4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S52–S76 | https://doi.org/10.2337/dc24-S004

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PERSON-CENTERED COLLABORATIVE CARE

Recommendations

4.1 A person-centered communication style that uses person-centered, culturally sensitive, and strength-based language and active listening; elicits individual preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize health outcomes and health-related quality of life. **B**

4.2 People with diabetes can benefit from a coordinated interprofessional team that may include and is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and behavioral health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the person with diabetes and the care team. The Chronic Care Model (1–3) (see Section 1, "Improving Care and Promoting Health in Populations") is a person-centered approach to care that requires a close working relationship between the person with diabetes and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interprofessional team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, behavioral health professionals, and community partners such as community health workers and community paramedics. Individuals with diabetes and their care partners must assume an active role in their care. Based on the preferences

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2024. *Diabetes Care 2024;47(Suppl. 1):S52–S76*

The BONE HEALTH subsection has received endorsement from the American Society for Bone and Mineral Research.

and values of the person with diabetes, elicited by the care team, the family or support group and health care team together formulate the management plan, which includes lifestyle management (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (**Fig. 4.1**). Treatment goals and plans should be cocreated with people with diabetes based on their individual preferences, values, and goals. This individualized management plan should take into account the person's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, and current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, access to health care services, and life expectancy. People living with diabetes should be engaged in conversation about these aspects of their lives and diabetes management, with routine reassessment as necessary given their changing circumstances across the life span. Various strategies and techniques should be used to support the person's self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Health care professional communication with people with diabetes and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–8). Thus, the goal of communication between health care professionals and people with diabetes is to establish a collaborative relationship and to assess and address self-management barriers without blaming people with diabetes for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (9). The familiar terms noncompliance and nonadherence denote a passive, obedient role for a person with diabetes in "following doctor's orders" that is at odds with the active role people with diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in management and the role systemic factors play may help minimize the person's resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the person said, can help facilitate communication. Perceptions of people with diabetes about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (10–12) and should be goals of ongoing assessment, education, and treatment planning.

