Aetiology, Diagnosis and classification of *Diabetes mellitus*

Dr Jane Nally  
(j.e.nally@gcu.ac.uk)  
Diabetes Education and Training Unit  
Glasgow Caledonian University
Fuelling the body

- Glucose - the primary fuel
- Normally the brain can ONLY use glucose
- Other cells can use other fuels:
  - Fatty acids, glycerol, amino acids and ketones
- Below 4 mmol/l glucose the brain may not receive sufficient glucose.
- Below 2.5 mmol/l is a threat to survival.
- Several hormones maintain normal glucose levels
  - Including insulin and glucagon
Insulin – from beta cells

- Increases glucose uptake to be stored as glycogen
- Increases uptake of amino acids to form proteins
- Increases storage of triglycerides as fat.
- Inhibits breakdown of glycogen
- Inhibits the release of amino acids from muscle and production of glucose from non-glycogen stores (gluconeogenesis)
- Inhibits lipolysis (fat breakdown)
- Release is stimulated by nutrients in the blood and hormones from the gut
Glucose

Time (0 - 90 mins)

Insulin levels mg/ml (20-80)

Phase 1 stored insulin
Phase 2 synthesised insulin
Glucagon - from alpha cells

- Stimulates glycogenolysis in the liver (i.e. glycogen into glucose)
- Stimulates hepatic gluconeogenesis
- Stimulates the transport of certain gluconeogenic amino acids to the liver for conversion to glucose.
- Stimulates lipolysis in adipose tissue.
- Release is stimulated by low blood glucose and inhibited by high blood glucose
Staining using Immunohistochemistry

Insulin secreting cells – with thanks to Alan Foulis
Glucagon secreting cells – with thanks to Alan Foulis
Other hyperglycaemic hormones

• Cortisol
• Adrenaline
• Growth hormone
• Oestrogen
• Cytokines (from inflammation – and obesity is a chronic inflammatory disease!)
Diabetes Mellitus

- *Dia* means through. *Betes* means flowing (Greek) *mellitus* derives from mel meaning honey (Latin)
- Usually just called diabetes
- Metabolic disease characterised by high blood glucose levels.
- Mentioned in an Egyptian manuscript from c. 1500 BC “too great emptying of the urine.”
- Mentioned around same time by Indian medics “honey urine”
- Result from defects in insulin secretion, action or both.
Current figures

- 284,122 people in Scotland have diabetes (2015)
- 5.3% (about 1 in 20) in Scotland have diabetes
- Plus 0.9% of the population undiagnosed
- 415 million adults with diabetes in 2015 worldwide (including 193 million undiagnosed)
- 318 million adults with impaired glucose tolerance
- Predicting 642m worldwide by 2040
- Accounts for 10% of all NHS expenditure.

Number of people recorded with diabetes in Scotland (all types).
In Asians

- Incidence of T2DM is at least 5x higher in native and migrant Asian populations.
- T2DM tends to develop 5yr sooner in people from African Caribbean and Asia.
- Asian populations have a substantially increased lifetime risk of developing cardiovascular disease.
- Has serious implications for some health practices within NHS GG&C.

4% in Scotland from minority ethnic groups – up 2% since 2001
2.7% of the total population (141,000) are Asian (up 1.3% from 2001)
Glasgow City, 12% minority ethnic group
In Pollokshields East, 48% minority ethnic.
Maxwell Park (24%), Woodlands (23%)
Strathbungo (21%). All wards from 2001
Economic Burden Of Diabetes

• In developing countries- T2DM mainly affects working age
• In poor countries- people bear almost the whole cost of medical care
• In poor countries such as Latin America, Mozambique, Mali, Vietnam and Zambia 40%-75% medical expenditure for diabetic care is paid by families themselves.
• The choice between healthcare expenses and food or clothing can trap the whole family in a downward spiral of worsening poverty and health.

• Extracted from Muhammad Irfan Ali Dissertation MSc  Diabetes Care and Management  August 2011
Economic Burden

- Pakistan – if death rate due to chronic diseases reduced by 2% annually - $1 billion saved in next 10 years (WDD06 – Karachi, 2006).
- Intensive management of Type 2 diabetes in Scotland can decrease hospital cost by £41 million by saving over 91,000 bed days a year in 2025 and will also save £78 million a year in lost work days (ABPI Report Scotland, 2005).
Types of *Diabetes mellitus*

- Three major forms (WHO)
  - Type 1 – Autoimmune – own immune cells attack beta cells of pancreas. Genetic susceptibility
  - Type 2 – Insulin resistance triggered mainly by obesity and inactivity. Genetic susceptibility
  - Gestational – Diabetes developing/identified in pregnancy
Other Types of Diabetes mellitus

