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56. Management of Type 2 Diabetes Mellitus

I. PREVALENCE (CDC 2014 National Diabetes Statistics Report)

A. Diabetes affects 29.1 million people, i.e., 9.3% of the US population. Of these, 8.1 million people have undiagnosed diabetes

B. In 2005–2008, 35% of adults aged over 20 years had prediabetes (50% of adults aged ≥65 years)

Section II through Section VIII summarize the guidelines in the 2014 ADA Standards of Medical Care in Diabetes (Reference 1). Following is a guide to using this chapter:

II. Classification; III. Diagnosis; IV. Management of Prediabetes; V. Diabetes Care; VI. Management of Type 2 Diabetes; VII. Prevention and Management of Diabetes Complications; VIII. Assessment of Common Comorbid Conditions; IX. Medications Used in the Treatment of T2DM; X. Insulin Therapy

II. CLASSIFICATION

A. Type 1 diabetes (T1DM)
1. β-cell destruction, leading to absolute insulin deficiency
2. Immune mediated and idiopathic
3. 95% with genetic marker of human leukocyte antigen DR3 and/or DR4

B. Type 2 diabetes (T2DM)
1. Insulin resistance with progressive insulin secretory defect
2. 50% of patients with T2DM present with end-organ damage at the time of diagnosis
3. As obesity rates in children have climbed, so has the incidence of T2DM among adolescents and children

C. Gestational diabetes (GDM):
1. Diagnosed during pregnancy
2. About 200,000 cases annually

D. Diabetes due to other causes, e.g., genetic defects, cystic fibrosis, drug-induced (such as in the treatment of HIV/AIDS or after organ transplant)

III. DIAGNOSIS

A. The diagnostic criteria for diabetes mellitus have recently been modified to include the use of A1C ≥6.5%
1. The A1C test should be National Glycohemoglobin Standardization Program (NGSP) certified and standardized to DCCT reference assay
2. Use of point-of-care A1C is not recommended at this time as proficiency testing is not mandated for performing the test

B. The ADA criteria for the diagnosis of diabetes are shown in Table 1

Table 1: Diabetes is diagnosed if meeting one of the following criteria:

Criteria	Comments
A1C ≥6.5%*	The A1C test should be certified by the NGSP and standardized to the DCCT assay
FPG ≥126mg/dL*	Fasting is defined as no caloric intake for at least 8 hr
2-h plasma glucose ≥200mg/dL during an OGTT (75-g)*	Use a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
Symptoms of diabetes plus a random plasma glucose ≥200mg/dL	Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing on a different day	

C. Categories of increased risk for diabetes (prediabetes)
1. FPG 100–125mg/dL, or
2. 2-h plasma glucose in the 75-g OGTT 140–199mg/dL, or
3. A1C 5.7–6.4%

D. Criteria for testing for diabetes in asymptomatic adult patients*

1. Testing should be considered in all adults who are overweight (BMI ≥25kg/m^2) and have additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who delivered a baby >9 lb or were diagnosed with GDM
   - Hypertension (≥140/90mmHg or on therapy for hypertension)
   - HDL cholesterol level <35mg/dL (0.90 mmol/L) and/or triglyceride level >250mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - History of CVD
2. In the absence of the above criteria, testing for diabetes should begin at age 45 years
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status

*Source: American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013; 36(1):S14. Table 4. © 2013 by the American Diabetes Association. Used with permission.

E. Testing for type 2 diabetes in asymptomatic children (age ≤18 y)

1. Screening for type 2 diabetes should be considered in children and adolescents who are overweight and have ≥2 additional risk factors for diabetes
2. Overweight is defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height
3. Risk factors:
   - Family history of type 2 diabetes in first- or second-degree relative
   - Race/ethnicity: Native American, African American, Latino, Asian American, Pacific Islander
   - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
   - Maternal history of diabetes or GDM during the child's gestation
4. Initiate testing at age 10 yrs or at onset of puberty, if puberty occurs at a younger age
5. Test every 3 years

F. Diagnosis of Gestational Diabetes Mellitus (GDM)

1. Screen for undiagnosed T2DM at the first prenatal visit in those with risk factors, using standard diagnostic criteria
2. Screen for GDM using one of the two following strategies:
   a. One-step (International Association of Diabetes and Pregnancy Study Groups—IADPSG consensus)
      - Screen at 24–28 weeks of gestation using a 75-g OGTT (oral glucose tolerance test)
      - The OGTT should be performed in the morning after an overnight fast of 8 h or more
      - Measure plasma glucose at fasting and at 1 and 2 h post OGTT
      - Use the diagnostic cut points listed below:
        Fasting: ≥92mg/dL
        1h: ≥180mg/dL
        2h: ≥153mg/dL

   b. Two-step (NIH consensus)
      - Step 1: At 24–28 weeks of gestation, perform a nonfasting 50-g GLT (glucose load test) and measure plasma glucose at 1 h after the load. If ≥140mg/dL, go to step 2
      - Step 2: Perform a 100-g OGTT when the patient is fasting. The diagnosis is

made when the plasma glucose at 3 h after the test is ≥140mg/dL
- The ACOG recommends a lower threshold of 135 mg/dL in high-risk ethnic minorities with higher prevalence of GDM

