

Diabetes mellitus

= syndrome characterised by hyperglycaemia due to absolute or relative lack of insulin and/or insulin resistance

Clinical presentation

- **Acute:** DKA, weight loss, polydipsia, polyuria
- **Subacute:** longer Hx, lethargy, infections (e.g. pruritus vulvae/balanitis, boils)
- **Through complications**

Primary and secondary DM

- Primary = types 1+2
- Secondary = roughly equivalent to types 3+4

ADA/WHO classification

Type 1 (IDDM), type 2 (NIDDM)

	Type 1	Type 2
Epidemiology <ul style="list-style-type: none"> • Frequency • Predominance • Sex 	0.02-0.4% Caucasians, esp. Northern Europeans (north-south gradient from Finland to Greece, plus Sardinia!) F=M (unlike other autoimmune diseases)	1-3% 85% of all diabetes Afro-Caribbeans and Asians F:M = 4:1
Clinical characteristics <ul style="list-style-type: none"> • Age • Weight • Onset • Ketosis • Endogenous insulin • Insulin sensitivity • Islet cell antibodies 	<40 years (but 30% diagnosed after age 30; LADA - latent autoimmune DM of adults) Low Rapid Common Absolute deficiency, no C peptide Yes Yes	>40 years Normal or increased Slow Under stress Relative deficiency, C peptide persists No (end-organ resistance) No
Pathophysiology <ul style="list-style-type: none"> • Genetic associations 	HLA associations (DQ2, DQ8, DR3, DR4 – together called <i>IDDM 1</i> ; DR2 and DR5 protective) Non-HLA association (part of insulin gene – <i>IDDM 2</i>) <i>IDDM 3-17</i> also described (both HLA and non-HLA) Associated with other autoimmune disease (esp. thyroid disease) 40% concordance rate amongst MZ twins suggests strong environmental influence 5% risk in first-degree relative	Polygenic <ul style="list-style-type: none"> • Familial • ~100% concordance rate amongst MZ twins

<ul style="list-style-type: none"> • Aetiology 	<p>Interplay of 3 factors:</p> <ul style="list-style-type: none"> • Viral infection (Coxsackie B4, rubella, mumps, EBV, CMV), also cow's milk protein¹ • Cytopathic effect and molecular mimicry of GAD • Islet cell antibodies, present in 90%, e.g. against GAD or PTP (protein tyrosine phosphatase) <p>“Hygiene hypothesis” – clean environment leads to defective immunoregulation</p>	<p>Ageing Obesity (BMI, waist circumference)</p>
<ul style="list-style-type: none"> • Pathogenesis 	<p>Two theories:</p> <ul style="list-style-type: none"> • Mostly CD8+ T cells present. Proposed to kill β-cells by cytotoxicity • Inflammatory process not specific for β-cells; cytokines such as IL-1 are known to be cytotoxic to β-cells <p>Autoantibodies² only of relevance in diagnosis. They cannot transfer the disease, neither between animals nor <i>in utero</i>, and are not even present in all affected patients.</p>	<p>Some loss of β-cell mass, partial replacement by amyloid</p> <p>Autoantibodies used to define subsets (latent autoimmune diabetes of adults)</p>

Type 1

Type 1a: an organ-specific autoimmune disorder. Absolute lack of insulin as a consequence of antibody-mediated destruction of β -cells.

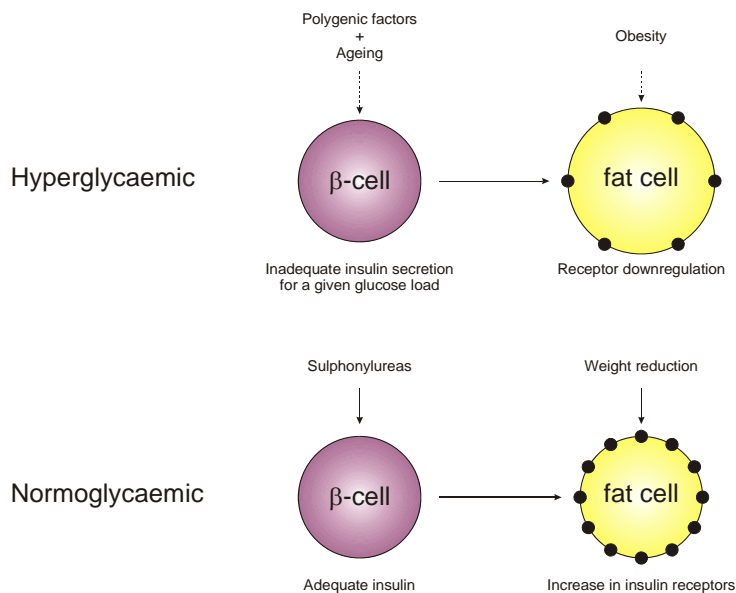
Type 1b: young obese Afro-Caribbean patients, initially type 1 + ketoacidosis, but no other autoimmune disease + fluctuating insulin requirements

Type 2

¹ Evidence: epidemiological association, viral isolation, animal experiments

²

Autoantibody	Antigen	Prevalence at diagnosis	Role in disease
Islet cell AB	?	75%	Predictive
Islet cell surface AB	?	40%	To be defined
Insulin autoantibody	Insulin	40%	Predictive, often the first to develop
Anti-GAD AB	GAD	75%	Predictive
Anti-phogrin and anti-IA-2 ABs	PTP	75%	Predictive



Type 2 diabetics may eventually require insulin – this does *not* mean that type 1 DM has developed.

