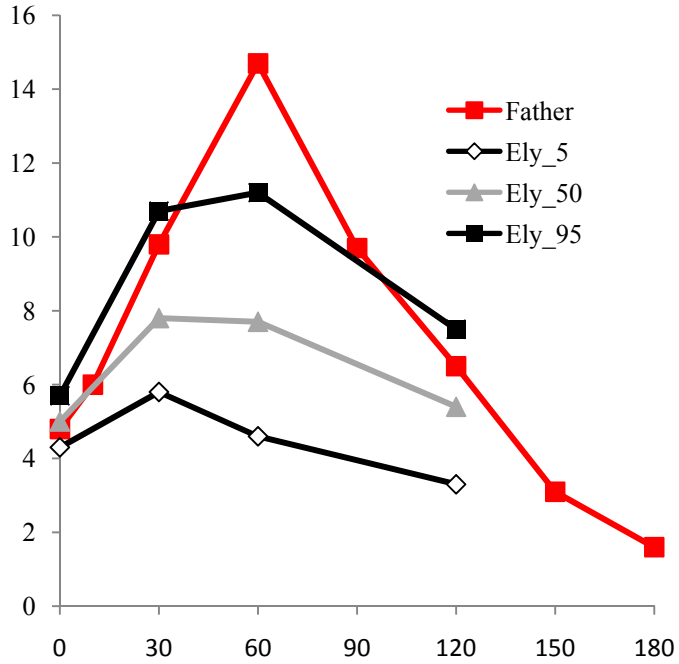
Ovaries and Severe Insulin Resistance



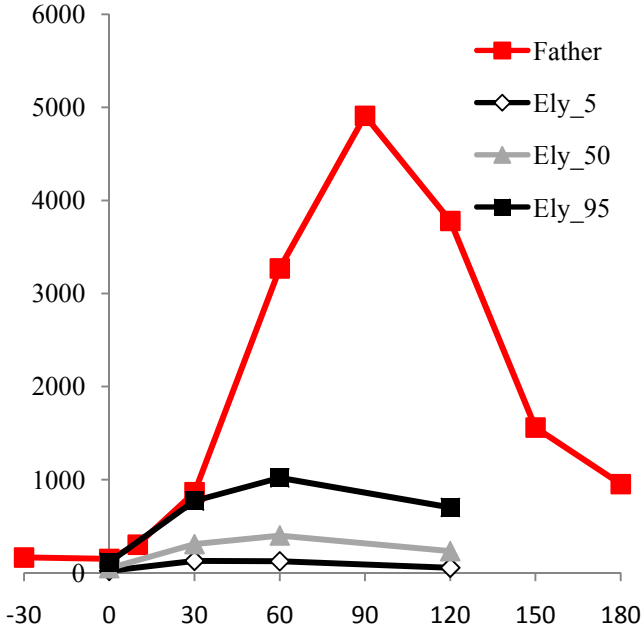
Semple *et al*, Endocrine Reviews 2011

Hypoglycaemia

Glucose



Insulin



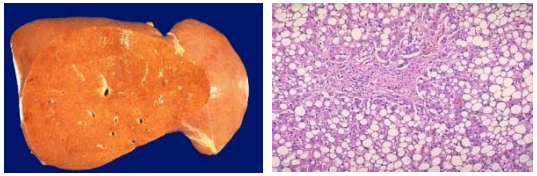
Patient with INSR mutation

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”

Lipotoxicity: “ectopic lipid deposition”

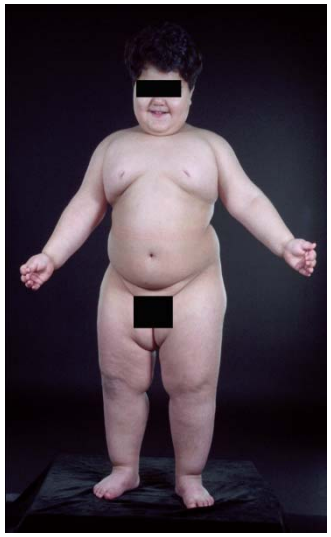


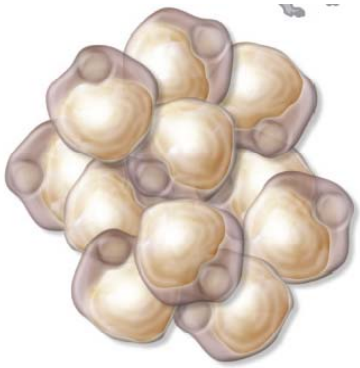
Liver

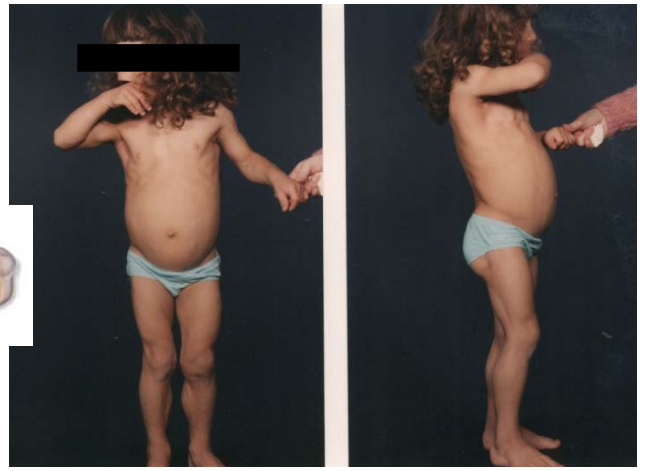
Muscle

Lipid spillover

(Dyslipidaemia)







Obesity

“Relative” Adipose Failure

Lipodystrophy

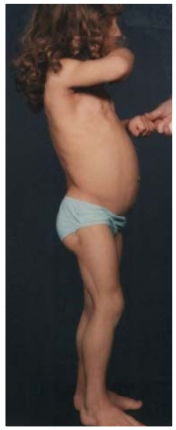
“Absolute” Adipose Failure

Clinical Presentation of Lipodystrophy

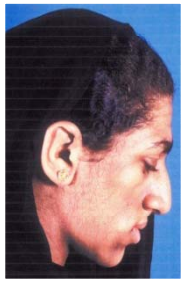
- Regional or global lack of adipose tissue, especially femorogluteal
- Muscular appearance
- Severe hypertriglyceridaemia
- Previous episodes of pancreatitis
- Severe fatty liver with or without inflammation/fibrosis
- Features of severe insulin resistance (acanthosis nigricans, DM, severe PCOS)

Lipodystrophy

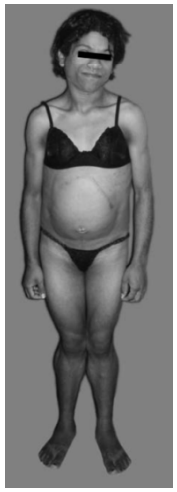
Generalised



BSCL2



AGPAT2



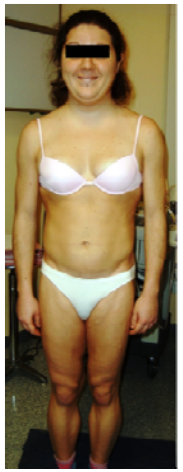
CAV1

acquired

PTRF
(with myopathy)