3. Glycemic goals in pregnant women with GDM:
   Preprandial: ≤95mg/dL, and either:
   1 h postmeal: ≤140mg/dL or
   2 h postmeal: ≤120mg/dL
4. Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using OGTT and nonpregnancy diagnostic criteria
5. Women with a history of GDM should be screened at least every 3 years

IV. MANAGEMENT OF PREDIABETES

A. Effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to ≥150 min/week of moderate activity (such as walking)

B. Metformin therapy especially for those with BMI ≥35 kg/m^2, age <60 yr, and women with prior GDM

C. Assess and treat cardiovascular risk factors

V. DIABETES CARE

A. A complete medical evaluation will assist the health care team to ensure optimal management of the patient with diabetes.

B. Components of a comprehensive diabetes evaluation are listed in Table 2

Table 2: Components of the Comprehensive Diabetes Evaluation

Medical history
- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, medication adherence and barriers thereto, meal plan, physical activity patterns, and readiness for behavior change
- Results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycemic episodes
  - Hypoglycemia awareness
  - Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications
  - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
  - Macrovascular: CHD, cerebrovascular disease, and PAD
  - Other: psychosocial problems*, dental disease*

Physical examination
- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination*
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination
- Inspection
- Palpation of dorsalis pedis and posterior tibial pulses
- Presence/absence of patellar and Achilles reflexes
- Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation
- A1C, if results not available within past 2–3 months

If not performed/available within past year
- Fasting lipid profile, including total, LDL and HDL cholesterol and triglycerides
- Liver function tests
- Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
- Serum creatinine and calculated GFR
- TSH in type 1 diabetes, dyslipidemia or women over age 50 years

Referrals
- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- DSME
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed

*See appropriate referrals for these categories.

Source: American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013; 36(1):S17. Table 7. © 2013 by the American Diabetes Association. Used with permission.

VI. MANAGEMENT OF TYPE 2 DIABETES INC. HBA1C GOAL

A. Glycemic control

1. Glycemic goals (A1C and capillary plasma glucose) should be individualized based on:
   - Duration of diabetes
   - Age/life expectancy
   - Comorbid conditions
   - Known CVD or advanced microvascular complications
   - Hypoglycemia unawareness
   - Individual patient considerations
2. A1C goal
   - A1C goal <7% for most adult patients: Lowering A1C to ≤7% has been shown to reduce microvascular complications of diabetes. Its effect on the risk of macrovascular disease especially in well-established diabetes is less certain
   - A1C <6.5% for selected patients if implemented safely, without significant hypoglycemia
   - A1C <8% for older patients with a history of severe hypoglycemia, or those with long-standing diabetes and cardiovascular disease
3. Frequency of A1C testing
   - Patients who are meeting treatment goals: at least 2 ×/yr
   - Patients whose therapy has changed or who are not meeting glycemic goals: every 3 months
4. Correlation of A1C with average glucose:

A1C (%)	Mean Plasma Glucose (mg/dL)
6	126
7	154
8	183
9	212
10	240
11	269
12	298

5. Capillary plasma glucose targets
   - Fasting or preprandial glucose: 70–130mg/dL
   - Peak postprandial (1–2 hr after the beginning of the meal) glucose level <180mg/dL
   - Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals
6. Self-monitoring of blood glucose (SMBG)
   - On multiple-dose insulin or insulin pump therapy: SMBG at least before meals and at bedtime; occasionally postprandially, prior to exercise, when low BG is suspected, after treating low BG until normoglycemic, prior to critical tasks such as driving
   - On less frequent insulin injections or noninsulin therapies: SMBG may be used to guide treatment decisions and/or patient self-management
7. Continuous glucose monitoring (CGM) may be used in T1DM, those with hypoglycemia unawareness, and/or those with frequent hypoglycemic episodes

B. Medical Nutrition Therapy (MNT)

1. Refer patients to a registered dietitian who should also be a certified diabetes educator (CDE). Goal is to educate on meal planning and healthy food choices
2. The ADA recommends a balanced diet that is rich in fiber, whole grains, and legumes. Monitor carbohydrate intake. Saturated fat intake should be <7% of total calories. Reduce intake of trans fat
3. Weight loss is recommended for all overweight or obese patients
4. Limit alcohol intake (≤1 drink/day for women, ≤2 drinks/day for men) and take precautions to prevent hypoglycemia

C. Physical activity

1. At least 150 min/wk of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over ≥3 days/wk with no more than 2 consecutive days without exercise
2. If no contraindication, perform resistance training ≥2 times/week

3. High-risk patients should be encouraged to start with short periods of low-intensity exercise and increase the intensity and duration slowly
4. Special populations
   - Patients with diabetic autonomic neuropathy should undergo cardiac evaluation before beginning physical activity that is more intense than what they are accustomed
   - Patients with proliferative diabetic retinopathy (PDR) or severe non-PDR should not do vigorous aerobic or resistance exercise because of the risk of triggering vitreous hemorrhage or retinal detachment
   - Patients with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early
   - Patients with a foot injury or open sore should be restricted to non-weight-bearing activities