Type 3 (other specific types)

- Insulin deficiency ('type 1-like')
 - Genetic/chromosomal syndromes, e.g. Down's and Turner's
 - Genetic defect in β-cell function, e.g.
 - MODY
 - AD
 - Type 2 DM under age 25, with strong FH
 - Defect in glucokinase (onset at birth, stable, dietary modification) or transcription factor gene (onset in adolescence, progressive, require insulin)
 - MIDD - mitochondrially inherited DM + deafness
 - Pancreatic exocrine diseases, e.g. chronic pancreatitis, haemochromatosis, CF
- Insulin resistance ('type 2-like')
 - Hormonal antagonism of insulin
 - Cushing's
 - Acromegaly
 - Pheochromocytoma
 - Glucagonoma, VIPoma
 - Thyrotoxicosis
 - PCOS
 - Drugs
 - Corticosteroids
 - Thiazide diuretics
 - Anti-insulin antibodies
 - Insulin receptor abnormalities (associations: partial lipodystrophy, acanthosis nigricans, leprechaunism)

NB hypothyroidism enhances insulin sensitivity

Metabolic syndrome ('syndrome X')³

Clustering of several vascular risk factors in the same individual.

Several definitions exist

- WHO
 - Insulin resistance plus at least two of the following: HT, dyslipidaemia, obesity, microalbuminuria
- American Treatment Panel III
 - At least three of: high fasting glucose, HT, raised triglycerides, low HDL, central obesity
- International Diabetes Federation

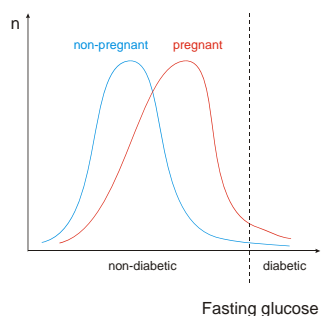
³ LAWLOR, D.A. ET AL. (2006): Obesity and vascular disease. *BMJ* 333:1060-1063.

- Central obesity plus at least two of: raised triglycerides, low HDL, HT, high fasting glucose

Overall involves: obesity, insulin resistance, hyperinsulinaemia, hyperglycaemia, hypertriglyceridaemia, HT, coronary artery disease.

Type 4 (gestational DM)

Altered CH metabolism and physiological antagonism of insulin by HPL, progesterone and cortisol shift the population curve to the right.



Gestational diabetics have a high chance of developing subsequent overt diabetes. Repeat OGTT $\geq 6w$ post-partum.

Diagnosis and monitoring

Diagnostic finding = hyperglycaemia.

Urine testing

Glucose: first-line screening test. Normally negative unless plasma glucose $>10\text{mmol/l}$; however, poor correlation with blood glucose because

- Time lag relative to changes in blood glucose
- Mean renal threshold variable (ca. 1% have low threshold), and increasing with age (many diabetics will not have glycosuria)
- No guidance if blood glucose below renal threshold

Sensitivity 32%, specificity 99%.

Ketones: not diagnostic of ketoacidosis; overnight fast can produce ++ketonuria in normals.

Blood glucose

Outside the lab: visual/electronic test strips

In the lab: blood is collected into tubes containing fluoride, an inhibitor of glycolysis

- RBG (random): the only test required in an emergency, but not diagnostic in the elective setting.
- FBG (fasting): after an overnight fast (at least 10h). Diagnostic if two high readings, or single high reading and symptomatic.
- OGTT: sitting comfortably without smoking or exercise, normal diet for at least 3 days.
 - Most are performed unnecessarily. Indications:
 - Borderline fasting glucose
 - Persistent glycosuria
 - Glycosuria in pregnant women
 - Pregnant women with a FH of DM, previously macrosomic babies or unexplained fetal loss

WHO criteria

	Fasting sample (at least 10h fast)	OGTT (2h after 75g glucose in 300ml in 5min)
Normal	$< 6 \text{ mmol/l}$	$< 7.8 \text{ mmol/l}$
Impaired glucose tolerance	$6-7 \text{ mmol/l}$	$7.8-11.1 \text{ mmol/l}$
DM	$\geq 7 \text{ mmol/l}$	$> 11.1 \text{ mmol/l}$

Impaired glucose tolerance: intermediate stage between normality and DM, but only 2-4% per year go on to develop frank diabetes. No microvascular complications, but x2 macrovascular risk/mortality (i.e. same as DM!). Should receive yearly follow-up, and dietary treatment may be used.

