Lec 4

Fourth year. Clinical Pharmacy

Endocrine disorders

Diabetes Mellitus Part II

α-Glucosidase Inhibitors

1-**Acarbose** and **miglitol delay the breakdown of sucrose and complex carbohydrates** in the small intestine, prolonging carbohydrate absorption.

2-Good candidates for these drugs are patients who are **near target A1C levels** with near-normal FPG but **high PPG levels**.

3-The most common side effects **are flatulence, abdominal pain, and diarrhea**, which can be reduced by slow dosage titration.

Meglitinides

1-**Nateglinide** and **repaglinide** stimulate insulin secretion from pancreatic β-cells by binding to a site adjacent to the sulfonylurea receptor.

2-They are similar to sulfonylureas except that they have **a faster onset and shorter duration** of action.

3-Similar to sulfonylureas, the main side effects **are hypoglycemia and weight gain**.

4-They may be a good option for patients **with erratic meal schedules**. However, **multiple daily dosing may decrease adherence**.

5-Meglitinides should be taken by mouth **with each meal**.

Bile Acid Sequestrants

Colesevelam. Its mechanism in lowering plasma glucose levels is unknown, and its role in therapy is unclear.

Dopamine Agonists

1-**Bromocriptine mesylate** is FDA approved for treatment of type 2 DM. The mechanisms by which it improves glycemic control are unknown .

2-Its role in the treatment of type 2 DM is unclear.

Amylin Analogs

1-**Pramlintide** is a synthetic amylin analog that reduces glucagon secretion, slows gastric emptying, and increases satiety. **It was the first noninsulin agent approved for patients with type 1 DM.**

2-It is used **primarily in type 1 DM as adjunctive therapy** for patients who are not achieving **PPG goals** despite maximizing mealtime insulin doses.

3-It can also **decrease weight** and may allow for lower mealtime insulin doses.

Treatment of Type 2 Diabetes

1-Upon diagnosis, **set a patient-specific A1C target**. **Implement comprehensive lifestyle modifications** .

2-**Initiate with metformin [**or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals] **(Unless there is a comorbidity in which other agents are preferred). Recommendations based on patient-specific comorbidities** include:

- ✔**High risk or established ASCVD**: SGLT2 inhibitor or GLP1RA.
- ✔**Heart Failure (HF)**: SGLT2 inhibitor. Avoid TZDs in patients with HF.
- ✔**CKD (with or without ASCVD):** SGLT2 inhibitor.

3-If the initial A1C is close to goal (eg, ≤7.5%) **consider initial treatment with lifestyle modifications alone** if the patient is motivated.

4-Consider **starting two medications** (e.g. metformin plus a second agent) if the initial A1C is >**1.5% higher than the target A1C.**

5-**Consider early introduction of basal insulin in patients with** very high A1C levels (>10%), or symptoms of hyperglycemia.

6-**See patients at least every 3 months if they are not meeting their goals and at least every 6 months if they are meeting goals.** Add additional therapy if glucose targets have not been met.

7-Most patients eventually require combination therapy.

8-If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug(s), **then triple therapy is warranted**, adding a drug from another class.

9-People with type 2 DM can often be managed with **oral medications for years before injectable medications are needed.**

10-Insulin is recommended for extreme (A1C >10%) or symptomatic hyperglycemia. Otherwise, **GLP-1 RAs are preferred over basal insulin** because they have equal or superior A1C lowering efficacy and lead to weight loss instead of weight gain with a low risk of hypoglycemia.

11-**Basal insulin can be initiated** if additional glucose lowering is needed after the GLP-1 RA dose has been maximized.

12-**If the A1C target is not reached by maximally titrating basal insulin**, PPG levels are likely elevated and **a GLP1-RA or SGLT-2 inhibitor should be considered** if the patient is not already taking one.

13-**Prandial insulin is also an option**. Titrate the dose over time to achieve target PPG levels <180 mg/dL. **A second or third injection can be added** to the other meals if needed.

Treatment of Hyperglycemia in Type 1 Diabetes

1-All patients with type 1 DM require exogenous insulin. Achieving adequate glycemic control usually requires **intensive insulin regimens designed to provide insulin in a manner that mimics normal physiologic insulin secretion**, with consistent secretion of insulin throughout the day to manage glucose levels overnight and in between meals (ie,

basal insulin), and bursts of insulin in response to glucose rises after ingestion of carbohydrates (ie, prandial insulin).

2-**Intensive insulin regimens** can be given with either **multiple daily injections** (MDI) or use of **continuous subcutaneous insulin infusion** (CSII) via an **insulin pump.**

3-A common MDI approach is **one injection of long-acting insulin** (eg, insulin glargine) for the basal component and **three injections** of rapid acting insulin (eg, insulin lispro) for the prandial component.

