Diabetes Mellitus 2
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Objectives:
- Scope of diabetes
- Making the diagnosis
- Pathophysiology
- Disease consequences
- Management
- Conclusion

References:
Step up / davidson- Black
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Extra explanation - Grey
Introduction:

Diabetes mellitus is a clinical syndrome characterized by an increase in plasma blood glucose (hyperglycemia). There are many causes of diabetes:

1. Type 1 diabetes characterized by a severe deficiency of insulin.
2. Type 2 diabetes.
3. Other specific types: it could be temporary or permanent but always have a specific cause for example Genetic defects of β-cell function, Genetic defects of insulin action and pancreatic disease like pancreatitis.

Type 2 diabetes is characterized by resistance to the action of insulin and an inability to produce sufficient insulin to overcome this ‘insulin resistance’. Hyperglycemia results in both acute and long-term problems. Type 2 diabetes was previously termed ‘non-insulin-dependent diabetes mellitus’ (NIDDM) because patients retain the capacity to secrete some insulin but exhibit impaired sensitivity to insulin (insulin resistance) and initially can usually be treated without insulin replacement therapy.

Type 2 diabetes, or its antecedent, impaired glucose tolerance, is one of a cluster of conditions thought to be caused by resistance to insulin action. Thus, patients with type 2 diabetes often have associated disorders including hypertension, dyslipidemia, non-alcoholic fatty liver and, in women, polycystic ovarian syndrome. This cluster has been termed the ‘insulin resistance syndrome’ or ‘metabolic syndrome’ and is much more common in patients who are obese.

In both of the common types of diabetes, environmental factors interact with genetic susceptibility to determine which people develop the clinical syndrome.

Genetic predisposition:

Genetic factors are important in type 2 diabetes, as shown by marked differences in susceptibility in different ethnic groups, Genome-wide association studies have identified over 65 genes or gene regions that are associated with type 2 diabetes, each exerting a small effect. The largest effect is seen with variation in TCF7L2; Most of the genes known to contribute to risk of type 2 diabetes are involved in β-cell function or in regulation of cell cycling and turnover, suggesting that altered regulation of β-cell mass is a key factor.

Environmental and other risk factors:

Diet and obesity increase the risk of developing type 2 diabetes increases tenfold in people with a body mass index (BMI) of more than 30 kg/m² However, although the majority of patients with type 2 diabetes are obese, only a minority of obese people develop diabetes, as the majority of obese patients are able to increase insulin secretion to compensate for the increased demand resulting from obesity and insulin resistance (will be explained more in pathophysiology). Age type 2 diabetes is more common in the middle-aged and elderly.

Researchers found that diabetes mellitus in Saudi Arabia is present in 20% of the adult population with one of two in people above the age of 50 years.
Before attempting to understand the pathophysiology of DM type 2 you should know the basic mechanism of glucose control, here is a brief reminder:

Blood glucose is tightly regulated and maintained within a narrow range by insulin & glucagon. This is essential for ensuring a continuous supply of glucose to the central nervous system. After ingestion of a meal containing carbohydrate, normal blood glucose levels are maintained by:

1. Suppression of hepatic glucose production.
2. Stimulation of hepatic glucose uptake.
3. Stimulation of glucose uptake by peripheral tissues.

Insulin, the primary regulator of glucose metabolism and storage is secreted from pancreatic β cells into the portal circulation in response to a rise in blood glucose, also A number of other factors released from the gut following food intake can augment insulin release, including amino acids and hormones such as glucagon-like peptide 1 (GLP-1) and gastrointestinal peptide (GIP).

As a result, insulin release is greater when glucose is administered by mouth than when the same rise in plasma glucose is achieved by intravenous glucose infusion, a phenomenon termed the ‘incretin’ effect.

◆ Pathophysiology is divided into:

A. Insulin resistance:
   - The primary cause of insulin resistance remains unclear, one theory is centered on the Intra-abdominal ‘central’ adipose tissue is metabolically active, and releases large quantities of FFAs, which may induce insulin resistance because they compete with glucose as a fuel supply for oxidation in peripheral tissues such as muscle.
   - In addition, adipose tissue releases a number of hormones adipokines which act on specific receptors to influence sensitivity to insulin in other tissues.
   - Several circulating peptides including the cytokines TNF-α and IL-6, RBP4, and the “adipokines” adiponectin and resistin produced and released from adipose tissue can modify insulin action.
   - Also diabetic patients have some degree of incretin hormones ((GLP-1) and (GIP)) resistance and deficiency (they play major role in management will be clarified later).
   - Another theory is physical activity as an important determinant of insulin sensitivity. Inactivity is associated with down regulation of insulin-sensitive kinases and may promote accumulation of FFAs within skeletal muscle. Moreover, physical activity allows non-insulin-dependent glucose uptake into muscle, reducing the ‘demand’ on the pancreatic β cells to produce insulin.
   - All those changes play a role in development of insulin resistance which is manageable by normal individuals.