NB: the distribution of blood glucose concentration in the population is unimodal. Diagnostic criteria are therefore arbitrary.

Long-term indices of glycaemic control

Many proteins undergo non-enzymatic glycation of lysine residues; the extent is determined by the ambient glucose level. It is virtually irreversible, and the concentration of a glycated protein reflects the mean blood glucose level during the life of that protein.

- **HbA_{1c}:** $t_{1/2}$ = 2 months, but recent glycaemic control has greater influence

4.9-6.3%	Normal range
>7%	DM likely (sensitivity and specificity >99%; however, HbA _{1c} should not be used as a screening test)
<8%	Acceptable glycaemic control (targets vary; e.g. NICE: <6.5% type 1 DM with high cardiovascular risk, 6.5-7.5% type 2 DM, <7.5% type 1 DM with lower cardiovascular risk)
8-10%	Increased risk of complications, desirable to improve control
>10%	High risk of complications

- **Fructosamine:** other plasma proteins (mostly albumin), $t_{1/2}$ = 3 weeks; useful if HbA_{1c} measurements not meaningful⁴

Microalbuminuria: albumin excretion between normality (2.5-25 mg/day) and macroalbuminuria (>250 mg/day). Not detected by albumin stick tests, requiring confirmation in a 24h urine specimen. Sign of early, reversible renal damage.

Other investigations

- Blood: lipids, U&E
- Urinalysis

Treatment

Type 1: insulin

Type 2: progressive decline of β -cell function, hence sequence of⁵

- Lifestyle modification
- Oral monotherapy (usually metformin)
- Dual combination therapy (add sulphonylurea or thiazolidinedione or basal insulin)
- Triple combination therapy (metformin + 2 of above)
- Intensive insulin + metformin \pm thiazolidinedione

Diet

- CHO 50-55% of energy
 - Complex rather than refined sugars
 - Fibre slows absorption
- Fat 30-35% of energy
- Protein 10-15% of energy
- Salt <6 g/day

⁴ Abnormally low in HbS, thalassaemia, haemolysis, blood loss; abnormally high in uraemia (causes carbamylated Hb), high triglycerides, high bilirubin, alcoholism

⁵ HEINE R.J. ET AL. (2006): Management of hyperglycaemia in type 2 diabetes. *BMJ* 333:1200-4.

- Regular snacks between meals avoid hypo's

Oral hypoglycaemics

Only given if diet does not achieve satisfactory control. All major classes (sulphonylureas, biguanides, thiazolidinediones) are roughly equally effective. Insulin may eventually be required (types 1 and 2!).

- Sulphonylureas (tolbutamide, glipizide – short-acting; gliclazide – intermediate-acting; glibenclamide, chlorpropamide – long-acting)
 - Close ATP-sensitive K⁺ channels on the β-cell membrane
 - CI: hepatic/renal impairment (exception: tolbutamide – hepatically metabolised)
 - SE: ↑appetite (hence use in slim patients), hypoglycaemia, sensitise collecting ducts to ADH (→ SIADH-like syndrome), flushing, P₄₅₀ inhibition, cholestatic jaundice
 - Chlorpropamide has long half-life and carries marked risk of hypoglycaemia
 - ↑effect by EtOH, sulphonamides, trimethoprim, fibrates, sulphinyprazole
 - Average ↓HbA_{1c}: 1.5%
- Biguanides (metformin)
 - Reduce hepatic gluconeogenesis and increase hepatic insulin sensitivity
 - CI: hepatic/renal impairment (worse offender than SUs; stopped if crea>150 as metformin is renally excreted and t_{1/2} is prolonged in proportion to decreased creatinine clearance), AMI
 - SE: ↓appetite, lactic acidosis, N&D&V – may occur late, poor B₁₂ absorption; *not* hypoglycaemia
 - Considered as an adjunct to insulin in type 1 diabetics if requiring large doses, overweight, or HbA_{1c} > 8%
 - Average ↓HbA_{1c}: 1.5%
- Thiazolidinediones/glitazones (roziglitazone, pioglitazone; troglitazone withdrawn due to drug-induced hepatitis)
 - PPAR_γ⁶-agonists
 - Sensitise adipose tissue, liver and muscle to insulin; reduce lipotoxicity
 - NICE guidance: only use if
 - Unable to tolerate combination of metformin and sulphonylurea
 - Metformin or sulphonylurea is contraindicated
 - Better combined with metformin than with sulphonylureas; next step is insulin
 - Slow onset of action over 6m
 - CI in hepatic impairment; may cause rise in LFTs, check every 2 months for first year and stop if ↑ALT more than 3-fold
 - SE: hypo (!), headache, fatigue, oedema (avoid in heart failure), GI upset
 - Average ↓HbA_{1c}: 0.5-1.5%
- Meglitinides (repaglinide, nateglinide)
 - Stimulates insulin secretion from β-cells (non-sulphonylurea insulin secretagogue)
 - Quick onset and short duration of action → given just before meals
 - Indications
 - Monotherapy in patients who are not overweight or in whom metformin is CI or not tolerated
 - Combined therapy with metformin
 - CI in hepatic impairment
 - Average ↓HbA_{1c}: 1-1.5%
- α-glucosidase inhibitors (acarbose)
 - Inhibits intestinal enzymes that break down starch (complex CHO), thus reducing absorption
 - Increase in fermentation in large intestine causes flatulence, abdo pain, diarrhoea; less if slow build-up
 - Average ↓HbA_{1c}: 0.5-0.8%
- Glucagon-like peptide and dipeptidyl peptidase-4 (DPP-4) inhibitors/gliptins (vildagliptin, sitagliptin)
 - Incretin effect: normally, an oral glucose load elicits a substantially greater release of insulin than the same amount of glucose given intravenously. Mediated predominantly by glucagon-like peptide-1 (GLP-1), which is secreted from the small intestine in response to luminal carbohydrate. Effect size reduced in type 2 DM.
 - GLP-1 effects: potentiation of insulin secretion, increased insulin sensitivity, inhibition of glucagon secretion, slowing of gastric emptying, decreased food intake
 - GLP-1 has to be given parenterally (exanatide), and has a short half-life due to degradation by DPP-4

