Diabetes Queensland

awareness • prevention • detection • management • cure
Outline

• Types of Diabetes
• LADA
• Case study
• Summary
Diabetes

• Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.*

• The name 'diabetes mellitus' derives from:
  Greek: 'diabetes' – “siphon” or “to pass through”
  Latin: 'mellitus' – “honeyed” or “sweet”**

* Diagnosis and Classification of Diabetes Mellitus. ADA 2009.
** http://science.jrank.org/pages/2044/Diabetes-Mellitus.html
# Diagnosis

## Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Glucose concentration, mmol l(^{-1}) (mg dl(^{-1}))</th>
<th>Whole blood</th>
<th>Capillary</th>
<th>Plasma*</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Venous</td>
<td>Capillary</td>
<td></td>
<td>Venous</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fasting</td>
<td>≥ 6.1 (≥ 110)</td>
<td>≥ 6.1 (≥ 110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>≥ 10.0 (≥ 180)</td>
<td>≥ 11.1 (≥ 200)</td>
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<tr>
<td>or both</td>
<td>≥ 10.0 (≥ 180)</td>
<td>≥ 11.1 (≥ 200)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (if measured)</td>
<td>&lt; 6.1 (&lt; 110)</td>
<td>&lt; 6.1 (&lt; 110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and</td>
<td>≥ 6.7 (≥ 120) and &lt; 10.0 (&lt; 180)</td>
<td>≥ 7.8 (≥ 140) and &lt; 11.1 (&lt; 200)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Impaired Fasting Glycaemia (IFG):</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>≥ 5.6 (≥ 100) and &lt; 6.1 (&lt; 110)</td>
<td>≥ 5.6 (≥ 100) and &lt; 6.1 (&lt; 110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and (if measured)</td>
<td>&lt; 6.7 (&lt; 120)</td>
<td>&lt; 7.8 (&lt; 140)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td></td>
<td></td>
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</tbody>
</table>

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Types of Diabetes:

- PreDiabetes
- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA (Latent Autoimmune Diabetes in Adults)
  - MODY (Maturity–Onset Diabetes of Youth)
  - Secondary Diabetes Mellitus
PreDiabetes

- Prediabetes is a term used to distinguish people who are at increased risk of developing diabetes. People with prediabetes have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Some people may have both IFG and IGT.

- IFG is a condition in which the fasting blood sugar level is elevated after an overnight fast but is not high enough to be classified as diabetes.

- IGT is a condition in which the blood sugar level is elevated (after a 2-hour oral glucose tolerance test), but is not high enough to be classified as diabetes.
PreDiabetes

• Progression to diabetes among those with prediabetes is not inevitable. Studies suggest that weight loss and increased physical activity among people with prediabetes prevent or delay diabetes and may return blood glucose levels to normal.

• People with prediabetes are already at increased risk for other adverse health outcomes such as heart disease and stroke.
Type 1 Diabetes

- Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.
- Type 1 diabetes develops when the body’s immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.
- This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.
- Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.
T1D

• Immune-mediated

• Type 1 diabetes is characterized by β-cell destruction, usually leading to absolute insulin deficiency
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T1D

• Absolute insulin deficiency

• Autoimmune destruction of the pancreatic β cells
  – Islet-cell antibodies (ICA)
  – Glutamic acid decarboxylase [anti-GAD]
  – IA-2
  – and anti-insulin

• Rapid onset

• Ketosis Prone
Type 1 Diabetes & Autoimmune Diseases

- Hypothyroidism
- Celiac disease
- Addison’s Disease
- Rheumatoid arthritis
- Pernicious anemia
- Vitiligo
Type 2 Diabetes

- Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.
- Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.
- It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.
- Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.
- Type 2 diabetes is increasingly being diagnosed in children and adolescents.
T2D

• Central feature: Insulin resistance

• Relative impairment in insulin secretion (hyperinsulinemia may exist)

• Associated metabolic features (hyperlipidemia)

• Ketosis occurs rarely
Type 2 Diabetes and Associated Factors

- Obesity
- Sedentary lifestyle
- Gradual onset
- History
  - Gestational diabetes
  - Family history
  - PCOS
- Hyperpigmented skin (acanthosis nigricans)
Gestational Diabetes

- A form of glucose intolerance that is diagnosed in some women during pregnancy.
- It is also more common among obese women and women with a family history of diabetes.
- During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant.
- After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes.
- Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the next 5-10 years.
Other types

• Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.

• Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.
MODY

- MODY – Maturity Onset Diabetes of the Young

- MODY is a monogenic form of diabetes with an autosomal dominant mode of inheritance:
  - Mutations in any one of several transcription factors or in the enzyme glucokinase lead to insufficient insulin release from pancreatic β-cells, causing MODY.
  - Different subtypes of MODY are identified based on the mutated gene.

- Originally, diagnosis of MODY was based on presence of non-ketotic hyperglycemia in adolescents or young adults in conjunction with a family history of diabetes.

- However, genetic testing has shown that MODY can occur at any age and that a family history of diabetes is not always obvious.
MODY features

Table 1. Features suggestive of monogenic diabetes

MODY (majority have HNF-1 alpha or HNF-4 alpha mutations)
• Young onset of diabetes (generally <25 years of age)
• Strong family history of diabetes (typically 2–3 generations affected)
• Sulfonylurea sensitivity
• Absence of insulin resistance phenotype: normal BP, TG, HDL-C

PNDM (50% have Kir6.2 mutations)
• Diabetes onset <6 months of age
• DEND syndrome
MODY

- Within MODY, the different subtypes can essentially be divided into 2 distinct groups: glucokinase MODY and transcription factor MODY, distinguished by characteristic phenotypic features and pattern on oral glucose tolerance testing.

- Glucokinase MODY requires no treatment, while transcription factor MODY (i.e. Hepatocyte nuclear factor -1alpha) requires low-dose sulfonylurea therapy and PNDM (caused by Kir6.2 mutation) requires high-dose sulfonylurea therapy.
Secondary Causes of Diabetes

Secondary causes of Diabetes mellitus include:

- Acromegaly,
- Cushing syndrome,
- Thyrotoxicosis,
- Pheochromocytoma
- Chronic pancreatitis,
- Cancer
- Drug induced hyperglycemia:
  - Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
  - Beta-blockers - Inhibit insulin secretion.
  - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
  - Corticosteroids - Cause peripheral insulin resistance and gluconeogenesis.
  - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
  - Naicin - They cause increased insulin resistance due to increased free fatty acid mobilization.
  - Phenothiazines - Inhibit insulin secretion.
  - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
  - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.
LADA - Latent Autoimmune Diabetes in Adults

• Different Names:
  – LADA
  – “Skinny Type 2 diabetes”
  – “Type 1.5 Diabetes,”
  – “Antibody-Positive Type 2 Diabetes,”
  – “Latent Type 1 Diabetes,”
  – “Double Diabetes,” and
  – “Youth Overt Diabetes of Maturity (YODM).”

• LADA may comprise up to 10-15% of adults diagnosed with Type 2 diabetes.
LADA

• Latent Autoimmune Diabetes in Adults (LADA) is a form of *autoimmune* *(type 1 diabetes)* which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes.

• Often, patients with LADA are mistakenly thought to have *type 2 diabetes*, based on their age at the time of diagnosis.
Latent Autoimmune Diabetes in Adults (LADA)

- Typical characteristics
  - Age of onset > 30 years of age
  - Gradual onset with initial improvement to oral agents/lifestyle changes.
  - BMI < 25 kg/m²
  - Personal or family history of autoimmune disease

A clinical screening tool identifies autoimmune diabetes in adults. Fourlanos S; Perry C; Stein MS; Stankovich J; Harrison LC; Colman PG. Diabetes Care. 2006 May;29(5):970-5
LADA cont’d

• About 80% of adults with recently diagnosed Type 2 diabetes but with GAD auto–antibodies (i.e. LADA) progress to insulin requirement **within 6 years**.