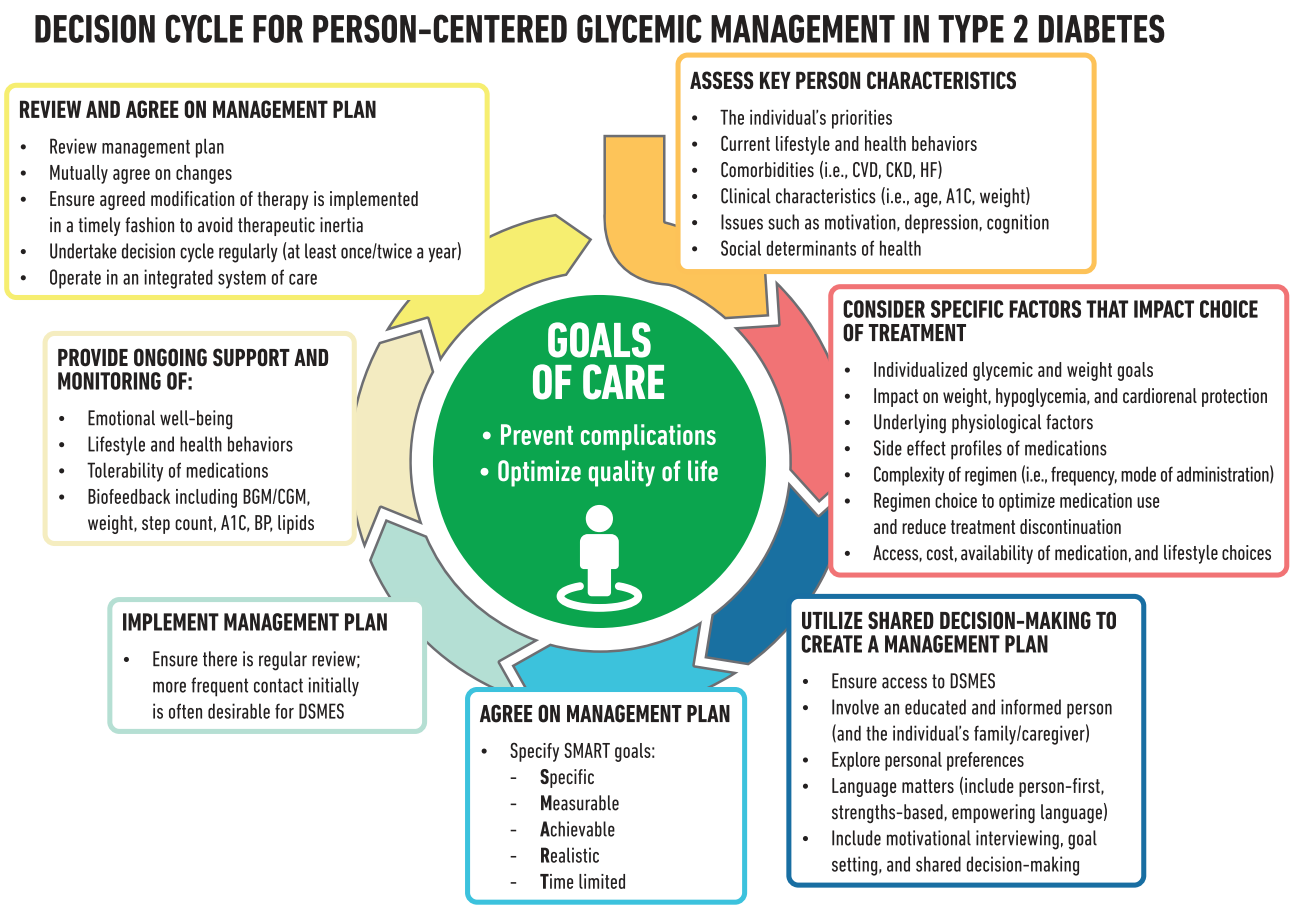

Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (294). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

Language has a strong impact on perceptions and behavior. Empowering language can help to inform and motivate, while shame and judgement can be discouraging. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly called the American Association of Diabetes Educators) joint consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (13). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between people with diabetes and health care professionals.
- Use language that is person centered (e.g., "person with diabetes" is preferred over "diabetic").

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit to:

- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications, potential comorbid conditions, and overall health status. **A**
- Identify care partners and support system. **E**
- Assess social determinants of health and structural barriers to optimal health and health care. **A**
- Review previous treatment and risk factor management in people with established diabetes. **A**
- Begin engagement with the person with diabetes in the formulation of a care management plan including initial goals of care. **A**
- Develop a plan for continuing care. **A**

4.4 A follow-up visit should include most components of the initial comprehensive medical evaluation (**Table 4.1**). **A**

4.5 Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, overall health, functional and cognitive status, and engagement of the person with diabetes throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the health care professional may need to prioritize the components of the medical evaluation given the available resources and time. Engaging other members of the health care team can also support comprehensive diabetes care. The goal of these recommendations is to provide the health care team information so it can optimally support people with diabetes and their care partners. In addition to the medical history, physical examination, and laboratory tests, health care professionals should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered. Interval follow-up visits should occur at least every 3–6 months individualized to the person and then at least annually.

Lifestyle management and behavioral health care are cornerstones of diabetes management. People with diabetes should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of behavioral health concerns as appropriate. People with diabetes should receive recommended preventive care services (e.g., immunizations and cancer screening); smoking cessation counseling; and ophthalmological, dental, podiatric, and other referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, "Cardiovascular Disease and Risk Management"), chronic kidney disease staging (see Section 11, "Chronic Kidney Disease and Risk Management"), presence of retinopathy and presence of neuropathy (see Section 12, "Retinopathy, Neuropathy, and Foot Care"), and risk of treatment-associated hypoglycemia should be used to individualize goals for glycemia (see Section 6, "Glycemic Goals and Hypoglycemia"), blood pressure, and lipids and to select specific glucose-lowering medication(s) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"), antihypertension medication(s), and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.3**). Clinicians should ensure that people with diabetes are appropriately screened for complications, comorbidities, and treatment burden. Discussing and implementing an approach to glycemic management with the person is a part, not the sole goal, of the clinical encounter.

