DIABETES

WHAT IS DIABETES?

Diabetes Mellitus (DM)
Chronic metabolic disorder with a predisposition of hyperglycaemia (increased blood glucose) .

Diabetes Insipidus (DI)
Condition in which the body has lack of control over fluid balance.

- Similar symptoms including polyuria (frequent urination)
- Mellitus "sweet"
- Insipidus "tasteless"

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- Mellitus "sweet"
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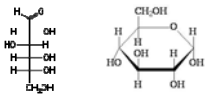
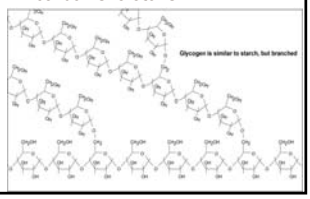
GLUCOSE

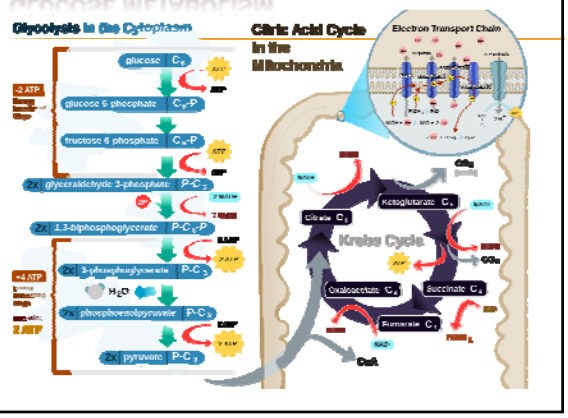
- Simply 6-carbon sugar
- Product of carbohydrate digestion
- Primary source of energy
- Exclusive source of energy in brain cells
- Blood glucose levels tightly controlled



- Uptake by cells involves glucose transporter proteins – $GLUT_{1\text{-}5}$
- Stored as glycogen
- Excess stored as fat
- Synthesised (recycled) from 3-carbon skeletons



GLUCOSE METABOLISM



GLUCOSE HOMEOSTASIS

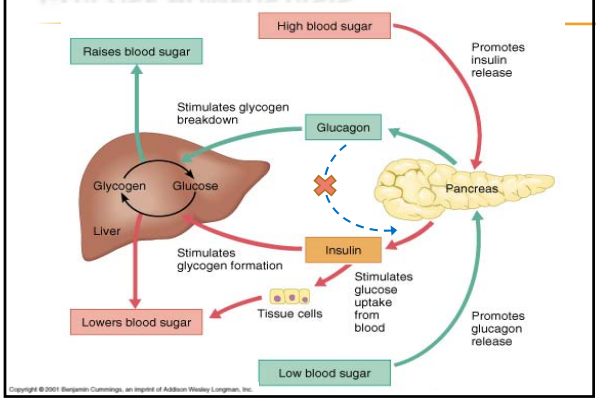
Insulin

- β cells of pancreas
- Released in response to ↑ glucose
- ↑ cellular uptake of glucose
- ↑ glycolysis
- ↑ glycogen synthesis
- ↓ lipolysis
- ↓ glycogenolysis
- ↓ gluconeogenesis

Glucagon

- α cells of the pancreas
- Released in response to ↓ glucose
- ↓ insulin secretion
- ↑ glycogenolysis
- ↑ gluconeogenesis

GLUCOSE HOMEOSTASIS



PATHOGENESIS OF DIABETES

- Commonest endocrine disorder
  - 171 million worldwide (2000)
- Characterised by persistent hyperglycaemia
- Absolute or relative lack of insulin
  - Subclasses of primary diabetes

TYPES OF DIABETES

TYPE 1 (~10%)

- Insulin deficiency
- Early & rapid onset (<18yrs)
- Low/Normal BMI - Weight loss
- Usually autoimmune
- Precipitating factor – stress/infection
- Often presents as a medical emergency – Ketosis
- Known genetic association
- Used to be called
  - Insulin dependant
  - Juvenile

TYPE 2 (~90%)

- Ineffective insulin
  - Reduced response in target cells
  - Reduced production
- Slow onset (>40yrs)
- Symptoms often present late (even after diagnosis)
- Normal or increased BMI
- Associated with obesity & inactivity
- Strong hereditary association
- Used to be called
  - Non-insulin dependant
  - Late onset