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<thead>
<tr>
<th>Carbohydrate metabolism</th>
<th>Decrease</th>
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<tbody>
<tr>
<td>Glucose transport (muscle, adipose tissue)</td>
<td>Gluconeogenesis</td>
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<td>Glucose phosphorylation</td>
<td>Glycogen synthesis</td>
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<td>Glycogen synthesis</td>
<td>Glycolysis</td>
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<td>Glycolysis</td>
<td>Pyruvate dehydrogenase activity</td>
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<td>Pentose phosphate shunt</td>
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<th>Lipid metabolism</th>
<th>Decrease</th>
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<tr>
<td>Triglyceride synthesis</td>
<td>Lipolysis</td>
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<tr>
<td>Fatty acid synthesis (liver)</td>
<td>Lipoprotein lipase (muscle)</td>
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<td>Lipoprotein lipase activity (adipose tissue)</td>
<td>Ketogenesis</td>
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<td>Fatty acid oxidation (liver)</td>
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<th>Protein metabolism</th>
<th>Decrease</th>
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<tr>
<td>Amino acid transport</td>
<td>Protein degradation</td>
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<tr>
<td>Protein synthesis</td>
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</table>
**Diagnosis:**

Symptoms of hyperglycemia and the Clinical examination of the patient with diabetes:

1. Thirst, dry mouth (polydipsia).
2. Polyuria.
3. Polyphagia.
4. Change in weight (usually weight loss).
5. Nocturia.
6. Tiredness, fatigue, lethargy.
8. Pruritus vulvae, balanitis (genital candidiasis).
11. Mood change, irritability, difficulty in concentrating, apathy.

**Investigations:**

Type 2 diabetes is a diagnosis of exclusion, i.e. it is made when type 1 diabetes and other types of diabetes are ruled out.

A-Urine tasting:

1. Testing the urine for glucose with dipsticks. The greatest disadvantage of urinary glucose measurement is the individual variation in renal threshold for glucose also drugs may interfere with urine glucose tests.
2. Ketones: Ketonuria may be found in normal people who have been fasting or exercising strenuously for long periods, who have been vomiting repeatedly, or who have been eating a diet high in fat and low in carbohydrate.
3. Protein: Microalbuminuria or proteinuria, in the absence of urinary tract infection.

B-Blood testing:

1. Glucose.
2. Ketones.
3. Glycated hemoglobin (HbA1c): slow non-enzymatic covalent attachment of glucose to hemoglobin (glycation) increases the amount in the HbA1c fraction relative to nonglycated adult hemoglobin (HbA0). Glycated hemoglobin provides an accurate and objective measure of glycemic control integrated over a period of 120 days life span of normal RBCs.

Glycaemia can be classified into three categories: normal, impaired (prediabetes) and diabetes the glucose cut-off that defines diabetes is based upon the level above which there is a significant risk of microvascular complications (retinopathy, nephropathy, and neuropathy). People categorized as having prediabetes have blood glucose levels that carry a negligible risk of microvascular complications but are at increased risk of developing diabetes. Also, because there is a continuous risk of macrovascular disease (atheroma of large conduit blood vessels) with increasing glycaemia in the population, people with pre-diabetes have increased risk of cardiovascular disease (myocardial infarction, stroke and peripheral vascular disease).
Diagnostic Criteria of Diabetes:
- Two fasting blood glucose >7.0 mmol/L (126 mg/dL)
- Glucose level 2 postprandial ≥ 11.1 mmol/L (200 mg/dL)
- Random plasma glucose >11.1 mmol/L (200 mg/dL)
- Oral glucose tolerance testing (OGTT) Less than 140 mg/dL or less than 7.7 mmol/L
- Hemoglobin A1C >6.5% is a diagnostic criterion and is the best test to follow response to therapy over the last several months.

Complications of DM type 2: (it’s going to be explained in complication lecture)

A-Macrovascular: coronary artery disease, peripheral artery disease and cerebrovascular disease.

Management:
The aims of management are to improve symptoms of hyperglycemia and to minimize the risks of long-term microvascular and macrovascular complications. Regardless of etiology, the choice of treatment is determined by the adequacy of residual β-cell function. However, this cannot be determined easily by measurement of plasma insulin concentration because a level which is adequate in one patient may be inadequate in another, depending upon sensitivity to insulin.