IMMUNIZATIONS

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.4**). **A**

Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (14,15). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.4** for selected vaccinations. The ACIP evidence review has evolved over time with the adoption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks in 2020 (16). Here, we discuss the particular importance of specific vaccines.

COVID-19

People with underlying medical conditions, including diabetes, are more likely

Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment plans and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam			✓
	▪ Visits to specialists			✓
	▪ Disability assessment and use of assistive devices (e.g., physical, cognitive, vision and auditory, history of fractures, podiatry)	✓	✓	✓
	▪ Personal history of autoimmune disease	✓		
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓
BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors; screen for obstructive sleep apnea	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication plan	✓	✓	✓
	▪ Medication-taking behavior, including rationing of medications and/or medical equipment	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
SOCIAL LIFE ASSESSMENT	**Social network**			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓
	▪ Assess daily routine and environment, including school/work schedules and ability to engage in diabetes self-management	✓	✓	✓

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Table 4.1 (cont.) - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination	✓		✓
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓	✓	✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, diabetes distress, fear of hypoglycemia, and disordered eating	✓		✓
	▪ Consider assessment for cognitive performance*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
	▪ Consider assessment for bone pain	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in people with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Complete blood count (CBC) with platelets	✓		✓
	• Serum potassium levels in people with diabetes on ACE inhibitors, ARBs, or diuretics+	✓		✓
	• Calcium, vitamin D, and phosphorous for appropriate people with diabetes	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; PAD, peripheral arterial disease.

*At 65 years of age or older.

+May be needed more frequently in people with diabetes with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see **Table 11.1**).

#May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications).

^In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent.

**Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations.

to become severely ill with coronavirus disease 2019 (COVID-19) (see DIABETES AND COVID-19 section below). COVID-19 vaccinations and boosters are recommended for everyone ages 6 months and older in the U.S. for the prevention of COVID-19 (17).

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis. Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged <60 years. For adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection (18).

Influenza

Influenza is a common, preventable infectious disease associated with high mortality

Table 4.2—Assessment and treatment plan

Assessing risk of diabetes complications • ASCVD and heart failure history • ASCVD risk factors and 10-year ASCVD risk assessment • Staging of chronic kidney disease (see **Table 11.1**) • Hypoglycemia risk (see Section 6, "Glycemic Goals and Hypoglycemia") • Assessment for retinopathy • Assessment for neuropathy • Assessment for NAFLD/NASH
Goal setting • Set A1C/blood glucose/time in range • If hypertension is present, establish blood pressure goal • Weight management and physical activity goals • Diabetes self-management goals
Therapeutic treatment plans • Lifestyle management • Pharmacologic therapy: glucose lowering • Pharmacologic therapy: cardiovascular and kidney disease risk factors • Weight management with pharmacotherapy or metabolic surgery, as appropriate • Use of glucose monitoring and insulin delivery devices • Referral to diabetes education, behavioral health, and medical specialists

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (19). In people with diabetes and cardiovascular disease, influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (20). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for people who are 2–49 years of age and who are not pregnant, but people with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals ≥65 years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (21).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for pneumococcal infection and have been reported to have a high risk of hospitalization and death, with a mortality rate as high as 50% (22). There are two types of vaccines available in the U.S., pneumococcal conjugate vaccines (PCV13, PCV15, and PCV20) and pneumococcal polysaccharide vaccine (PPSV23), with distinct schedules for children and adults.

It is recommended that all children receive a four-dose series of PCV13 or PCV15 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6 and 18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

Adults aged ≥65 years whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. If PCV15 is used, it should be followed by PPSV23.

Adults aged 19–64 years with certain underlying risk factors or other medical conditions whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. As for adults aged ≥65 years, if PCV15 is used, it should be followed by PPSV23.

The recommended interval between PCV15 and PPSV23 is ≥1 year. If PPSV23 is the only dose received, PCV15 or PCV20 may be given ≥1 year later.

For adults with immunocompromising conditions, cochlear implant, or cerebrospinal fluid leak, a minimum interval of 8 weeks can be considered for dosing of PCV15 and PPSV23 when PCV15 has been used.

