Lec 3
Fourth year. Clinical Pharmacy

Endocrine disorders:
Diabetes Mellitus Part I

Introduction

1-**Diabetes mellitus** (DM) is a **group of metabolic disorders characterized by chronically elevated blood glucose (BG)** and abnormal carbohydrate, fat, and protein metabolism.

2-Without effective treatment, **DM can lead to acute complications such as diabetic ketoacidosis (DKA)** and **hyperosmolar hyperglycemic syndrome** (**HHS**).

3-**Chronic hyperglycemia** can cause **microvascular**, **macrovascular**, and **neuropathic complications.**

Pathophysiology

1-**Type 1 DM** (5%–10% of cases) usually results **from autoimmune destruction of pancreatic β-cells (**islet cell antibody**), leading to absolute deficiency of insulin.**

2-It usually presents **in children and adolescents but can occur at any age**.

3-**Type 2 DM (90%–95% of cases) is characterized by multiple defects:**

- **Impaired insulin secretion**:
- **Reduced incretin effect:** Normally, the gut incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and **stimulate insulin secretion in response to a meal**. **Patients with type 2 DM have a reduced incretin effect**.
- **Insulin resistance:** This is manifested by excessive hepatic glucose production, decreased skeletal muscle uptake of glucose, and increased lipolysis and free fatty acid production.
- **Excess glucagon secretion.**
- **Sodium-glucose cotransporter-2 (SGLT-2) upregulation in the kidney:** This **increases reabsorption of glucose**, which further contributes to hyperglycemia.

4-**Gestational diabetes** (GDM) is DM **that occurs in women during pregnancy**.

5-**Microvascular complications** include **retinopathy**, **neuropathy**, and **nephropathy**.

6-**Macrovascular complications** include **coronary heart disease** (CHD), **stroke**, and **peripheral vascular disease**.

Clinical presentation

Type 1 Diabetes Mellitus

1-Patients often **have symptoms in the days or weeks preceding the diagnosis**. The most common initial symptoms are **polyuria**, **polydipsia**, **polyphagia**, **weight loss**, **fatigue**, and **lethargy**.

2-Individuals are often **thin** and are **prone to develop DKA** in the absence of an adequate insulin supply; many patients initially present with DKA.

3-Symptom onset can be **triggered by infection, trauma, or psychological stress**.

Type 2 Diabetes Mellitus

1-**Most patients are asymptomatic** or have **only mild fatigue at the time of diagnosis**. Many patients are **incidentally found to have type 2 DM after routine laboratory testing** (eg, plasma glucose or A1C) or development of complications (eg, myocardial infarction, stroke).

2-**Because mild hyperglycemia may exist for years prior to the diagnosis**, microvascular and macrovascular **complications are often present at the time of diagnosis**.

3-**Most patients are overweight** or obese.

Diagnosis

1-Criteria for diagnosis of DM include any one of the following:

1. **A1C ≥6.5%** 2. Fasting (no caloric intake for at least 8 hours) plasma glucose (FPG) **≥126 mg/dL** 3. Oral glucose tolerance test **(OGTT) ≥200 mg/dL** 4. **Random plasma glucose ≥200 mg/dL** with **classic symptoms of hyperglycemia or hyperglycemic crisis.**

2-**Prediabetes** is a condition of abnormal BG that is not sufficiently high to meet the thresholds that define DM but often progresses to the diagnosis.

3-**Screening for type 1 DM in asymptomatic children or adults is not recommended** due to low disease prevalence and the acute onset of symptoms.

4-**Screening for type 2 DM is recommended for asymptomatic adults who are overweight** (BMI ≥25 kg/m^2) and **have at least one other risk factor for developing type 2 DM.**

5-**All adults, even those without risk factors, should be screened every 3 years starting at 45 years old**. Children at risk for developing type 2 DM should undergo screening every 3 years starting at age 10 years.

Treatment

1-**Goals of Treatment:** The **primary goal is** to prevent or delay progression of long-term microvascular and macrovascular complications.