The management of type 2 diabetes mellitus is divided by three main categories:

A-Diet and lifestyle:
In new cases of diabetes, adequate glycemic control can be obtained by diet and lifestyle advice alone in approximately 50%, 20–30% will need oral anti-diabetic medication, and 20–30% will require insulin. Weight loss suggests worsening β-cell function.

During continuing follow-up, the majority of patients will require combinations of anti-diabetic drugs, often with additional insulin replacement, to obtain satisfactory glycemic control.

B-Antidiabetic drugs (oral hypoglycemic agents):

1- Biguanides (Metformin):
Is potent blood glucose lowering treatment that is weight neutral, does not cause hypoglycemia and has established benefits in microvascular disease. It is employed as first-line therapy in all patients who tolerate it, and its use is maintained when additional agents are added as glycaemia deteriorates.

Approximately 25% of patients develop mild gastrointestinal side-effects with metformin, but only 5% are unable to tolerate it even at low dose. The main side-effects are diarrhea, abdominal cramps, bloating and nausea.

Mechanism of action: it lowers insulin levels; its main effects are on fasting glucose and are insulin independent. Metformin reduces hepatic glucose production, may also increase insulin-mediated glucose uptake, and has effects on gut glucose uptake and utilization.

Q: why Metformin is contraindicated in patients with renal failure? b/c the fear of developing Lactic Acidosis

2- Sulphonylureas (Glibenclamide, Glimepiride, Glipizide):
They are an effective therapy for lowering blood glucose and are often used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone, they promote pancreatic β-cell insulin secretion.

The main adverse effects of sulphonylureas are weight gain and hypoglycemia.

Mechanism of action: Sulfonylureas act by closing the pancreatic β-cell ATP-sensitive potassium (K ATP) channel, decreasing K+ efflux, which ultimately trigger insulin secretion.
3- Alpha-glucosidase inhibitors:

The α-glucosidase inhibitors delay carbohydrate absorption in the gut by inhibiting disaccharides. The main side-effects are flatulence, abdominal bloating and diarrhea.

4-Thiazolidinediones (Pioglitazone, Rosiglitazone, etc.):

Pioglitazone can be very effective at lowering blood glucose in some patients and appears more effective in insulin-resistant patients. But it exacerbates cardiac failure by causing fluid retention, and recent data show that it increases the risk of bone fracture, and possibly bladder cancer. These observations have reduced the use of pioglitazone dramatically.

Mechanism of action: bind and activate peroxisome proliferator activated receptor γ, a nuclear receptor present mainly in adipose tissue that regulates the expression of several genes involved in metabolism. TZDs enhance the actions of endogenous insulin, in part directly (in the adipose cells) and in part indirectly (by altering release of ‘adipokines’). Plasma insulin concentrations are not increased and hypoglycemia does not occur.

5- Incretin-based therapies: DPP-4 inhibitors and GLP-1 analogues:

(GLP-1) and (GIP) are rapidly broken down by the peptidase DPP-4, DPP-4 inhibitors, prevent breakdown and therefore enhance concentrations of endogenous GLP-1 and GIP.

The GLP-1 receptors analogues have been modified to resist breakdown by DPP-4. These agents are not orally active and have to be given by subcutaneous injection. Unlike sulphonylureas, both incretin-based therapies only promote insulin secretion when there is a glucose ‘trigger’ for insulin secretion. Thus, when the blood glucose is normal, the insulin secretion is not augmented and so these agents do not cause hypoglycemia.

6- SGLT2 inhibitors:

Glucose is filtered freely in the renal glomeruli and reabsorbed in the proximal tubules. SGLT2 is involved in Inhibition of reabsorption glucose. Inhibition results in approximately 25% of the filtered glucose not being reabsorbed. Although this helps to lower blood glucose and results in calorie loss and subsequent weight loss, the glycosuria does result in increased urinary tract and genital fungal infections.
C- Insulin therapy:

<table>
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<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Rapid-acting</td>
<td>&lt; 0.5</td>
<td>0.5–2.5</td>
<td>3–4.5</td>
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<tr>
<td>(insulin analogues:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ispro, aspart, glulisine)</td>
<td></td>
<td></td>
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<tr>
<td>Short-acting</td>
<td>0.5–1</td>
<td>1–4</td>
<td>4–8</td>
</tr>
<tr>
<td>(soluble (regular))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intermediate-acting</td>
<td>1–3</td>
<td>3–8</td>
<td>7–14</td>
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<tr>
<td>(isophane (NPH), lente)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Long-acting</td>
<td>2–4</td>
<td>6–12</td>
<td>12–30</td>
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<tr>
<td>(bovine ultralente)</td>
<td></td>
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<tr>
<td>Long-acting</td>
<td>1–2</td>
<td>None</td>
<td>18–24</td>
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<tr>
<td>(insulin analogues:</td>
<td></td>
<td></td>
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<tr>
<td>glargine, detemir)</td>
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Summary:

Side-effects of insulin therapy:

1- Hypoglycemia.
2- Weight gain.
3- Peripheral edema.
4- Insulin antibodies (with animal insulins)
5- Local allergy (rare).
6- Lipohypertrophy or lipoatrophy at injection sites so repeated injection at the same site should be avoided.

