Diabetes Mellitus

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Islets of Langerhans

- 3 cell types
  A Glucagon
  B Insulin
  D Somatostatin

Insulin

- 2 chains (A + B)
- 51 aas
- (minor) differences between species
- Preproinsulin, proinsulin
- Stored in granules (insulin + c-peptide)

Insulin Secretion Stimulation

- Sugars
  • Glucose
  • Fructose
  • Sucrose
  • Ribose
- Amino Acids
  • Leucine
  • Arginine
- Fats
  • MCT in man
- Hormones
  • Glucagon
  • Gut glucagon
  • GIP
  • ß adrenergic
  • Secretin
- Vagal Stimulation
- Drugs
  • Sulphonylureas
  • (Nucleotides)
  • Adenosine in man

Insulin Secretion Inhibition

- Alpha adrenergic stimulation
- Drugs
  • ß blockers (Propranolol)
  • Dianatin
  • Diazoxide
  • Thiazide diuretics

Insulin Action

1. Glucose transport into cells
2. Stimulation of lipogenesis
3. Inhibition of lipolysis
4. Amino acid transport
5. Protein Synthesis
6. Growth Factor
Insulin Secretion

- Hyperinsulinaemia
  - Marker of insulin resistance
- Early abnormality in animal models of diabetes
- Impaired in Type 2 diabetes
  - Loss of first phase
  - Reduced secretion to glucose load
  - “Glucose toxicity”

Insulin

- Receptor
  - Cell surface
  - Dimer (2 chains)
- Binding
- Phosphorylation of receptor
- IRS
- Kinases & phosphorylases alter enzymes

Glucose transporters

- Family
- Single polypeptide chain about 500 residues
- 12 transmembrane domains (alpha helices)
- Transport achieved by conformational change
- Some in membrane
- On insulin stimulation, recruited from intracellular pool

Glucose Transporters

- Liver and islets non-insulin sensitive transporters
  - GLUT2
    - High Km (15mM) – glucose enters in “time of plenty”
- Insulin responsive tissues (muscle, adipose tissue)
  - GLUT4
    - Km 5mM
- Basal Transport
  - GLUT 1 and 3
- small intestine
  - GLUT 5
  - Plasma membrane side of the enterocyte
  - Works in conjunction with Na-glucose symporter (luminal surface)

Classification of Diabetes Mellitus

- Type 1
- Type 2
- Other specific types
  - MODY (glucokinase)
  - Starvation/malnutrition
  - Proinsulin, receptor mutations
- Gestational (GDM)

Diabetes Mellitus

- Type 1
  - Insulin Deficient
  - Younger (<35)
  - Thin
  - Auto-immune
  - Not as strongly inherited
  - Mainly caucasian
- Type 2
  - Insulin Resistant
  - + Relative Insulin deficiency
  - Older (>40)
  - adolescents now
  - Obesity
  - Strongly inherited
  - All ethnic groups
Diabetes Diagnosis

• Fasting plasma glucose > 7.0 mmol/L
• Random blood sugar > 11.1 mmol/L
• Impaired fasting glucose (IFG) > 5.5 and < 7.0

• Glucose Tolerance Test (oGTT)
  – 75g glucose
  – Fasting < 7.0
  – 2h < 7.8
  – Max < 11.1

• IGT
  – 1 point abnormal

3. Insulin Resistance
• Obesity, inherited
• Illness/operation, pregnancy

Aetiology

1. Genetic
• Runs in families
• Twin studies
• Islet cell surface antibodies
• Insulin gene polymorphism
• Chlorpropamide/alcohol flush

2. Environment
• Viruses
• Nutrition
• Urbanisation

5. Gestational

6. Other
• Pancreatic damage
• Low K

Viruses & Diabetes

• Coxsackie B4
• Mumps
• EB Virus
• Rubella
• ? EMC

Diabetes prevalence

• Varies country to country
• Increasing !!!

