Definition – Diabetes Mellitus

- Loss of control of glucose homeostasis.
- → hyperglycaemia

Secondary to:
- inability to secrete insulin (DM1)
- resistance of cells to insulin (DM2) (Insulin resistance)
- both of the above (DM2)

Pathological consequences of DM:

- Are secondary to hyperglycaemia

And

to dyslipidaemia (80% of deaths amongst diabetics – CAD – the atherosclerosis process in DM is accelerated – esp. when poorly controlled)
DM = a growing health concern of epic proportions / concern

And there are several types of DM – all unified by an inability to maintain the blood glucose homeostasis.

→ serious ST & LT repercussions including CVD & premature death

LT consequences:

→ DM → increased risk of serious morbidity and premature mortality e.g. atherosclerosis, CHD (AMI), heart failure, stroke, hypertension, PAD, peripheral nerve damage, renal and retinal damage (?? → failure)

→ Morbidity escalates if blood glucose is not adequately controlled by pharmacology plus life-style modification

NHS estimates it spends ...

→ ~10% of its budget managing DM & its complications

→ £14 billion per year or £1.5 million per hour

→ Greatest costs incurred treating the complications of DM

→ http://www.diabetes.co.uk/cost-of-diabetes.html
DM = loss of glucose homeostasis:

- Normal Physiological range: 4-8mmol/L
- Normally fluctuate within this range i.e. high after meal – low on waking in the am

Diagnosis:
- FPG = 7.0mmol/L (fasting plasma glucose test)
- 2hr oral glucose tolerance test = >11.1mmol/L
- Random blood test - >11.1mmol/L (non-fasting plasma glucose test)

Types of diabetes mellitus:

1. Type 1 (insulin dependent IDDM) - failure to produce insulin
2. Type II (previously non-insulin dependent NIDDM) – insulin resistant diabetes. Poor response +/- poor secretion
- i.e some can produce insulin++ but the cells do not respond adequately ⇔ hyperinsulinaemia & still glucose is not transported into cells ⇔ hyperglycaemia.

Other types of diabetes mellitus:

3. Gestational diabetes
4. Congenital diabetes – genetically defective insulin secretion
5. CF – related diabetes
6. Secondary diabetes
- Other causes – many causes – lower incidence
Focus of this Lecture = **type 2 diabetes**
because:
- It has the greatest prevalence
- It demonstrates a high & rising incidence
- It is associated with chronic ill-health, loss of independence, health costs ++, premature death
- It is very largely **preventable**

People with DM2 will very commonly be your patients.

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**Epidemiology of DM:**
- Currently ~ 2.5 million people with DM in UK (x100% by 2030)
- ~ 1 million not aware of their condition – (Diabetes UK report “State of the Nation 2012)
- ~ 7 million who are known pre-diabetics
- ??? X many unknown pre-diabetics

Incidence ofDM1 shows – stable / slow ↑
Incidence of insulin resistant DM2 growing steadily yearly – mirroring the obesity trend

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![Prevalence Trends in England (2006-2010)](image)
Risk factors associated with DM2

- Being over-weight or obese
- High waist: hip (VAT)
- Being over 40 years old (or 25 if of black or Asian ethnicity)
- Have a close relative with DM (genes/shared philosophy?)
- Poor lifestyle philosophy – e.g., sedentary & diet,

Exercise & DM2 prevalence Cardiorespiratory fitness

Swada et al 2003 Diabetes Care 26: 2918-2922
http://care.diabetesjournals.org/content/26/10/2918.full.pdf

Prevalence of diabetes by age and aggregated ethnic groups

http://qmed.oxfordjournals.org/content/102/4/261
Age-adjusted relative risk of developing diabetes over an 8 year period


Type 2 DM & children

- Risk factor for DM type 2 = > 40 years old (Caucasian)
- But last 30 years has seen a 3-fold ↑ in incidence of childhood DM2
- Reflecting the dramatic rise in childhood obesity.
DM2 & weight loss:

