Diabetes Mellitus Guidelines Summary

Prevention/Delay of Diabetes

- No data to suggest any known lifestyle or pharmacologic intervention can delay the onset of T1DM.
- Lifestyle modifications and certain medications can reduce the incidence of T2DM.
  - Most impressive clinical outcomes are associated with dietary and exercise programs that lead to mild to moderate weight loss (5%-7% reduction) in overweight or obese patients.
  - Prediabetic patients using metformin results in mild reductions in the incidence of progression to diabetes
  - Though pharmacologic intervention was significantly less effective than lifestyle changes.

Screening

- No recommendation to screen individuals for T1DM.
- The US Preventive Services Task Force recommends screening for T2DM in asymptomatic adults with sustained blood pressure (BP; treated or untreated) >135/80 mm Hg.
- American Diabetes Association (ADA) recommends screening patients who are **overweight or obese (body mass index >25 kg/m^2) and who have risk factors:**
  - BP >140/90 mm Hg
  - Dyslipidemia: [high-density lipoprotein levels <35 mg/dL (0.9 mmol/L) and/or triglyceride levels >250 mg/dL (2.8 mmol/L)]
  - first degree relative with diabetes
  - member of a high-risk ethnic group
  - polycystic ovary syndrome
- Asymptomatic patients without risk factors should consider screening at age 45 years.

Diagnosis

- **Fasting plasma glucose** ≥126 mg/dL (7.0 mmol/L)
- **2-hour plasma glucose** ≥200 mg/dL (OGTT) (11.1 mmol/L) during the 75-g oral glucose tolerance
  - **Both** tests are highly specific for the diagnosis.
- **Glycated hemoglobin (HbA_{1c})** ≥6.5% is adequate to establish the diagnosis
- **Random plasma glucose level** of ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
- **All tests must be confirmed by repeating the test**

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

- Once diabetes is diagnosed, these investigations are performed to screen for complications and establish baseline values:
    - HbA_{1c} measurement
    - fasting lipid profile
    - serum electrolyte panel
    - urinalysis (including testing for moderately increased albuminuria [microalbuminuria])
    - electrocardiography

- **Individuals whose glucose levels are higher than normal but do not meet the criteria for diabetes are considered prediabetic:**
    - HbA_{1c} ranging from 5.7% to 6.4%
    - impaired fasting glucose (100 mg/dL [5.6 mmol/L] to 125 mg/dL [6.9 mmol/L])
    - impaired glucose tolerance test (2-hour postprandial serum glucose level of 140 mg/dL [7.8 mmol/L] to 199 mg/dL [11.0 mmol/L])

- *Important to identify these patients to offer appropriate preventive measures.*
- *HbA_{1c} between 5.5% and 6.0% have an incidence of diabetes ranging from 9% to 25% within a 5-year period*
- *HbA_{1c} of 6.0% to 6.5% have an incidence of 25% to 50%.*

Type 2 Diabetes Management

- Type 2 diabetes is conventionally treated **first with diet, weight loss (for overweight or obese patients), and exercise.**
    - Such lifestyle modifications reduce insulin resistance and blood glucose levels and improve cardiovascular risk factors.
    - However, these steps are usually **insufficient to attain glucose targets.**
- Various pharmacotherapies should be individualized based on a patient's known risk factors, comorbidities, medication side effects, and cost burden.
- Many patients fail to achieve optimal glucose control with monotherapy.

- **Metformin** is the preferred **first-line monotherapeutic agent in patients with creatinine levels <1.6 mg/dL (141.4 µmol/L; men) and <1.5 mg/dL (132.6 µmol/L; women)**
    - And without known liver disease or alcohol abuse.
    - Must be discontinued before receipt of radiocontrast agents.
    - Patients should be counseled about the risk of loose stools, bloating, gas, or other gastrointestinal side effects.

- **Sulfonylureas:**
    - Can be given as **first-line agents or in combination with metformin.**
    - can cause hypoglycemia and should be used with caution in the elderly
    - Caution especially in the presence of chronic kidney disease.