21.28 Duration of action (in hours) of insulin preparations

Typical age at onset
- Type 1: < 40 yrs
- Type 2: > 50 yrs

Duration of symptoms
- Type 1: Weeks
- Type 2: Months to years

Body weight
- Type 1: Normal or low
- Type 2: Obese

Ketonuria
- Type 1: Yes
- Type 2: No

Rapid death without treatment with insulin
- Type 1: Yes
- Type 2: No

Autoantibodies
- Type 1: Positive in 80–90%
- Type 2: Negative

Diabetic complications at diagnosis
- Type 1: No
- Type 2: 25%

Family history of diabetes
- Type 1: Uncommon
- Type 2: Common

Other autoimmune disease
- Type 1: Common
- Type 2: Uncommon

Confirming the diagnosis of type 2 diabetes:

- Fasting plasma glucose: 126 mg/dL or higher on 2 separate occasions
- HbA1c: 6.5% or higher on 2 separate occasions
- Oral glucose tolerance test (OGTT): 2-hour post OGTT blood glucose 200 mg/dL or higher

FBG, HbA1c or OGTT high on 2 occasions

Diabetes
Observation
- Weight loss in insulin deficiency
- Obesity in type 2 diabetes
- Mucosal candidiasis
- Dehydration—dry mouth, tissue turgor
- Air hunger—Kussmaul breathing in ketoacidosis
MCQ’s

Q1: A 53-year-old man comes to the physician because of tingling in his feet and recurrent blurry vision. He is an obese man who rarely exercises and who eats an excessive amount of fatty, high-caloric food. He takes no medications. A fasting plasma glucose level is 169 mg/dL on this visit and 172 mg/dL on a subsequent visit. Which of the following drugs used in the treatment of his condition has no effect on the secretion of insulin?

(A) Acetohexamide
(B) Chlorpropamide
(C) Glyburide
(D) Metformin
(E) Tolbutamide

Q2: A 45-year-old woman comes to the physician because of persistent blurred vision for the past month. She also reports three episodes of Candida vaginitis during the past year. She is 167 cm (66 in) tall, and weighs 84 kg (185 lb). Her blood pressure is 130/84 mmHg. Funduscopic examination reveals dot retinal hemorrhages and increased tortuosity of retinal veins. Her family history is significant for obesity, coronary artery disease, and type 2 diabetes mellitus in several relatives. Examination reveals no significant abnormalities. Dipstick urinalysis is normal. Which of the following is the most appropriate next step in diagnosis?

(A) Blood test for c-peptide
(B) Fasting blood glucose level
(C) Glucose tolerance test
(D) Glycosylated hemoglobin
(E) Urine glucose levels

Q3: An obese 18-year-old woman is brought to the emergency department by her mother, who noted that she had been lethargic all day, and suffered a brief, seizure-like episode. One month earlier, the patient had been started on medication for type 2 DM. Lactic acid levels are normal. Which of the following medications most likely played a role in the patient’s current presentation?

(A) A statin
(B) A sulfonylurea
(C) A thiazolidinedione
(D) An α-glucosidase inhibitor
(E) Metformin

Q4: An obese patient with a long-standing history of type 2 DM presents to his primary care physician. On examination he has decreased sensation in both lower extremities. Upon questioning of his compliance with his prescribed medications, he reports that he has stopped taking one medication because it gave him flatulence and abdominal pain. Which of the following did this man most likely stop taking?

(A) An α-glucosidase inhibitor
(B) Meglitinide
(C) Metformin
(D) Sulfonylurea
(E) Thiazolidinedione

Q5: A 49-year-old man presents to the clinic for a health maintenance visit. He has a family history of type 2 DM. His medical history is significant for gastroesophageal reflux disease, for which he takes omeprazole and over-the-counter antacids. He smokes one pack of cigarettes per day and drinks an average of two beers per night. The patient’s body mass index is 32 kg/m². Which of the following most greatly reduce(s) the patient’s risk of future coronary artery disease, renal failure, and retinopathy?

(A) Alcohol avoidance
(B) Daily multivitamin
(C) Diet rich in fruit and vegetables
(D) Smoking cessation
(E) Weight loss and exercise