• Genetic susceptibility + Environment
  • Nutrition
    • Sedentary
    • Abdominal adiposity
  • Intrauterine undernutrition (FOAD)

Age-specific Diabetes Prevalence

AUSDIAB 2000

Age & gender prevalence of diabetes

AUSDIAB 2000
Type 1 Diabetes

- Insulin deficiency and absolute insulin requirement
- Loss of weight
- Thirst (polydipsia) and Polyuria
- Diabetes Keto-acidosis

Type 2 Diabetes

- general consensus

  Insulin Resistance + Insulin Deficiency

  needed for Type 2 Diabetes

Insulin Resistance

- difficult to define
- depends on individual experiment
- generally accepted

  “A situation in which more insulin (than in appropriate control) is required to achieve same response.”

Comparison

- Ketoadiogenesis
  - No insulin
  - High glucose
  - High ketone bodies
  - Acidosis
  - Increased HGO
  - Uncontrolled lipolysis
  - Beta-oxidation
  - High glucagon

- Starvation
  - Low insulin
  - Low, normal glucose
  - Some ketones
  - Normal pH
  - Controlled HGO
  - Controlled lipolysis
  - Beta-oxidation
**Cause of Insulin Resistance**

- Hyperinsulinaemia
- Increased hepatic glucose production (hyperglycaemia)
- Decreased non-oxidative glucose disposal (glycogen synthase)
- Increased lipid availability & oxidation (glucose fatty acid cycle)

**Possible Mechanisms of Insulin Resistance**

- Intracellular
  - Insulin Signalling
  - Glucose Transporter Induction
  - Enzyme Structure
  - Synthesis
  - Action
  - Response

**Insulin Resistance**

- Reduced glucose disposal
  - Glycogen synthesised slowly
  - Less glucose oxidation
- Glycogen content normal
- Less lipid oxidation (Zars et al., 1996)
- Increased glycolytic flux
- Recycling to liver of 3C units
- Increased gluconeogenesis

**Insulin Resistance**

- Excess abdominal fat & fat oxidation
  - Abdominal fat - increased NEFA flux
- Hyperinsulinaemia
- Uncontrolled Hepatic Glucose Output (HGO)
  - Role of leptin
    - Increased lipid oxidation

**Insulin Resistance (sensitivity) and abdominal fat.**

**Type 2 diabetes**

- Obesity (abdominal)
- Not a dramatic presentation, insidious
- Often diagnosed on blood testing for something else
- Thirst, polyuria
- Tired, not well
- Infections (thrush)
- May present with complications
Type 2 Diabetes - Metabolic Abnormalities

- High BSL
- Dyslipidaemia
  - High Triglycerides
  - Low HDL cholesterol
- Normal ketones and pH
- Fatty liver

Management of Diabetes

- Eating
- Exercise
- Education
- Oral Hypoglycaemics
- Insulin
- Other medications
- Complications Screening

Eating

- Appropriate caloric intake
  - Growth
  - Obesity etc
- CHO spread
- Reduce saturated fat
- GI

Exercise

- Regular activity reduces BSL
- May need to alter
  - Diet
  - insulin
- Walking, jogging, gym etc.

Diabetes Education

- No evidence that it improves control
  - Blood sugar readings
- Better understanding
- Take control of own disease
- Early presentation with problems
- Reduce complications

Diabetes Centre

- Team
  - physician, educator, dietitian
  - podiatrist, physiotherapist
- Education
- Special Services
  - ambulatory stabilisation
  - complications assessment
  - foot care, vascular care
  - renal clinic, retinopathy treatment
- Data Base
Home Glucose Monitoring

- Urine testing
- Blood Glucose strips
- Glucose meters (memory, ketones)

NB Patient MUST be educated

- Use of strips
- Meters
- Interpretation of results
- Alteration of therapy

Complications of Diabetes

- Macrovacular
  - Heart Disease
  - Hypertension
  - Stroke
  - Peripheral Vascular disease
- Microvascular
  - Renal disease
  - Retinopathy
  - Infections
    - Gangrene

- Neuropathy
  - Peripheral
  - Autonomic
  - Cranial
- The Diabetic Foot
- Diabetic Comas
- Dyslipidaemia
- Skin disease
- Pregnancy

Complications screening

- Yearly
- Check
  - Eyes
  - Kidneys
  - BP
  - Neuropathy (peripheral & autonomic)
  - Vascular disease
  - FEET
- Alter management

