Investigation and management of severe disorders of insulin sensitivity – a practical update

ABCD, London, November 2012

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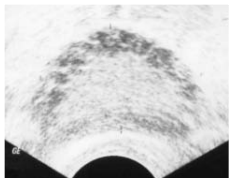
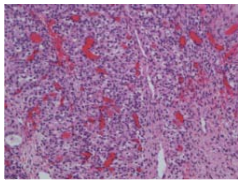
Metabolic Research Laboratories,

Institute of Metabolic Science

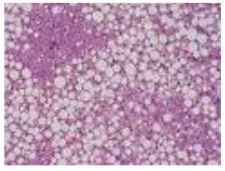
IMS MRL





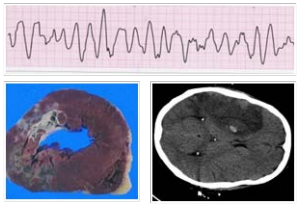
"P.C.O.S.", subfertility

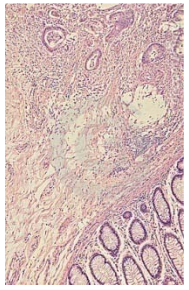
cirrhosis



NAFLD
+
Metabolic dyslipidaemia

atherosclerosis



Increased risk of malignancy

Acanthosis nigricans

β cell failure

hyperglycaemia

retinopathy

+

nephropathy

+

neuropathy

INSULIN

OBESITY

RESISTANCE

Monogenic Severe Insulin Resistance

Lipodystrophy

BSCL2

PPARG

PLIN

AGPAT2

CAV1

LMNA

CIDEC

Signal Transduction Defects

AKT2

PIK3R1

INSR

Complex syndromes

- Werner
- Bloom
- MAD
- Myotonic Dystrophy
- Alström
- MOPDII
- Bardet Biedl

Severe Insulin Resistance: Clinical Features

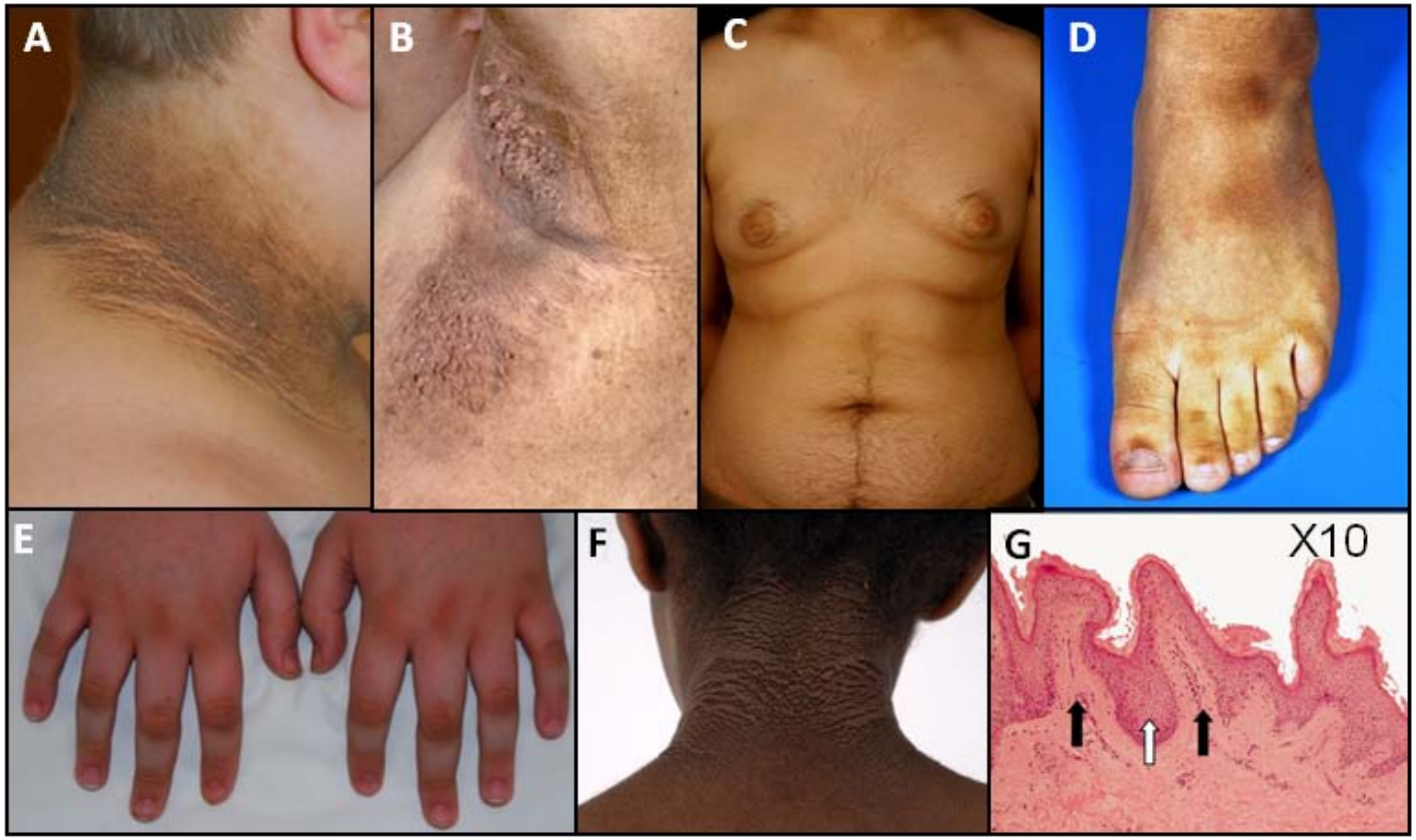
Common to all Causes
(Consequences of impaired insulin action/hyperinsulinaemia)

- **Glucose Homeostasis: Hypoglycaemia (fasting or reactive), IGT, Diabetes**
- **Skin: Acanthosis Nigricans/Skin tags/abnormal hair growth**
- **Ovary: PCOS, clitoromegaly.**
- **Growth: Impaired linear growth, acral enlargement, muscle hypertrophy**