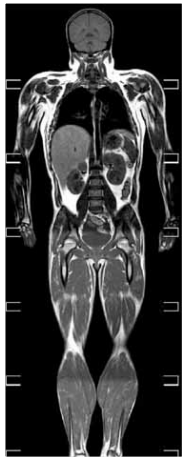
Partial

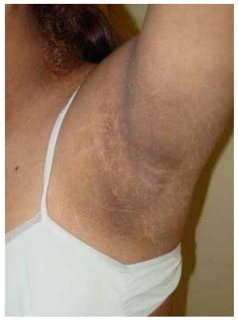
PPARG



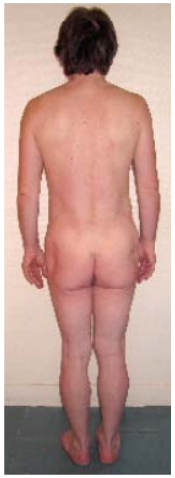
LMNA

acquired





CIDEC

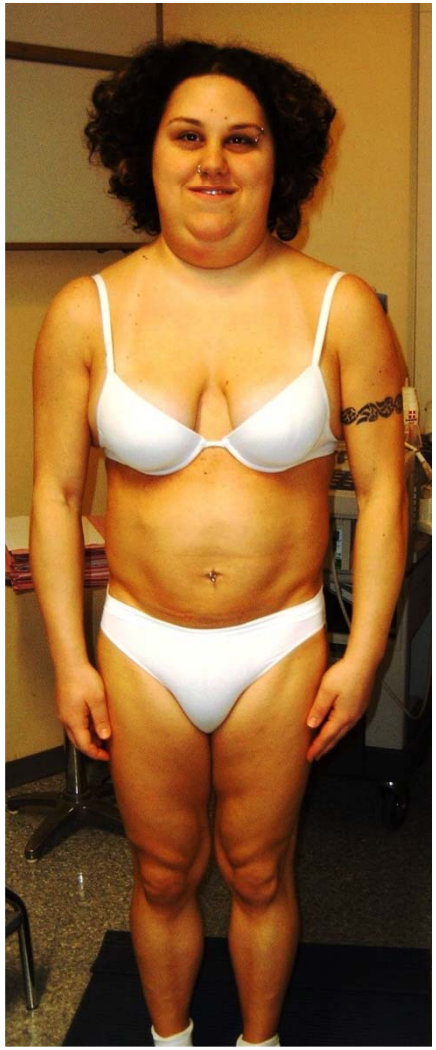


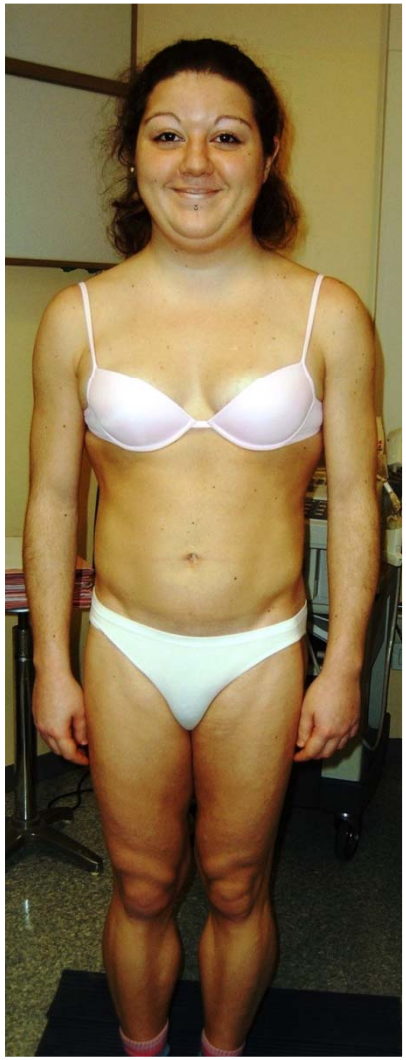
PLIN

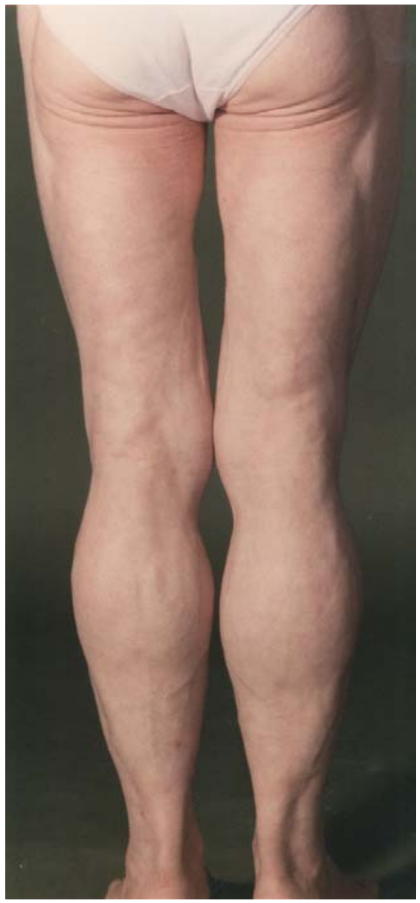
AKT2

Dunnigan Köbberling Lipodystrophy

(FPLD2; LMNA exon 8-12 mutations)

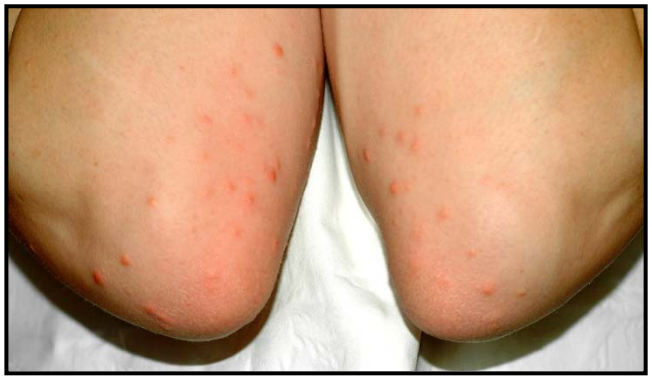


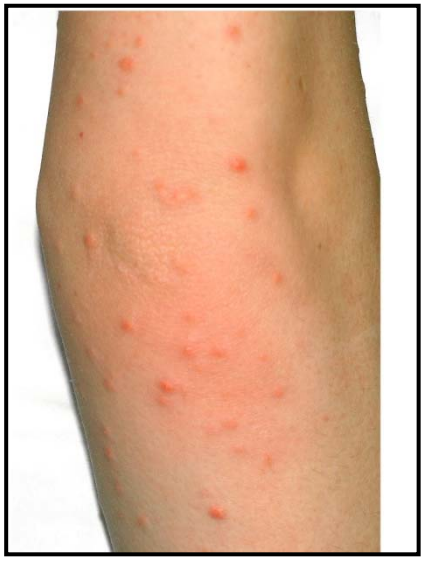




PPARγ Ligand Resistance Syndrome

(FPLD3; PPARG mutations)





PPARγ Ligand Resistance Syndrome

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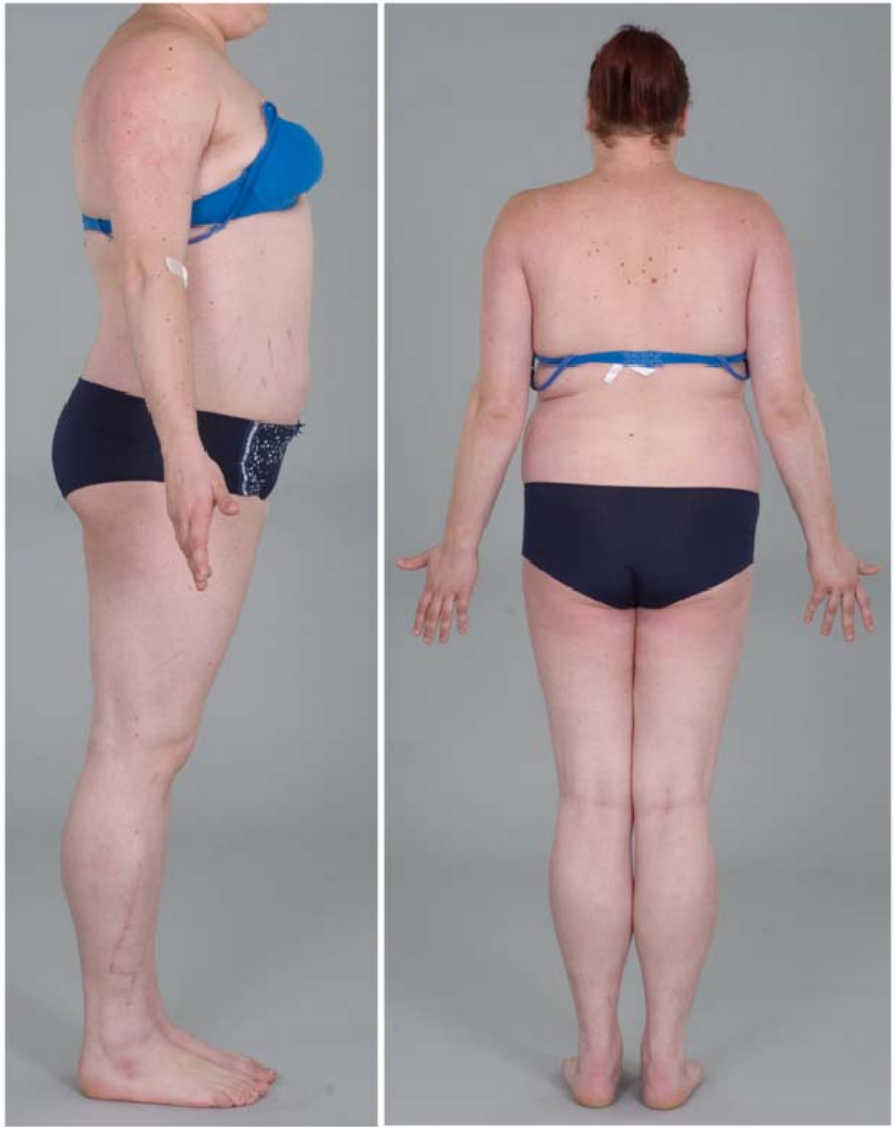


Familial Partial Lipodystrophy Type 1

FPLD1

- Most common type
- “Cushingoid” fat topography
- May be familial
- Most likely genetically heterogeneous
- Role of sex hormones?
- Role of intra-adipose steroid metabolism?