Regular visits

- BP, complications
- Blood
  - Glycated haemoglobin (fructosamine)
  - Glucose (fasting or random)
  - Lipids
- Urine
  - Microalbumin (timed specimen)

Management of Diabetes

- Type 1
  - Diet
    - Appropriate energy
    - Spread through day
  - Exercise
  - Glucose uptake
  - Utilisation
    - Education
  - INSULIN

- Type 2
  - Diet
    - Reduced energy
    - Spread
  - Exercise
  - Education
  - Oral hypoglycaemics
    - Biguanides
    - B cell stimulation
    - 3H sulphonylureas
    - Insulin occasionally

Control

- Awareness of need
- Team Approach
- Medications
  - oral
  - insulin
    - combination
- Complications Assessment
Oral Hypoglycaemics

1. Metformin
2. Sulphonylureas
   - gliclazide
   - glibenclamide
   - glipizide
   - tolbutamide
   - chlorpropamide etc

Oral Hypoglycaemics 2

3. Other agents
   - alpha glucosidase inhibitors
   - Repaglinide etc
4. Thiazolidinediones
5. Adjunctive agents
   - Weight loss agents (orlistat, sibutramine)
6. Incretins (GLPs)

Insulin - Practical Points

- Human Insulin
- Multiple Injections
- Site - Abdomen
- Get used to a few preparations
- ? Need for Premixed Insulins
- ? syringes or "pens"

Insulin Pumps

- Available
  - Better now
  - Need implanted port
- Expensive
- Use leads to good control
- Patient Selection & Education Essential

Insulin in T2DM

- criteria - fasting BSL > 8
  - post prandial BSL > 10
  - Hba1c 2.5% > normal
  - on 3 consecutive occasions 2 months apart
- personal preference - insulin or combined
- no evidence combined therapy gives better control
- some evidence
  - nocturnal insulin less hyperinsulinaemia
  - possibility of “weaning” with combined therapy

Problems

1. Control vs Lifestyle
2. Hypoglycaemia
3. Vascular Disease
4. Obesity
5. Other complications
### Insulin Resistance

1. **Weight**
   - fluoxetine
   - sibutramine
   - orlistat

2. **Fat Metabolism**
   - \(\beta\)-oxidation (etomoxir)
   - glitazones

3. **Thermogenesis**
   - \(\beta_3\) agonists

4. **Glucose Metabolism**

### Insulin Secretion

1. **Glucose Delivery**
   - Glucosidase inhibitors

2. **Insulin Delivery**
   - pens
   - pumps

3. **Insulin Analogues**
   - LysPro
   - Monomers (B9asp B27glu)
   - Dimers (B10asp)
   - Monomer/dimer (B26asp)
   - Insulin glargine

### Implications of DCCT

1. **Intensive therapy**
   - Multiple injections
   - Dietary support / Exercise
   - Frequent contact

2. **Treatment “Group”**
   - ? Centres

3. **Cost**
   - Hypoglycaemia
   - Individual
   - Health System

### Type 2 Diabetes - UKPDS

- **Better control**
  - Risk reduction 12% for any diabetes endpoint
  - 25% less microvascular complications

- **GHb 7.0% - down from 7.9%**

- **Adverse**
  - More hypoglycaemia
  - Weight gain

### Type 2 Diabetes - UKPDS

- **BP control essential & beneficial**
- **Macrovascular disease important**
- **Treat in multiple ways**
  - Glucose control
  - BP
  - Lipids
  - Weight

### UKPDS - Hypertension

- **Tight control**
  - BP 142/88 vs 154/87

- **Results - risk reduction**
  - 32% deaths
  - 44% strokes
  - 24% diabetes, 37% microvascular endpoints

- **Captopril and atenolol similarly effective**
- **Cost effective**

UKPDS - Macrovascular Disease

- Major cause of mortality
- No increase with intensive treatment
- No deleterious effect of type of treatment

Complications

1. Microvascular
   - Retinopathy
   - Nephropathy
2. Macrovascular
   - Coronary
   - Peripheral/Cerebral
   - Hypertension
3. Neuropathy
   - Peripheral
   - Autonomic
   - Cranial
   - Atrophy

Complications 2

4. Metabolic
   - Coma
   - Dyslipidaemia
   - Hyperinsulinaemia
5. The Diabetic Foot
6. Infection
7. Pregnancy
8. Tissue glycosylation

Diabetic Coma

- Hypoglycaemia
  - Most common
  - Iatrogenic
- Hyperglycaemic
  - Ketoacidosis
    - Hypoglycaemic, non-ketotic
  - Lactic Acidosis
  - Stroke
  - Infection
  - Trauma

Hypoglycaemia.