- **Initiating an incretin-based therapy while continuing oral medications:**
  - Currently available incretin therapies include **glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors.**
  - This class of drug can reduce HbA_{1c} by approximately 0.5% to 1.5%.
  - **Glucagon-like peptide-1 agonists: no increasing of the risk of hypoglycemia or weight gain**
  - Nausea, diarrhea, vomiting, and bloating are well known side effect.
  - expensive than other medications

- **Initiating a third oral medication:**
  - Thiazolidinediones (pioglitazone, rosiglitazone) can result in further reductions in HbA_{1c} of approximately 0.5% to 1.0%
  - However, current evidence suggests that rosiglitazone (and possibly pioglitazone) may not be optimal for treating T2DM.
  - associated with increased cardiovascular adverse events
  - Contraindicated in patients with heart failure or liver dysfunction and have been associated with increased risk of bladder cancer and osteoporotic fracture.

- **Initiate insulin therapy if the desired level of glycemic control is not achieved with these other strategies.**
  - Most popular method is to **begin with a single nighttime injection of basal (long-acting) insulin**
  - Basal insulin, although effective in many patients, **does not address postprandial glucose excursions so short- or rapid-acting insulin is added before each meal.**
  - Some oral agents can be continued with the initiation of basal insulin
  - Although insulin secretagogues (sulfonylureas and glinides) are usually discontinued **because of the additive risk for hypoglycemia.**
  - Patients should be counseled that consistency in their routine (both timing of insulin administration and eating patterns) is paramount to success in managing their diabetes.
  - **Insulin therapy is also considered the standard of care for treating diabetes during pregnancy**

Pharmacokinetic Properties of Insulin Products			
Human Insulins and Insulin Analogues	**Onset**	**Peak**	**Duration**
Rapid acting (lispro, aspart, glulisine)	10-15 min	1-2 h	3-5 h
Short acting (regular)	0.5-1 h	2-4 h	4-8 h
Intermediate acting (NPH)	1-3 h	6-10 h	10-16 h
Long acting: Glargine	2-3 h	None	24+ h
Long acting: Detemir	1 h	None	12-24 h
NPH = neutral protamine Hagedorn.			

Drug Class (Examples)	Mechanism of Action	Benefits	Risks/Concerns
Sulfonylureas (glyburide, glipizide, glimepiride)	Bind to sulfonylurea receptor on β-cells, stimulating insulin release; long duration of action	Long-term safety; can be once-daily oral pill; substantial HbA_{1c} reduction (1.0%-1.5%); low cost	Hypoglycemia; weight gain
Glinides (repaglinide, nateglinide)	Bind to sulfonylurea receptor on β-cells, stimulating insulin release; short duration of action	Target postprandial glucose	Only modest glycemic effect; potential hypoglycemia; weight gain; no long-term studies; expensive
Biguanides (metformin)	Decrease hepatic glucose production	Long-term safety; substantial HbA_{1c} reduction (1.0%-1.5%); no hypoglycemia; weight loss or weight neutral; possible macrovascular benefit; low cost	Loose stool, mild abdominal discomfort; lowers vitamin B_{12} levels; contraindicated when kidney disease is present (creatinine >1.5)
Thiazolidinediones (pioglitazone, rosiglitazone)	Activate the nuclear receptor PPARγ, increasing peripheral insulin sensitivity; may also reduce hepatic glucose production	No hypoglycemia; may improve lipid profile	Edema and heart failure risk; weight gain; possible increased myocardial infarction risk with rosiglitazone; expensive; increased risk for bladder cancer and fracture
Incretin modulators (exenatide, liraglutide)	Activate GLP-1 receptors, increasing glucose-dependent insulin secretion, decreasing glucagon secretion, delaying gastric emptying, and enhancing satiety	No hypoglycemia; weight loss; may prevent further β-cell decline (theoretical)	Injectable; nausea, vomiting; possible pancreatitis (rare); expensive
DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin)	Inhibit degradation of endogenous GLP-1 and GIP, thereby enhancing the effect of these incretins on insulin and glucagon secretion	No hypoglycemia; weight neutral; once-daily oral dosing	Possible urticaria/angioedema (rare); no long-term studies; weight neutral; expensive
α-glucosidase inhibitors (acarbose, miglitol, voglibose)	Inhibit polysaccharide absorption in the gut	No hypoglycemia; weight neutral	Minimal HbA_{1c} effect (~0.5%); flatulence, abdominal discomfort
SGLT2 inhibitor (dapagliflozin, canagliflozin)	Inhibit SGLT2 in proximal renal tubules to reduce renal reabsorption of filtered glucose resulting glucosuria	No hypoglycemia; weight neutral; possible lower blood pressure	Genital infection such as vulvovaginal candidiasis and possible urinary tract infection; long-term efficacy and safety data are pending

DPP-4 = dipeptidyl peptidase-4; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; PPARγ = peroxisome proliferator–activated receptor-γ; SGLT2 = sodium glucose co-transporter 2.