- Mature Onset Diabetes in the Young
- Neonatal Diabetes Mellitus
- Latent Autoimmune Diabetes in Adults
- Secondary Diabetes e.g: pancreatic damage, endocrine disease, therapy (e.g. with corticosteroids, anti-viral, or anti-psycho#c drugs).
- Brittle diabetes
- Type 3 diabetes
- Mixed pathologies in T1DM with obesity and insulin resistance
Proportions of diabetes population by type

- Type 2: 88.3%
- Type 1: 10.8%
- Other types of diabetes: 0.9%
TYPE 1

- Genetic Influences
- Environmental factors eg; diet, infection, obesity?

- T-helper cells attack beta cells in pancreas
- Higher incidence of other autoimmune diseases, especially coeliac disease and thyroid disease
- Ketones in plasma and urine (ketoacidosis)
Pathogenesis of Type I Diabetes

- Genetic abnormality
- Environment? Viral infection?

Autoimmune attack on pancreatic cells

β cell destruction

Severe Insulin deficiency

Type I diabetes
PRESENTATION TYPE 1

• Unexplained loss of weight
• Polyuria
• Polydipsia
• Change in vision
• Thrush
• Lethargy
• Change in menstruation
• Change in hair texture
• Disturbance of libido
• Bedwetting in a previously dry child
Diagnosis of Type 1 (see later slides)

- Random Glucose usually high 15-20 mmols/l and associated with ketones.
- Confirmed if patient displays symptoms and has a random venous plasma glucose concentration higher than 11.1 mmol/litre.
- **Immediate same day telephone referral!!**
  Even if no ketones. Don’t ask for FPG or OGTT
Importance of diagnosis

- 25% of children are in Diabetic Ketoacidosis on diagnosis of T1DM
- Over 30% in children under 5 yr
- One third of these cases has seen a Health Care Professional in the weeks before but the diagnosis has been missed
- Delayed diagnosis = greater likelihood of poor outcome
Diabetes UK have become concerned about the failure to diagnose type 1 in children and young people.
Diabetic teenager died hours after GP ‘laughed off’ fears

Failure to spot condition will haunt me, says doctor

By Glen Keogh

A GP who failed to diagnose diabetes in a critically ill teenager hours before she died broke down in tears yesterday as she told a tribunal the mistake would stay with her the rest of her life.

Dr Michelle Watts, 47, had been called to a home visit to treat Claire Taylor, 17, but allegedly ‘laughed off’ concerns from the schoolgirl’s mother that she needed hospital treatment.

She also failed to properly examine the teenager when she attended her Kettering Health Centre practice in Anson Road the previous day.

When Dr Watts had visited Claire at her home after she began feeling violently unwell, the teenager was said to have lost weight, had a blue pallor, sunken cheeks and was struggling to eat or drink. But Dr Watts left the house suggesting she take a course of sleeping tablets.

‘The keen dancer died from diabetic ketoacidosis a few hours later with her mother in a chair beside her on November 8, 2012 at her home in Anson Road, Kettering, a coroner was told yesterday.

Her mother Helen, 55, had earlier informed Dr Watts that her family had a history of the condition.

Giving evidence at the Medical Practitioners’ Tribunal Service in Manchester yesterday, Dr Watts acknowledged her mistake had ‘catastrophic consequences’.

She said: ‘I am deeply, deeply sorry. I wish I could go back and change things but I can’t. This will be with me for the rest of my life. I feel that if I could miss a diagnosis like this then somebody else could. I can’t go back and change anything. However much I want it I can’t go back and change what has been done.

‘I can do everything I can to make sure it doesn’t happen to another family or another clinician. Dr Watts said she had considered diabetes but the condition was ‘at the back of her mind’. It is alleged she did not associate Claire’s symptoms with diabetes.

Claire had been taken to see four doctors before her home consultation with Dr Watts, when she lost 10lb in weight and became nauseous.

At the end of that meeting on November 7, Dr Watts tried to test Claire for diabetes using the finger prick method, but she refused.

She arranged for Claire to have a blood test at the hospital the following morning but when it arrived it was ‘too late’.

But Claire died before it could be performed. Dr Watts added: ‘Looking back now, with the benefit of hindsight, and hindsight is a wonderful thing, I saw Claire was losing weight and was connecting them in a slightly wrong way to make the wrong picture.’

Describing her distress on learning of Claire’s death, she said: ‘As more information came in over those days and I began to reflect and understand what had happened, and when the post-mortem results came through and it all fit together, I couldn’t understand why a clinician who had been working for more than 20 years, who had never had anything like that happen before, would laugh it off.