D. Diabetes Self-Management Education (DSME)

1. DSME should be provided to all patients when diabetes is diagnosed and as needed thereafter
2. DSME should be provided according to the National Standards for Diabetes Self-Management Education and Support
3. Effective self-management and quality of life are key outcomes of DSME
4. Psychosocial issues should be addressed in DSME
5. DSME also apply to the education and support of people with prediabetes

E. Psychosocial assessment and care

1. Assessment of psychological and social situation should be an ongoing part of the medical management of diabetes
2. Psychosocial screening and follow-up include attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources, and psychiatric history
3. When self-management is poor, consider screen for depression, diabetes-related distress, anxiety, eating disorders, and cognitive impairment

F. Bariatric surgery

1. Adults with T2DM and BMI ≥35kg/m^2, especially if the diabetes or associated comorbidities are difficult to control with lifestyle or drug therapy, may consider bariatric surgery as a weight loss treatment option
2. Benefit of bariatric surgery in patients with T2DM and BMI 30–35 kg/m^2 has not been proven
3. Patients with T2DM who have undergone bariatric surgery need life-long lifestyle support and medical monitoring

G. Immunizations

1. Annual flu vaccination for all diabetic patients (≥6 mo of age)
2. PPSV23 (Pneumovax) vaccination for all diabetic patients (≥2 yr of age)
   - A one-time revaccination at/after age 65 (use a minimum interval of 5 years between PPSV23 doses)
   - Repeat vaccination in those with nephritic syndrome, chronic renal disease, and other immunocompromised states (e.g., after transplantation). Use a minimum interval of 5 years between PPSV23 doses
3. Hepatitis B vaccination for adults aged 19–59 years with diabetes
   - 3-dose series: 0, 1, 6 months
   - Diabetics aged ≥60 yrs may be vaccinated at the clinician's discretion

VII. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. Hypertension (HTN)

1. General information
   - Affects 20–60% of patients with diabetes
   - In T1DM, HTN is often the result of underlying nephropathy
   - In T2DM, HTN usually coexists with other cardiometabolic risk factors
2. Screening
   - Measure BP at every visit
   - Diagnose HTN when BP elevated in 2 separate days

3. Goals
   - <140/80 for most patients
   - <130/80 for younger patients and those without undue treatment burden
   - 110–129/65–79 for pregnant patients with diabetes and chronic HTN
4. Treatment
   - Patients with BP >120/80: lifestyle modification
   - Patients with BP >140/80: lifestyle and drug therapy
   - Lifestyle: weight loss if overweight; DASH (reduce sodium and increase potassium intake; alcohol in moderation; increase physical activity)
   - Drug therapy
     a. The regimen should include either an ACE inhibitor or ARB
     b. ≥2 drugs at maximal doses is generally required to achieve BP goals
     c. Administer ≥1 antihypertensive agents at bedtime
     d. Monitor serum creatinine or eGFR and serum potassium levels if ACE inhibitor, ARB, or diuretics are used
     e. Note: ACE inhibitors and ARBs are contraindicated during pregnancy
     f. Antihypertensive agents that are effective and safe in pregnancy: **Methyldopa, Labetalol, Diltiazem, Clonidine, Prazosin**

B. Dyslipidemia

1. Prevalence
   - Increased in patients with T2DM
   - Contributes to high CVD risk
2. Screening
   - Fasting lipid profile at least annually
   - Adults with low-risk lipid values (LDL<100, HDL >50, TG <150) may repeat lipid assessment every 2 years
3. Treatment
   - Lifestyle modification recommended for patients with diabetes
     a. Reduce saturated fat, *trans* fat, and cholesterol intake
     b. Increase n-3 fatty acids, viscous fiber, and plant stanols/sterols
     c. Weight loss if overweight
     d. Increase physical activity
   - Statin therapy regardless of baseline lipid levels in diabetes patients:
     a. With overt CVD
     b. Without CVD who are >age 40 and have ≥1 other CVD risk factors (family history of CVD, HTN, smoking, dyslipidemia, or albuminuria)
   - Statin therapy for lower-risk patients (e.g., without overt CVD and <40 y/o) with LDL>100mg/dL or in those with multiple CVD risk factors
4. Primary target: LDL
   - In individuals with overt CVD, LDL goal <70mg/dL, using a high dose of a statin, is an option
   - In individuals without overt CVD, LDL goal <100mg/dL
   - If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL of ~30–40% from baseline is an alternative therapeutic goal
5. Triglycerides goal: <150mg/dL
6. HDL goal: Men >40mg/dL; Women >50mg/dL
7. Combination therapy is not generally recommended due to the lack of additional CV benefit above statin therapy alone
8. Note: Statin therapy is contraindicated in pregnancy