Cushing’s Disease

Acquired Lipodystrophy

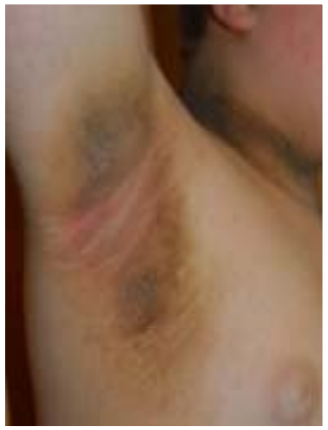
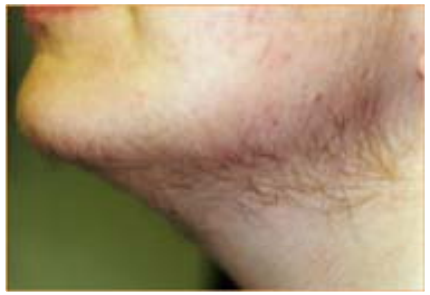
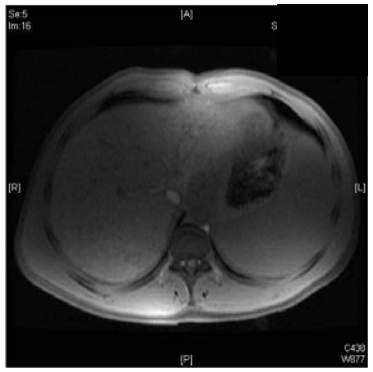
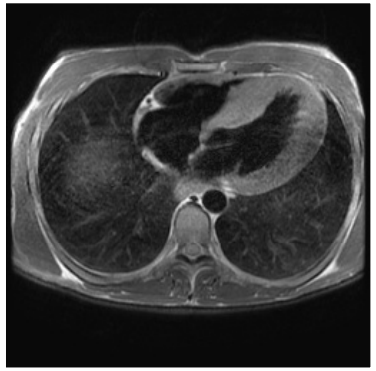
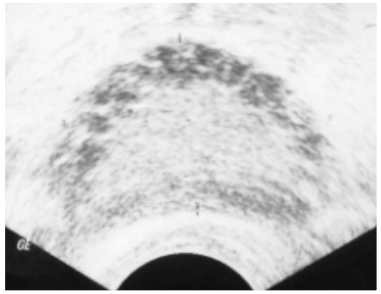
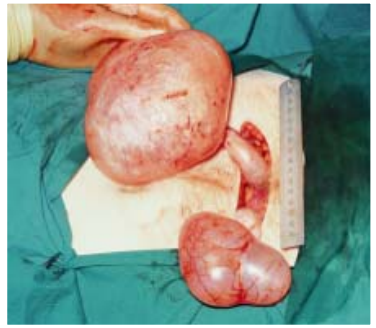
GENERALISED

PARTIAL

- Usually upper body only
- Relatively little IR/DM
- Risk of MCGN; surveillance needed

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
   - Low fat, hypocaloric diet
   - "obesity therapies" – orlistat, GLP1 agonists, bariatric surgery
   - leptin
2. Maximise insulin sensitivity
   - Exercise
   - Metformin, (pioglitazone)
3. Rationally targeted therapy (for the future)
   - Anti-lipolytic agents in "lipid droplet" LD?
4. Treat dyslipidaemia, hypertension

Other management issues

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

Severe Insulin Resistance as a Late Effect of Childhood Cancer Therapy

Case 1

- 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^2. 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

Case 2

- 22-year-old with insulin resistant T2D and severe hypertriglyceridemia.
- **ALL** treated with chemotherapy between 3-6 years old.
- At 7 years CNS relapse treated with focal irradiation, chemotherapy, TBI, and allogeneic BMT.
- Serum transaminases elevated, liver biopsy documented hepatic steatosis.
- Bilateral cataracts, short stature, and secondary oligomenorrhea.
- At age 16 T2DM was diagnosed; poorly controlled despite insulin Oligomenorrhea was treated with oral conjugated estrogens/ medroxyprogesterone.
- Height 160 cm, BMI 22.4 kg/m^2. Preponderance of central adiposity, no frank lipoatrophy. Acanthosis nigricans and acrochordons over chest, abdomen, shoulders, back.
- U-500 insulin and fenofibrate started; subsequent improvement in serum triglycerides to around 8 mmol/l, and HbA1c to 7%. Despite this, pancreatitis developed attributed to hypertriglyceridemia.

Case 3

- 32 year-old man
- **ALL** at 6 years old treated with chemotherapy, cranial irradiation and, TBI, allogeneic BMT.
- At 13 years old height velocity diminished. GH response to insulin and arginine stimulation was diminished and GH therapy commenced
- Leydig cell failure diagnosed at 14 years old and testosterone commenced
- Examination at 13 years old prior to GH therapy revealed severe acanthosis nigricans. BMI was normal.
- OGTT at 18 years revealed extreme hyperinsulinaemia (3180pmol/L at 60mins) with diabetes (11.6mmol/L at 2hours).
- At 25 years old HbA1C 12.2%; random glucose 12.7 mmol/l. Acanthosis nigricans still present, with multiple neck and axillary acrochordons. Metformin was commenced.
- Anterior pituitary function tests at 31 years revealed ongoing hypogonadism and additional hypothyroidism (T_4 = 11), prompting thyroxine introduction.

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

 Diabetic Medicine, **18**, 849–853

Childhood Cancer Survivors

- Increased risk of impaired glucose tolerance, type 2 diabetes, insulin resistance, dyslipidemia.
- Typically normal BMI, but often increased whole body adiposity, with preferential truncal deposition.
- GH deficiency, hypogonadism, hypothyroidism may contribute, but total body irradiation is commonest correlate.
- Risk of overt T2D is particularly strong with TBI, with presentation a median of 9 years following exposure.

Animal Model

Adipose Tissue Sensitivity to Radiation Exposure

The American Journal of Pathology, Vol. 174, No. 1, January 2009

Sandrine Poglio, Sylvain Galvani, Sandy Bour,
Mireille André, Bénédicte Prunet-Marcassus,
Luc Pénicaud, Louis Casteilla,
and Béatrice Cousin

From the Institut Louis Bugnard, Toulouse, France

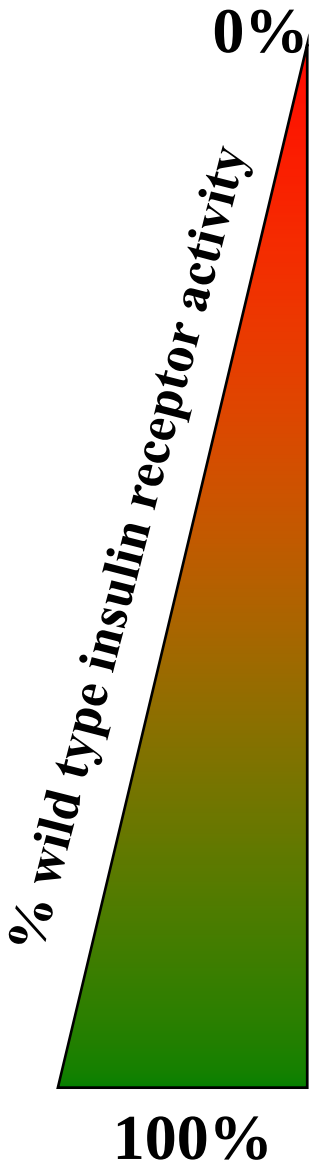
- Direct evidence provided by animal studies.
- Female *ob/ob* mice exposed to 8 Gy TBI plus transplantation with syngeneic or wild-type bone marrow
- No change in hyperphagia but reduced weight due to impaired accumulation of fat, but not lean, body mass.
- Despite this reduction in fat, treated mice had more severe IR and hepatic steatosis than untreated control ob/ob animals.
- Morphometric analysis indicated a reduced proportion of small adipocytes in irradiated animals, and reduced expression of the preadipocyte marker MCP-1.

Clinical Implications of "Adipose Failure" Model

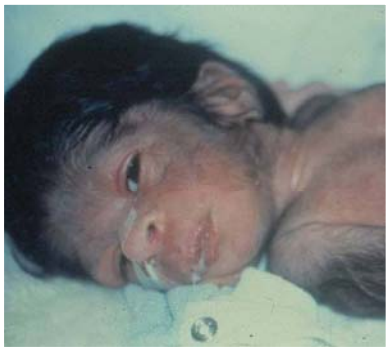
- Patients with impaired adipose expandability after cancer treatment in childhood may exhibit signs of "adipose failure" (dyslipidaemia, insulin resistance, type 2 diabetes) at normal BMIs, sometimes in association with altered adipose topography.
- Principles of management are similar to those for the metabolic consequences of severe obesity, but BMI-based thresholds for therapeutic intervention may be inappropriate
- Therapy aimed at offloading adipose tissue (e.g. Incretin mimetics) or at increasing adipose lipid storage (e.g. Pioglitazone) may be effective: comparative trials are warranted in patients with post-cancer adipose tissue failure.