⁶ Peroxisome-Proliferator-Activated Receptor Gamma (part of nuclear receptor superfamily; normally activated by free fatty acids; upregulates e.g. GLUT transporters + LPL)

- Current approach is via DDP-4 inhibition
- Add-on to metformin or sulphonylurea
- Well tolerated; hypoglycaemia rates similar to placebo
- Average \downarrow HbA_{1c}: 0.5-1%

Type 2 diabetics may require insulin if

- Sudden onset
- Glucose >25mmol/l
- Ketonuria
- Dehydration

Parenteral hypoglycaemics

- Exenatide
 - Synthetic analogue of the Gila monster salivary gland product exendin-4, which has similar characteristics to, but a much longer half-life than, glucagon-like peptide
 - Causes weight loss
 - GI side-effects
 - Average \downarrow HbA_{1c}: 0.5-1%
- Pramlintide
 - Slowing of gastric emptying, inhibition of glucagon release
 - Causes weight loss
 - GI side-effects
 - Average \downarrow HbA_{1c}: 0.5-1%

Insulin

Physiology

- Pancreas secretes 30-40 units of insulin per day
- Insulin has half-life of ca. 5 min

Injection

- Either by syringes or pens
- Given at 45° into a pinch of skin on thigh, abdomen, buttocks or upper arm
- Rotate injection site to prevent complications
- Absorption rate
 - Abdomen > buttock > arm > thigh; IM > SC
 - Accelerated by exercise, heat or massage

Insulin preparations

- Insulin is made chemically identical to human insulin by recombinant yeasts or chemical modification of pork insulin⁷
- Concentration 100U/ml
- Formulations
 - Ultra-short-acting Lispro/Aspart
 - Altered $\alpha\alpha$ sequence accelerates dispersion of insulin hexamers that form around zinc core
 - Use same number of units
 - Less hypos, but need more injections/BMs
 - Little impact on HbA_{1c}
 - Short-acting neutral/soluble
 - Use in emergencies
 - Intermediate-acting isophane, lente
 - NPH, zinc
 - Mixtures of intermediate and short-acting insulins widely used (e.g. 70/30)
 - Long-acting ultralente
 - Zinc but larger particles
 - Peakless basal glargine/Lantus
 - NICE (2002): should be available to

⁷ In practice, porcine insulin is not more immunogenic than human insulin. Compared to human insulin, 1 amino acid is different in porcine insulin and 2 in bovine insulin.

- Type 1 diabetics
- Type 2 diabetics
 - Who require assistance with injecting
 - Whose lifestyle is significantly restricted by hypoglycaemic symptoms
 - Who would otherwise need twice-daily basal insulin injections in combination with oral hypoglycaemics

Insulin in clinical use

- ‘Honeymoon’ period with low insulin requirements shortly after presentation. Requirements then increase up to 2U/kg/day.
- In normal subjects, a sharp increase in insulin occurs after meals (50% of total), superimposed on a constant background of secretion (50%)
- Insulin therapy attempts to reproduce this pattern but fails because
 - Absorption is variable
 - Onset and offset are too slow
 - In normal subjects, insulin concentration is high in the portal circulation and low in the systemic circulation. Insulin injected subcutaneously passes directly into the systemic circulation. Insulin-treated patients therefore have lower portal and higher systemic levels.
 - Basal insulin levels are constant in the normal state, but injected insulin gives fluctuating levels
- Administration
 - Combination of short- and long-acting insulin injections
 - Bd: mixture of short- and intermediate-acting insulin at e.g. 7am and 6pm; give 2/3 in the morning and 2/3 as intermediate-acting
 - Tds: short-acting before every meal, with evening dose of long-acting (‘basal bolus’; mixtures available)
 - Infusion devices
- Social implications
 - DVLA
 - Insurance
 - Employer