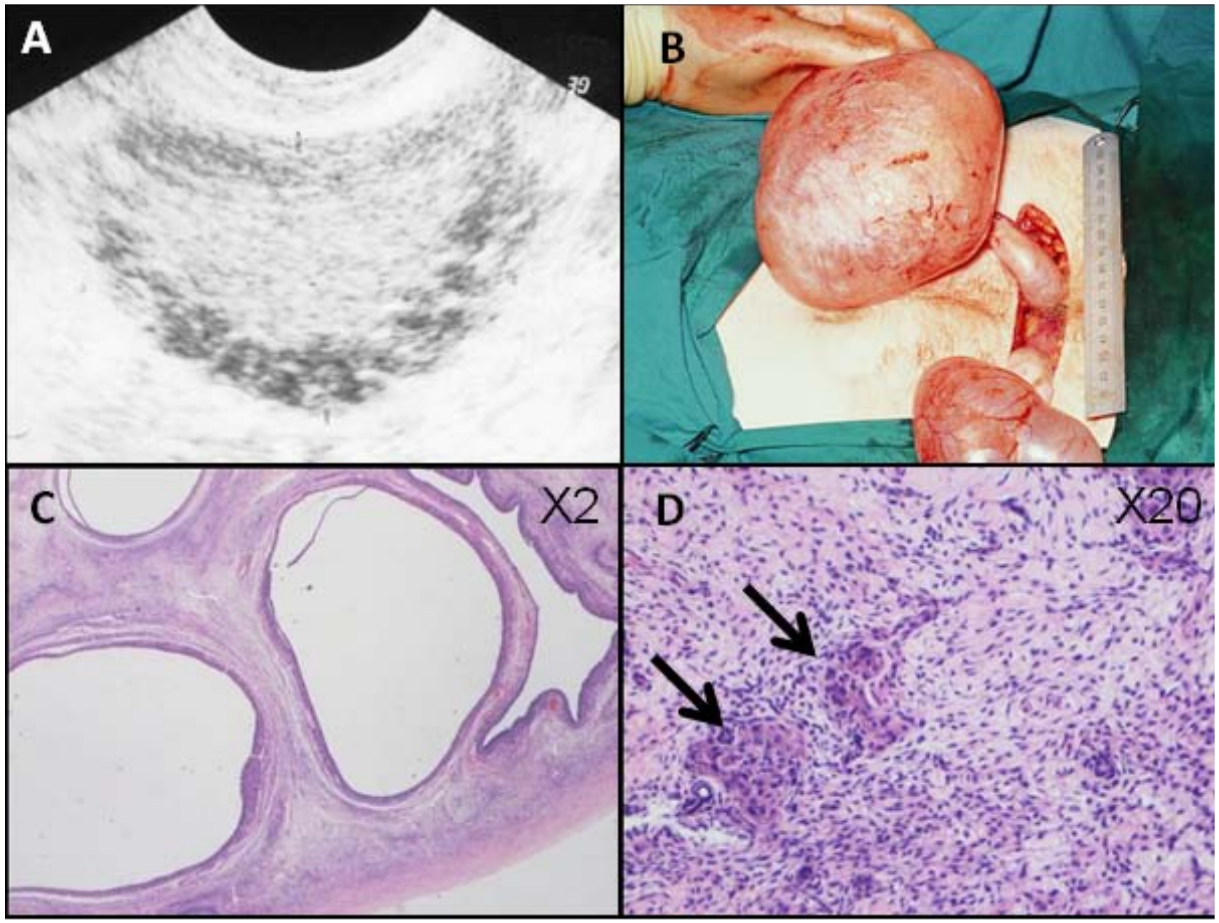
Variable

- **Hypertension**
- **Obesity**
- **Dyslipidemia**
- **Steatohepatitis**
- **Syndromic features e.g lipodystrophy**

Acanthosis Nigricans



Ovaries and Severe Insulin Resistance



Pseudoacromegaly

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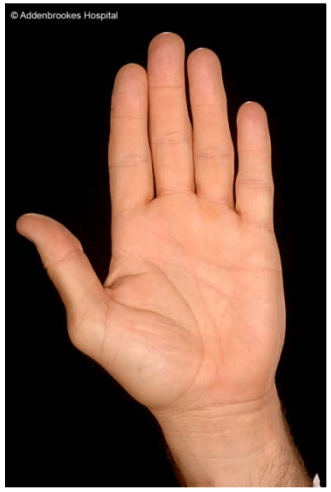
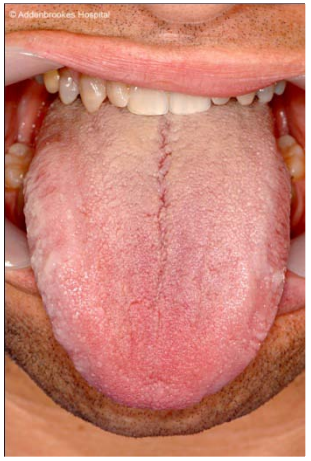




Lipodystrophy

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

- 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)

Inherited Lipodystrophies

Congenital Generalised (AR)

1) ***BSCL2***
   - most severe
   - developmental delay common
   - commonest in Caucasians
2) ***AGPAT2***
   - Some sparing
   - No developmental delay
   - Commonest in Africans
3) ***PTRF***
   - Myopathy common
4) ***CAV1***
   - Single case
5) **Unknown (<5%)**

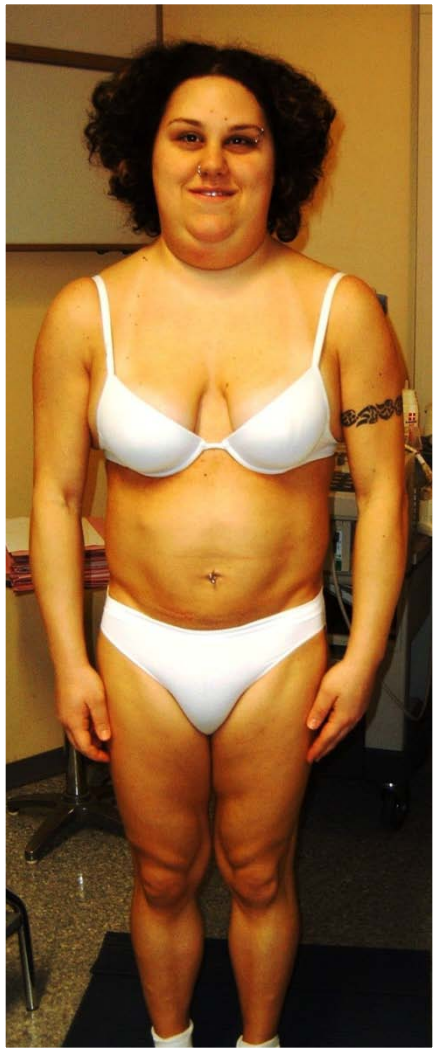
Familial Partial (AD)