OTHER TYPES OF DIABETES

- Gestational diabetes
- Maturity onset diabetes of the young (MODY)
- Secondary causes
  - Endocrine
    - Cushing's syndrome/disease
    - Acromegaly
    - Conn's syndrome
    - Phaeochromocytoma
  - Pancreatitis
  - Pancreatic cancer
  - Pancreatectomy
  - Haemochromatosis
  - Drugs

SYMPTOMS OF DIABETES

- Polyuria
- Polydipsia
- Increased appetite
- Weight loss
- TAT
- Frequent/reoccurring infection
- Blurred vision

DIAGNOSIS

What needs to be detected……

- Raised blood glucose with symptoms
- Persistent hyperglycaemia without symptoms

When does it get detected…..

- Medical presentation
  - Symptoms or complications
- Family history
- Health check
- CVD screen

LABORATORY ISSUES

- Plasma glucose ~11% higher than whole blood (dependant on haematocrit)
- Capillary and venous glucose is comparable in fasting state but after glucose load capillary glucose is higher.
- Enzymatic methods for glucose are gold standard and must be used for diagnosis.
- In vitro glycolysis continues after collection in un-separated blood
  - Fluoride anticoagulant inhibits glycolysis
  - Separation ASAP (& kept on ice pre-separation)

IMPORTANCE OF DIAGNOSIS

- Increased risk of microvascular disease
  - Retinopathy, ultimately blindness
  - Nephropathy, ultimately renal failure
  - Neuropathy, commonly foot ulcers & impotence
- Increased risk of marcovascular disease
  - Ischemic heart disease
  - Stroke
  - Peripheral vascular disease
- Reduced life expectancy with significant morbidity
- Diminished quality of life

WHO GUIDELINES

- Fasting Glucose ≥ 7.0 mmol/L
  - with classic symptoms
  - On 2+ occasions excluding any other cause
- Random Glucose ≥ 11.1 mmol/L
  - with classic symptoms
  - On 2+ occasions excluding any other cause
- HbA1c ≥ 48 mmol/mol
  - Only if appropriate to use HbA1c

"PRE-DIABETES"

- Impaired Fasting Glycaemia (IFG)
  - Mildly raised glucose in a fasting state
- Impaired Glucose Tolerance (IGT)
  - Glucose remains mildly elevated for too long

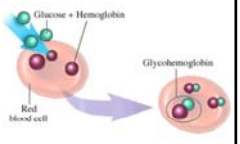
ORAL GLUCOSE TOLERANCE TEST (GTT)

- Used to confirm diagnosis but also to identify those at risk of diabetes
- Determines ability to handle a fixed load of glucose (75g) within 2 hours.
- Relies on
  - Complete fasting state at start
  - Accurate measure of glucose load
  - No activity that increases glucose utility before 2hrs

Diagnosis	Fasting Glucose		2hr post load
Normal	≤6.0 mmol/L	AND	≤7.8 mmol/L
Diabetic	≥7.0 mmol/L	AND / OR	≥11.1 mmol/L
Impaired Glucose Tolerance (IGT)	≤6.0 mmol/L	AND	7.9 - 11.0 mmol/L
Impaired Fasting Glycaemia (IFG)	≥6.1 but <7.0 mmol/L	AND	≤7.8 mmol/L

HBA1C

- Glycated haemoglobin proportional to glucose concentration
- Used for diagnosis since 2009
- ≥48 mmol/mol is sufficient to diagnose but ≤47 mmol/mol does not exclude diabetes



Why.....