- Although wt gain dramatically increases risk of developing DM
- Wt loss can reduce risk of developing DM i.e. each 1kg wt reduction → 16% decrease risk of developing DM2

Pathology of diabetes:

Normal glucose regulation

- Action of glucagon → glycogen breakdown to glucose → raising blood glucose levels
- Action of insulin promotes
  - 1. cellular uptake of plasma glucose lowering blood glucose levels
  - 2. storage of glucose in the liver as glycogen – lowering blood glucose levels
- Hormones interact to maintain blood glucose level at 4- 8 mmol/L
Liver, Adipose & Skeletal mm

Insulin Actions:

1. Skeletal muscle – liver - fat cells take up glucose for metabolic fuel or conversion to fats for storage or glycogen for storage.

2. Insulin also promotes fat (FFA → triglyceride) storage → natural reduction in circulating FFAs (triglycerides)

So postulate a lack of insulin or ↓ sensitivity to insulin → derangement of glucose & fat metabolism

Insulin lack / receptor sensitivity

- Leads to:
  - Decreased cellular uptake of glucose → hyperglycaemia → glycosylation of e.g. vessel endothelium → tissue dysfunction
  - Decreased fat uptake / storage → high levels of circulating triglycerides & lipids dyslipidaemia → high risk of atheroma formation
Central adiposity, high BMI & DM2:

- Many (but not all) with DM2 have:
  - high waist circumferences & W:H ratios
  - central adiposity (VAT)
  - high BMI > 30 Caucasians or > 23 Asians

**NB The fat thin exist with:**
- proportionally little SCAT but VAT or
- normal VAT & SCAT but proportionally little mm

The link between DM2 & VAT

- not only is fat metabolism a consequence of the diabetic process its also implicated in the evolution of the condition.
- VAT not subcutaneous fat
- VAT is biochemically distinct from other fats and as such plays a pivotal role in DM2 genesis.
  - **NB:/ High BMI – high VAT / normal BMI – high VAT**
Visceral Adipose Tissue (VAT) & DM2

⇒ VAT \rightarrow Insulin resistance

VAT is a metabolically active secretory / regulatory and inflammatory tissue!

A complex mix of inflammatory mediators & factors released from VAT \rightarrow \downarrow insulin receptor sensitivity

⇒ VAT \rightarrow\uparrow insulin resistance because ...

- Inflammatory mediators (e.g. TNF, CRP & IL-6):
  - \rightarrow \uparrow insulin receptor insensitivity
  - \& \rightarrow \downarrow secretion of NO & \uparrow secretion endothelin

- VAT \rightarrow secretion of resistin \rightarrow \uparrow insulin receptor insensitivity (more VAT = more secretion)

- VAT \rightarrow \downarrow secretion of adiponectin \rightarrow \uparrow insulin receptor insensitivity

Adipose tissue & insulin resistance:

- Insulin resistant adipose tissue (loses normal insulin mediated tendency to fat storage & instead) undergoes accelerated lipolysis \rightarrow generation FFAs++ which are then liberated into the circulation.

- Liberated FFAs do exactly the opposite of what insulin would do at the tissue level i.e.
  - - Inhibit SK mm uptake of glucose \rightarrow \uparrow plasma glucose levels
  - - promote glucogenesis in the liver \rightarrow release of glucose into the circulation \rightarrow \uparrow plasma glucose levels
**FFAs: Link between obesity & DM2**

- Insulin resistant adipose tissue → accelerated lipolysis
- Free Fatty acids ++
- Sk mm utilization of glucose → Rising plasma glucose levels
- Glucose production - liver

**FFAs & atheroma formation:**
- FFAs liberated by VAT lipolysis are taken up by the liver converted to LDLs & liberated back into the circulation.
- → significant atheroma risk esp in combination with: hyperglycaemia, hyperinsulinaemia & a pro-inflammatory state (+/- poor life-style choices)