Complications

- Injection site: scarring, abscesses, lipodystrophy
- Insulin resistance, most commonly due to obesity
- Weight gain, esp. if non-compliant with diet or insulin doses
- Hypoglycaemia – major limiting factor in achieving euglycaemia

New developments

Treatment

Other routes of insulin administration

- Inhaled insulin
 - Activity ca. 10% of injected insulin on a weight basis
 - Smoking increases and asthma decreases absorption
 - First preparation: Exubera[®]
 - First non-pulmonary drug licensed for administration by inhalation
 - Prandial insulin: onset similar to analogue insulin, offset similar to human insulin
 - Equivalent efficacy to SC insulin in glycaemic control
 - CIs: lung disease (incl. FEV₁<70%), heart failure
 - SEs: cough, insulin antibody formation (more than with SC insulin; levels subside on discontinuation), ↓FEV₁ (subsides after discontinuation); insuling is a growth factor and may have further long-term side effects
 - Was endorsed by NICE as a treatment option in type 1 and 2 DM with poor glycaemic control, when routine insulin therapy could not be started or intensified due to severe injection phobia or due to severe lipohypertrophy
 - Voluntarily withdrawn due to disappointing sales, possibly due to the complex device, dosing difficulties, price (ca. 4x that of standard insulin), and continued concerns about long-term effects
 - Under development
 - AERx Insulin Diabetes Management System: breath-activated, dose adjustments similar to injectable insulin, electronic compliance monitoring
 - Mannkind Technosphere Insulin system: insulin encapsulated in a carrier ‘technosphere’
 - Oral

- Delivery via portal system, thus mimicking normal physiology
- Main challenge: insulin degradation by gastric acid and proteolytic enzymes
- Capsulin is one promising formulation that delivers insulin in an enteric-coated capsule to the small intestine
- Nasal

Islet transplantation

Monitoring⁸

- Future aim is minimally or non-invasive monitoring
 - Continuous Glucose Monitoring System (CGMS): laser microporation of skin, followed by continuous drawing of interstitial fluid for glucose estimation.
 - GlucoWatch[®]: glucose molecules drawn through skin by reverse iontophoresis, concentration measured by an electrochemical reaction catalysed by glucose oxidase.
 - Near-infrared: measures absorption of 940nm light through the earlobe.
 - Main drawbacks: frequent calibration required, poor accuracy, cost, currently no means of harnessing the amount of data generated – a ‘closed-loop’ system with an insulin pump would require accurate readings in real time
 - Increasingly smaller amounts of blood required by glucometers may lead to near-painless lancets and prolong the lifespan of the traditional glucometer

Targets

ADA targets: HbA_{1c} < 7% and fasting glucose 4.4-6.7mmol/l
Set individually, e.g. tight in the young/pregnancy, relaxed in the elderly

Other medical aspects

- ACE-I
- Aspirin
- Statin

Also consider

- Exercise
- Specialist nurse/dietician/chiroprapist/diabetic association
- Follow-up

Complications

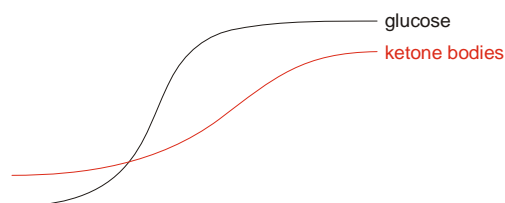
Acute: metabolic decompensation

Diabetic ketoacidosis

Precipitating factors

- Unrecognised onset of DM
- Stopping/reducing insulin – in error or deliberately
- Resistance to insulin during infection/surgery/MI

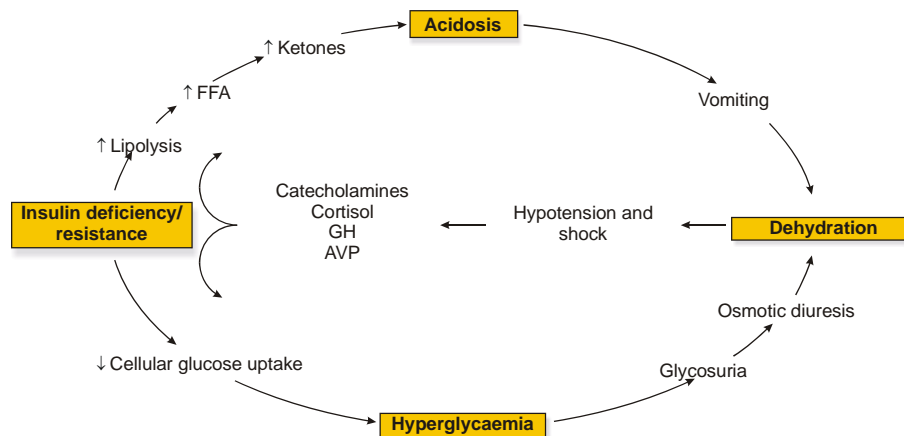
If no insulin to type 1 diabetic:



⁸ SINGH, G. (2008): Revolution at our fingertips. *Cambridge Medicine* **22(1)**:41-3.