1) ***LMNA***
   - lack of truncal/limb fat
   - xs on face and neck
2) ***PPARG***
   - lack of limb fat
   - xs hypertension
3) ***AKT2***
   - lack of limb fat
4) ***PLIN***
   - lack of limb fat
5) ***CIDEC***
   - lack of limb fat; DKA
6) ***Unknown*** **(c. 40%)**

Complex

Dunnigan Köbberling Lipodystrophy

(FPLD2; LMNA exon 8-12 mutations)



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PPARγ Ligand Resistance Syndrome

(FPLD3; PPARG mutations)

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Familial Partial Lipodystrophy Type 1

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

Congenital Generalised Lipodystrophy Type 1 (biallelic mutations in *BSCL2*)

DEFECTIVE ADIPOCYTE DIFFERENTIATION

Acquired Lipodystrophy

GENERALISED

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PARTIAL

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

Acquired Lipodystrophy/ Adipose Failure After Childhood Malignancy

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Principles of Management of Lipodystrophy

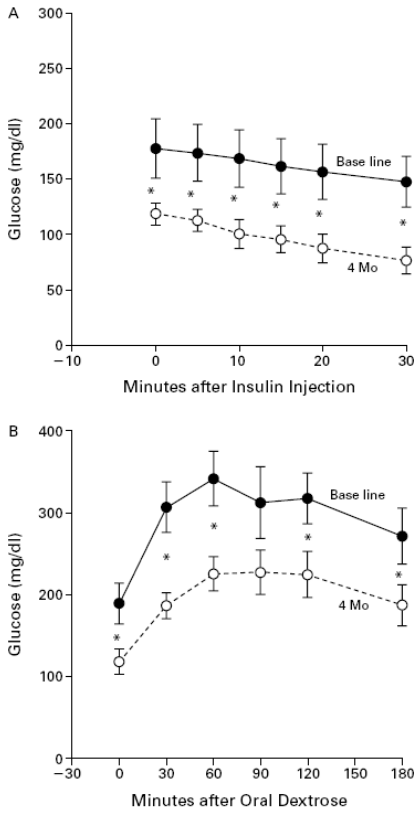
Lipodystrophy = "Adipose Failure"

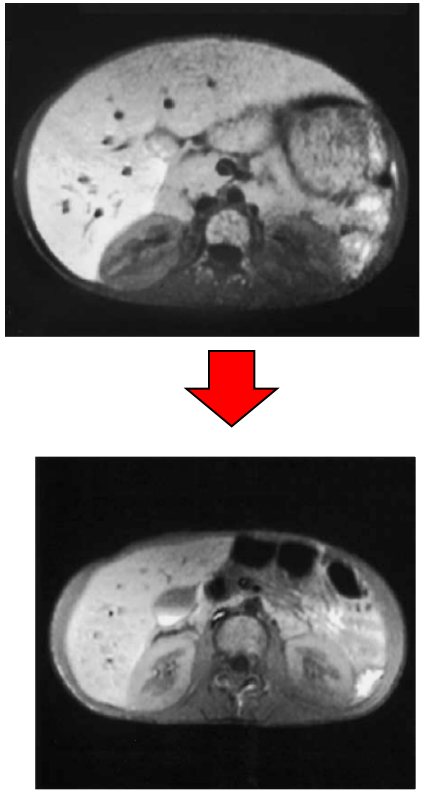
1. Offload adipose tissue
   - Low fat diet
   - "obesity therapies" – orlistat, bariatric surgery
   - leptin
2. Maximise insulin sensitivity
   - Exercise
   - Metformin, (pioglitazone)
3. Rationally targeted therapy (for the future)
   - Anti-lipolytic agents in "lipid droplet" LD?
4. Treat dyslipidaemia,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

Leptin Therapy in Lipodystrophy

LEPTIN-REPLACEMENT THERAPY FOR LIPODYSTROPHY

ELIF ARIOGLU ORAL, M.D., VINAYA SIMHA, M.D., ELAINE RUIZ, N.P., ALEXA ANDEWELT, B.S., AHALYA PREMKUMAR, M.D., PETER SNELL, PH.D., ANTHONY J. WAGNER, PH.D., ALEX M. DEPAOLI, M.D., MARC L. REITMAN, M.D., PH.D., SIMEON I. TAYLOR, M.D., PH.D., PHILLIP GORDEN, M.D., AND ABHIMANYU GARG, M.D.