Primary Insulin Signalling Defects

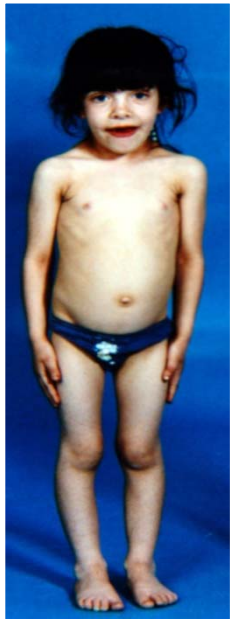
Genetic Insulin Receptoropathies

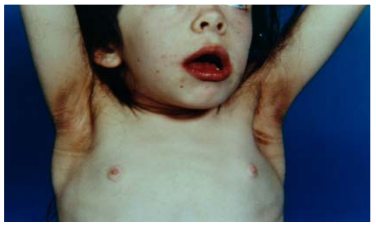


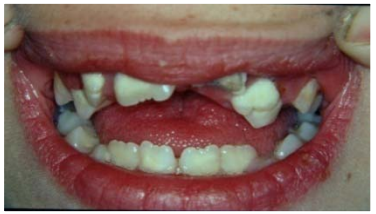
- Donohue Syndrome



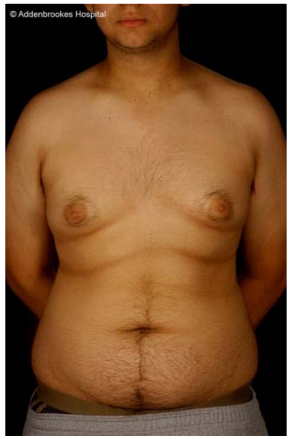
- Rabson-Mendenhall Syndrome

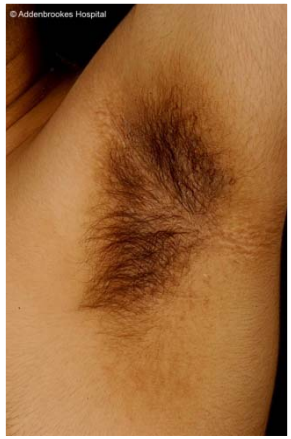






- Type A Insulin Resistance
- HAIR-AN

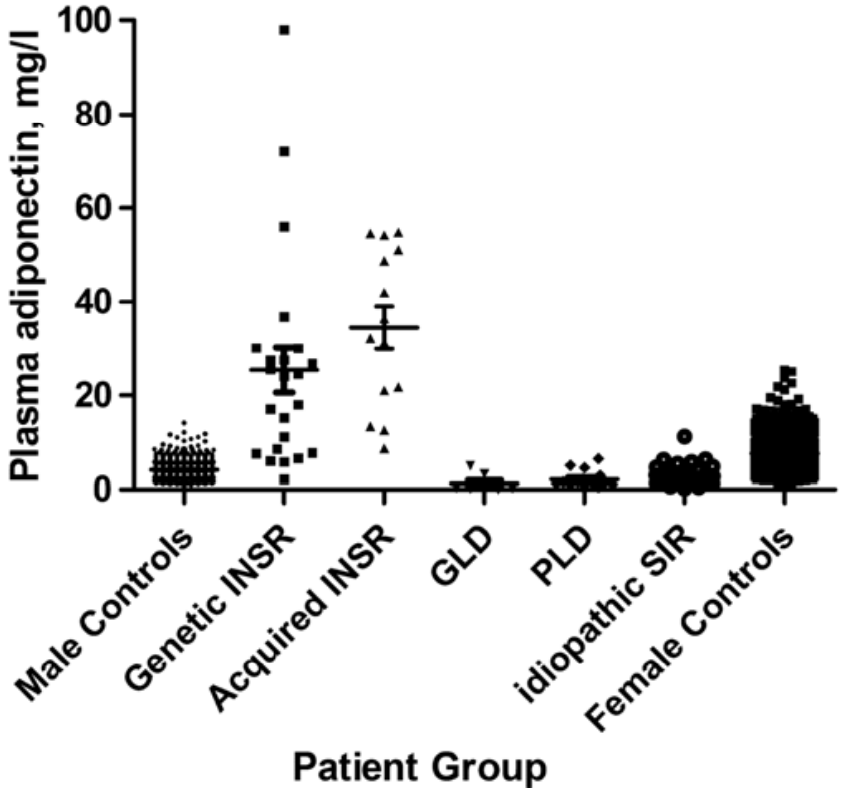


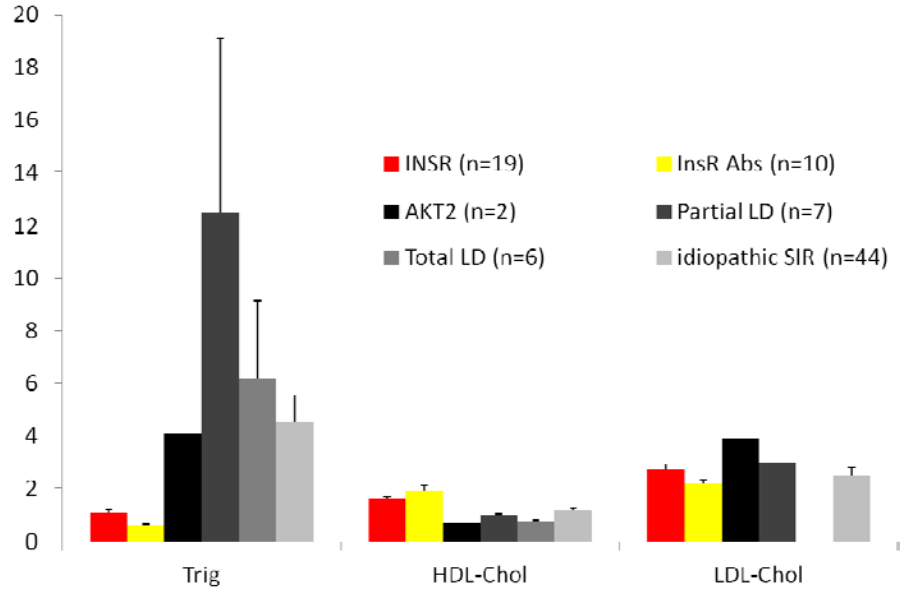


Type A Insulin Resistance

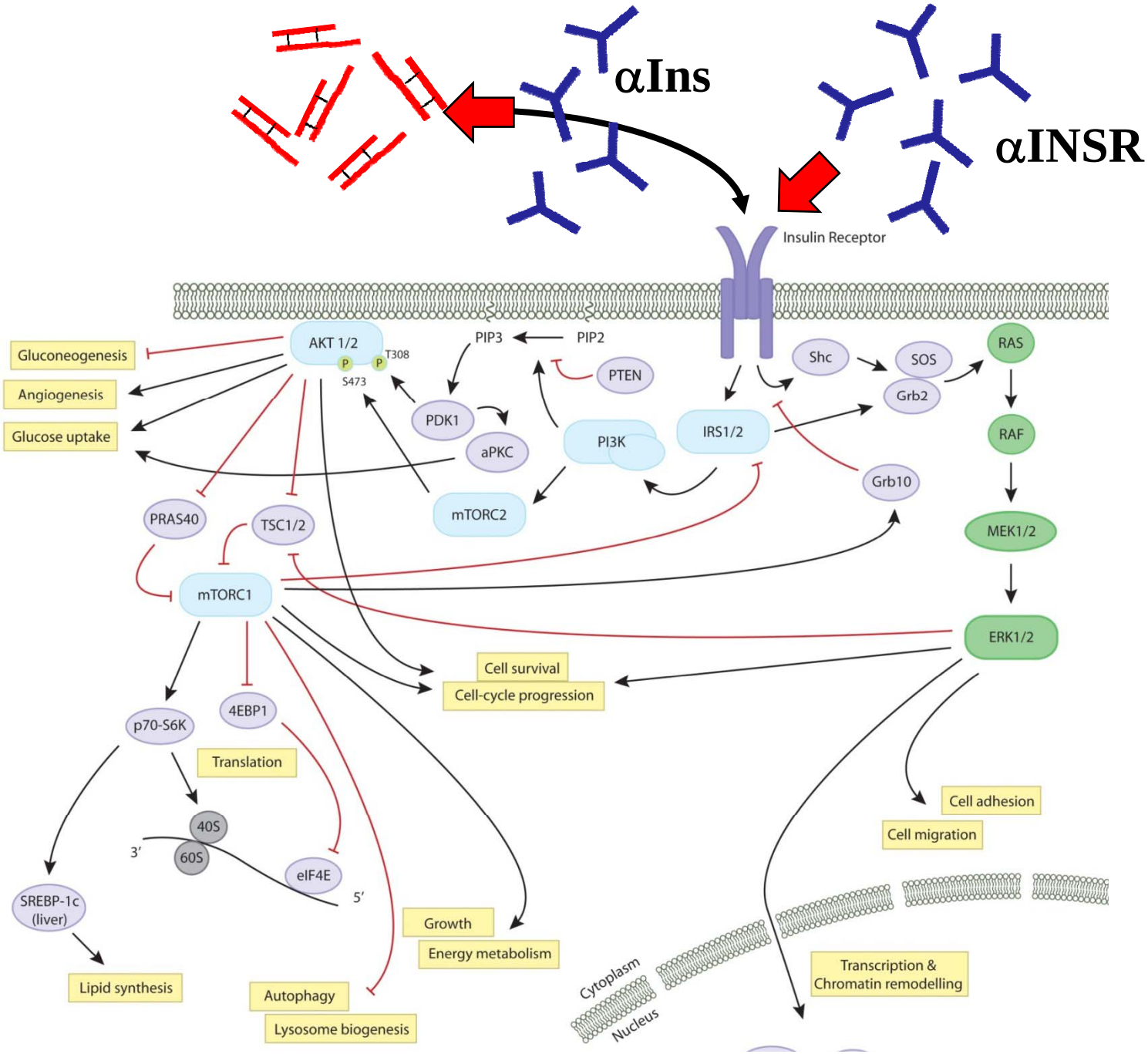
- Presentation usually peri-puberty
- Precocious puberty
- Oligomenorrhoea/amenorrhoea
- Hyperandrogenism
- Cystic ovaries
- Acanthosis nigricans
- Severe hyperinsulinaemia
- Hypoglycaemia
- Insulin-resistant diabetes