C. Antiplatelet agents

1. **Aspirin**: 75–162mg/day
   - Primary prevention
     a. Consider **Aspirin** therapy in those with T1DM or T2DM who are at increased CV risk (10-year risk >10%). This includes most men aged >50 or women aged >60 who have at least one additional major risk factor (family history of CVD, HTN, smoking, dyslipidemia, or albuminuria)
     b. Use clinical judgment to determine the need for **Aspirin** therapy in patients

with moderate CVD risk (10-year 5–10%)

c. **Aspirin** is not recommended in diabetic adults at low CVD risk (10-year risk <5%)

• Secondary prevention: Use **Aspirin** in those with diabetes with a history of CVD

2. **Clopidogrel:** 75mg/day should be used in patients with CVD and documented **Aspirin** allergy
3. **Aspirin** (75–162mg/day) and **Clopidogrel** (75mg/day) as dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome

D. Smoking cessation (See Chapter 39, Smoking Cessation)

1. Advise all patients not to smoke
2. Management: Smoking cessation counseling and other forms of treatment

E. CHD screening and treatment

1. Screening: in asymptomatic patients, routine screening is not recommended
2. Treatment
   - In patients with known CVD, consider **ACE inhibitor**, **Aspirin** and **Statin** therapy
   - In patients with prior MI, continue **β-blockers** for at least 2 years after the event
   - Avoid **Thiazolidinedione (Pioglitazone [Actos])** in patients with symptomatic heart failure
   - **Metformin** may be used in patients with stable CHF if renal function is normal; should be avoided in unstable or hospitalized patients with CHF

F. Nephropathy

1. General information
   - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of ESRD
   - Optimize glucose and BP control to reduce the risk or slow the progression of nephropathy
2. Definitions of abnormalities in albumin excretion
   - Screen for increased urinary albumin excretion with the albumin to creatinine ratio in a random spot collection
   - Normal: <30ug/mg creatinine
   - Increased urinary albumin excretion: ≥30μg/mg creatinine
   - Historically, ratios between 30 and 299 have been called microalbuminuria and ≥300 have been called macroalbuminuria (clinical albuminuria)
   - Exercise within 24 h, infection, CHF, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values
   - 2 of 3 specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed increased urinary albumin excretion or had a progression in albuminuria
3. Screening
   - Annual assessment of urine albumin excretion in:
     a. T1DM with diabetes duration ≥5 years
     b. All T2DM starting at diagnosis
        - Assess serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. Use serum creatinine to estimate GFR and stage the level of chronic kidney disease (CKD), if present
4. Treatment
   - In nonpregnant patients with modestly elevated (30–299mg/day) or higher levels (≥300mg/day) of urinary albumin excretion, an ACE inhibitor or ARB (but not both in combination) is recommended
     a. In hypertensive T1DM with any degree of albuminuria, ACE inhibitors have shown to delay the progression of nephropathy
     b. In hypertensive T2DM with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria
     c. In T2DM with hypertension, macroalbuminuria, and renal insufficiency (serum creatinine>1.5), ARBs have been shown to delay the progression of nephropathy
     d. Monitor serum creatinine and serum potassium when using ACE inhibitors,

ARBs, or diuretics
- Reduction of protein intake:
  a. 0.8–1.0g/kg/day for patients with diabetes and earlier stages of CKD
  b. 0.8g/kg/day in later stages of CKD
- Continue to monitor urine albumin excretion to assess both response to therapy and progression of disease
- Evaluate and manage potential complications of CKD when eGFR <60mL/min/1.73m^2
- Referral to nephrology in patients with advanced kidney disease

G. Retinopathy

1. General information
   - Prevalence is strongly related to the duration of diabetes
   - The most frequent cause of new cases of blindness among adults aged 20–74 years
   - Glaucoma, cataracts and other eye disorders occur earlier and more frequently in diabetic patients
   - Optimize glucose and BP control to reduce the risk or slow the progression of retinopathy
2. Screening
   - T1DM: adults and children aged ≥10 years should have an initial dilated and comprehensive eye exam within 5 years after the onset of diabetes
   - T2DM: initial dilated and comprehensive eye exam shortly after the diagnosis of diabetes
   - Frequency of exam: annually for T1DM and T2DM patients.
     a. Less frequent exams (every 2 yr) may be considered if no retinopathy is present for one or more eye exams
     b. More frequently if retinopathy is progressing
   - High-quality fundus photographs can detect most clinically significant diabetic retinopathy. A trained eye care provider should interpret the images
     a. Retinal photography may be used as a screening tool
     b. It is not a substitute for a comprehensive eye exam
   - Women with pre-existing diabetes who are planning pregnancy or who have become pregnant should have:
     a. A comprehensive eye examination and be educated on diabetic retinopathy
     b. Eye exam should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum
3. Treatment
   - Prompt referral to ophthalmology specialists
   - Laser photocoagulation therapy is indicated to reduce vision loss in high-risk PDR, clinically significant macular edema, and in some cases of severe NPDR
   - Anti-vascular endothelial growth factor (VEG) therapy is indicated for diabetic macular edema
   - Aspirin therapy for cardioprotection does not increase the risk of retinal hemorrhage. **Aspirin** is not contraindicated in patients with retinopathy