baseline

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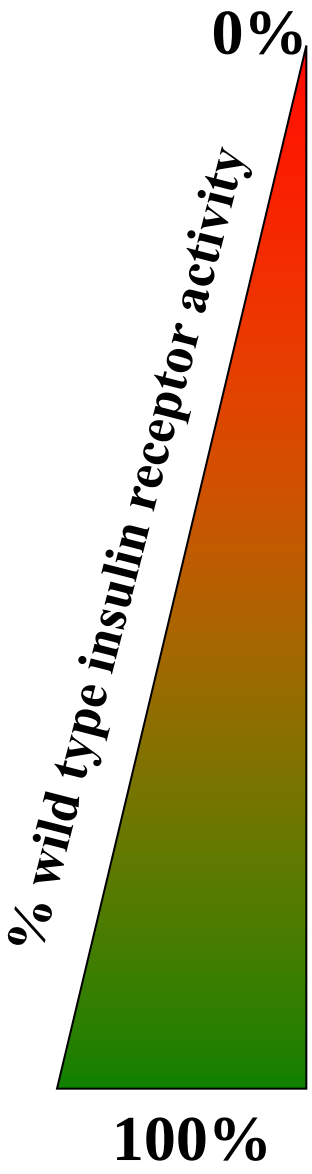
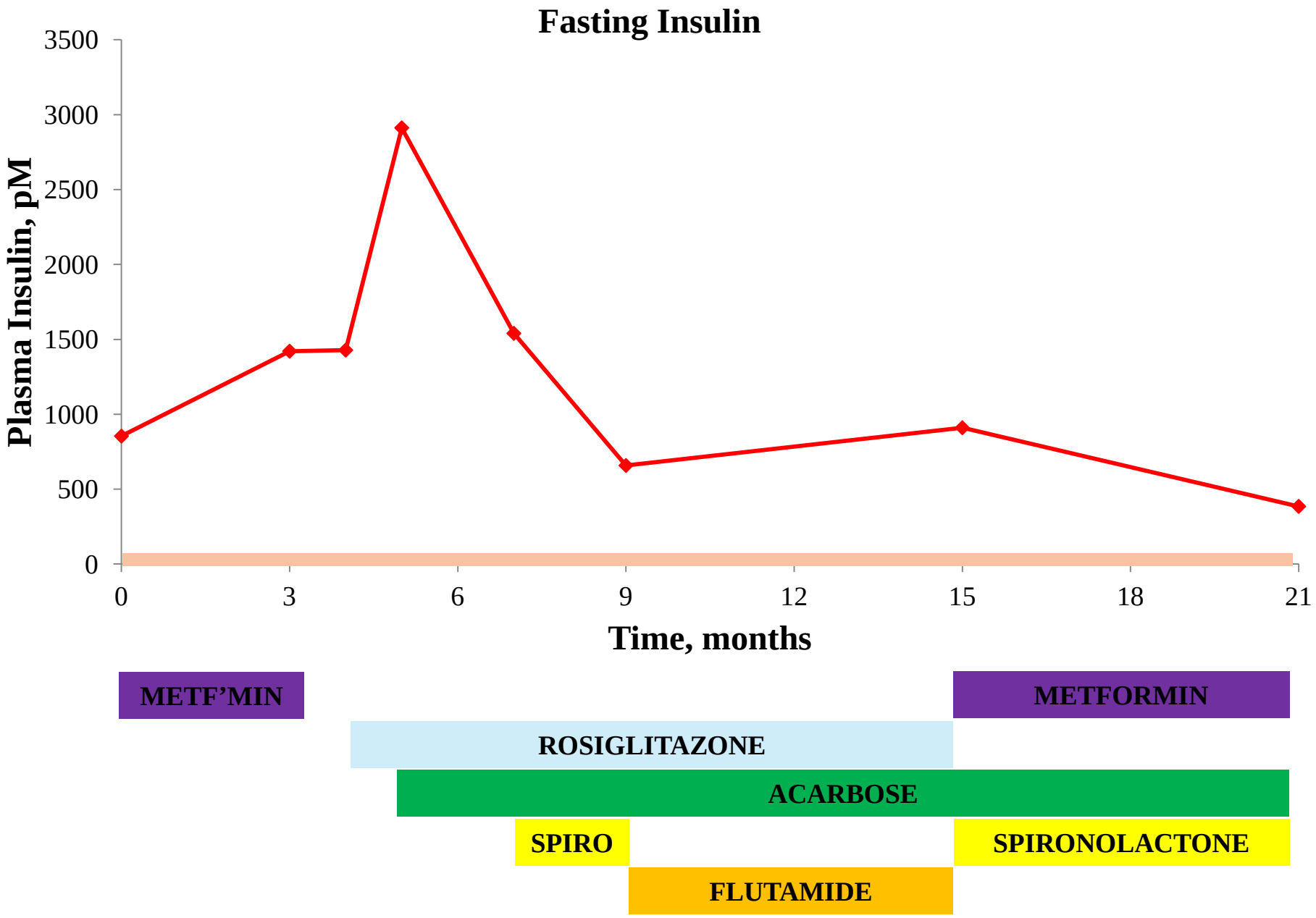
Primary Insulin Signalling Defects