2-**Additional goals are** to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse effects.

3-**General glycemic targets** for most nonpregnant adults with DM are listed in **Table-1.**

Table-1: Glycemic Target Recommendations for Most Nonpregnant Adults with Diabetes

Parameter	American Diabetes Association (ADA)	American Association of Clinical Endocrinologists (AACE)
A1C	<7.0% (53 mmol/mol Hb)	≤6.5% (48 mmol/mol Hb)
Fasting plasma glucose (FPG)	80–130 mg/dL (4.4–7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Postprandial glucose (PPG)	<180 mg/dL (10 mmol/L)	<140 mg/dL (7.8 mmol/L)

4-Glycemic targets should be individualized. More stringent or less stringent goals may be appropriate for some patients.

Nonpharmacologic Therapy

1-Medical nutrition therapy (MNT): Implement a healthy meal plan that is moderate in calories and carbohydrates and low in saturated fat with all of the essential vitamins and minerals. Target an initial weight loss goal of at least 5% in all type 2 DM patients who are overweight or obese through calorie restriction.

2-**Aerobic exercise**: Physical activity goals include at least 150 min/week of moderate intensity exercise spread over at least 3 days/week with no more than 2 days between activity. Resistance/strength training is recommended at least 2 times/week for patients without proliferative diabetic retinopathy.

3-Patients **must be involved in decision making and have strong knowledge of the disease and associated complications.**

Pharmacologic Therapy

Insulin

1-The main advantage of insulin over other antihyperglycemic agents is **that the** dose can be individualized based on glycemic levels.

2-**Disadvantages** include the **risk of hypoglycemia**, **need for injections**, **and weight gain**.

3-Most insulin products are administered **subcutaneously** (SC) **for chronic diabetes management**, except for **inhaled human insulin**, which is a dry powder of regular insulin that is inhaled and absorbed through pulmonary tissue.

4-The **pharmacokinetics of insulin products** is characterized by their onset, peak, and duration of action (**Table**-2).

5-**Basal insulin** (or background insulin) **refers to longer-acting insulins** that regulate BG levels in **between meals**. Options include the following insulins:

- **NPH** is the least ideal product because it **has a distinct peak** and usually requires **twice daily dosing**.
- **Detemir also has a peak** and often lasts <24 hours; it can be given once daily in some patients **but should be dosed twice daily at low doses**.
- **Glargine** and **degludec** are longer acting-agents that have no **peak and are given once daily.**

6-**The longer-acting products have a lower risk of hypoglycemia** (particularly nocturnal hypoglycemia). However, they are more expensive.

7-**Bolus insulin refers to short- or rapid-acting insulins that cover meals** (also called prandial insulin) or glycemic excursions (also called correction insulin).

8-**Basal insulin** is the preferred and most convenient **initial insulin formulation for patients with type 2 DM,** whereas patients with **type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control**.

Table-2: Pharmacokinetics of Select Insulins Administered Subcutaneously

Type of Insulin by Generic (Brand) Name (U-100 unless otherwise noted)	Onset	Peak[a]	Duration[a]
Ultra-rapid acting			
Insulin aspart (Fiasp)	15–20 min[b]	90–120 min	5–7 hours
Insulin lispro aabc (Lyumjev)	15–17 min[c]	120–174 min	4.6–7.3 hours
Insulin human—inhaled (Afrezza)	12 min	35–55 min	1.5–4.5 hours
Rapid-acting			
Insulin aspart (NovoLog)	10–20 min	30–90 min	3–5 hours
Insulin lispro U-100, U-200 (Humalog, Admelog)			
Insulin glulisine (Apidra)			
Short-acting			
Regular (Humulin R, Novolin R)	30–60 min	2–4 hours	5–8 hours
Intermediate-acting			
NPH (Humulin N, Novolin N)	2–4 hours	4–10 hours	10–24 hours
Regular U-500 (Humulin R 500)	15–30 min	4–8 hours	13–24 hours
Long-acting			
Insulin detemir (Levemir)	1.5–4 hours	6–14 hours[c]	16–20 hours
Insulin glargine (Lantus, Basaglar)	2–4 hours	No peak	20–24 hours
Insulin glargine U-300 (Toujeo)	6 hours	No peak	36 hours
Insulin degludec U-100, U-200 (Tresiba)	1 hour	No peak	42 hours
Combination Products			
70% NPH/30% Regular (Humulin 70/30, Novolin 70/30)	30–60 min	Dual	10–16 hours
75% NPL, 25% lispro (Humalog 75/25)	5–15 min		10–16 hours
50% NPL, 50% lispro (Humalog 50/50)	5–15 min		10–16 hours
70% insulin aspart protamine, 30% insulin aspart (NovoLog 70/30)	5–15 min		15–18 hours