• The potential value of identifying this group at high risk of progression to insulin dependence includes:
  – the **avoidance of using metformin** treatment (ketoacidosis risk)
  – the **early introduction of insulin** therapy (basal–bolus regimen)
Keys to recognising LADA

- Negative family history for Type 2 DM
- Positive family history for Type 1 DM
- Non obese
- Ketones in urine
- Early failure of oral agents
  - Most type 2 patients do well on oral agents for several years

Diagnosis

- Measure GAD antibody
  - Positive very likely LADA

- Serum C-peptide level; A high C-peptide level, which often occurs in type 2 diabetes at onset, rules out LADA and anti-GAD antibody level assays need not be performed. However, if the C-peptide level is low or in the normal range, the anti-GAD antibody level should be measured.
Antibody testing

• Adults who should be considered for antibody testing*:
  – age of onset <50 years
  – acute symptoms
  – BMI <25 kg/m²
  – personal or family history of autoimmune disease

*A clinical screening tool identifies autoimmune diabetes in adults. Fourlanos S; Perry C; Stein MS; Stankovich J; Harrison LC; Colman PG. Diabetes Care. 2006 May;29(5):970-5
LADA Diagnosis

• LADA is distinguished from type 2 diabetes by the presence of islet autoantibodies that are common to type 1 diabetes.

• Patients with type 1 diabetes commonly have one or more of four islet autoantibodies — islet cell antigens (ICAs), glutamic acid decarboxylase autoantibodies (GADs) or tyrosine phosphatase proteins (IA-2s) — whereas patients with LADA typically only have one autoantibody (GAD). LADA patients have a far less incidence of IA-2 and ICA autoantibodies than patients with T1D.
Diagnosis Criteria

- The Immunology of Diabetes Society released the following criteria to determine if patients have LADA, specifying that patients be:
  1. aged at least 30 years or older
  2. positive for at least one of the autoantibodies found in type 1 diabetes
  3. and free from insulin treatment for the first six months after diagnosis

- This definition distinguishes LADA from type 1—because people diagnosed with type 1 typically need to start insulin immediately—and from type 2, because of the presence of autoantibodies in the blood.
- Performing a GAD antibody test is the most common method of diagnosing LADA, but not all patients have these antibodies. In the very early stages of LADA, it is possible that there are no detectable antibodies, but they can develop over time. Therefore GAD test alone cannot rule out LADA.
Body habitus

- Type 2 diabetes
- LADA
- Type 1 diabetes

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## Characteristics of Type 1, Type 2 and LADA:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
<th>LADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>&lt;35</td>
<td>&gt;35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Speed of Onset</td>
<td>Rapid</td>
<td>Slow</td>
<td>Slow</td>
</tr>
<tr>
<td>Response to lifestyle modification or oral agents</td>
<td>Poor</td>
<td>Good</td>
<td>Initial mixed then worsening</td>
</tr>
<tr>
<td>Frequency of DKA</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Family History of DM</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Personal/Family History Autoimmune Disease</td>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Body Habitus</td>
<td>Fit or lean</td>
<td>Overweight to Obese</td>
<td>Normal to overweight</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>C Peptide Level</td>
<td>Undetectable</td>
<td>Normal</td>
<td>Low/Normal</td>
</tr>
<tr>
<td>Anti-GAD/Anti-ICA/Anti-IA2</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

## Diabetes Types

Key characteristics of type 1, LADA (latent autoimmune diabetes in adults), and type 2.

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>LADA</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age of onset</td>
<td>Youth or adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>Progression to insulin dependence</td>
<td>Rapid (days/weeks)</td>
<td>Latent (months/years)</td>
<td>Slow (years)</td>
</tr>
<tr>
<td>Presence of autoantibodies*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Insulin dependence</td>
<td>At diagnosis</td>
<td>Within 6 years</td>
<td>Over time, if at all</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>No</td>
<td>Some</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Proteins that indicate the body has launched an autoimmune attack on the insulin-producing beta cells in the pancreas.
LADA Treatment

- Dietary guidelines for patients with LADA are similar to those for patients with type 1 diabetes. Obese LADA patients should follow a healthy reduced-calorie diet and increase their physical activity levels.
LADA Treatment

• LADA is generally considered to be a slowly progressive form of Type 1 diabetes
• LADA patients do not require insulin early in the disease
• Oral agents may work initially but generally fairly early
LADA Treatment

• Distinguishing LADA from patients with type 2 diabetes is important to ensure that patients are not prescribed drugs that stimulate β-cell insulin production. Sulfonylureas, such as glimepiride and glipizide, and incretin drugs, such as sitagliptin (Januvia) and exanatide (Byetta, Amylin) should be avoided.
Treatment of LADA