H. Neuropathy

1. Screening for distal symmetric polyneuropathy (DPN)
   - All T2DM at diagnosis and at least annually thereafter
   - All D1DM 5 years after the diagnosis and at least annually thereafter
2. Screening for signs and symptoms of cardiovascular autonomic neuropathy (CAN)
   - T2DM: at diagnosis
   - T1DM: 5 years after diagnosis
3. Medications are recommended for the relief of specific symptoms related to painful DPN and autonomic neuropathy. Drugs approved for the treatment of pain related to DPN:
   - **Duloxetine (Cymbalta):** 60mg QD
   - **Pregabalin (Lyrica):** 50mg TID

I. Foot care

1. All patients with diabetes should have an annual comprehensive foot exam to identify risk factors predictive of ulcers and amputations. Foot exam should include:

- Inspection
- Assessment of foot pulse
- Testing for loss of protective sensation (LOPS): 10-g monofilament plus testing any one of the following:
  a. Vibration using tuning fork
  b. Pinprick sensation
  c. Ankle reflexes
  d. Vibration perception threshold

2. All patients with diabetes should receive general foot self-care education
3. A multidisciplinary approach is recommended for patients with foot ulcers and high-risk feet
4. Refer patients who smoke, have LOPS and structural abnormalities, or have history of prior lower-extremity complications to foot care specialists for ongoing monitoring and lifelong surveillance
5. Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI)
6. Refer patients with significant claudication or a positive ABI for further assessment and treatment

VIII. ASSESSMENT OF COMMON COMORBID CONDITIONS

A. Hearing impairment
1. High frequency loss is associated with history of CHD and with peripheral neuropathy
2. Low/mid frequency loss is associated with low HDL and with poor reported health status

B. Obstructive sleep apnea
1. A risk factor for CVD
2. Age-adjusted rates are 4- to 10- fold higher with obesity
3. Prevalence in general population with T2DM may be up to 23% and in obese patients with T2DM exceeding 80%
4. Treatment significantly improves quality of life and BP control

C. Fatty liver disease
1. Unexplained elevation of LFTs is associated with higher BMI, waist circumference, TG, and fasting insulin, and with lower HDL
2. T2DM and HTN are independent risk factors in women
3. Interventions: improve metabolic abnormalities

D. Low testosterone in men
1. Obesity is a major cofounder
2. Screening and treatment of men without symptoms are not recommended

E. Periodontal disease
1. More severe in patients with diabetes than those without diabetes
2. Evidence that periodontal disease treatment improves glycemic control is mixed

F. Cancer: Recommend age- and sex-appropriate cancer screenings and reduce modifiable cancer risk factors

G. Fracture: Avoid **Thiazolidinediones** in patients with T2DM and fracture risk factors

H. Cognitive impairment

I. Depression

IX. MEDICATIONS USED IN THE TREATMENT OF T2DM

A. Criteria for selecting a drug to achieve glycemic targets:
1. A1C reduction needed
2. Effect on weight
3. Risk for hypoglycemia
4. Comorbidities
5. Tolerability
6. Side effect profile
7. Ease of use
8. Cost

B. Pharmacologic treatment

1. Oral therapies (Table 3)
   - **Sulfonylurea**
   - **Meglitinides (Non ulfonylurea)**
   - **Metformin**
   - **Thiazolidinediones (Glitazones)**
   - **Dipeptidyl peptidase-4 (DDP4) inhibitors**
   - **Alpha glucosidase inhibitors**
   - **Bile acid sequestrants (Colesevelam)**
   - **Dopamine-2 agonists (Bromocriptine)**
   - **Sodium-glucose co-transporter 2 (SGLT2)**
2. Oral combination products (Table 4)
3. Parenteral therapies
   - Amylin analog
   - GLP-1 receptor agonists **(Exenatide, Liraglutide)**
   - Insulin (Basal, Bolus, Mixed)—Table 5

C. Therapeutic strategies (Note: For a detailed outline in chart form of this topic, see Figure 2 in the second citation in the References at the end of this chapter, located online at http://care.diabetesjournals.org/content/35/6/1364/F2.expansion.html)