Insulin Receptoropathy: Distinct from Prevalent Insulin Resistance





Acquired Insulin Signalling Defects

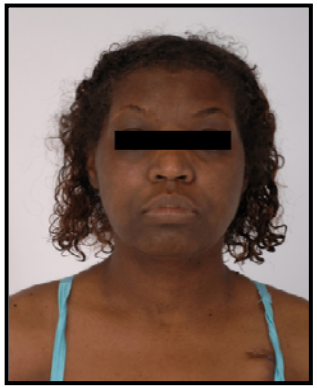

αIns
αINSR
Insulin Receptor
AKT 1/2
T308
S473
PIP3
PIP2
PTEN
PDK1
aPKC
PI3K
IRS1/2
Shc
SOS
Grb2
RAS
RAF
MEK1/2
ERK1/2
Grb10
mTORC2
PRAS40
TSC1/2
mTORC1
Gluconeogenesis
Angiogenesis
Glucose uptake
Cell survival
Cell-cycle progression
p70-S6K
4EBP1
Translation
40S
60S
3′
5′
eIF4E
SREBP-1c
(liver)
Lipid synthesis
Growth
Energy metabolism
Autophagy
Lysosome biogenesis
Cell adhesion
Cell migration
Cytoplasm
Nucleus
Transcription &
Chromatin remodelling

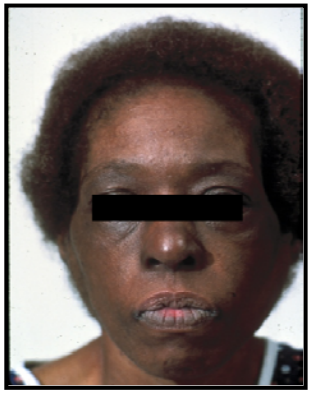
αINSR Abs: Type B insulin resistance

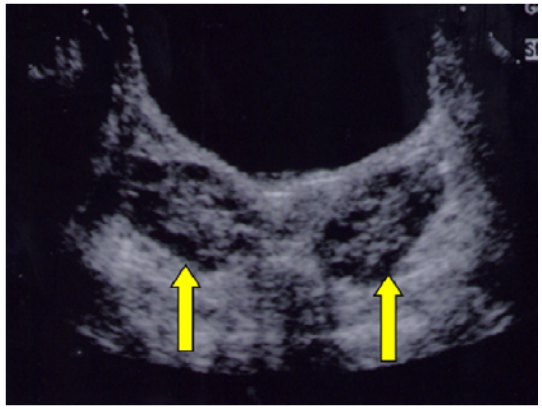
- A syndrome of acquired, extreme insulin resistance mediated by insulin receptor antibodies
- Very rare disorder (Exact prevalence unknown)
- High mortality
- Often in association with other Ab-mediated autoimmune disease
- May be paraneoplastic
- Many cases remit spontaneously with time
- 85% female and African-American

Clinical Manifestations

- Hyperglycemia
- Extreme insulin resistance
- Extreme weight loss
- Severe polyuria
- Acanthosis nigricans
- Ovarian enlargement
- Elevated testosterone levels







Before Type B IR

Type B IR

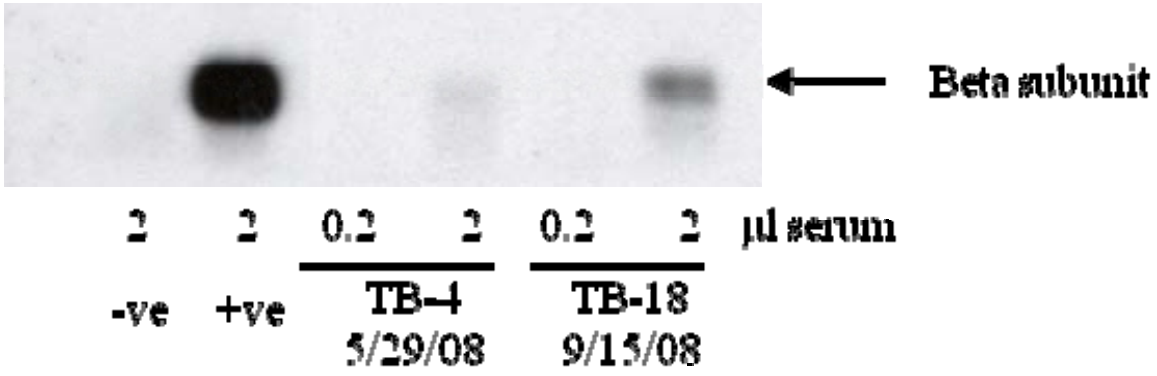
Laboratory Investigation

- Hyperglycemia
- Hyperinsulinemia
- Often high insulin:C peptide ratio
- Often leukopenia, thrombocytopenia, anaemia
- Low or normal serum triglycerides
- Normal serum HDL cholesterol
- No fatty liver
- Elevated adiponectin, often SHBG, IGFBP1

Definitive Diagnosis

Immunoprecipitation Assay:

- Patient serum incubated with a preparation of cell lysate expressing a high concentration of human insulin receptor
- Human IgG pulled out and washed
- Resulting immunoprecipitate blotted for presence of human INSR



Hypoglycaemia due to αINSR Abs

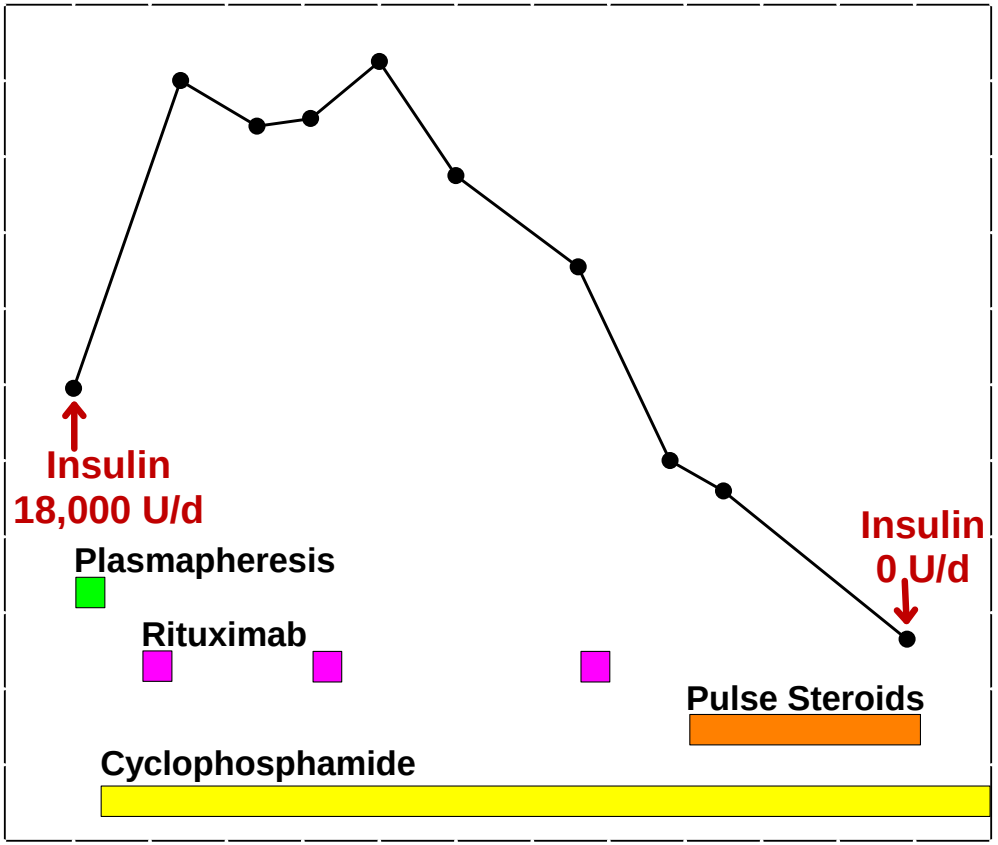
- 24% of patients experience hypoglycaemia at some point in their illness, and this may be the presenting feature
- May be fasting or postprandial
- Often associated with low Ab titres
- Many studies have shown Abs to be activators of the INSR. ?Partial agonists
- Strong female preponderance
- Key clinical discriminators are acanthosis nigricans, new onset oligomenorrhoea/hyperandrogenism

