Diabetes Mellitus

Classification

Primary

Type 1 (old terms: insulin-dependent DM, IDDM) – **15% DM cases**

- Characterized by insulin deficiency. & beta cell destruction. Patients prone to DKA.
- 30-50% concordance in identical twins (so environment also important). M=F.
- Polygenic (incl 6q). Assoc with HLA DR3 and DR4 and 90% have islet cell antibodies at Dx.
- Norm juvenile onset. Type 1A – immune-mediated (adult), Type 1B (non-immune, ↓↓insulin)
- May be assoc with other autoimmune disease.

Type 2 (old terms: non-insulin-dependent DM, NIDDM, maturity onset DM) – **85% DM cases**

- Due to impaired insulin secretion and insulin resistance
- ~100% concordance in identical twins. F>M.
- No HLA association
- Mature gradual onset, often obese (Syndrome X). 5% MODY (mainly AD, β-cell dysfn.)

Secondary

- *Drugs:* steroids, thiazides, phenytoin, diazoxide, antipsychotics, αINF, β-agonists
- *Endocrine:* Cushing's, acromegaly, phaeochromocytoma, hyperthyroid, glucagonoma
- *Pancreatic:* acute & chronic pancreatitis, surgery (>80%), haemochromatosis, CF, cancer
- *Infections:* CMV, Coxsackie B virus
- *Chromosomal syndromes:* Down, Kleinfelter, Turner
- *Others:* acanthosis nigricans, congenital lipodystrophy with insulin receptor antibodies, PCOS, Wolfram syndrome (DIDMOAD) and glycogen storage diseases, schizophrenia.

Epidemiology

Prevelance: 3-5% (UK) and increasing in all age groups

Risk Factors:

- Race: Aborigine, South Asian, African and African-Caribbean and Middle-Eastern.
- Family history
- Obesity/inactivity (T2DM)
- Gestational diabetes and impaired glucose tolerance

Presentation

Patients may be asymptomatic. Complications may be the presenting feature: infections, neuropathy and ulcers, retinopathy, arterial disease (e.g. MI or claudication).

Acute:

- Ketoacidosis - unwell, hyperventilation, ketones on breath.
- Few weeks of weight loss, polyuria and polydipsia.

Subacute:

- History as above, but longer.
- In addition lethargy, infection, pruritis vulvae, boils.

Initial Assessment

History

- Diabetic history, symptoms of potential complications
- Other medical conditions, Drug history, current medications, Family history
- Occupation and social history e.g. level of exercise, diet, smoking, EtOH

Examination

- General examination – including height/ weight/ BMI
- Examination of feet (e.g. ulcers, loss of sensation) & eyes (e.g. cataracts, retinopathy)
- Blood pressure measurement & examination of peripheral pulses

Diagnosis

WHO criteria:

- Symptoms of diabetes (weight loss, polyuria, polydypsia)
- A fasting blood glucose ≥7.0mmol/L
- Random or 2h post-OGTT (75g glucose) plasma glucose >11.1mmol/L

Investigations

- BMI
- Urine albumin excretion (microalbuminuria 30-300mg/day)
- Urine protein (diabetic nephropathy if albumin loss >300mg/day)
- HbA1c
- U&Es, estimated GFR
- TFTs in young diabetic & lipid profile
- ± Islet cell antibodies/ C peptide deficiency
- Test for coeliac disease in young diabetic.

Complications

Microvascular: neuropathy, nephropathy and vision disorders (eg retinopathy, glaucoma, cataract and corneal disease).
Macrovascular: heart disease, CVA, PVD
Other: DKA, HONK, hypoglycaemia (from Rx), infections, metabolic probs, impotence, autonomic neuropathy and pregnancy probs.

General Management

General aims: prevent, identify & treat diabetes and Cx (may be ↓ by good/tight BSL control)
Usual goals:

- Lifestyle changes – weight, diet, exercise, smoking cessation
- Fasting blood glucose levels of 4-7 mmol/l
- 3-6monthly HbA1c levels of 6.5% or below
- BP ≤130/80 mm Hg
- Total cholesterol level should be ≤4.0 mmol/l, LDL level ≤2.0 mmol/l

Regular reviews (at least annually) - check goals, feet, eyes. Also rpt UEC, urine protein.