Pathogenesis

A series of interlocking vicious circles:



Sick day rules

- Never stop insulin – need to increase dose when ill
 - Insulin-treated, mild illness (e.g. gastroenteritis): maintain calorie intake with PO fluids, test BM/urine bd, increase insulin if consistently >10mmol/l
 - Insulin-treated, moderate illness (e.g. pneumonia): normal insulin and supplementary sliding scale qds before meals
 - Insulin-treated, severe illness (e.g. MI): IV sliding scale
 - Diet and tablet-treated, moderate/severe illness
 - Metformin: stop
 - Sulphonylurea: continue and supplement with insulin
- Maintain CHO intake
- Increased frequency of testing
- Test urine for ketones

Clinical features

- Decreased conscious level
- Kussmaul's breathing, ketotic fetor (acetone)
- Abdominal pain, vomiting, dehydration
- Polyuria, polydipsia

Investigations

- Lab glucose, U&E, HCO_3^- (hourly)
- Amylase
- ABG
- FBC
- Septic screen
- Urinalysis: ketones
- ECG: features of hypokalaemia

Management

- Fluid replacement
 - Dehydration rather than hyperglycaemia is life-threatening
 - 1l 0.9% NaCl stat., followed by 1l over 1-2-4-6h
 - Use dextrose-saline when glucose <15mmol/l
 - If >65 or in CCF, need less saline more cautiously
 - Monitor fluid balance; catheter if no urine for >4h, CVP line if shocked.
- Insulin
 - IV
 - 50U soluble insulin in 50ml saline

Hourly glucose result	Insulin dose	If infection/insulin resistance
0-4	0.5	1
4-8	1	2
8-12	2	4

12-16	3	6
>16mmol/l	4U/h	8U/h

- IM
 - If no pump, load with 10U IM (SC not absorbed well), then give 4-6U/h IM while glucose is >14mmol/l
- Potassium replacement
 - Despite apparently normal serum potassium levels, all patients with DKA have whole body potassium depletion. Treatment precipitates hypokalaemia since insulin stimulates K⁺ transport into cells.
 - NONE should be given in the first bag of saline while awaiting lab result
 - Thereafter, given according to 2 hourly lab K⁺ samples
 - <3mmol/l: give 40mmol/h
 - <4mmol/l: give 30mmol/h
 - <5mmol/l: give 20mmol/h
- Additional treatment
 - NG tube for aspiration/nil by mouth, if patient at all drowsy. Acidosis inhibits gastric emptying.
 - Thromboprophylaxis
 - Treatment of any underlying condition
- Back to normal
 - Daily urinalysis
 - Re-introduce diet
 - Once ketones ≤1 and eating, re-start SC insulin. Insulin infusion should be continued for half an hour after first SC dose given.
 - Patient education

Pitfalls

- Failure to recognise: deceptively well patients
- Ketonuria vs. ketoacidosis: starvation produces ketonuria but not ketoacidosis.
- Creatinine: may be falsely elevated due to cross-reaction of assay with ketones
- Hyponatraemia: common, due to osmolar compensation for hyperglycaemia. As treatment commences Na⁺ rises. Na⁺ is also low due to an artefact caused by hyperglycaemia.
- High WCC: may be seen in absence of infection
- Amylase: may be raised up to 10x even without pancreatitis
- ↑chloride: chloride required in collecting duct for bicarb/chloride exchange
- ↑K⁺: acidosis impairs renal K⁺ excretion
- Infection: often without fever – give broad-spectrum ABx early if suspected, but ideally not just on the basis of ↑WCC
- Failure to educate patient

Complications

- Hypokalaemia, hypomagnesaemia
- Cerebral oedema
- Aspiration pneumonia
- DVT/PE

HONK

Develops slowly in elderly type 2 diabetics.

Low level of insulin persists

- Sufficient to prevent ketosis (no acidosis)
- Does not prevent hyperglycaemia (often glucose >35mmol/l) and osmotic diuresis (plasma osmolality >340mosm/kg)

Precipitating factors include severe illness, surgery, dialysis, dehydration, diuretics, glucocorticoids and parenteral nutrition.

Management principles

- As for DKA, but much slower: aim to rehydrate over 48h, with little or no insulin (e.g. 1U/h after 1h without insulin).
- Hyponatraemia often profound, Na >150 mmol/l, and dilute saline (0.45%) may need to be used.
- High DVT risk – thromboprophylaxis

High mortality/morbidity.