Adults who received PCV13 should follow the previously recommended PPSV23 series (23–26). Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a cause of respiratory illness in older adults. People with chronic conditions such as diabetes have a higher risk of severe illness. The Food and Drug Administration (FDA) approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years. On 21 June 2023, ACIP voted to recommend that adults aged ≥60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making. The ACIP Respiratory Syncytial Virus Vaccines Adult Work Group continues to monitor the efficacy

Table 4.3—Referrals for initial care management

• Eye care professional for annual dilated eye exam
• Family planning for individuals of childbearing potential
• Registered dietitian nutritionist for medical nutrition therapy
• Diabetes self-management education and support
• Dentist for comprehensive dental and periodontal examination
• Behavioral health professional, if indicated
• Audiology, if indicated
• Social worker/community resources, if indicated
• Rehabilitation medicine or another relevant health care professional for physical and cognitive disability evaluation, if indicated
• Other appropriate health care professionals

Table 4.4—Highly recommended immunizations for adults with diabetes (Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention)

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
COVID-19	Recommended for all 6 months of age and older	Current initial vaccination and boosters		Centers for Disease Control and Prevention, Interim Clinical Considerations for Use of COVID-19 Vaccines, 2023 (295)
Hepatitis B	Recommended for adults with diabetes aged <60 years; for adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection			Weng et al., Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (18)
Influenza	All people with diabetes advised not to receive live attenuated influenza vaccine	Annual		Centers for Disease Control and Prevention, Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2023–24 Influenza Season (296)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) (23)
	≥65 years of age	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (24)
PCV20 or PCV15	Adults 19–64 years of age, with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose of PCV15 or PCV20 is recommended by the Centers for Disease Control and Prevention	3	Kobayashi et al., Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (25)
	19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the CDC recommends one dose of PCV15 or PCV20		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care professionals	One dose of PCV15 or PCV20; PCSV23 may be given ≥8 weeks after PCV15; PPSV23 is not indicated after PCV20		
RSV	Older adults ≥60 years of age with diabetes appear to be a risk group	Adults aged ≥60 years may receive a single dose of an RSV vaccine		Centers for Disease Control and Prevention, CDC Recommends RSV Vaccine for Older Adults (29)
Tetanus, diphtheria, pertussis (Tdap)	All adults; pregnant individuals should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (297)

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Table 4.4—Continued

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (298)

For a comprehensive list of vaccines, refer to the Centers for Disease Control and Prevention web site at cdc.gov/vaccines/. Advisory Committee on Immunization Practices recommendations can be found at cdc.gov/vaccines/acip/recommendations. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV 20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1, randomized controlled trials (RCTs) or overwhelming evidence from observational studies; 2, RCTs with important limitations or exceptionally strong evidence from observational studies; 3, observational studies or RCTs with notable limitations; 4, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

of these vaccines among adults aged ≥60 years (27–29).

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and people with diabetes need to be aware of common comorbidities that affect people with diabetes and that may complicate management (30–32). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in people with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendations

4.7 People with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**

4.8 Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (33). Other associated conditions include autoimmune liver disease, primary adrenal insufficiency (Addison disease), collagen vascular diseases, and myasthenia gravis (34–37). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (38). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all people with type 1 diabetes. Screening for celiac disease should be considered in adults with diabetes with suggestive symptoms (e.g., diarrhea, malabsorption, and abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, and iron deficiency anemia) (39,40). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Table 4.5—General and diabetes-specific risk factors for fracture

General risk factors
- Prior osteoporotic fracture
- Age >65 years
- Low BMI
- Sex
- Malabsorption
- Recurrent falls
- Glucocorticoid use
- Family history
- Alcohol/tobacco abuse
- Rheumatoid arthritis

Diabetes-specific risk factors
- Lumbar spine or hip T-score ≤−2.0
- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylurea
- A1C >8%
- Peripheral and autonomic neuropathy
- Retinopathy and nephropathy

Bone Health

Recommendations

4.9 Fracture risk should be assessed in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities. **A**

4.10 Monitor bone mineral density using dual-energy X-ray absorptiometry of high-risk older adults with diabetes (aged >65 years) and younger individuals with diabetes and multiple risk factors every 2–3 years. **A**