**Beta cell response to insulin resistance**
- As insulin receptor responsivity worsens – beta cell production of insulin increases
- → state of hyperinsulinaemia
- Eventually beta cells fail
- Pt moves from a non-insulin to insulin dependent state
Insulin resistance & atheromas

- Combination of:
  - 1. Raised plasma LDLs
  - 2. Inflammatory mediators released from VAT in circulation
  - = pro-atherogenic
  - NB/
  - Insulin resistance also often co-existent with other life-style factor mediated issues e.g. hypertension, smoking & sedentarism

Diabetes & hypertension

- Mediated via VAT +/- obesity.
- Increased obesity → increased secretion of leptin (sateity) as leptin resistance rises.

- Switch on renal sympathetics → activation of the RAS
- Increased VC → increased TPR
- Increased fluid retention → increased blood volume
The diabetic journey

- Developing VAT – increasing release of inflammatory / chemical mediators
- Increasing insulin resistance
- Rising plasma glucose levels
- Increasing dyslipidaemia
- Rising insulin secretion
- Insulin secretion failure
- Artificial insulin dependency

The pre-diabetic state - IGT:

- Characterised by insulin resistance or impaired glucose tolerance (IGT)
  - i.e. reduced responsivity of insulin receptors
  - \[ \text{persistently high plasma glucose } 6.1 \text{ – } 6.9 \text{ mmol/L} \]
- Associated with risk of developing DM2, & premature death from CVD
- Prime targets for health promotion.

Tipping from insulin resistance to full blown DM2 = a picture of …

1. Increasing insulin resistance
   - (Often mirrored by uncorrected life-style choices)
2. rising profile of hyperglycaemia & dyslipidaemia
   - compounded by increasing failure of \( \beta \) cell activity to over-produce insulin to compensate for decreased receptor sensitivity (state of hyperinsulinaemia)
Summary

- ↑ insulin resistance due to a number of factors e.g. adiponectin, resistin, TNF, IL-6 etc...
- VAT is clearly implicated in the process of ↑ insulin resistance & development of DM2

- Resistance →
- ↑ plasma glucose (impaired liver/sk mm uptake)
- ↑ circulating FFAs → stimulate liver gluconeogenesis → ↑ plasma glucose & raise plasma LDL levels

Consequences of diabetes:

- In DM2 pathological consequences are 2ndary to: dyslipidaemia, hyperglycaemia & hyperinsulinaemia (early DM2)
- Glycosylation – binding of glucose molecules to lipids & proteins → structural dysfunction e.g. at capillary basement membranes

Consequences of diabetes:

- May be many & severe but could be significantly fewer & more manageable if:
- diabetes is well controlled & therefore blood sugar levels are well regulated.
- NB/ such consequences start to develop in the pre-diabetic state!
Measuring diabetic control:

1. Glucose levels (mmol/L) – informs re: hr by hr / day to day glycaemic control

2. HBA1c – glycosylated Hb (i.e. Hb + glucose) = a longer term view of control & predictor of morbidity – measured in mmol/mol

GP target – to check HBA1c every 2-6 mths

<table>
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<th>Average Blood Glucose mmol/L</th>
<th>Average Blood glucose mmol/mol</th>
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<td>10.0</td>
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</tbody>
</table>

A 1% ↓ in HbA1c level →

19% ↓ cataracts
16% ↓ in heart failure
43% ↓ amputation or death due to PVD

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Good DM2 control = < 48 mmol/mol or %Hb 1Ac < 6.5

To maintain acceptable glycaemic control:

A pt may need:

- drugs – including insulin (refer to workbook)
- weight-loss
- Lifestyle modification
Insulin & Hypoglycaemia

- **Causes:**
  - Insulin excess per se (mis-calculations)
  - Insufficient glucose (food) intake – usually in combination with vigorous exercise without adequate calculation of insulin
  - Hypoglycaemia → predominantly neuro & stress hormone signs e.g. (next slide)