Lactic acidosis

Type I: excessive peripheral lactate production in hypoxic subjects

Type II: impaired lactate metabolism in liver

Both are characterised by extreme metabolic acidosis ($[H^+] > 100\text{nmol/l}$). There is a high anion gap with low or absent ketones, and high blood lactate.

Treatment: large amounts of IV bicarbonate. Alternatively dialysis against a bicarbonate-containing solution.

Hypoglycaemia

Defined as blood glucose $<2.5\text{mmol/l}$

Causes

In *type 1 diabetic* (99%)

- Major hazard of insulin therapy, and major fear of every diabetic. Lifestyle implications huge, e.g. DVLA, unable to hold HGV license⁹
- Precipitating factors
 - Insufficient CHO
 - Excessive insulin, mistakenly or deliberately. This can include erratic absorption from 'lumpy' injection sites.
 - Excessive activity
 - Misc.: alcoholic binge, hot weather, pregnancy

In *type 2 diabetic* on sulphonylureas

Others

- Fasting
 - Cancer
 - Insulinoma
 - Non-pancreatic neoplasms: retroperitoneal fibrosarcoma, haemangiopericytoma
 - Hodgkin's: associated with insulin-R antibody
 - Hepatic disease
 - Addison's disease
 - Sepsis: mechanism is not fully explained
- Reactive (exogenous stimulus)
 - Drugs: surreptitious insulin (therefore measure C peptide)
 - Food: post-prandial hypoglycaemia: may be due to idiopathic exaggerated insulin response, or accelerated gastric emptying ('dumping syndrome' after gastric surgery)
 - Alcohol

Clinical features

- Autonomic¹⁰: sweating, tremor, hunger, palpitations
- Neuroglycopenic: double vision, confusion, altered behaviour, altered conscious state, seizures
- Beware of hypoglycaemic unawareness in longstanding diabetics on tight control
- No evidence that β -blockers cause hypoglycaemic unawareness

Investigations

- Blood glucose: act on basis of BM and send for lab result
- Admit for 72h fast
- Plasma insulin, C peptide

Management (must be rapid to avoid brain damage)

- 50ml 50% dextrose IV, may cause thrombophlebitis
- If no improvement consider dexamethasone 4mg/4h IV to combat cerebral oedema
- If IV access fails try glucagon 1mg IM, can cause profound nausea
- Identify cause

⁹ Other career paths closed to diabetics on insulin: armed forces, working offshore or aboard ships, pilot, police, fire, driving in the post office. Regulations for taxi licenses vary according to local authority.

¹⁰ Hypoglycaemia \rightarrow catecholamine secretion \rightarrow clinical features

- o If tight glycaemic control, consider relaxing control for 3-4m until hypoglycaemic awareness is regained
- Education

Chronic

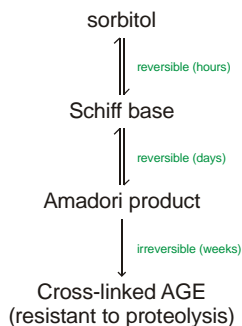
Microangiopathy esp. type 1
Premature atherosclerosis esp. type 2

Precipitating factors

- Longstanding disease
- Poor glycaemic control
 - o Metabolic memory: a period of poor glycaemic control increases the risk of complications for longer than the duration of poor control
- Co-morbidity
- Genetic factors

Pathogenesis

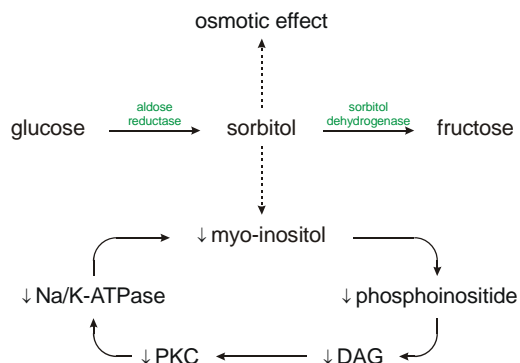
In hyperglycaemia, glucose is channelled into non-insulin dependent pathways. Non-enzymatic glycation involves many proteins, lipoproteins and nucleic acids, forming **AGEs** (advanced glycosylation end products).



They exert widespread pathogenic effects:

- Thickened BM
 - o Affects collagen, resulting in cross-linking, trapping of non-glycosylated proteins including lipoproteins, and resistance to proteolysis by collagenase
 - o Accelerated by hypertension
 - o Functional significance of thick BM
 - Structurally weak, ballooning out to form microaneurysms
 - Abnormally permeable
 - Obliterates lumina
- Receptors
 - o Binds to endothelial cells, phagocytes, lymphocytes
 - o Causes emigration of leukocytes, increased permeability, release of cytokines, procoagulant state, collagen secretion by fibroblasts
- Increase in superoxides, causing oxidative stress

Also, increased intracellular glucose is converted to **sorbitol**, exerting an **osmotic effect** and indirectly **inhibiting Na/K-ATPase**.