9-**Bolus insulin options include**:

- **Aspart**, **lispro**, and **glulisine**, the rapid-onset, short-duration insulins
- Inhaled human insulin, fast-acting insulin aspart (Fiasp®), and insulin lispro (Lyumjev®): the ultrarapid onset insulins

10-Rapid-acting insulins offer a **faster onset and shorter duration of action than regular insulin**, and **ultra-rapid acting insulins offer an even faster onset**; this may more closely **mimic prandial endogenous insulin release**.

11-Rapid-acting insulins have **a modestly lower risk of hypoglycemia** than regular insulin.

12-**Various premixed insulin products** containing both a basal and a prandial component are also available (**Table-2**). However, **these products are limited by fixed mixed formulations, which can make it challenging to tailor the dosing regimen.**

13-**The insulin dose must be individualized.** In type 1 DM, **the average daily requirement** is 0.5–0.6 units/kg, with **approximately 50% given as basal insulin** and the remaining **50% dedicated to meal coverage.**

14-**Hypoglycemia is the most common adverse effects of insulin therapy**. Insulin also causes dose-dependent weight gain.

15-SC administration can result in **lipoatrophy** or **lipohypertrophy**, which can be prevented by **routinely rotating injection sites.**

Biguanides

1-Metformin **decreases hepatic glucose production** and **enhances insulin sensitivity** in peripheral (muscle) tissues, **allowing for increased glucose uptake into muscle cells**.

2-Metformin is recommended **as first-line pharmacotherapy in patients with type 2 DM** (unless a contraindication or intolerability exists).

3-It **does not cause weight gain** and may **lead to a modest (2–3 kg) weight loss.**

4-It has a **low risk of hypoglycemia** because it does not directly increase pancreatic insulin secretion.

5-Metformin **decreases plasma triglycerides** and **low-density lipoprotein cholesterol** (LDL-C) and **modestly increases high-density lipoprotein cholesterol** (HDL-C).

6-**Metformin frequently causes GI side effects** (diarrhea, abdominal discomfort, stomach upset); these effects are usually dose-dependent, transient, mild, and can be **minimized with slow dose titration and taking metformin with or immediately after meals.**

7-**Extended-release metformin** may lessen some of the GI side effects**.**

8-**Metformin may cause a metallic taste and may lower vitamin B12 concentrations**; B12 levels or methylmalonic acid should be measured annually or if a deficiency is suspected, **with vitamin B12 supplementation given if indicated**.

9-**Lactic acidosis occurs rarely**, usually in the setting of **severe illness or acute kidney injury**. **Because symptoms are often nonspecific, the diagnosis must be confirmed by laboratory measurement of high lactic acid levels and acidosis**.

10-Metformin is renally excreted and accumulates in renal insufficiency; Due to the risk of **acute renal failure with use of IV contrast dye**, **withhold metformin therapy starting the day of the procedure and resume it 2–3 days later** if normal renal function has been documented.

11-Metformin can be **used in combination with any other antihyperglycemic therapy** and is often continued when insulin therapy is initiated.