‘I was really angry with myself for any contribution I may have made to any deterioration. She added that Claire’s menopausal symptoms, which included frequent urination and lower abdominal pain when she visited her at home because she hadn’t specifically mentioned it to her.

‘Shamefully denying her not making was dishonest, she added: ‘I am extremely open and honest and we all make mistakes. Dr Watts said that since the incident she had reduced her clinical work from five days each week to

Claire died on November 8, 2012, from diabetic ketoacidosis.
TYPE 2

• Insulin resistance
• Beta cell gradually declines in function before diagnosis.
• Accelerated decline after onset of T2DM.

• Insidious onset
• Very rarely associated with ketoacidosis but Hyperosmolar Hyperglycaemic State can occur
• (HHS (formerly HONK))
Insulin resistance (reduced biological response to insulin)

Increased β-cell secretion of insulin
Hyperinsulinaemia

β-cell compensation declines

Insulin secretion cannot keep pace with insulin resistance

Glucose intolerance and frank type 2 diabetes
Development of Type 2 Diabetes

- Normal
- Impaired glucose tolerance
- Type 2 diabetes

- Insulin resistance
- Glucose level
- Insulin production

β-cell dysfunction
In Asians

- Incidence of T2DM is at least 5x higher in native and migrant Asian populations.
- T2DM tends to develop 5yr sooner in people from African Caribbean and Asia.
- Asian populations have a substantially increased lifetime risk of developing cardiovascular disease.
- Has serious implications for some health practices within NHS GG&C.

4% in Scotland from minority ethnic groups – up 2% since 2001

2.7% of the total population (141,000) are Asian (up 1.3% from 2001)
PRESENTATION TYPE 2

- Unexplained loss of weight
- Polyuria, Polydipsia
- Change in eyesight
- Thrush or other recurrent infections
- Lethargy
- Change in Libido
- Discoloured or ulcerated feet
- Hypertension
- Obesity
Presentation type 2

- Evidence of chronic complications:
  - Kidneys
  - Eyes
  - Nerves
  - Cardiovascular events
  - Cerebrovascular events
  - Peripheral vascular disease
Diagnosis of Type 2 (see later slides)

- Random Blood Glucose, OGTT, Fasting glucose, HBA1c

Consider:
- Lipids, Liver Function Test
- Blood pressure
- Beta Ketones
- Urine – estimated Glomerular Filtration Rate
- (eGFR) & Microalbuminuria
Double diabetes

- Occurs when patients with type 1 diabetes become obese
- Insulin resistance plus type 1 inability to produce insulin (resistance to insulin administered)
Gestational Diabetes

Increases risk of developing type II in later years
Gestational Diabetes

- Test for diabetes six weeks after delivery – most women will no longer have diabetes.
- Women with a history of GDM have a 60% chance of developing diabetes (usually T2DM) within the subsequent 20 years – risk increased by obesity. For this reason they should be advised to control their weight and have an annual fasting glucose measurement performed. * NHS GGC Guidelines
Gestational Diabetes

- On the rise:
- E.g. NHS AAA;
- 2011  31
- 2012  94
- 2013  110
- “No you can’t eat for two – eat moderately!”
- Reported that many women miss follow up appointments to check diabetes – too busy looking after baby
Monogenic forms of diabetes

- 1 – 2% of cases
- Reduces ability of β cells to produce insulin – patient may need insulin but diet alone maybe sufficient
- 90% initially mis-diagnosed as T2DM or T1DM
- Diagnosed by Genetic testing
- If parent has gene mutation child has 50% of MODY
- At least 6 types (4 common)

NDM - neonatal diabetes mellitus

- Occurs in first six months of life
- Rare
- Single gene defect
- Do not produce enough insulin
- High Plasma glucose – mistake for T1DM
- At birth, babies are small
- Do not gain weight as quickly as expected.
LADA
(Latent Autoimmune Diabetes of Adults)

- Slow destruction of Beta Cells. Symptoms insidious without osmotic symptoms or ketoacidosis
- Eventual full Type 1 diabetes?
- Diagnosis – Glutamic Acid Decarboxylase autoantibody test (may also have other diabetes-associated antibodies)
- > 25yrs (30-50)
- Masquerades as non obese Type 2
- Control achieved with diet and or tablets
- Usually insulin requirement in months to years (≈4yr)
- Therefore needs very close monitoring to maintain wellbeing
Brittle Diabetes – rare form of T1DM

- Frequent large changes in blood glucose levels for no apparent reason - hyperglycaemia and hypoglycaemia.
- May be seen in people with T1DM who have absorption difficulties in the GI tract.
Type 3 diabetes

• A title that has been proposed for a specific form of Alzheimer’s Disease which results from resistance to insulin in the brain.