4.11 Clinicians should consider the potential adverse impact on bone health when selecting pharmacological options to lower glucose levels in people with diabetes. Prioritizing medications with a proven safety profile for bones is recommended, particularly for those at elevated risk for fractures. **A**

4.12 To reduce the risk of falls and fractures, glycemic management goals should be individualized for people with diabetes at a higher risk of fracture. **C** Prioritize use of glucose-lowering medications that are associated with low risk for hypoglycemia to avoid falls. **E**

4.13 Advise people with diabetes on their intake of calcium and vitamin D to ensure it meets the recommended daily allowance for those at risk for fracture, either through their diet or supplemental means. **B**

4.14 Antiresorptive medications and osteoanabolic agents should be considered for people with diabetes who have low bone mineral density with a T-score ≤−2.0 or have experienced fragility fractures. **B**

Fracture risk has traditionally relied on measurements of bone mineral density (BMD) and the World Health Organization–defined T-score of ≤−2.5 SD. However, it is now established that the consideration of other risk factors improves the categorization of fracture risk (**Table 4.5**). There are factors beyond BMD testing that contribute to bone strength in people with diabetes.

Hip or vertebral fracture with low trauma in people aged ≥65 years is diagnostic for osteoporosis independent of BMD and is one of the strongest risk factors for subsequent fractures, especially in the first 1–2 years after a fracture (41,42). Osteoporotic hip fractures are associated with significant morbidity, mortality, and societal costs (43). It is estimated that 20% of individuals do not survive to 1 year after hip fracture, while 60% do not regain their prior functionality, living with permanent disability (44).

Hip fractures in people with diabetes are associated with higher risk of mortality (28% in women and 57% in men), longer recovery, and delayed healing (45) compared with individuals without diabetes.

Epidemiology and Risk Factors

Age-specific fracture risk is significantly increased in people with type 1 or type 2 diabetes in both sexes, with a 34% increase in fracture risk compared with those without diabetes (46).

Type 1 Diabetes. Fracture risk in people with type 1 diabetes is increased by 4.35 times for hip fractures, 1.83 times for upper limb fractures, and 1.97 times for ankle fractures (47). Fractures occur even at young ages, 10–15 years earlier than they do in people without diabetes, and are less frequent at the vertebral level. Type 1 diabetes is often associated with low bone mass, although BMD underestimates the high risk of fracture observed even in young individuals (47).

Type 2 Diabetes. In people with type 2 diabetes, hip fracture risk is increased by 1.79 times, and risk throughout life is 40–70% higher than in it is in individuals without diabetes (46,48). Fracture risk is increased also in the upper limbs and ankle. Hip fracture risk is increased even at early stages of the disease despite normal or higher BMD (49,50). However, bone loss is accelerated, and low BMD remains an independent risk factor for fractures (51).

Glucose control significantly impacts fracture risk in people with diabetes. A meta-analysis revealed an 8% increased fracture risk per 1% rise in A1C level (risk ratio [RR] 1.08 [95% CI 1.03–1.14]) (52). Poor glycemic control (A1C >9%) over 2 years in individuals with type 2 diabetes correlated with a 29% heightened fracture risk (53). Notably, this risk was higher in the White demographic than in other racial groups. Hypoglycemia also escalated the risk of fractures at the hip and other skeletal sites (RR 1.52 [95% CI 1.23–1.88]) (52). A Japanese study echoed these findings, showing a fracture risk increase (hazard ratio [HR] 2.24 [95% CI 1.56–3.21]) with severe hypoglycemia episodes (54).

Longer disease duration further elevates fracture risk (55); data indicate individuals with T2D for >10 years and those with type 1 diabetes for >26 years face significantly higher fracture risks, which are largely attributed to ensuing microvascular and macrovascular damage affecting the skeleton. Additionally, high fracture risk is seen in people with cardiovascular issues, nephropathy, retinopathy, neuropathy, and frequent falls (45, 56–59).