Chronic Complications and Their Prevention

- Microvascular complications of diabetes involve the:
  - Kidneys (diabetic nephropathy)
  - Retina (diabetic retinopathy)
  - Peripheral nerves (diabetic neuropathy).

- **Nephropathy:**
  - Recommended that all patients with T1DM and T2DM be tested for **urine albumin excretion with a spot urine sample for albumin-creatinine ratio**
  - **Presence of moderately increased albuminuria (approximately 30-300 mg/g) should prompt initiation of ACEI or ARBs for its renoprotective effects.**
  - Optimizing glycemic control and BP control may reduce the risk and slow the progression of nephropathy.

- **Retinopathy**
  - Responsible for most cases of legal blindness among adults in the United States
  - Early changes (background diabetic retinopathy):
    - Hard exudates
    - Microaneurysms
    - and minor hemorrhages
  - *Mechanism: Although diabetic background retinopathy is not typically associated with any decline in visual acuity, it is associated with retinal infarcts and growth of abnormally fragile blood vessels (neovascularization) that predispose to retinal and vitreous hemorrhage resulting in visual loss.*
  - **Laser photocoagulation** can preserve sight in these individuals.
  - In addition, BP reduction and glycemic control slow the progression of eye disease.

- **Foot ulcers:**
  - foot-care strategies should be instituted for all patients with diabetes, particularly those with documented diabetic neuropathy
  - foot ulcers defined as: Any transdermal interruption of skin integrity, and is predictive of amputation.
  - **patients must be educated about daily foot inspections, appropriate footwear and avoiding barefoot activities, and testing water temperature before bathing.**
  - Orthotic footwear should be prescribed for patients with foot deformities to cushion high-pressure areas.
  - Testing sensation using **a 5.07/10-g monofilament** has been shown to predict ulcer and amputation risk
  - using a 5.07/10-g monofilament have superior predictive value, compared with other sensory test modalities (tuning fork, pinprick, and cotton wisps), for the presence or absence of neuropathic symptoms.

- **Autonomic neuropathy:**
    - Cardiovascular autonomic neuropathy is an often underdiagnosed autonomic neuropathy in diabetic patient that may present with nonspecific symptoms such as exercise intolerance, orthostatic hypotension, or cardiovascular lability.
    - associated with increased risk of silent myocardial ischemia and mortality.
    - Autonomic neuropathy can also involve the genitourinary tract, resulting in neurogenic bladder and, in men, erectile dysfunction and retrograde ejaculation.
    - optimal glycemic control can prevent the development of neuropathies. However, once neuropathies are present, glycemic control can only slow progression but not reverse the disease process.

- **To reduce the risk of macrovascular complications, BP and cholesterol levels should be aggressively managed.**
    - **ADA guidelines recommends a target BP of <140/80 mm Hg.**
    - Lipid control is usually achieved with the assistance of statin therapy:
        - AHA/ACC guidelines recommend **moderate-intensity statin therapy** (to lower the low-density lipoprotein cholesterol [LDL-C] concentration by 30% to <50%) **in patients with diabetes,**
        - **high-intensity statin therapy** (to lower the LDL-C concentration by ≥50**%**) **if the 10-year cardiovascular risk is ≥7.5% in patients aged 40 to 75 years.**
    - ADA and AHA **recommend aspirin for secondary prevention in patients with a history of myocardial infarction**, vascular bypass, stroke or transient ischemic attack, peripheral arterial disease, claudication, or angina.

Follow-Up

- Glycemic control should be monitored with **HbA_{1c} measurements every 3 to 6 months.**
- **Annual investigations include:**
    - Fasting lipid profile, including LDL-C, triglyceride, high-density lipoprotein cholesterol, and total cholesterol levels
    - Nephropathy: spot urine test for moderately increased albuminuria (microalbuminuria).
    - foot examination at each visit.
    - annual dilated funduscopic examination from a specialist
- Reinforce the key issues of diabetes self-management, hypoglycemia prevention and treatment, appropriate use of medications, blood glucose monitoring, and lifestyle measures.

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