1. Initial drug therapy
   - **Metformin**, if no contraindication, is the preferred and most cost-effective first drug. To minimize GI side effects, Metformin should be started at a low dose with gradual titration
   - If **Metformin** cannot be used, consider another oral drug such as **Sulfonylurea/ Glinide**, **Pioglitazone**, or a **DDP-4 inhibitor**
   - If A1C ≥9%, a combination of two noninsulin agents or with insulin itself may be necessary
   - If patient presents with significant hyperglycemic symptoms and/or has plasma glucose >300–350 mg/dL or A1C ≥10–12%, insulin should be considered at the outset
2. Advancing to dual combination therapy
   - If A1C is not at target after ~3 months of monotherapy, add a second oral agent, a sulfonylurea, TZD, DDP-4 inhibitor, GLP-1 receptor agonist or basal insulin
   - The higher the A1C, the more likely insulin will be required
   - Choice is based on patient and drug characteristics, with the goal to improve glycemic control while minimizing side effects
3. Advancing to triple combination therapy
   - If A1C is not at target after ~3 months of dual therapy, proceed to 3-drug combination
   - Use agents with complementary mechanisms
   - Insulin usually provides the most robust response at this juncture where many patients would have progressive beta-cell loss
4. Transitions to and titrations of insulin
   - Basal insulin (long-acting insulin or NPH) alone is usually the optimal initial insulin regimen in conjunction with 1 or 2 oral agents
     a. Start at a low dose 0.1–0.2 units/kg/day. Depending on the degree of hyperglycemia, larger doses (0.3–0.4 units/kg/day) may be used
     b. Titrate by 1–2 units (or increments of 5–10%) to the daily dose once or twice weekly if FBG > preagreed target
     c. Give long-acting insulin (Lantus or Leremir) once daily or NPH at hs
     d. As the target is neared, dosage adjustments should be more modest and occur less frequently
     e. Downward titration is needed if any hypoglycemia occurs
     f. Daily self-monitoring of blood glucose (SMBG) is important during this phase
   - Prandial or mealtime insulin (typically the rapid insulin analogs)
     a. If FBG is at target but A1C is >7%, add prandial insulin to on-going basal insulin (basal-bolus therapy)

b. First step is to get more SMBG data to verify that postprandial hyperglycemia is occurring (e.g., >180mg/dL)

c. Two approaches

i. Gradual approach over several weeks: Add the first prandial insulin before the biggest meal, often the evening meal. Then, a second prandial insulin can be added before the meal with the next glucose excursion, often breakfast. Finally, a third prandial insulin is added before the smallest meal, often lunch

ii. Progression from basal insulin to a twice-daily premixed insulin (before breakfast and evening meals)

d. Insulin secretagogues (sulfonylureas, meglitinides) are typically stopped once basal-bolus regimens are utilized

Table 3: Oral Drugs For Type 2 Diabetes Mellitus

Drug	Usual Dosage	Efficacy	Adverse Events	Cost/ mo
Sulfonylureas- 2nd generation (↑ insulin secretion)				
Glimepiride (Amaryl, generic) 1, 2, 4 mg tabs	1-4 mg qd	↓ HbA1c: 1.5-2 % ↓ FPG: 50-70 mg/dL No effect on lipids	Hypoglycemia, weight gain	$13-30
Glipizide (Glucotrol, generic 5, 10 mg tabs) (Glucotrol XL, generic 2.5, 5, 10 mg tabs)	10-20 mg qd or 5-20 mg XL qd			$7-28
Glyburide (DiaBeta, Micronase, generic 2.5, 5 mg tabs) (Glynase, generic 1.5, 3, 6 mg tabs)	5-20 mg qd or 1.5-12 mg qd (micronized)			$17-38
Non-sulfonylurea Secretagogues (↑ insulin secretion)				
Nateglinide (Starlix, generic) 60, 120 mg tabs	60-120 mg tid before meals	↓ HbA1c: 1.5-2 % (Prandin); 0.7-1.4 (Starlix) ↓ FPG: 50-70 mg/dL No effect on lipids	Hypoglycemia if a meal is missed, weight gain	$144-150
Repaglinide (Prandin) 0.5, 1, 2 mg tabs	1-4 mg tid before meals			$249-480
Biguanides (↓ hepatic glucose output, ↑ peripheral glucose uptake, ↑ intestinal glucose use)				
Metformin (Glucophage, generic) 500, 850, 1000 mg tabs	500-1000 mg qd-bid	↓ HbA1c: 1.5-2 % ↓ FPG: 50-70 mg/dL ↓ LDL& TG, ↓ weight	Nausea, diarrhea, abdominal pain, metallic taste, lactic acidosis (rare), vit B12 deficiency	$13-36
Metformin ER-24h (Glucophage XL generic, Fortamet, Glumetza) 500, 1000mg tabs	500 -2000 mg qd or 1000 mg bid with meals			$35-140
Thiazolidinediones ("Glitazones") (improve peripheral insulin sensitivity)				
Pioglitazone (Actos, generic) 15, 30, 45 mg tabs	15-45 mg qd	↓ HbA1c: 1.2-1.5% ↓ FPG: 35-40 mg/dL ↑ LDL, HDL	Weight gain, CHF risk, CVD risk (rosiglitazone) peripheral edema, macular edema, fractures risk, bladder cancer (pioglitazone)	$194-294
Rosiglitazone (Avandia) 2, 4, 8 mg tabs (Prescribing restriction-REMS requirement)	4-8 mg qd^			$182-250
Alpha-glucosidase inhibitors (delay carbohydrate absorption)				
Acarbose (Precose, generic) 25, 50, 100 mg tabs	50-100 mg tid with meals	↓ HbA1c: 0.5-1 % ↓ FPG: 20-30 mg/dL	GI disturbances, ↑ LFTs & liver failure (acarbose)	$86-110
Miglitol (Glyset) 25, 50, 100 mg tabs	50-100 mg tid with meals			$118
DPP-4 Inhibitors (↑ insulin secretion and ↓ glucagons secretion)				
Alogliptin (Nesina) 6.25, 12.5, 25 mg	25 mg qd	↓ HbA1c: 0.5-0.8 %	URI, pancreatitis, hypersensitivity, dose adjustment required in renal insufficiency except linagliptin	$270
Linagliptin (Tradjenta) 5 mg tabs	5 mg qd			$270
Saxagliptin (Onglyza) 2.5, 5 mg tabs	2.5-5 mg qd			$270
Sitagliptin (Januvia) 25, 50, 100 mg tabs	100 mg qd			$270
GLP-1 Agonists (injections) (↑ insulin secretion; ↓ glucagons secretion; slows gastric emptying; ↑ satiety)				
Exenatide (Byetta) 250 mcg/mL in 1.2 and 2.4 mL pre-filled pens Exenatide QW (Bydureon): 2 mg vial	5-10 mcg SC bid before breakfast and dinner Bydureon 2 mg SC q 7 d	↓ HbA1c: 0.5-1 %	N/V, diarrhea, acute pancreatitis, thyroid tumor (liraglutide)	$282-385
Liraglutide (Victoza) 6 mg/mL in 3 mL pre-filled pen	1.2-1.8 mg SC qd			$340/ 2 pens
SGLT2 Inhibitors				
Canagliflozin (Invokana) Dapagliflozin (Farxiga)	100-300 mg qd 5-10 mg qd	↓ HbA1c: 0.5-1 %	Myotic genital infections, ↑risk of bladder infection (Dapagliflozin)	$300
Miscellaneous				
Colesevelam (Welchol) 625 mg tabs	3.8 g (6tabs) qd or divided bid	↓ HbA1c: 0.5 %	Constipation, dyspepsia, ↑TG, drug interaction	$245
Bromocriptine (Cycloset) 0.8 mg tabs	1.6-4.8 mg qd	↓ HbA1c: 0.5 %	N/V, fatigue, headache, dizziness, rhinitis	$71-312
Pramlintide (Symlin) 1000 mcg/mL in 1.5 and 2.7 mL pre-filled pens	60-120 mcg SC tid immediately prior to meals	↓ HbA1c: 0.3-0.6 %	N/V, anorexia, headache	$462/ pen