- Most common diabetic coma
- Iatrogenic
- Educate
  - occurrence
  - symptoms
  - therapy
- Choice of therapy
  - oral agents do cause hypoglycaemia!
- Treatment
  - glucose
  - glucagon

Diabetic ketoacidosis

- No insulin
  - Low glucose transport
  - Increased HCO
  - therefore high plasma glucose
- Uncontrolled lipolysis
  - Beta-oxidation
  - Ketone body production
- Acidosis (short of breath)
  - H/K exchange (buffering)
- Osmotic diuresis
  - Loss of electrolytes
**Blood results DKA**

- Increased
  - Glucose
  - Na
    - Variable depends on hydration
  - K (usually)
  - Ketones
    - Acetoacetate
    - βOH butyrate

- Decreased
  - pH
  - HCO3
  - Cl

- Creatinine (consider)

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**DKA - Treatment Principles**

1. Fluids
2. Electrolytes
3. Insulin
4. (Bicarbonate - NO!!)
5. Treat Cause
6. Maintenance

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**Diabetic Nephropathy**

- Common - a major cause of death
- Hyperfiltration & Hyperperfusion
  - ? Due to reduced O2 availability & osmotic effect
  - High creatinine clearance; large kidneys
  - Increased albumin excretion
- Basement membrane thickening
  - Altered permeability
  - Creat clearance falls
  - Increased albumin excretion, then overt protein excretion
- Overt Renal disease
  - Inexorable progression

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**Diabetic Nephropathy**

- Investigations
  - Creatinine
  - Creatine clearance
  - Albumin excretion (microalbuminuria)
    - Specific, sensitive assay
    - Timed specimen best
    - Repeated measurements
  - U. Protein
  - Watch lipids

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**Diabetic Nephropathy**

- Therapy
  1. Control of diabetes
  2. Treat “micro” hypertension
  3. Diet
    - Low protein
  4. Dialysis (Haemo or CAPD)
  5. Transplantation

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**Neuropathy**

1. Peripheral
   - Symmetrical
   - Mononeuropathy
2. Autonomic
3. Cranial
4. Diabetic Amyotrophy
Peripheral Neuropathy

- Theories
  1. Metabolic - glucose
  2. Metabolic - sorbitol/inositol
  3. Hypoxic damage
  4. Immunological

Peripheral neuropathy

- Treatment
  1. Protection
  2. Control (7)
  3. Analgesia
  4. Oxygen (7)

Autonomic Neuropathy

- Therapy
  1. Control of diabetes
  2. Diarrhoea
    - Diphenoxylate
    - Metoclopramide
    - tetracycline
  3. Vomiting
    - Metoclopramide
    - Domperidone
    - cisapride
  4. BP
    - mineralocorticoid

The Diabetic Foot

- Major problem
  - “Take off socks” - prevent amputation
  - Regular check
  - Podiatrist - regular care
  - Cast/prostheses
  - Treat infection

The Diabetic Foot 2

- Causes
  - Infection
  - Peripheral Vascular disease
  - Neuropathy

Retinopathy

- Diabetes is major cause of blindness in developed world
- Types
  - Background
  - Proliferative
## Retinopathy 2
- Regular screening of all patients
- Good BSL control
- Laser therapy
  - New vessels (possibly specific)
  - Central vessels, Maculopathy (Pancoagulation)

## Pregnancy & Diabetes
- High Mortality previously
- Problems
  - Macrosomia
  - Congenital defects
  - Hypoglycaemia
- Good control
  - As early as possible
  - 1st trimester - organ formation

## Pregnancy & Diabetes
- Planning
- Screening
- Therapy
  - Diet
  - Insulin
- Close Monitoring
- Admit if Problems
- Labour
  - Insulin infusion + glucose infusion