Certain glucose-lowering medications also factor into fracture risk. Studies have reported increased fracture incidences in women using thiazolidinediones (TZD), with the risk doubling with 1–2 years of TZD use (HR 2.23 [95% CI 1.65–3.01]) (60,61). According to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, reduced risk is noted in women who had discontinued TZD use for 1–2 years (HR 0.57 [95% CI 0.35–0.92]) or >2 years (HR 0.42 [95% CI 0.24–0.74]) compared with current users (62). Furthermore, individuals with type 2 diabetes on insulin (RR 1.49 [95% CI 1.29–1.73]) or sulfonylurea (RR 1.30 [95% CI 1.18–1.43]) treatment exhibit a heightened fracture risk (63).

Screening

Most evidence on screening in individuals at risk for fracture is available from people with type 2 diabetes, while fracture risk prediction in type 1 diabetes has not been explored. Health care professionals should assess fracture history and risk factors in older people with diabetes and recommend measurement of BMD if appropriate according to the individual's age and sex.

Type 2 Diabetes. People with type 2 diabetes have 5–10% higher BMD than people without diabetes. A T-score adjustment of −0.5 has been proposed to improve fracture prediction by dual-energy X-ray absorptiometry (DXA). For example, a T-score ≤−2.0 should be interpreted as equivalent to −2.5 in a person without diabetes (51). Notably, the Fracture Risk Assessment Tool (FRAX), although useful, does not factor in type 2 diabetes; an inclusion of the condition is estimated to mirror the effect of either a 10-year age increase or a 0.5 SD reduction in BMD T-score (64). Fracture risk was higher in large observational studies in participants with diabetes compared with those without diabetes for a given T-score and age or for a given FRAX score (51). Additionally, integrating the diagnosis of rheumatoid arthritis in FRAX can potentially improve fracture risk prediction for people with type 2 diabetes. Growing evidence suggests that fracture risk prediction is enhanced by use of trabecular bone score (64), although such studies are not available for individuals with type 1 diabetes and are based on data from the U.S. or Canada.

In people with type 2 diabetes, in the absence of other comorbidities, DXA scan should be performed at least 5 years after the diagnosis of diabetes, and reassessment is recommended every 2–3 years (64) depending on the screening evaluation and the presence of additional risk factors (**Table 4.5**). According to the European Association for the Study of Obesity (EASO), DXA should be performed every two years in subjects undergoing bariatric-metabolic surgery.

Bone turnover markers are commonly used in clinical practice, although they are suppressed in people with diabetes and have not been shown to predict fracture risk (65).

Type 1 Diabetes. Because hip fracture risk in type 1 diabetes starts to increase after the age of 50, clinicians may consider assessing BMD after the 5th decade of life (47). In people with type 1 diabetes, BMD underestimates fracture risk, but studies do not address the extent of underestimation of fracture risk.

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), regular assessment of bone health using bone densitometry in youth with type 1 diabetes is still controversial and not recommended, but it may be considered in association with celiac disease because of the involvement of inflammatory pathways (66).

Management

Maintaining glucose control and minimizing hypoglycemic episodes are crucial for bone health in people with diabetes. Individuals with prolonged disease, microvascular and macrovascular complications, or frequent hypoglycemic episodes face higher fracture risks and fall risks due to factors like sarcopenia and impaired gait. Health care professionals should advocate moderate physical activity to enhance muscle health, gait coordination, and balance as part of fracture preventive strategies (58,59,67).

Aerobic and weight-bearing exercise should be recommended to counteract the potential negative effect of weight loss on bone; specific guidelines have been published for older adults with type 2 diabetes (68).

Osteoporosis and fracture prevention are first based on measures applied to the general population. All people with diabetes should receive an adequate daily intake of proteins, calcium, and vitamin D, stop smoking, and have regular physical activity (69–71).

Intake of calcium should reflect the age-specific recommendations of the general population and should be obtained through diet and/or oral supplements (72).

The optimal level of 25-hydroxyvitamin D is a matter of controversy (73), although serum levels $\geq$20 ng/mL are generally thought to be sufficient (74). Because diabetes is a risk factor for fractures, other guidelines suggest a goal $>$30 ng/mL (75).

The safe upper limit is also a matter of debate, and there is substantial disagreement over whether to treat to a specified serum level. In the U.S., the recommended daily allowance of vitamin D is 600 IU for people aged 51–70 years and 800 IU for people aged $>$70 years (74). In clinical practice, this dose of supplement is often not enough to reach recommended goals, and higher doses of D2 or D3 may be needed.