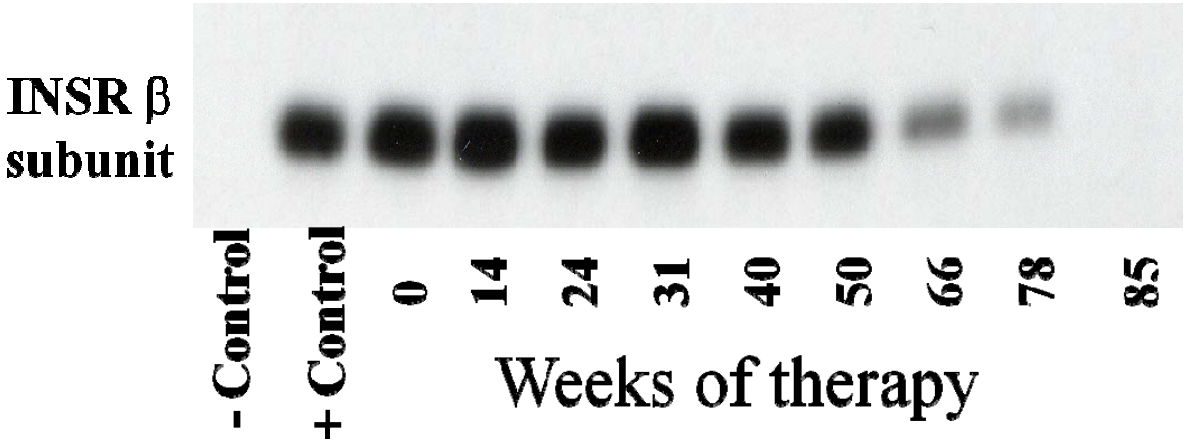
Lupsa *et al*, Medicine (Baltimore), 2009

Multimodal Immunosuppression

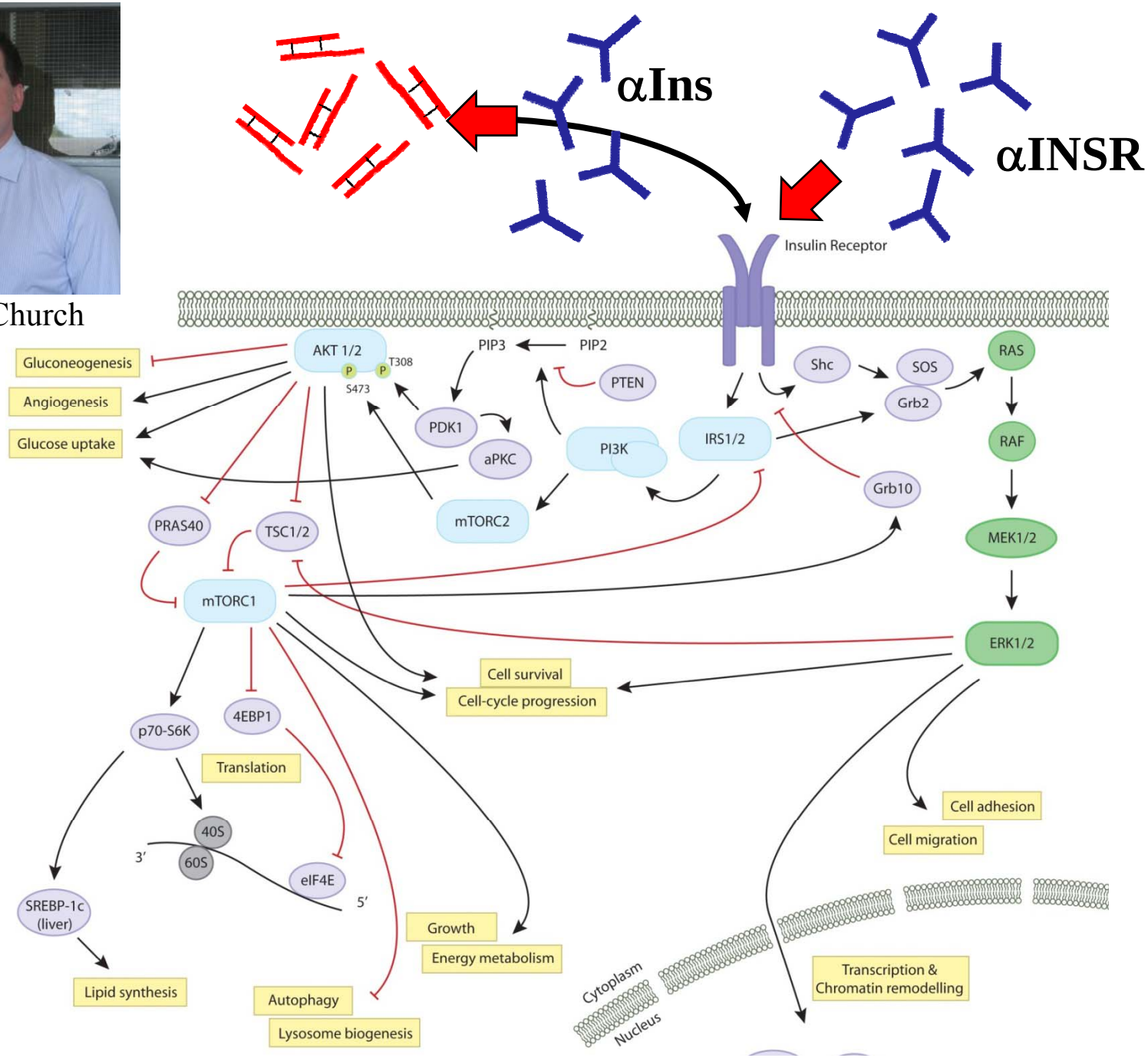
Goal: elimination of auto-antibody

- Rituximab: antibody against CD-20, expressed by B-cells
- High dose pulse steroids: reduce pre-existing antibody-producing plasma cells
- Mild generalized immunosuppression to control T-cell function (low dose)
  - Cyclophosphamide
  - Cyclosporine


Insulin
18,000 U/d
Plasmapheresis
Rituximab
Insulin
0 U/d
Pulse Steroids
Cyclophosphamide


INSR β
subunit
- Control
+ Control
0
14
24
31
40
50
66
78
85
Weeks of therapy

David Church



Case History

- 83 year old man - 60 year history of T1DM
- Historical HbA1c 7.3 – 8.0%
- Peripheral neuropathy/ PVD/ rheumatoid arthritis
- Stable insulin regime for years
  - Levemir 10 units pm, Humalog 7/7/7 units
- No recent weight loss

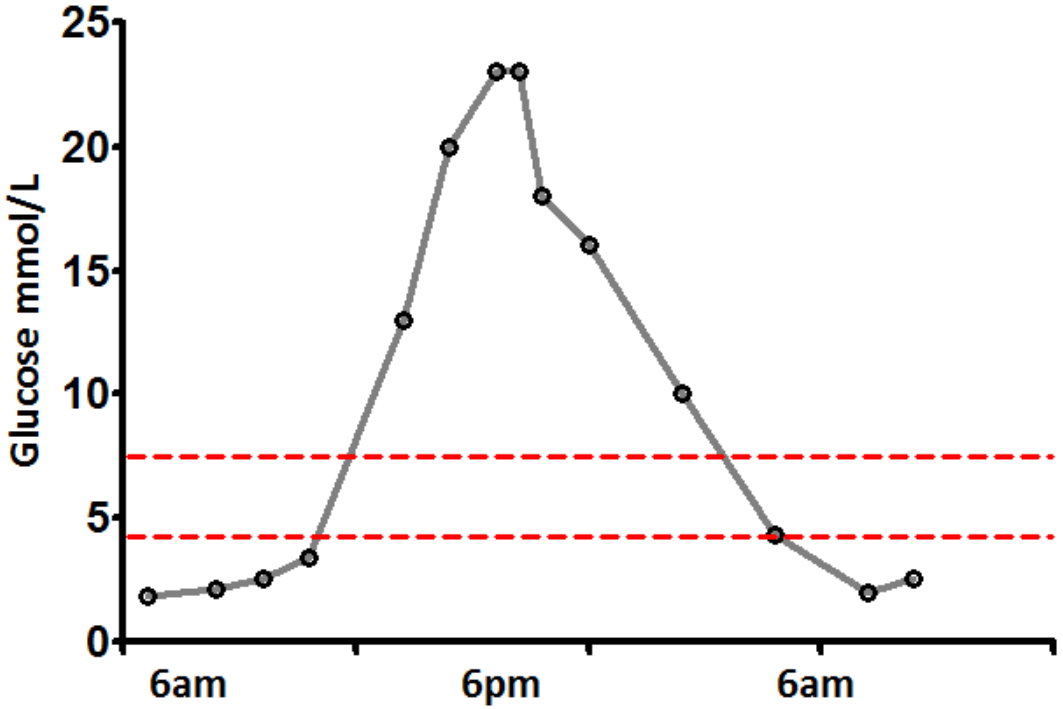
Case History

Several months intractable morning hypoglycaemia (< 2mM) + daytime hyperglycaemia. Dose adjustment ineffectual

Currently on:

Detemir 10, -

Lispro 24,22, 7



HbA1c 10%

Normal renal, hepatic, thyroid and adrenal function

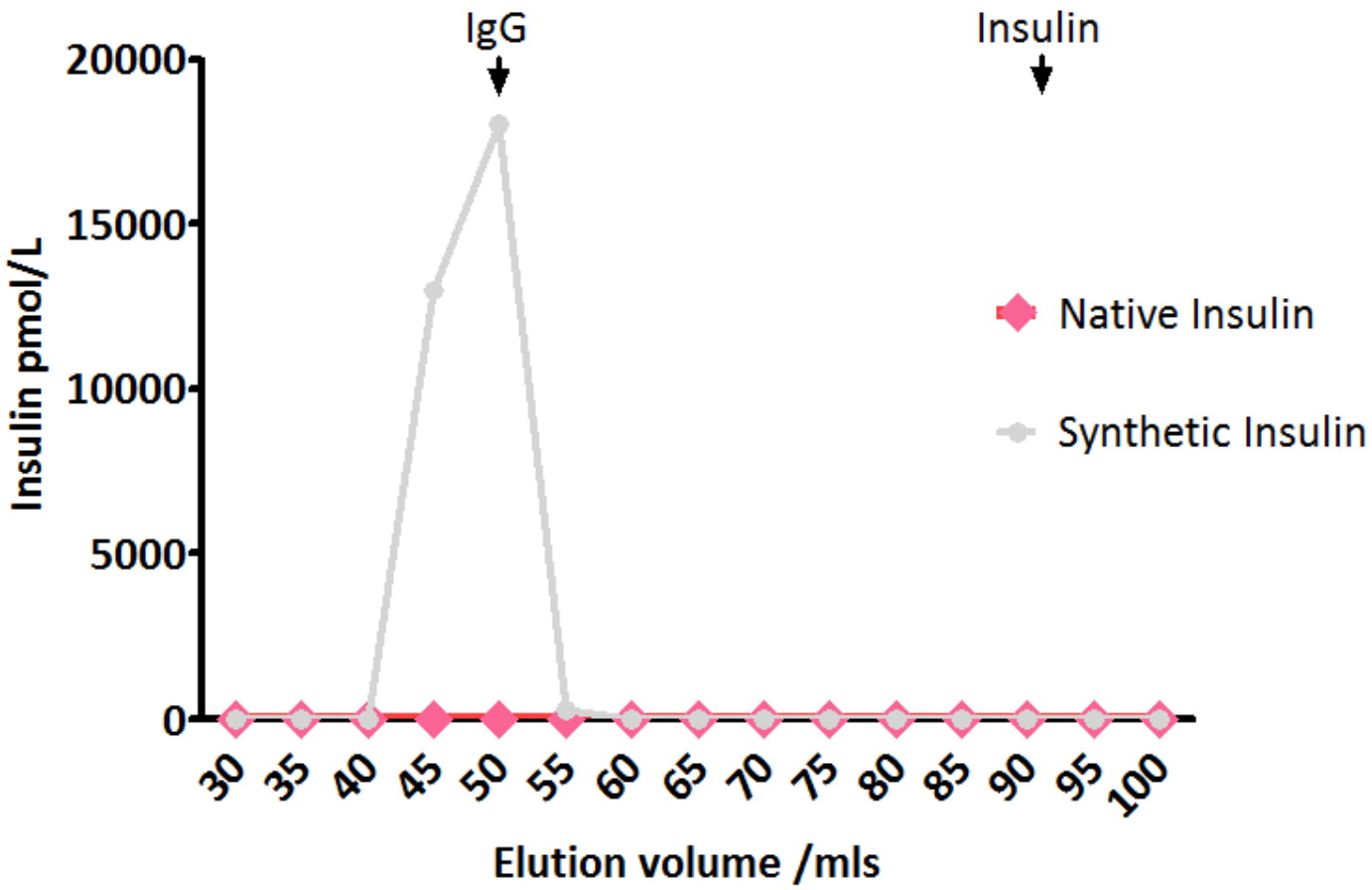
Insulin 2h after 24u Lispro:

- DELFIA assay [native human insulin]: undetectable
- MERCODIA assay [native AND short acting analogue insulin]: 37,108 pmol/L (expected c. 500pmol/L)
- C-peptide undetectable

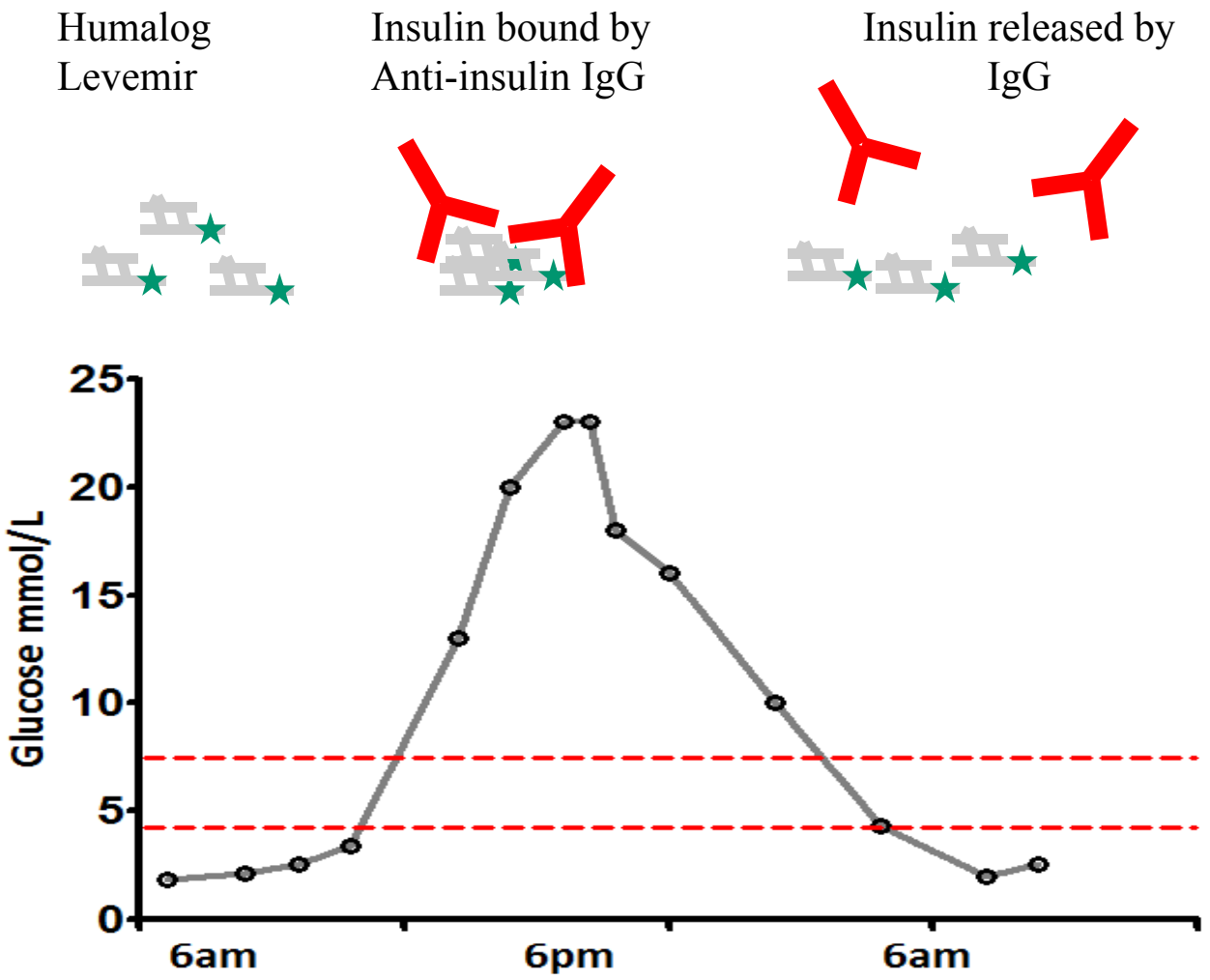
Rheumatoid factor 194 iu/ml (0-30)

αIns Abs strongly positive

Insulin Present as HMW Species on Gel Filtration



Proposed Mechanism



Management

Started on prednisolone 30mg od

- Reduced hypoglycaemia
- No evidence of change in insulin binding capacity of serum
- HBA1C improved to 78 mmol/mol (9.3%)
- Rheumatoid arthritis improved

CASE 2

17 year old

Type 1 diabetes – 2 year history.

HbA1c 96mmol/mol (10.9%). **Erratic CBG.**

DKA. Denied missing insulin doses. Required **250 units of insulin in 48 hours**.