Table 4: Oral Combination Products

Drug (Formulations)	Usual Dosage	Cost/month*
Actoplus Met (pioglitazone/metformin generic) 15/500, 15/850, 15/1000 XR, 30/1000 XR	15/500 mg bid or 15/1000 mg XR qd	$143-429, $156-458 XR
Avandaryl^ (glimepiride/rosiglitazone) 1/4, 2/4, 2/8, 4/4, 4/8 mg tab	1 tab qd	$250
Avandamet^ (rosiglitazone/metformin) 2/500, 4/500, 2/1000, 4/1000 tabs	2/500 mg bid	$130-280
Duetact (glimepiride/pioglitazone, generic) 2/30, 4/30 mg tabs	4/30 mg qd	$130-297
Glucovance (glyburide/metformin, generic) 1.25/250, 2.5/500, 5/500 mg tabs	1 tab bid with meals	$23-101
Jentadueto (linagliptin/metformin) 2.5/500, 2.5/850, 2.5/1000 mg tab	1 tab bid	$135
Kazano (alogliptin/metformin) 12.5/500, 12.5/1000 mg tabs	1 tab bid	$140
Kombiglyze XR (saxagliptin/metformin) 5/500, 2.5/1000, 5/1000 XR tabs	5/1000 mg to 5/2000 mg qd	$230-240
Metaglip (glipizide/metformin, generic) 2.5/250, 2.5/500, 5/500 mg tabs	2.5/500mg or 5/500 mg bid	$34-172
Oseni (alogliptin/pioglitazone) 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg tab	1 tab qd	$274
Prandimet (repaglinide/metformin) 1/500, 2/500 mg	1/500-2/500 mg bid-tid	$95
Janumet (sitagliptin/metformin) 50/500, 50/1000, 50/500 ER, 50/1000 ER, 100/1000 ER mg tabs	50/500 mg bid	$217
Juvisync (sitagliptin/simvastatin) 50/10, 100/10, 50/20, 100/20, 50/40, 100/40 tab	1 tab qd	$271

^The Avandia-Rosiglitazone Medicines Access Program (a REMs program) now restricts Avandia use to patients who have already been on Avandia, or Type 2 diabetics who have not achieved adequate glucose control with the other antidiabetic medications.

*Cost/month with usual dosage range starting with starting dose and going up to max dose, rounded to the nearest dollar, based on price listed at www.goodrx.com (assessed 3/17/2013). Generic prices are used if available.