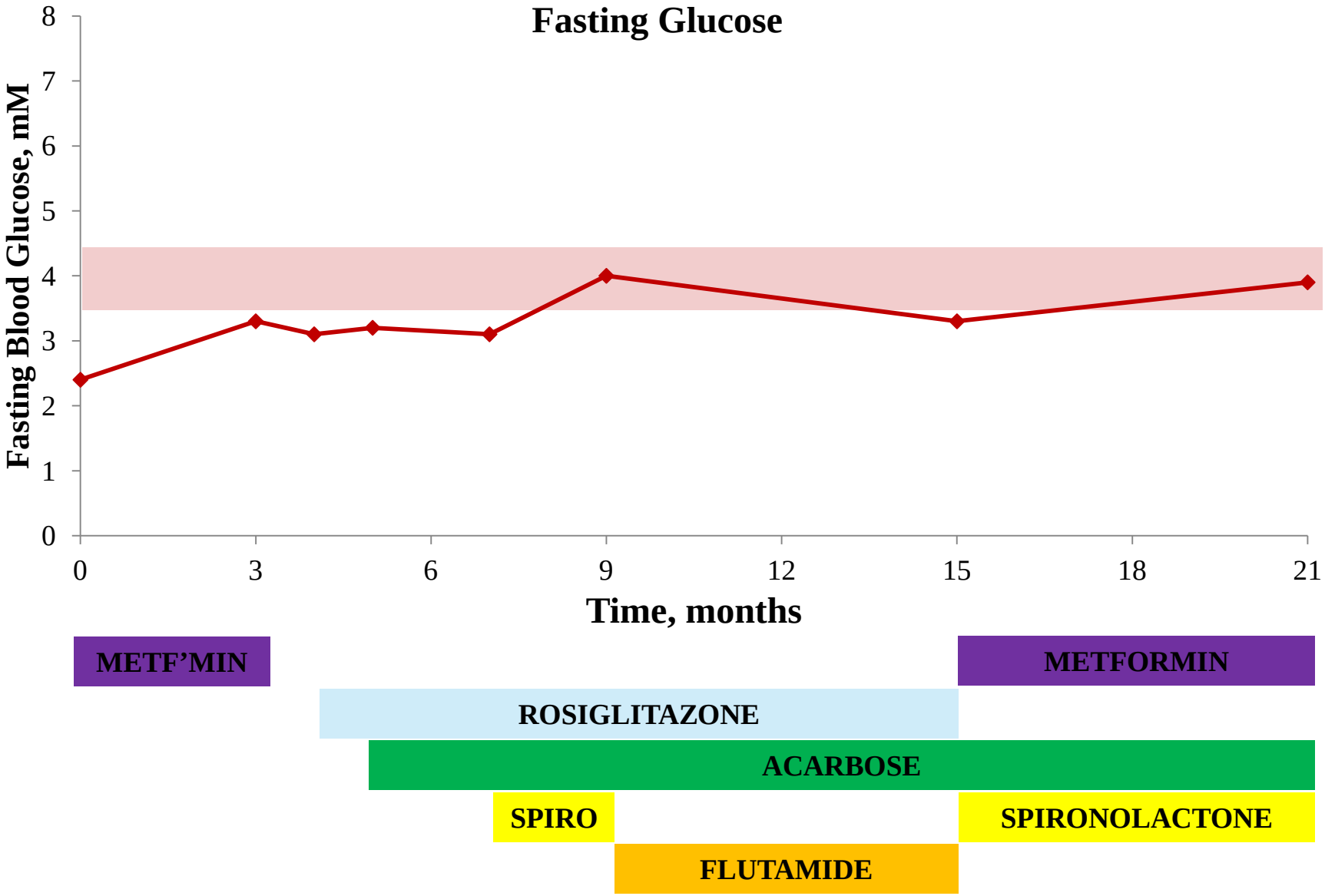
Genetic Insulin Receptoropathies

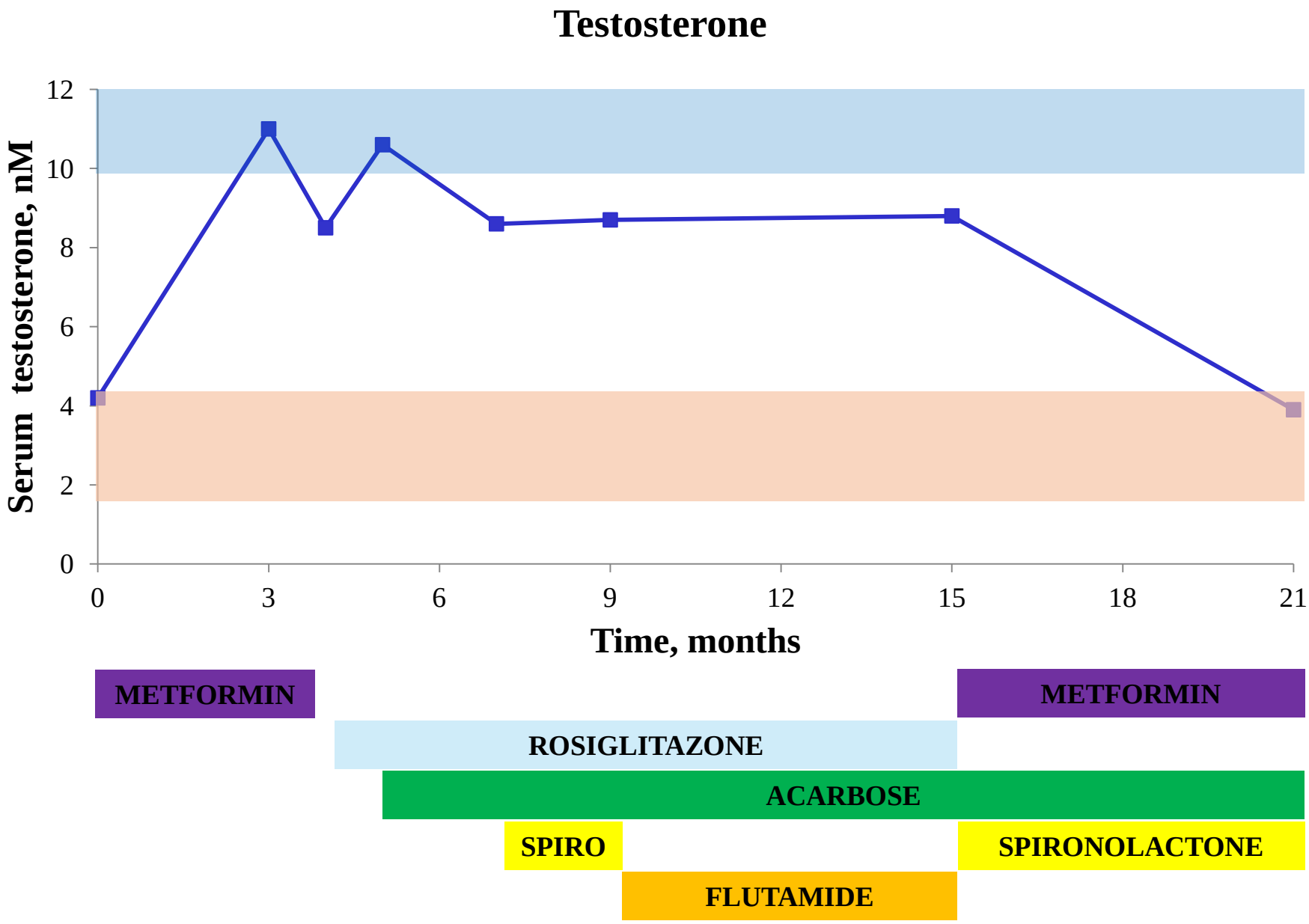


- Donohue Syndrome

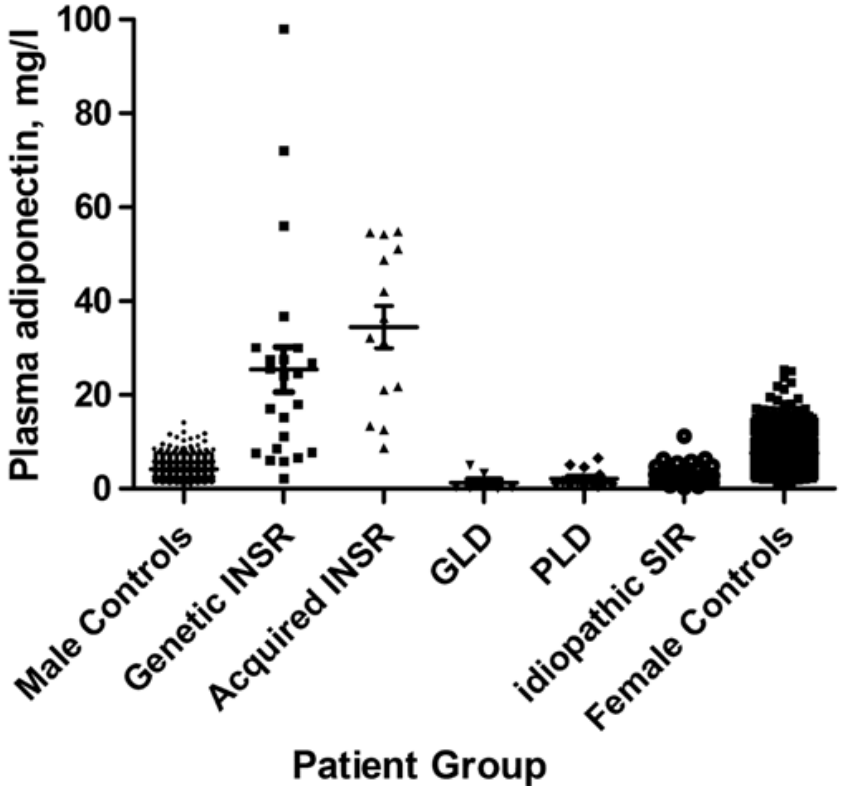
- Rabson-Mendenhall Syndrome
- Type A Insulin Resistance
- HAIR-AN

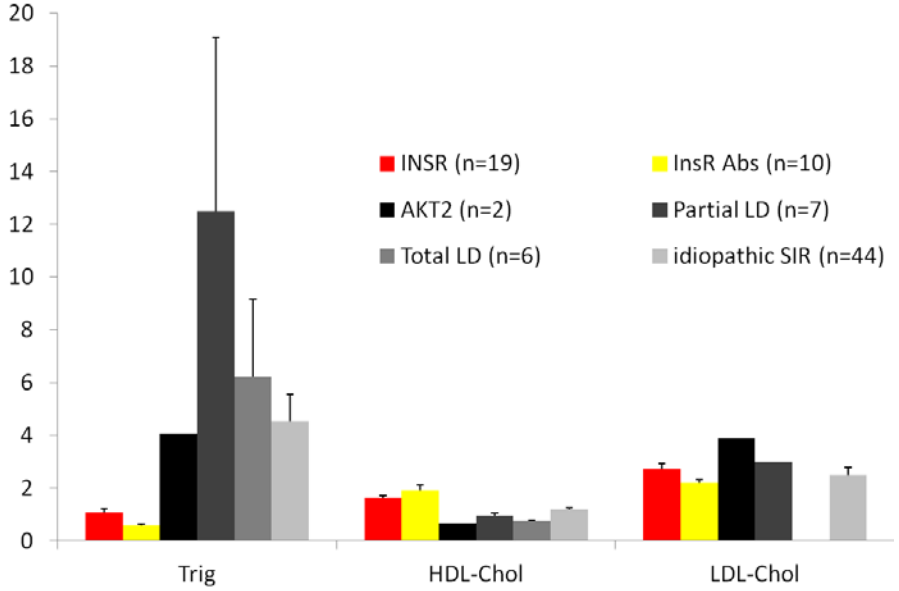

Fasting Insulin
Plasma Insulin, pM
3500
3000
2500
2000
1500
1000
500
0
0
3
6
9
12
15
18
21
Time, months
METF'MIN
METFORMIN
ROSIGLITAZONE
ACARBOSE
SPIRO
SPIRONOLACTONE
FLUTAMIDE


Fasting Glucose
Fasting Blood Glucose, mM
0
1
2
3
4
5
6
7
8
0
3
6
9
12
15
18
21
Time, months
METF'MIN
METFORMIN
ROSIGLITAZONE
ACARBOSE
SPIRO
SPIRONOLACTONE
FLUTAMIDE


Testosterone
Serum testosterone, nM
12
10
8
6
4
2
0
0
3
6
9
12
15
18
21
Time, months
METFORMIN
METFORMIN
ROSIGLITAZONE
ACARBOSE
SPIRO
SPIRONOLACTONE
FLUTAMIDE

Insulin Receptoropathy: Distinct from Prevalent Insulin Resistance





Type B insulin resistance

- A syndrome of acquired, extreme insulin resistance mediated by insulin receptor blocking antibodies
- Often in association with other antibody-mediated autoimmune disease
- Many cases remit spontaneously with time
- May be treated effectively with multimodal immunosuppression