4-**A less expensive option consists of two injections of intermediate-acting insulin (eg, NPH insulin) and two injections of short-acting insulin (eg, regular insulin).** However, the ADA Standards of Care recommend that most patients should **use rapid-acting insulins** rather than regular insulin to reduce the risk of hypoglycemia.

5-**Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs** . The pump infuses a basal rate constantly throughout the day and allows **the patient to give bolus doses using a bolus dose calculator** based on current glucose levels, carbohydrate intake, and insulin on board.

6-**The total daily insulin dose is divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals).** The insulin doses would then be adjusted based on self-monitoring of blood glucose (**SMBG**) data. Ideally, patients should learn to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake.

7-Patients should also **SMBG before each meal or use continuous glucose monitoring (CGM) to evaluate the insulin regimen and make treatment decisions**. Bolus insulin doses can be better individualized by using carbohydrate-to-insulin ratios (C:I ratios) and correction factors (CF).

8-**Pramlintide is indicated as adjunctive treatment** in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin.

9-Assess patients every 3 months if uncontrolled and every 6 months if controlled. Patients on intensive insulin therapy should SMBG at least four times daily, before meals and at bedtime.

10-**Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur**. SMBG is crucial during times of intercurrent illness or stresses for early detection and prevention of DKA.

11-Current guidelines recommend **CGM in patients with type 1 DM who are not meeting glycemic goals.** They are also recommended in patients with **hypoglycemia unawareness** to better detect and prevent hypoglycemic events.

Common insulin regimens.

(A) Multiple-component insulin regimen consisting of **one injection of long-acting** insulin (detemir, glargine degludec) to provide basal glycemic coverage and **three injections of rapid-acting insulin** (aspart, lispro, glulisine) to provide glycemic coverage for each meal.

(B) Insulin regimen consisting of **two injections of intermediate-acting insulin** (NPH) and rapid-acting insulin (aspart, lispro, glulisine), or short-acting regular insulin.

(C) **Insulin administration by insulin infusion device**. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump.

Hypoglycemia

1-**Hypoglycemia is a common complication** of some diabetes medications.

2-The severity of hypoglycemia is classified as follows:

- **Level 1** (hypoglycemia alert value; ≤70 mg/dL: May not cause symptoms but should be treated **with a fast-acting carbohydrate** and may need medication dose adjustment.
- **Level 2** (clinically significant hypoglycemia; <54 mg/dL: Serious, clinically important hypoglycemia
- **Level 3** (severe hypoglycemia): Associated with cognitive impairment requiring external assistance for recovery and can be life threatening.

3-**Initial autonomic symptoms include** tachycardia, palpitations, sweating, tremors, and hunger. **Neuroglycopenic symptoms** often occur with BG <60 mg/dL and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness.

4-Some patients have **hypoglycemia unawareness** and are unable to detect the early warning symptoms of hypoglycemia; they are at increased risk for the serious sequelae associated with severe hypoglycemia.

5-**SMBG and CGM can be useful in preventing hypoglycemia**. Patients must be educated to understand situations that increase risk of hypoglycemia (eg, delaying meals, during or after exercising, or fasting).

6-**Treatment of hypoglycemia** requires ingestion of carbohydrates, preferably glucose. Patients should carry a source of fast-acting glucose with them at all times and use the **"rule of 15" f**or proper treatment:

- First use SMBG to confirm BG <70 mg/dL and then **ingest 15 g** of fast-acting carbohydrates such as 1/2 cup (4 oz or 125 mL) of milk, juice, or soda; 1 tablespoon of honey; hard candy; jelly beans; or glucose tablets.
- **Repeat SMBG in 15 minutes**; if the BG is <70 mg/dL, **repeat the process.**
- **Once the BG is normalized**, **eat a snack or meal that includes complex carbohydrates** and protein to prevent further hypoglycemic episodes.

7-If the patient is unconscious, **give IV glucose or glucagon injection**. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV glucose cannot be rapidly administered.

8-**A glucagon kit should be prescribed and readily available to all patients on insulin who have a history of or high risk for severe hypoglycemia**. It can take 10–15 minutes before glucose levels start to rise, and patients often **vomit**.

9-**Position the patient on the side with the head tilted slightly downward to avoid aspiration.**

10-Clinicians **should monitor hypoglycemia at every visit**.

11-**Reevaluate the treatment regimen** of patients with frequent or severe hypoglycemia to minimize future episodes.

Complications and Comorbidities

Macrovascular Complications

1-Macrovascular complications (eg, CHD, stroke) **are the leading causes of death in people with diabetes.**

2-The ADA recommends **low-dose aspirin therapy** (75–162 mg daily) **in all patients with established ASCVD.** Clopidogrel may be used in patients allergic to aspirin.