Sodium-Glucose Cotransporter-2 Inhibitors

1-Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin reduce plasma glucose by **preventing the kidneys from reabsorbing glucose back into the bloodstream**, leading to increased glucose excretion in the urine.

2-SGLT-2 inhibitors **lower both FPG and postprandial glucose (PPG).**

3-SGLT-2 inhibitors **can be added** to metformin or other second-line agents. **They** can be used as monotherapy in patients who cannot tolerate or take metformin ..

4-They are recommended for patients at high risk for or with established **ASCVD, heart failure, or CKD.**

5-They are **unlikely to cause hypoglycemia** unless combined with medications such as sulfonylureas, meglitinides, or insulin.

6-**The most common adverse effect is genital mycotic infections**, which are more common in women and uncircumcised men. There is also a slightly increased risk of **urinary tract infections**. Polyuria, dehydration, dizziness, or hypotension may occur because of the osmotic diuresis effects.

Glucagon-like Peptide 1 Receptor Agonists (GLP1-RAs)

1-Dulaglutide, exenatide, exenatide XR, lixisenatide, liraglutide, and semaglutide stimulate insulin secretion and suppress inappropriately high postprandial glucagon secretion, decreasing hepatic glucose output. They also slow gastric emptying, increase satiety, and **cause weight loss (average 1–3 kg).**

2-**Short-acting agents** (exenatide, lixisenatide) predominantly **lower PPG levels**, whereas **long-acting agents** (dulaglutide, liraglutide, exenatide XR, semaglutide) **lower both FPG and PPG**, but with larger effects on FPG.

3-Dulaglutide, liraglutide, and semaglutide are FDA approved to reduce the risk of major adverse CV events in adults with type 2 DM and established ASCVD

4-GLP1RAs can be used as monotherapy in patients who cannot tolerate or take first line therapy. Six GLP1RAs are administered SC. Semaglutide is available as SC and oral preparations.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

1-Alogliptin, linagliptin, saxagliptin, and sitagliptin prolong the half-life of endogenously produced GLP-1 and GIP, thereby increasing glucose-dependent insulin secretion from the pancreas and reducing inappropriate postprandial glucagon secretion, resulting in lower glucose levels **without an increase in hypoglycemia when used as monotherapy**.

2-They do not alter gastric emptying, or cause weight gain/loss.

3-DPP-4 inhibitors are considered **second- or third-line therapy**.

4-Advantages include **once-daily dosing**, **oral administration**, **weight neutrality**, **low risk of hypoglycemia, and good tolerability**.

Thiazolidinediones (TZDs)

1-TZDs bind to the peroxisome proliferator activator receptor-γ (PPAR-γ) located primarily on fat and vascular cells, enhancing insulin sensitivity in muscle, liver, and fat tissues.

2-Maximum effects may **not be seen until 3–4 months of therapy**.

3-TZDs are considered **second- or third-line agents** and can be used in combination with metformin and other commonly prescribed medications for type 2 DM.

4-**Fluid retention may occur**. This may result in **peripheral edema**, HF, **hemodilution** of hemoglobin and hematocrit, **and weight gain.**

5-**TZDs are contraindicated in patients with New York Heart Association Class III or IV HF** and should be used with caution in patients with Class I or II HF.

6-**Weight gain** is dose related and results from both fluid retention and fat accumulation.

Sulfonylureas (e.g. glyburide, glipizide, and glimepiride)

1-Sulfonylureas enhance insulin secretion by binding to the sulfonylurea receptor SUR1 on pancreatic β-cells.

2-Sulfonylureas are widely used because they have an extensive record of safety and effectiveness, are given orally, and are inexpensive. **However, current treatment guidelines either discourage their use or suggest caution due to the risk of hypoglycemia and weight gain.** In addition, **tachyphylaxis** to the insulin secretion effect occurs, leading to poor long-term durability of response in most patients.

3-**The most common side effect is hypoglycemia**.

4-**Weight gain is common** (typically 1–2 kg). **Patients with sulfa allergy rarely experience crossreactivity with sulfonylureas.**

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

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