- HbA1c reflects "average" glucose over 8-12 weeks
- Does not fluctuate daily – no need to fast
- Strong evidence emerging relating HbA1c levels with diabetic related mircovascular disease (retinopathy)
- Easy test to confirm non-symptomatic hyperglycaemia

CANNOT USE HBA1C FOR DIAGNOSIS

- ALL children and young people
- Patients of any age suspected of having Type 1 diabetes
- Patients with symptoms of diabetes for less than 2 months
- Patients who are acutely ill and risk of diabetes (e.g. those requiring hospital admission)
- Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics
- Patients with acute pancreatic damage, including pancreatic surgery
- In pregnancy
- Presence of genetic, haematologic and illness-related factors that influence HbA1c and its measurement

Factors affecting HbA1c	Increased HbA1c	Decreased HbA1c
Erythropoiesis	Iron deficiency, vitamin B12 deficiency, decreased erythropoiesis.	administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
Altered Haemoglobin	haemoglobinopathies, HbF, methaemoglobin	haemoglobinopathies, HbF, methaemoglobin
Glycation	alcoholism, chronic renal failure, decreased intraerythrocyte pH.	aspirin, vitamin C and E, certain haemoglobinopathies, increased intraerythrocyte pH.
Erythrocyte destruction	increased erythrocyte life span: Splenectomy, haemoglobinopathies.	decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals
Assays	Haemoglobinopathies, hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use.	Haemoglobinopathies, hypertriglyceridaemia.

MANAGEMENT

- Life long dietary modifications
- Recommended increase in physical activity
- Glucose lowering medication
- Insulin replacement

MONITORING

- Severity of hyperglycaemia
- Response / compliance to treatment
- Identification of complications
  - Introduction of treatments for long-term complications
- New-patient review
- Stable patient annual review
- "Special needs"
  - Poor control
  - Complications

LABORATORY INVOLVEMENT IN MONITORING

- Blood glucose levels
  - Normally self-monitored with point of care meters
  - Investigate discreptancies
  - Confirm extremes
- Glycated proteins
  - Non-enzymatically, dependant on prevailing glucose conc over life span of protein
  - HbA1c ~120 days
    - Factors affecting absolute HbA1c hence diagnosis can still provide effective monitoring (may have reduced life span)
  - Fructosamine ~3-4 weeks
    - Albumin is the major contributing protein
    - Used when HbA1c cannot be used – some haemoglobinopathies
    - Can be mis-leading in obese patients or in diabetes with long standing renal impairment

LABORATORY INVOLVEMENT IN MONITORING

Mircovascular complications

- Mircoalbuminuria (ACR)
  - Risk marker of CVD
  - Progression of renal failure
  - Hypertension treatment

Macrovascular complications

- Lipids for CVD risk assessment
  - Total cholesterol, HDL, Triglycerides

Dyslipidaemia in Diabetes

- Diabetes independent risk factor for CVD
- ↑serum triglycerides due to increase in VLDL
- Decrease in HDL
- Glycation of lipoproteins
- Altered modulation of lipoprotein lipase
  - Sensitive to insulin
  - Breakdown of triglyceride stores
  - Utilisation of fat stores for energy in fasting state

OTHER TESTS

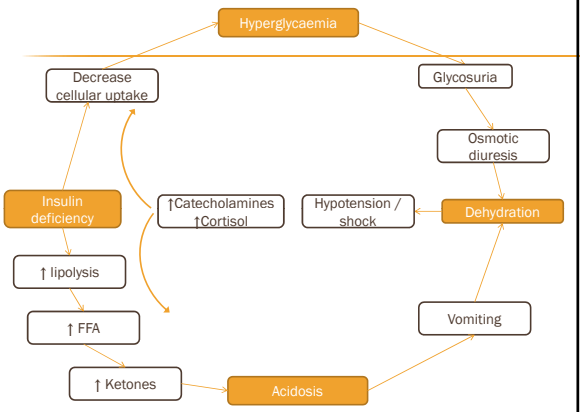
- Urine Glucose
  - Identifies glycosuria not diabetes
- Plasma insulin & C-peptide
  - Only useful in evaluating hypoglycaemia
- Lactate & ketone bodies
  - Essential in investigation and treatment of diabetic comas
  - Useful in investigation of high anion gap / acidosis

ACUTE COMPLICATIONS

- Diabetic Ketoacidosis (DKA)
  - Precipitating factors include infextion, trauma, MI
  - Omission of insulin

Metabolic disturbance

- Glycosuria causes osmotic diuresis
- Loss of water & electrolytes
- Increased ketone production and acidosis
- Vomiting hence loss of more water and elecrolytes