• Furthermore, evidence that diabetes complications increase the risk of dementia has been published.

*Chan W-C et al., J Clin Endocrinol Metab, (2015)*
Diagnosis - Venous Plasma glucose Concentrations

- FASTING: >7 mmol/l and symptomatic – diabetes
- 6.1 – 7 mmol/l or >7mmol/l and asymptomatic - impaired glucose tolerance, possible T2DM refer for HbA1c
- Below 6.1 - mmol/l normal – not diagnostic of T2DM
- OGTT: > 11.1 mmol/l 2h after 75g anhydrous glucose
- Plasma glucose tests should be kept on ice

Glycosylated Haemoglobin (HbA$$_{1c}$$)

- The attachment of glucose to haemoglobin brings about glycosylation.
- Glycosylated Hb provides an indication of glycaemic control over ≈ the previous 60 days (The life span of an erythrocyte is 120 days)
- HbA$$_{1c}$$ - ideal for monitoring control of blood glucose levels – now used for diagnosis
HbA$_{1c}$ and good glycaemic control

- Glycosylated Hb has been reported as a % - now reported as mmol/mol in UK (e.g. 7% = 53 mmol/mol; 9% = 75 mmol/mol)
- Diabetes UK target for good control is 6.5% (≈48 mmol/mol)
- SIGN 116 – target is 7.0%
- UKPDS* - tight glycaemic control of 7.0% has significant benefits in reducing complications
- Currie et al. (2010) have found a higher mortality in people with HbA1c below 6.5% than in those with a HbA1c of 7.5%.
- Mortality/morbidity increases with increasing HbA1c above 7.5%

Currie et al. (2010); Lancet, 375. Lancet 1998
Tight glucose control

DCCT Group, Diabetes 1996
<table>
<thead>
<tr>
<th>Old units (%)</th>
<th>Minus 2</th>
<th>Minus 2</th>
<th>New units (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>6 - 2 = 4</td>
<td>4 - 2 = 2</td>
<td>42</td>
</tr>
<tr>
<td>7.0</td>
<td>7 - 2 = 5</td>
<td>5 - 2 = 3</td>
<td>53</td>
</tr>
<tr>
<td>9.0</td>
<td>9 - 2 = 7</td>
<td>7 - 2 = 5</td>
<td>75</td>
</tr>
</tbody>
</table>
Use of HbA1c in the Diagnosis of Diabetes Mellitus

- “HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.”
- HbA1c of 48mmol/mol and above – diabetes
- 42 – 47 mmol/mol – impaired glucose tolerance or prediabetes
- 41 mmol/mol and below – diabetes unlikely but review limitations of test
- <4.8mmol/mol does not exclude diabetes diagnosed by FPG – accept either as a diagnosis.
HbA1c

- HbA1c can be done at any time of day
- Does not require fasting
- More reproducible than glucose
- Does not need to be stored on ice
When not to use HbA1c

- **Rapid onset (HbA1c too slow to respond)**
  - Children (likely T1DM)
  - Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics
  - Pancreatic damage or after surgery
- **Pregnancy**
  - HbA1c lowered in pregnancy

When not to use HbA1c

- Factors that reduce red blood cells/haemoglobin
  - Haemoglobinopathy, e.g. sickle disease, thalassaemia.
  - Anaemia
  - Severe blood loss
  - Splenomegaly
  - Antiretroviral drugs
- Increased red blood cells
  - Splenectomy
- Renal dialysis (reduced HbA1c) esp. if given EPO
- Patients at high diabetes risk who are acutely ill
Good news

- Traditionally 50% of patients had chronic complications of T2DM on diagnosis with damage starting 5-6 yrs prior.
- Alex Neil MSP (Cabinet Secretary for Health & Well-being) reported to the Science and Parliament event on 13 November 2013 that:
  - Number of amputations due to diabetes reduced by 40%
  - Blindness due to diabetes reduced by 80%
  - Anecdotal evidence from consultants for reductions in all complications at diagnosis

The ancient Greek physician, Hippocrates (460-370BC), wrote: Eating alone will not keep a man well; he must also take exercise. For food and exercise ... work together to produce health.
Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

North America and Caribbean  
2015: 44.3 million  
2040: 60.5 million  

Europe  
2015: 98.8 million  
2040: 71.1 million  

Middle East and North Africa  
2015: 35.4 million  
2040: 72.1 million  

South and Central America  
2015: 29.6 million  
2040: 48.8 million  

Africa  
2015: 14.2 million  
2040: 34.2 million  

World  
2015: 415 million  
2040: 642 million