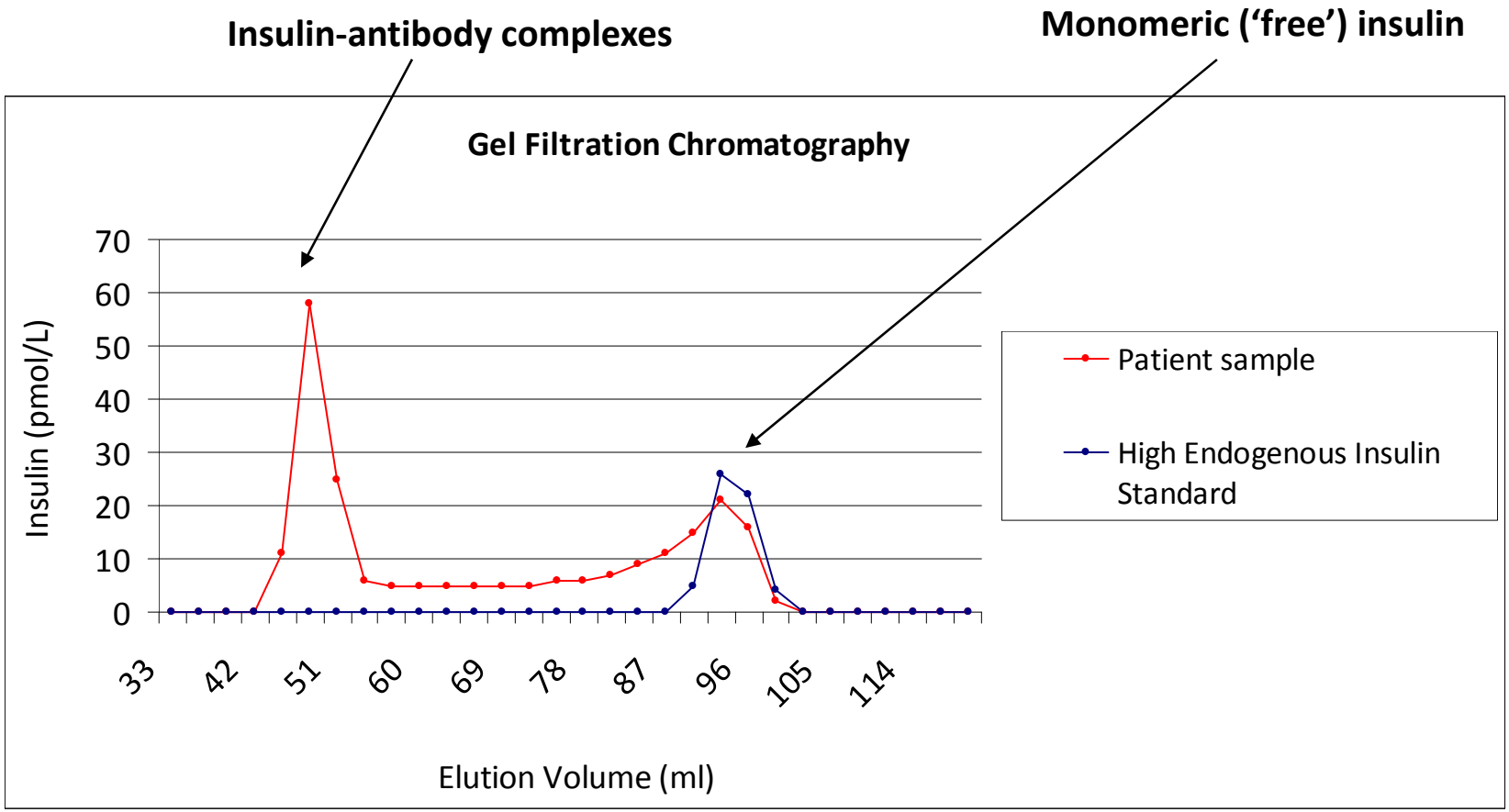
Hypoglycaemia during day/night in spite of **not taking any insulin** for several days.

Admission for investigation of hypoglycaemia. Glucose 10. Not taken insulin in several days. **Measured insulin 2850 pmol/L.**

Insulin antibodies positive. Urine sulphonylurea screen negative.

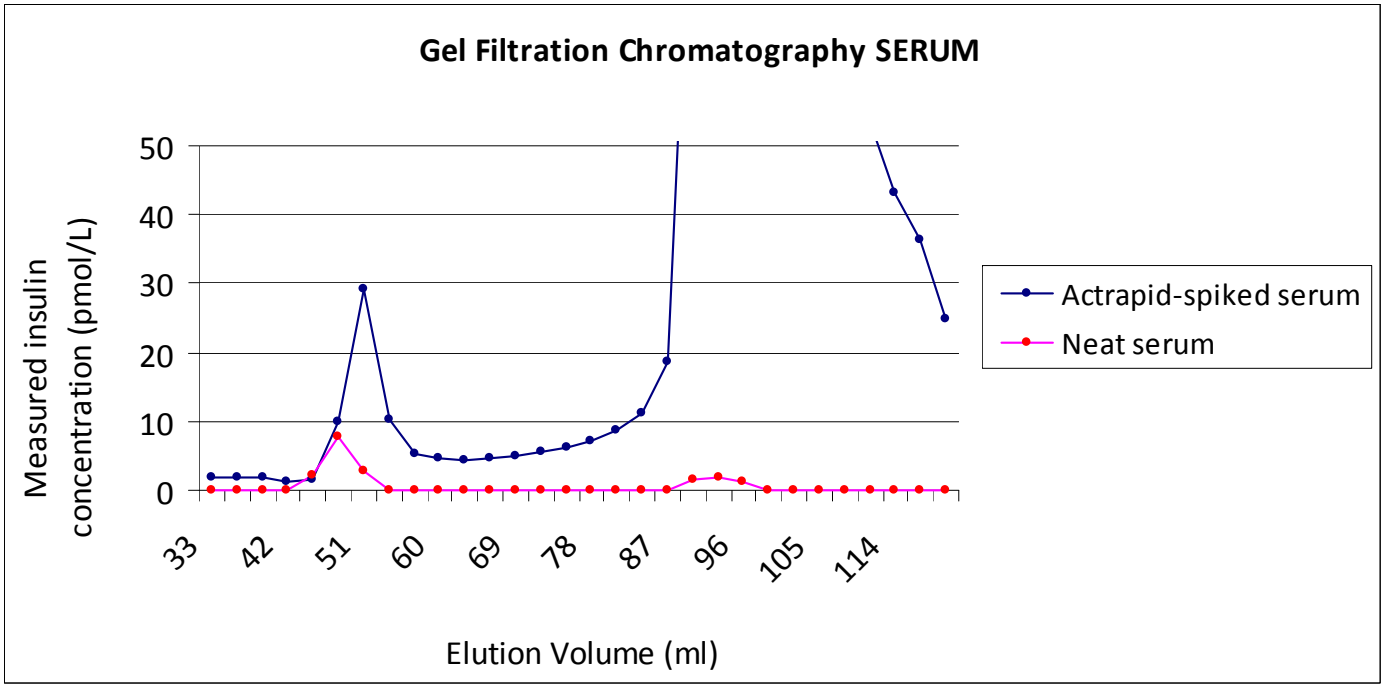
Patient taking Actrapid. No other insulin.

Apparent increase in insulin concentration following sample dilution (233% recovery following 1:20 dilution)



Following plasma exchange
Insulin-antibody complexes were still present

Insulin: Insulatard and Novorapid
Assay used has low cross-reactivity with Novorapid.



Increase in high molecular weight insulin immunoreactivity following insulin spike

- Supports presence of insulin-antibody complexes rather than heterophilic antibody interference

Questions

- Relationship between cutaneous hypersensitivity and systemic anti-Ins Abs?
- What is the optimal mode of Ab depletion therapy in young patients?
- In whom should this be used?
- How common are pharmacokineticlly significant anti-Ins Abs in labile diabetes?

Severe Insulin Resistance – Summary I

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

Summary II: Investigation

Initial

- Fasting glucose, insulin*, OGTT
- Fasting lipids
- Testosterone
- Leptin, adiponectin, IGFBP-1, SHBG
- Clinical photography/MRI/DXA

**Consider type of insulin assay, and ability to pick up native and analogue insulins*

More targeted

- Genetic testing (most commonly LMNA, PPARG, INSR)
- Anti-Ins Abs ("macroIns")
- Anti-InsR Abs
- C3, C4, C3 nephritic factor

National Severe Insulin Resistance Service Team

- Professor Sir Stephen O'Rahilly
- Dr Robert Semple
- Dr David Savage
- Dr Anna Stears
- Professor David Dunger (paediatrics)
- Dr Rachel Williams (paediatrics)
- Catherine Hames – dietitian
- Claire Adams - specialist nurse
- Julie Harris – specialist nurse
- Charlotte Jenkins-Liu – specialist nurse
- Elaine Withers– administrator
- Barbara Williams – administrator

NHS

Specialised Services

Cambridge University Hospitals NHS
NHS Foundation Trust

IMS MRL

UNIVERSITY OF CAMBRIDGE
Metabolic Research Laboratories,
Institute of Metabolic Science

insulinresistanceservice@addenbrookes.nhs.uk

Referral Criteria

- **Patients with severe insulin resistance and/or lipodystrophy:**
  - **Donohue Syndrome** or **Rabson Mendenhall Syndrome** with confirmed extreme hyperinsulinaemia
  - Clinically diagnosed **lipodystrophy** (generalised or partial)
  - **Unexplained severe insulin resistance**:

    with a BMI<30 kg/m^2 AND acanthosis nigricans AND/OR severe hyperinsulinaemia

insulinresistanceservice@addenbrookes.nhs.uk