TREATMENT

- Give fluids to re-hydrate & expand ECF to restore circulation
- Give insulin to reduce hyperglycaemia
- Replace potassium if required
  - Note K is re-distributed in acidosis and will change when acidosis is corrected
- Management of DKA is best monitored by blood ketones - POCT

HYPEROSMOLAR NON-KETOTIC COMA

- Essentially DKA but with sufficient insulin to prevent ketosis
- Severe dehydration results in reduced consciousness
- Treatment similar to DKA

PREGNANCY

- Established diabetes is high risk for mother and baby
  - Higher rate of miscarriage, congenital malformations and stillbirth
- Poor glycaemic control can cause neonatel hypoglycaemia, respiratory distress & jaundice
- Significant deterioration of retinal & renal disease in mother

GESTATIONAL DIABETES

- Diabetes first detected during pregnancy
- Requires close monitoring of mother and neonate
- Diabetes may resolve post-natel but increases risk of diabetes

Case

- 43 yr old women
- BMI = 28
- Disturbed sleep
- No medication
- General health ok, often feel tired.

- All tests within reference limits (U&E, LFT's, TFT'S) except random glucose = 10.5 mmol/L

- What next?

SUMMARY OF DIAGNOSTIC TEST

- Fasting glucose - ≥ 7.0 mmol/L
- Random or 2hr glucose - ≥ 11.1 mmol/L
- HbA1c – 48 mmol/mol

- Any of the above + symptoms
- Any of the above on 2 or more separate occassions.

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- BMI = 28
- Disturbed sleep
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- General health ok, often feel tired.

- All tests within reference limits (U&E, LFT's, TFT'S) except random glucose = 10.5 mmol/L
- 2 weeks later
  - fasting glucose = 7.3 mmol/L
  - HbA1c = 49 mmol/mol

Cases

- 43 yr old women
- BMI = 28
- Disturbed sleep
- Thirsty
- No medication
- General health ok, often feel tired.

DIABETIC

- All tests within reference limits (U&E, LFT's, TFT'S) except random glucose = 10.5 mmol/L
- 2 weeks later
  - fasting glucose = 7.3 mmol/L
  - HbA1c = 49 mmol/mol

CASE – GTT CLINIC

	Patient 1	Patient 2	Patient 3	Patient 4
Fasting glucose	7.5 mmol/L	5.8 mmol/L	6.4 mmol/l	5.5 mmol/L
2 hour post	10.3 mmol/L	12.9 mmol/L	9.5 mmol/L	7.0 mmol/L
HbA1c	52 mmol/mol	42 mmol/mol	50 mmol/mol	46 mmol/mol
Diagnosis				

Diagnosis	Fasting Glucose		2hr post load
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2 hour post	10.3 mmol/L	12.9 mmol/L	9.5 mmol/L	7.0 mmol/L
HbA1c	52 mmol/mol	42 mmol/mol	50 mmol/mol	46 mmol/mol
Diagnosis	Diabetic	Diabetic	Diabetic	Normal

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Impaired Fasting Glycaemia (IFG)	≥6.1 but <7.0 mmol/L	AND	≤7.8 mmol/L

Case 2

- 54 yr old Asian man complaining of increased frequency of angina during cold spell of weather
- Weight = 97Kg, BMI = 30 Kg/m2, BP 139/89
- Doctor requests lipid profile
  - Total cholesterol = 8.3 mmol/L
  - Trigs = 17.0 mmol/L
    - Advised to screen for diabetes

Case 2

- Random glucose = 15 mmol/L
- HbA1c = 61 mmol/mol

- Diabetes confirmed & started on calorie restricted diet
- 3 months later
  - Random glucose = 8.2 mmol/L
  - HbA1c = 56 mmol/mol
  - Total cholesterol = 4.3 mmol/L
  - Trigs = 4.3 mmol/L
  - HDL = 0.9 mmol/L

Hyperlipidaemia

- Always consider diabetes
- Other causes include alcohol excess and hypothyroidism
- Lipid lowering medication is often used as treatment for diabetics even when lipids are only marginally raised.

Questions

1. What are the gold standard tests for diagnosis?
2. What situations alter which tests are used?
3. What are the common presentations of diabetes?
4. What tests should be performed as routine on a new diabetic?
5. How often should these be repeated?
6. What other “teams” are involved with monitoring a diabetic patient?