Aldose reductase inhibitors have limited effect. Hence, there must be other mechanisms, too.

Microvascular

Kidney/urinary tract

Renal artery stenosis

Nephropathy

- BM thickening produces diffuse glomerulosclerosis. Pathognomonic Kimmelstiel-Wilson lesions form from nodular accumulations of BM material in the mesangium¹¹.
- Clinical definition: proteinuria >0.5g/day
 - Surrogate of 24h urinary protein excretion = alb:crea ratio, measured on first morning sample
 - If $\geq 2.5/3.5$ mg/mmol (M/F) indicates microalbuminuria
 - If ≥ 30 mg/mmol indicates proteinuria
- Functional significance:
 - Bursting microaneurysms cause haematuria
 - Permeable BM causes albuminuria
 - Obliteration of capillary lumina causes renal failure
- Stages
 - Incipient nephropathy
 - Microalbuminuria, 25-250 mg/day
 - Mesangial expansion
 - Increased GFR
 - Nephropathy
 - Macroalbuminuria, >250 mg /day
 - Kimmelstiel-Wilson nodules
 - Decline in GFR, creatinine raised
 - Relentless progression to ESRF
 - Type 1: 5y lag post-Dx, peak at 15-17y, low risk if >35y
 - Type 2: steady rise in incidence over time, may rapidly develop nephropathy
- Lower incidence in type 2; however majority of patients with diabetic nephropathy are type 2 as it is much more common than type 1
- Progression to ESRF
 - Type I: 50%
 - Type II: 15%
- ACE-Is proven to slow progression.

UTI

- Papillary necrosis
- Pyelonephritis

Eyes

See lists.

Neuropathy

Progressive: diffuse polyneuropathy, mostly sensory and autonomic

- Peripheral neuropathy
 - Symmetrical sensory
 - Usually lower limb, stocking distribution
 - Small fibres: pain & temperature
 - Burning pain and hyperalgesia (no sheets)
 - Proximal asymmetrical motor neuropathy (diabetic amyotrophy)
 - Middle-aged/elderly males
 - Caused by lumbosacral plexus disease
 - Classically quadriceps weakness with loss of knee jerks
- Autonomic neuropathy
 - Clinical features: tachycardia, cardiac arrhythmia ('dead-in-bed' – hence rationale to use β -blockers), reduced appreciation of cardiac pain, postural hypotension, gustatory sweating, gastroparesis, diarrhoea, neurogenic bladder, impotence
 - Diagnostic tests: heart rate response, BP response, pupil response to light

Reversible: mononeuropathies, esp. CN palsies; acute painful neuropathies

¹¹ Cellular network in the glomerulus that supports capillaries, also phagocytic

- Mononeuropathy
 - Rapid onset, eventual recovery
 - Esp. III and VI CN palsies
- Acute painful neuropathy
 - Any stage of diabetes
 - Disabling pain
 - Thigh common site

Infection

Increased risk, esp. urinary tract, and skin with bacteria or fungi.

Skin&joints

- Infections
- Cheiroarthropathy¹²
- Diabetic dermopathy¹³
- Diabetic bullae¹⁴
- Necrobiosis lipoidica diabetorum¹⁵
- Granuloma inguinale

Neuropathic joint: Charcot joint¹⁶

- Destruction of articular surfaces, opaque subchondral bones, loose bodies, deformity, dislocation

Diabetic foot

- Neuropathic vs. ischaemic
 - Neuropathic: callus, ulcers (infections: esp. *Staph. aureus*), sepsis, Charcot
 - Ischaemic: painful, pink, cold, pulseless

Teratogenesis

Risk of fetal malformations if uncontrolled DM in first trimester (e.g. sacral dysgenesis).

Macrovascular: premature atherosclerosis

Occurs earlier than in the normal population, and is more severe.

Prevention

Primary

- Blood glucose (esp. type 1)
- BP (esp. type 2)

Secondary

- Laser photocoagulation
- Chiropody

Literature

DCCT (Diabetic Control and Complications Trial) for type 1 DM
 UKPDS (UK Prospective Diabetes Study Group) for type 2 DM

DAFNE (Dose Adjustment for Normal Eating): improved dietary freedom, HbA_{1c}, and QOL

US Diabetes Prevention Programme: patients with impaired glucose tolerance were randomised to placebo, metformin, or an intensive programme of diet and exercise. New cases of diabetes were reduced by 58% in the diet and exercise group compared with 31% in patients randomised to metformin.

¹² Cheiro = to do with hands; prayer sign

¹³ Dull papules on shins → atrophic brown scars

¹⁴ Blisters on extremities of elderly diabetics

¹⁵ Degeneration of subcutaneous collagen over shins produces sharply demarcated violet rings with yellow atrophic centre

¹⁶ Swollen, deformed joint, often the knee, resulting from repeated minor trauma to asensate joint

www.diabetes.org.uk
www.diabetes.org