- If glycemic control is at goal on oral agents, continue them
- Watch closely for worsening control on oral agents
  - If 2 agents are failing (A1c>7.0%) change to insulin
  - Usually need to go to basal/bolus insulin
- If GAD +ve, start insulin
- Recognition is important so insulin treatment is not delayed as A1c climbs
<table>
<thead>
<tr>
<th>Features</th>
<th>Type 2 diabetes</th>
<th>Type 1 diabetes [corrected]</th>
<th>Latent autoimmune diabetes in adults [corrected]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>Usually absent</td>
<td>Will develop rapidly unless patient receives insulin replacement therapy</td>
<td>Absent at diagnosis, but may be present when patient becomes severely insulinopenic</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>Risk 2–4 times higher than individuals who are euglycemic</td>
<td>Increased risk of cardiovascular morbidity and mortality related to strokes, acute coronary events, and coronary revascularizations; high incidence rates compared with euglycemic individuals, especially in women</td>
<td>Same risk as patients with T2DM</td>
</tr>
<tr>
<td>Microvascular complications (retinopathy, nephropathy, neuropathy)</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Peripheral insulin resistance; reduced pancreatic beta-cell mass and function; reduced insulin secretion</td>
<td>Autoimmune destruction of pancreatic beta-cells</td>
<td>Latent autoimmune destruction of pancreatic beta-cells</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Negative</td>
<td>• GAD-65 autoantibodies</td>
<td>• GAD-65 autoantibody is typically the only one detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Islet-cell antigen-2</td>
<td>• Islet-cell antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insulin autoantibodies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NOTE: Unlike LADA, T1DM patients typically are positive for all three autoantibodies</td>
<td></td>
</tr>
<tr>
<td>Insulin requirements for treatment</td>
<td>Usually late in the disease when the remaining beta-cell mass and function can no longer support acceptable glycemic control achieved by oral agents or incretin mimetics</td>
<td>Insulin is required from the time of diagnosis</td>
<td>Insulin should be initiated as soon as the patient develops autoantibodies</td>
</tr>
</tbody>
</table>

T2DM indicates type 2 diabetes mellitus; GAD-65 indicates glutamic acid decarboxylase; LADA indicates latent autoimmune diabetes in adults; T1DM indicates type 1 diabetes mellitus.

Case Study

- 42 year old woman presenting with new onset diabetes
- HPI: 6 week history of fatigue, thirst, blurred vision, polyuria
- PMH: hypothyroidism, hyperlipidemia, depression.
- Medications: thyroxine, rosuvastatin, sertraline
- Family Hx: Son Type 1 DM
- SH: Married with 5 children (normal birthweight), Secretary
Case Study cont’d

• Physical exam
  – Ht – 156cm Wt. – 63kg (BMI 26) BP 135/80, HR 76,
  – Normal HEENT, Neck, Chest, Cardiovascular, Abdominal, Neurological

• Pathology
  – HbA1c – 10.0%, normal renal and liver function, normal urine microalbumin

What do you think of her diagnosis?
Type 1, Type 2 or LADA?
Case Study cont’d

• Follow up pathology
  – Glutamic Acid Carboxylase (GAD-65) – 94.9 (Reference 0-1.5)
  – C Peptide – 0.9 (1.1-5.0)

Your thoughts on this woman’s diagnosis????
Type1 . . . Type 2 . . . LADA
Clinical Pearls

- LADA is adult-onset diabetes with positive pancreatic autoantibodies and slowly progressive β-cell failure.
- LADA does not present like type 1 diabetes with significant weight loss and ketoacidosis from rapidly progressive β-cell failure. Because of the slow progressive β-cell failure, LADA presents similarly to type 2 diabetes, with elevated blood glucose values and typical symptoms of hyperglycemia, such as polyuria, polydipsia, polyphagia, and visual blurring.
- The three keys to diagnosis of this disease are adult onset, positive antibodies, and lack of ketosis.
- LADA occurs in ~10% of adults who appear to present with type 2 diabetes.
- Screening requires clinical suspicion, and it is recommended to test for ICA and GAD antibodies. Clinical suspicion should be raised by a history of autoimmune disorders and lower BMI, but not excluded by elevated BMI or family history of type 2 diabetes.
- Within a few years, β-cell failure requires insulin therapy. Therefore, to preserve β-cell function, it is recommended that insulin therapy be started early.
Thank You!