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Anti-Ins Abs: Case History

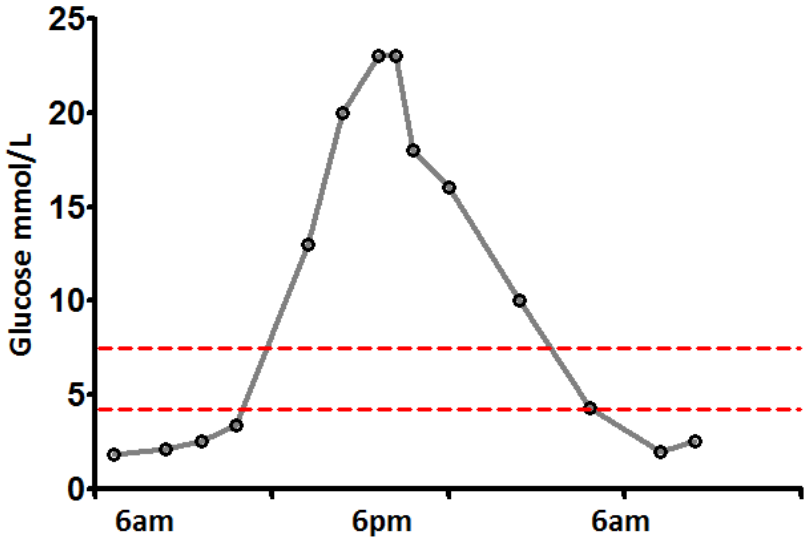
86 year old man

60 years well–controlled T1DM

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

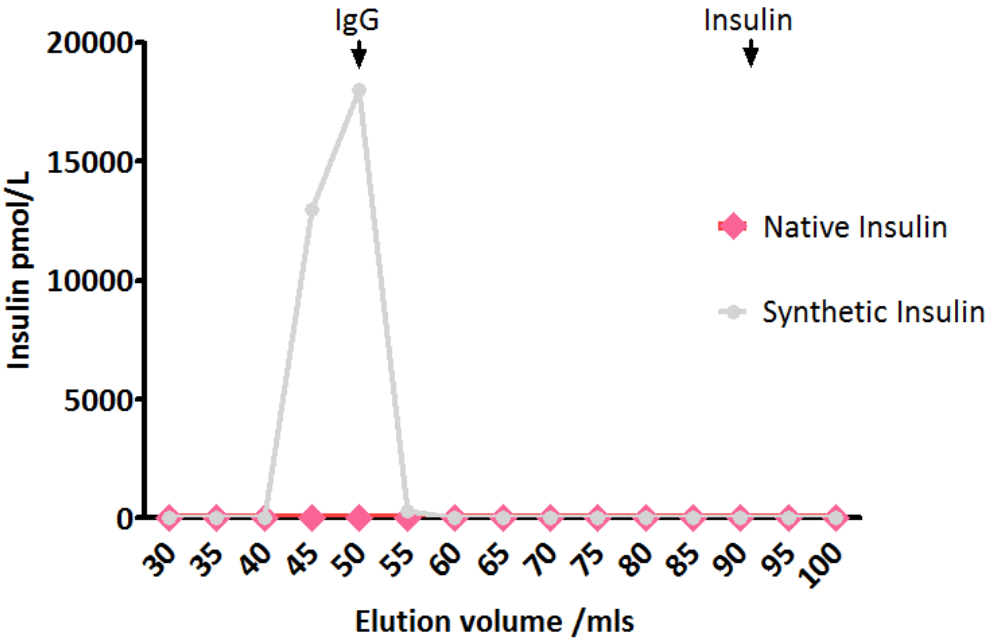
Previously good control on Levemir/Lispro.

Dose adjustment ineffective

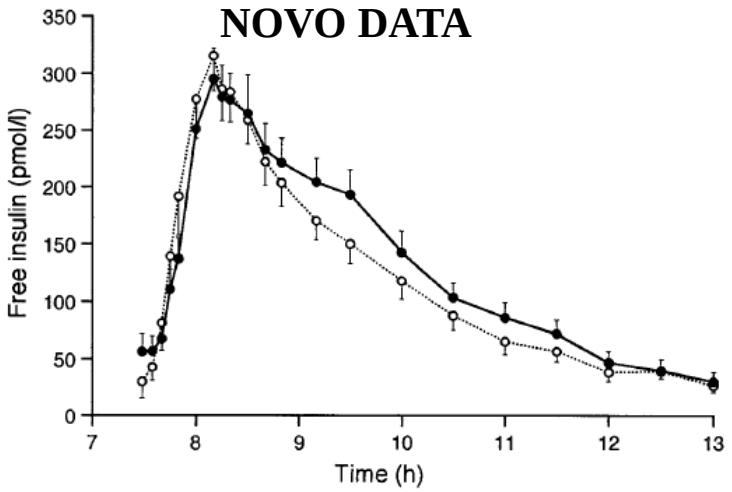


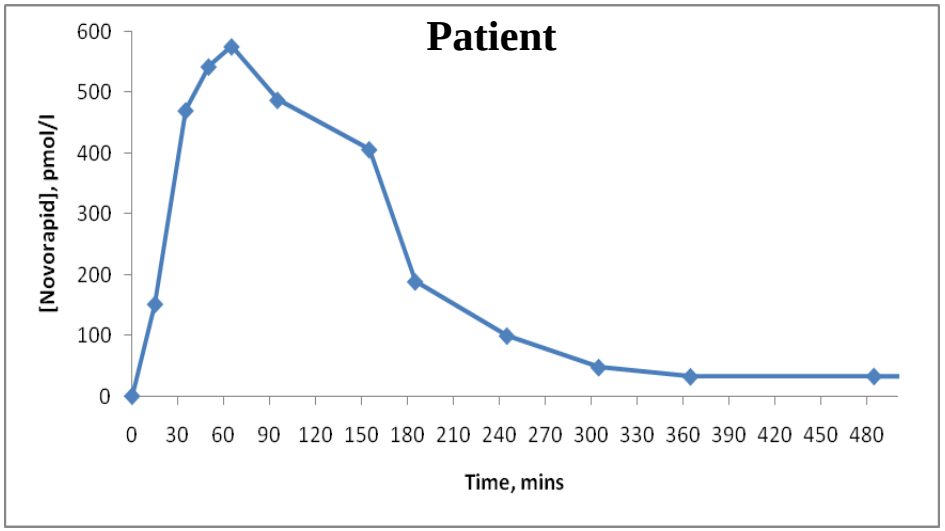
Insulin 2h after 24u Lispro:

- 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



“Subcutaneous IR”: Analogue Insulin Absorption Test





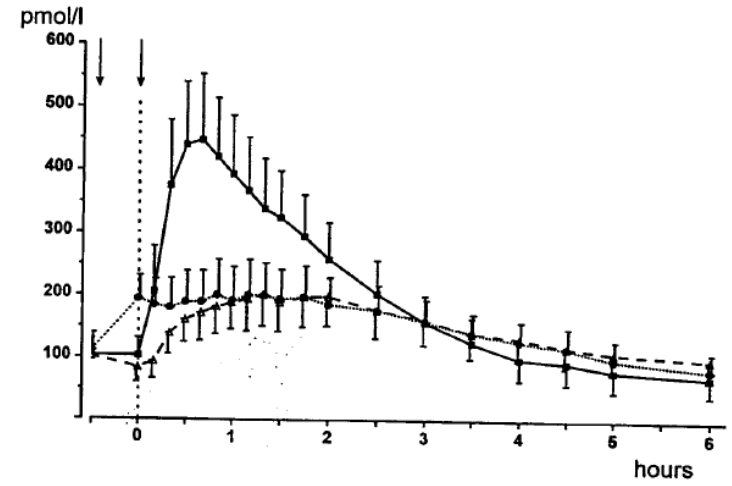
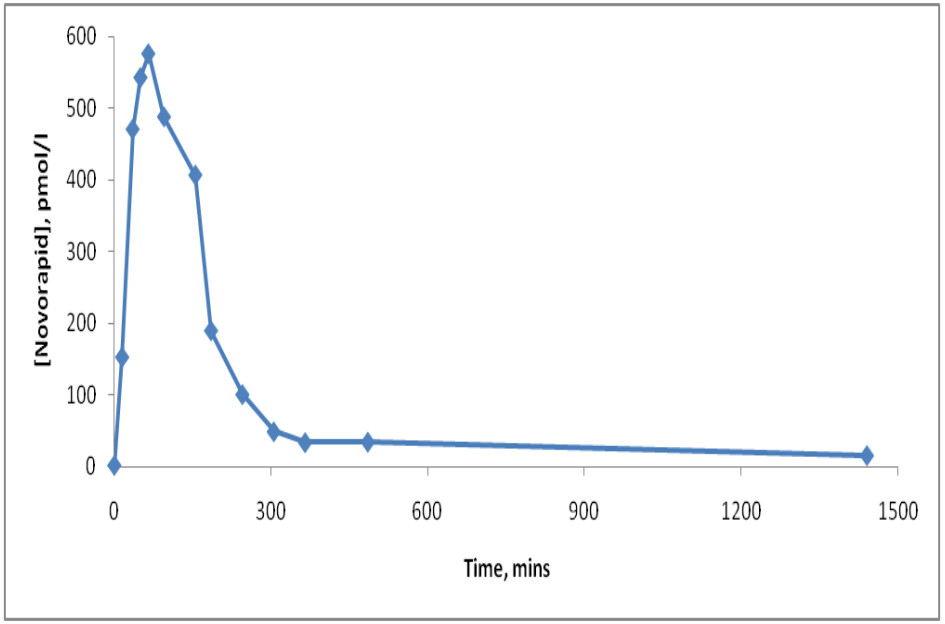