**Signs of hypoglycaemia**
- Sweating
tremors
- Anxiety
hunger
- Dizziness
headaches
- Cloudy vision
confusion
- Abnormal behaviour
stupor
- Convulsions
loss of consciousness
- Coma
death

What should you do if hypoglycaemia occurs?
- Eat / drink carbohydrates immediately / iv glucose ??
- Subcutaneous glucagon injection

Hyperglycaemia & ketoacidosis

- Hyperglycaemia – reduced ability to use glucose:
  - Common in DM1 – need an insulin injection
  - Rare in DM2 – often presents with acute infection – which further impairs ability to access glucose (?? Mechanism)
  - Unable to access glucose metabolism switches to fats.
  - Production of ketone bodies
Symptoms of ketoacidosis:

- **Early**: – PU++, nausea, lethargy, SOB, dehydrated
- **Advanced**: – tachycardia, tachypnea, dizziness, vomiting, confusion, drowsiness, ketone breath, LoC, coma, death

The glycaemic continuum:

- Glucose homeostasis
  - 4-8 mmol/L
  - Increasing severity of complication
- **Hypoglycaemia**
- **Ketoacidosis**

- Serious complications associated with DM – are mainly vascular in nature resulting in a number of secondary pathologies and premature death
- **Prime cause of death in DM = CVD**
Persistent hyperglycaemia predisposes to

Macrovascular damage

Microvascular damage

Mainly via complex chemical reactions involving glycation – the bonding of glucose molecules to lipids & proteins esp. within capillary walls (basement membrane)

Generally → CV complications – mainly mediated via atherosclerosis

1. Macrovascular disruption

(Affecting arteries & arterioles)

→ atherosclerosis – younger & more severe cf general population.

CVD – leading cause death in DM2 (70 - 80%)

CHD & MI - ↑ risk x 5 fold of AMI

CVA - ↑ risk 2-4 fold

Hypertension ~ 50% of DM2 pop-

• 130/80mmHg – target BP

PAD ~ 15 times more likely to have an amputation cf general population.

2. Microvascular disruption: - affecting capillary membrane exchange functions → impaired nutrient & hormonal Tx often resulting in ischaemic damage e.g

Retinopathy → visual loss / blindness

Nephropathy → to progressive renal dysfunction → failure

Peripheral neuropathy – mainly feet, mainly sensory → neuropathic foot ulceration - & enhanced falls risk
50 – 70% of diabetics will develop some form of neuropathy – usually sensory &/or autonomic

- Early signs of peripheral neuropathy often include the following sensations in fingers & toes:
  - Numbness  tingling  P&N
  - Prickling  burning  coldness
  - Pinching  buzzing  sharp

- Motor neuropathy uncommon e.g diabetic drop foot

- Neuropathy associated with minor injury
  - Poor healing – due to ..
    - 1. Poor blood supply – atherosclerosis

Chronically ulceration → secondary infection

- Major cause of hospitalisation of the diabetic pt.
- Significant cause of a large number of amputations.
Autonomic neuropathies

- Microvascular damage → malfunction of the autonomic n.s. esp affecting function of the:
  - GI tract – bloating, diarrhoea, flatulence
  - cardiac function, abnormal HR & loss of VMC control → orthostatic hypotension – reduced anginal symptoms. Also loss of normal exercise responses → exercise intolerance & deconditioning.
  - genito-urinary system – frequency, urgency, retention

Diabetes and MH:

- 2008 “Mind the Gap” report commissioned by Diabetes UK estimated that:
  - around 41% of people with diabetes suffer with poor psychological well-being.
  - & the rate of depression is doubled in people with diabetes.