GEN

Table 5: Types Of Insulin

Insulin Type	Common Insulin Product (Brand Name)	Onset of Action	Time to Peak	Duration of Action	Cost*
Rapid-acting	Lispro (Humalog), aspart (Novolog), glulisine (Apidra)	15-30 min	0.5-1.0 h	4-6 h	$160/v, $300/5 pens
Short-acting	Human Regular (Humulin-R, Novolin-R, ReliOn/Novolin R)	0.5-1 h	2-3 h	6-8 h	$86/v, $25 (ReliOn)
Intermediate	Human NPH (Humulin N, Novolin N, ReliOn/Novolin N)	2-4 h	4-10 h	10-16 h	$86/v, $25 (ReliOn)
Long-acting	Detemir (Levemir)	2-4 h	Flat	17-23 h	$150/v, $250/5 pens
	Glargine (Lantus)	2-4 h	Flat	~24 h	$150/v, $242/5 pens
Premixed Combinations	70% NPH/30% Regular (Humulin 70/30, Novolin 70/30, ReliOn/Novolin 70/30)	0.5-1 h	Dual	10-16 h	$86/v, $25 (ReliOn)
	70% NPA/30% Aspart (Novolog Mix 70/30)	<0.25 h	Dual	10-16 h	$300/5 pens
	75% NPL/25% Lispro (Humulog Mix 75/25)	<0.25 h	Dual	10-16 h	$300/5 pens
	50% NPL/50% Lispro (Humulog Mix 50/50)	<0.25 h	Dual	10-16 h	$300/5 pens

#The time course may vary considerably in different individuals or at different times in the same individual. NPL = neutral protamine lispro; NPA = neutral protamine aspart.

Source: ADA Practical Insulin. 2002 and Manufacturer Product Information

*Cost rounded to the nearest dollar, based on price listed at www.goodrx.com (assessed 3/17/2013). Generic prices are used if available.

Table 6: Which Insulin to Adjust

Out of Range Blood Glucose Value	Insulin Adjustment
Morning fasting blood glucose	PM or bedtime NPH or glargine or detemir
Before lunch	Morning rapid/short-acting insulin
Before dinner	Morning NPH or lunchtime rapid/short-acting insulin
Before bedtime	Dinner rapid/short-acting
During the night (low)	Evening NPH or move dinner NPH to bedtime

X. INSULIN THERAPY

A. Basal-bolus insulin regimens

1. Dosage calculations for multiple dose injection (MDI):
   - *First*, estimate the patient's total daily dose of insulin (TDD)
     TDD = 0.4–0.5 u/kg/d × patient's weight (kg)
   - *Second*, calculate the basal insulin dose
     Glargine or Detemir or NPH dose = TDD × 50%
   - *Third*, calculate the insulin coverage for each meal (HumaLog, Novolog, Regular)
     Pre-meal insulin dose = TDD × 50% ÷ 3
   - *Fourth*, calculate the corrective insulin ratio (supplemental scale)
     1800 ÷TDD = fall in blood glucose per 1 unit of HumaLog or Novolog
     1500 ÷TDD = fall in blood glucose per 1 unit of Regular insulin
     Or use:
     An arbitrary carb: insulin ratio (CIR): 1 unit per 50mg/dL
     An arbitray insulin: carb = 1:15g CHO

B. Twice-daily, mixed insulin regimen

1. Dosage calculations:
   - *First*, estimate the patient's total daily dose of insulin (TDD)
     TDD = 0.4–0.5 u/kg/d × patient's weight (kg)
   - *Second*, calculate the dose before breakfast (AM dose)
     AM dose = TDD × ⅔ (⅔ as NPH and ⅓ as rapid- or short-acting insulin)
   - *Third*, calculate the dose before dinner (PM dose)
     PM dose = TDD × ⅓ (½ as NPH ½ as rapid- or short-acting insulin)

C. Other considerations

1. Use lower starting dosage in patients who have normal weight, physically active, or unusual eating, in elderly or those with severe renal impairment
2. SMBG: fasting, pre-meal or 2 h post-meal, and bedtime
3. Insulin dose adjustment (refer to Table 6)

D. Writing insulin prescriptions and ordering supplies

1. Write insulin name in full. Avoid abbreviation "U" for units
2. Insulin is available in 10mL vials of 100 units/ml concentration. Each vial contains 1000 units
3. Some insulin products are also available in disposable pens (300 U/3mL). They are useful for patients who have difficulty drawing up accurate doses
4. Insulin syringes package in boxes of 100 ($16–26). They are available in sizes of 0.3mL (30 U), 0.5mL (50 U), 1mL (100 U). Needle size: 29, 30, 31 gauge; needle length: 12, 8, 6mm (no pitch if use short needles)
5. Disposable pens require single-use needle tips in 100/box (29, 30, 31, 32 gauge) ($30–40), needle length: 8, 6, 5, 4mm
6. Alcohol wipes in boxes of 200 ($3)
7. Refer the patient for Diabetes Education

CLINICAL PEARLS

- Diabetes mellitus is a progressive disease which requires multidisciplinary treatment approach and ongoing patient self-management of the disease
- Comprehensive CV risk reduction must be a major focus of therapy. Care should be focused on treatment of blood pressure, glycemic control, dyslipidemia, and smoking cessation
- Select appropriate medication management to get to goals
- Glycemic targets and hypoglycemic therapies must be individualized to meet the patient's needs
- Diet and lifestyle modifications are the cornerstone of T2DM treatment
- **Metformin** is recommended as the first-line drug. It is common to require 2–3 drug combinations to achieve glycemic control. Ultimately, many T2DM patients will require insulin therapy

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