Figure 2—*Mean postprandial serum insulin profiles in 22 subjects with type 1 diabetes after injection of insulin aspart (■—), human insulin immediately before the meal (Δ– –), or human insulin 30 min before the meal (●· · ·). The two arrows indicate subcutaneous injection times, and the vertical dotted line indicates the time of meal.*



Summary: Investigation of Severe IR

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

Summary: Management of Extreme Insulin Resistance

Managing the consequences

Acanthosis Nigricans

PCOS:
Hirsutism, Amenorrhea, Alopecia

Reactive hypoglycemia

Diabetes (e.g. U500 insulin)

Dyslipidemia

Steatohepatitis

Maxillofacial Surgery

Improving Insulin sensitivity

Diet and Exercise

Metformin

TZDs

Acarbose

GLP1 agonists

DPPIV inhibitors

Leptin

rhIGF-1

National Severe Insulin Resistance Service

- **National Specialised Commissioning Team (NSCT)** funding from April 2011
- Specialised service defined as <400 patients
- **Weekly multidisciplinary clinic**
  - Aim 30 new/70 follow up outpatients per annum
  - 4 patients per week
- **Weekly MDT meeting:** Consultants (adult/paediatric), dietitian, specialist nurses, admin support
- **Inpatients**
  - 8 per annum
- **To date 56 patients; 12 on leptin**

Cambridge University Hospitals NHS
NHS Foundation Trust

NHS
Specialised Services

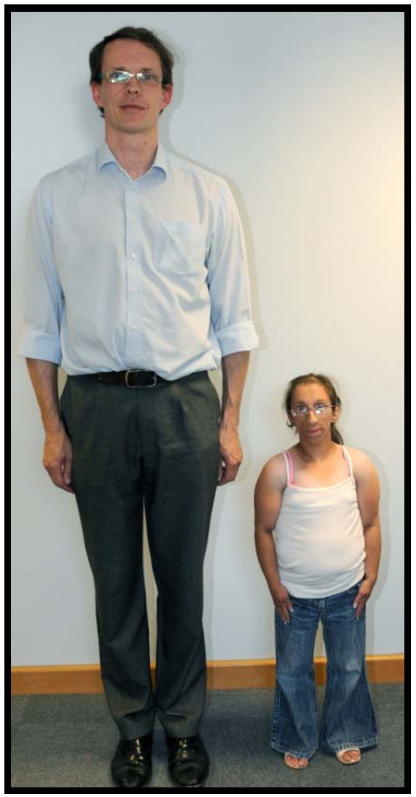
severeinsulinresistance@addenbrookes.nhs.uk

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 (fasting insulin>150pM or peak plasma insulin on oral glucose tolerance testing >1,500pM

Rarer Conditions



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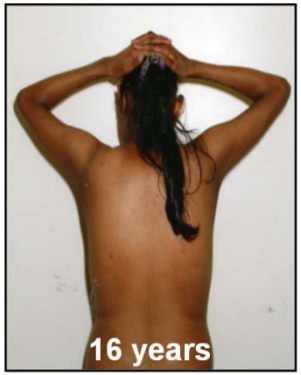

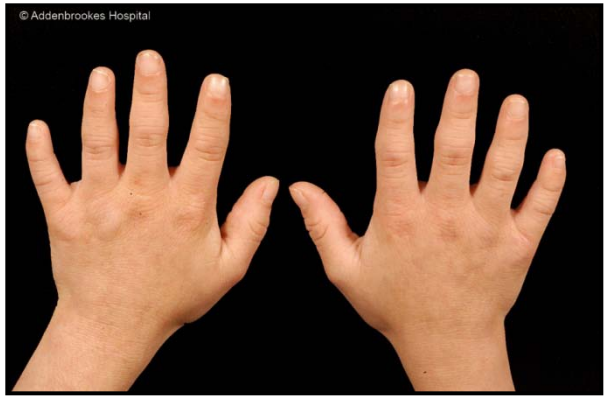

Summary

- Severe IR should be suspected in anyone with acanthosis nigricans
- Aggressive “PCOS” is the commonest manifestation in women of reproductive age
- Hypoglycaemia may commonly be seen in the early stages
- Careful clinical assessment of adipose distribution is essential.
- Determined insulin sensitisation and replacement are key
- Leptin and IGF1 have an important place in management for some cases
- It is rational to treat patients with lipodystrophy and severe metabolic deranegement in a similar manner to patients with morbid obesity with metabolic complications, though large scale evidence for efficacy of GLP1 agonists, bariatric surgery and other treatments is not yet available.

National Severe Insulin Resistance Service Team

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

Dr David Halsall
Mr Keith Burling
Dr Becky Treacy

..and many in research labs

wellcome trust Fellow

NHS Specialised Services

MRC Centre for Obesity and Related Metabolic Diseases

NHS National Institute for Health Research