3-The role of antiplatelet therapy for primary CV prevention is unclear because the benefits may be offset by a higher risk of bleeding; **some practice guidelines recommend aspirin if the 10-year risk of a CV event is >20%.**

4-In patients with **established ASCVD**, use of a **GLP1-RA or an SGLT-2 inhibitor should be strongly considered.**

5-For all patients whose **BP exceeds 120/80 mm Hg,** the ADA recommends dietary changes, physical activity, and weight loss in overweight or obese patients.

6-Drug therapy using agents proven to reduce CV events should be started **for BP >140/90 mm Hg.** A combination of **two medications should be used for BP >160/100 mm Hg**.

7-Initiate **high-intensity statin** therapy in all patients with diabetes and preexisting ASCVD regardless of baseline lipid levels. In the absence of ASCVD, prescribe a **moderate-intensity statin t**o all patients with type 1 or type 2 DM over the age of 40.

8-In patients <40 years of age, a **moderate intensity statin** may be appropriate for patients with multiple CV risk factors.

9-A **fibrate** (e.g., fenofibrate), **omega-3 fatty acid**, or **niacin** can be added for patients with marked **hypertriglyceridemia**.

10-**Peripheral arterial disease** can lead to claudication, nonhealing foot ulcers, and limb amputation. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies. **Cilostazol** may be useful in select patients to reduce symptoms. **Revascularization** surgery can be considered in some situations.

Microvascular Complications

Efforts to improve glucose control significantly reduce the risk of developing microvascular complications and slow their progression.

Nephropathy:

1-**Albuminuria is a marker of renal damage**. The ADA recommends screening for albuminuria upon diagnosis and annually thereafter in persons with type 2 DM.

2-Screening **with type 1 DM** should begin with puberty **and after 5-years'** disease duration.

3-**Glucose and BP control** are important for preventing and slowing progression of nephropathy.

4-**The SGLT2 inhibitors** empagliflozin, canagliflozin, and dapagliflozin significantly **reduce the decline in kidney function in patients with CKD, with or without diabetes**.

5-**ACE** inhibitors and **ARBs** can slow the progression of renal disease in patients with diabetes.

6-**Diuretics** are often necessary due to volume expanded states and are recommended **second-line therapy**.

7-The ADA recommends a **BP goal <140/90 mm Hg in patients with nephropathy** but a **lower target** (e.g., <130/80 mm Hg) **if it can be achieved without undue burden or side effects**. **Three or more antihypertensives are often needed to reach goal BP.**

Retinopathy:

1-Patients with diabetes should have **routine eye examinations to fully evaluate the retina.**

2-**Early retinopathy may reverse with improved glycemic control and optimal BP control**. More advanced retinopathy will not fully regress with improved glycemia.

3-**Laser photocoagulation** has markedly improved sight preservation. **Intravitreal antivascular endothelial growth factor (VEGF) therapy** is also highly effective for sight preservation.

4-**Bevacizumab** (used off-label) and **ranibizumab** are **anti-VEGF monoclonal antibodies**, and **aflibercept** is a VEGF **decoy receptor**.

Neuropathy:

- **Peripheral neuropathy** is the most common complication in patients with type 2 DM. **Paresthesias, numbness**, or **pain** are **the predominant symptoms**. The feet are involved far more often than the hands. **Improved glycemic control is the primary treatment and may alleviate some symptoms.** Pharmacologic therapy is symptomatic and includes low-**dose tricyclic antidepressants** (nortriptyline or desipramine), **duloxetine**, **gabapentin**, **pregabalin**, **venlafaxine**, **topical capsaicin**, and **tramadol**.

- **Gastroparesis**. Improved glycemic control and use of **metoclopramide** or **low-dose erythromycin** may be helpful.

- **Diabetic diarrhea** is often **nocturnal** and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.

- **Orthostatic hypotension** may require mineralocorticoids (eg, **fludrocortisone**) or adrenergic agonists (**midodrine**).

- **Erectile dysfunction** is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil**, **vardenafil**, or **tadalafil**).

Evaluation of therapeutic outcomes

1-**Measure A1C every 3–6 months to follow long-term glycemic control for the previous 2–3 months**.

2-For patients with type 1 DM, **SMBG is typically performed 4–6 times per day**—prior to food intake and physical activity and at bedtime.

3-The optimal **frequency of SMBG in patients with type 2 DM on oral agents is controversial**.

4-**At each visit**, ask patients with type 1 DM **about the frequency and severity of hypoglycemia**.

5-Screen for complications (**eye exams**, assess **BP, examine the feet, screen for albuminuria, check fasting lipid panel)**

6-Administer an **annual influenza vaccine** and assess for administration of the **pneumococcal vaccine and hepatitis B vaccine** series along with management of other CV risk factors (e.g., smoking).

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

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