Drug Management of Type 1 Diabetes

Insulin Therapy and Blood Glucose Monitoring

- Agree on most appropriate insulin regime:
    - Twice daily regimes using isophane (NPH) insulin or long acting insulin analogues (insulin glargine).
    - Multiple injection regimes using unmodified or "soluble" insulin or rapid-acting insulin analogues, with a longer acting insulin at night are suitable for well motivated individuals with a good understanding of disease control, or those with active or erratic lifestyles.
- Monitoring of blood glucose
- Give advice on how to change the regime in case of illness and how to recognise a hypoglycaemic episode and what action to take

Drug Management of Type 2 Diabetes

Treatment ladder

- Step 1: **Metformin** improves all endpoints, esp useful if overweight. **CI**: GFR<60ml/min. **SE:** GIT diarrhoea/bloating, rarely lactic acidosis
- Step 2: Add insulin secretagogue (sulphonylurea), e.g. **gliclazide**, **glibenclamide** **SE:** ↑wt, hypoglycaemia or if more erratic lifestyles can use rapid-acting meglitinides **nateglinide** or **repaglinide**. **SE:** hypoglycaemia
- Step 3: Add/substitiute a thiazolidinediones ("glitazone") e.g. **pioglitazone**, **rosiglitazone**. **CI:** if on insulin, Hx of liver disease, CCF, IHD, or renal impairment. **SE:** ↑F. arm/foot #s.
- Step 4: **Acarbose** if unable to use any of the above. **SE:** GIT diarrhoea/flatulence.
- Step 5: **Insulin** with the first line agent continued, either **metformin** or a sulphonylurea.
- Other possible drug treatments:
    - **Orlistat** may be considered to help weight loss in patients with type 2 diabetes.
    - Thiazides and/or ACEI if HT. If microalbuminuria or proteinuria use ACEI.
    - Newer PO drugs **sitagliptin** and **vildagliptin** ↑insulin & ↓glucagon secretion, used 3rd line with metformin or a glitazone. **SE:** hypersensitivity (incl. anaphylaxis, SJS)
    - **Exenatide** sc bd ac may be used with metformin/sulphonylureas if don't want to use insulin. **SE:** wt loss, hypoglycaemia, GIT SE, interacts with warfarin.

Types of insulin

Short-acting insulins

- Ultra-short or rapid-acting insulin analogues e.g. insulin **aspart** [**NovoRapid**], **lispro** [**Humalog**] & **glulisine**. Genetically engineered analogues of human insulin. Mimic prandial insulin release. Given sc, onset ~15min, peak @1hr, and last 3-4hr. Inject with/after meal.
- Soluble insulins e.g. **regular** or **neutral insulin** [**Actrapid**, **Humulin R**] - conventional short-acting insulins. Given sc, onset ~30min, peak @2-5hr, and last 6-8hr. Inject 30mins before meal. If given by infusion $T_{\frac{1}{2}}$ ~5mins.
- Inhaled insulin – A newer Rx, onset ~10mins, peak @30-90min. May have some prolonged action. It should be taken 10 minutes before meals.

Intermediate-acting insulins

- **Isophane** (**Neutral Protamine Hagedorn** or **NPH**, **Protophane**). Onset 1-2hr, peak 4-12hr & last 16-24hr.

Long-acting insulin analogues (e.g. **detemir** [**Levemir**] and **glargine** [**Lantus**])

- Genetically modified analogues. Onset 3-4hr, then plateau, and lasts up to 12hr (detemir) or 24hr (glargine). Used od (or up to bd with detemir), and achieve a steady-state similar to endogenous basal insulin secretion.

Biphasic insulins

- E.g. **Mixtard 30/70** (70% intermediate-acting **isophane**, 30% short-acting **neutral**).

Typical insulin regimens

Normal basal secretion: varies with age. ~0.5-1u/kg/day, split ~1/3 non-prandial & 2/3 prandial.
T1DM: Twice daily biphasic insulin, or basal+bolus regimen, (insulin pump occ an option)
T2DM: Basal od/bd long-acting insulin, twice daily biphasic insulin, or basal+bolus regimen

Acute intercurrent illness

Don't stop insulin/sulphonylurea, may need ↑dose. If dehydration, consider stopping metformin.

Prognosis

Life expectancy is reduced by 15 years in Type 1 diabetes; 5-7 years in Type 2 diabetes.