The ‘costs’ of untreated depression in DM2 are high, due to its negative impact on self-care & medication adherence, → hyperglycaemia & increased complications and healthcare costs.
Management of diabetes:

Role of Primary Health promotion:
- Through the successful adoption of healthy life-style choices with respects to:
  - Diet
  - Physical activity
  - Exercise
  - Wt gain
  - Smoking
  - Alcohol

DM2 can be totally avoided in 90% of cases Hu et al 2001

Role of Secondary Health promotion
- Through the successful adoption of healthy life-style choices with respects to:
  - Diet
  - Physical activity
  - Exercise
  - Wt gain
  - Smoking
  - Alcohol

The complications of DM2 & DM1 can be significantly reduced.
Healthy life-styles & Diabetes:

- It is absolutely vital to adopt healthy lifestyle choices - these choices prolong life and reduce the incidence/severity of diabetic complications.
- Exercise specifically has been shown to be of benefit in risk reduction for DM2, reversal of pre-diabetes, amelioration of complications - via VAT/obesity reduction, improved insulin receptor sensitivity & enhanced glycaemic control.

Exercise and risk of DM

- A dose-related relationship.
- 3 hours vigorous exercise per week → 46% ↓ risk of DM
- 3 hours per week of brisk walking (> 4.8 km/h or > 2.9 mph) → ↓ risk of DM by 42%
- So a 30 min daily brisk walk significantly ↓ risk of DM

Hu et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women. JAMA 1999 282: 1433-39

DM2 & CV Exercise:

- As per national guidelines – to start...
- F At least 5 times per week
- I Moderate intensity exs RPE 12-13
  65-75% HRmax, or 40 – 60% HRR
- T Initial goal 150 mins p.w
- T Aerobic / continuous
CV Exs & DM2 with obesity:

- Duration: as per tolerated getting to 300 mins per week min = a priority target.
- Ideally need prolonged sessions i.e. 60 mins
- May need to be on low side of 40-60% HRR to achieve this
- Prolonged mod exercise → fat burn

DM & CV exs; The benefits:

- Improves glycaemic control via increased insulin receptor sensitivity
- ↓ body fat – including VAT – maintains lean mm mass (improves glycaemic control)
- Atherosclerosis regression / slowing
- ↓ incidence / severity of debilitating complications and premature death

DM & strength training – The benefits

- ↑ the mass of lean tissue.
- ↓ mass of fatty tissue
- ↑ insulin sensitivity in trained mm
- Target all major groups
- F 2-3 times p.wk
- I – aim 8-12 reps (60-80%1RM)
- T 8 – 10 exs involving major mm groups
Whilst robust empirical data++ supports the very significant role of exercise in the prevention and management of diabetes ~ 80% of diabetics remain inactive.

**Barriers ???**
- Physical discomfort - too overwt?
- Lack of support
- Fear of having a hypoglycaemic episode
- Low exercise self-efficacy / depression
- Low belief in role of exercise
- Etc..

**Solutions ???**

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**Management of DM**

- Good glycaemic control essential.
- Dietary regulation
- Exercise
- Drug therapy - may include use of insulin

**(combination of above)**

- Good glycaemic control significantly\down the incidence of diabetic complications

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**Pharmacological management: BBL**

- **Insulin** – injections – oral – type I & in severe cases type II (β cell failure)
- **Metformin** - sensitivity of insulin receptors,
- **Sulfonylureas** – boost insulin secretion
- **Statins** = routine + anti-hypertensives as necessary.–
- Pills alone – are not the answer.
- Good glycaemic control requires lifestyle modification.
- However it may not be possible to effectively manage DM2 by lifestyle modification alone.

Increases in VAT appear to be driving increases in DM2 prevalence.

DM2 in turn increases the risk of CVD.

Lifestyle intervention & physical activity has a massive role in preventing & managing VAT & obesity & in preventing/delaying the development of DM2.

Physical activity lowers the risk of CVD in those with & without DM2.
Conclusion:

- Brief look at DM - characterised by varying degrees of insulin resistance and insulin deficiency
- Acknowledged - importance of glycaemic control in the prevention of LT 2ndary pathology & premature death
- Acknowledged - role of exercise in prevention of type 2 diabetes & as a potent inhibitor of secondary disease progression in types 1 & 2

- http://clinical.diabetesjournals.org/content/26/2/77 - useful review of microvascular & macrovascular damage