Fractures are main determinants of frailty, a predisability condition that should be mitigated with individualized interventions to prevent falls, maintain mobility, and delay disability (68). In many circumstances, conservative management (calcium, vitamin D, and lifestyle measures) are not enough to reduce fracture risk. When pharmacological treatment is needed, medication decision-making strategies are the same as those used for the general population. Antiosteoporosis medications reduce bone resorption (bisphosphonates, selective estrogen receptor modulators, and denosumab), stimulate bone formation (teriparatide and abaloparatide), or have dual actions by stimulating bone formation and reducing bone resorption (romosozumab). These agents improve bone density and reduce the risk of vertebral and nonvertebral fractures. Although there are no studies specifically designed for people with diabetes, data on antiresorptives and osteoanabolic agents suggest similar efficacy in type 2 diabetes compared with individuals without diabetes (76–78). Using individual patient data from randomized trials, antiresorptive therapies show similar effects in people with and without type 2 diabetes for vertebral, hip, and nonvertebral fractures (76). No similar studies of efficacy of antiosteoporosis treatment in people with type 1 diabetes have been published.

Primary Prevention of Fragility Fractures in People With Diabetes. In the general population, a T-score ≤ -2.5 is the threshold to consider pharmacological treatment for osteoporosis. In type 2 diabetes, since T-score underestimates fracture risk (as discussed above), a T-score ≤ -2.0 may be more appropriate for considering initiation of a first-line drug, including bisphosphonates (alendronate, risedronate, and zoledronate) or denosumab.

Denosumab is preferred in individuals with estimated glomerular filtration rate $<$30–35 mL/min/1.73 m^2. Self-management abilities of the person with diabetes should be considered in medication selection, as there can be rebound bone loss with missed doses of denosumab or delays in care. Zoledronic acid may be more appropriate in these cases.

Secondary Prevention of Fragility Fractures. The risk of subsequent fracture in individuals with hip or vertebral fracture is significantly high, especially in the first 1–2 years after a fracture. Antiosteoporosis treatment reduces the risk of fracture in older individuals with prior hip or vertebral fracture.

As in the general population, people with diabetes who experience fragility fracture should *1*) be given the diagnosis of osteoporosis regardless of DXA data and *2*) receive therapy to prevent future fractures (79). Individuals at particularly high risk (or those with multiple comorbidities) should be referred to a bone metabolic specialist. In these cases, a specialist may choose to initiate an osteoanabolic agent to optimize bone formation and reduce immediate fracture risk (80). It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation, if needed, as early as possible, even during hospitalization (79).

There are some additional considerations related to medication selection in people with diabetes. Data from a phase 3 trial and population studies have indicated positive effects of denosumab on fasting glucose and on diabetes prevention. The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial and its 10-year extension have shown that people with diabetes treated with denosumab experience significant improvements in BMD and lower vertebral fracture risk but higher risk of nonvertebral fractures (81). Romosozumab, a newer anabolic medication, may be associated with increased risk of myocardial infarction and stroke, limiting its use in people with diabetes at higher risk for cardiovascular compilations (82,83).

Glucose-Lowering Medications and Bone Health

Care plans for type 2 diabetes treatment should consider individual fracture risk and the potential effect of medications on bone metabolism. Medications other than TZD are advisable for postmenopausal women or elderly men with type 2 diabetes due to their safer bone health profiles. While several studies have shown metformin has a safe profile, special attention

should be paid to the wide use of sulfonylureas because of the high risk of hypoglycemic events and fractures (84). Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have been used in clinical practice for more than 15 years, and both clinical trials and postmarketing data suggest a neutral impact on bone health (85,86). Tirzepatide may play a positive effect through glucose-dependent insulinotropic polypeptide (GIP) receptor agonism, preventing bone loss associated with weight loss (87).

Use of sodium–glucose cotransporter 2 inhibitors has raised some concerns. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study showed that subjects treated with canagliflozin had a significant increase in fracture risk compared with placebo (HR 1.55). Further analyses from the same trial and from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study found a neutral effect on fracture risk (88–91). Although few data are available, use of empagliflozin, ertugliflozin, or dapagliflozin has not been associated with negative effects on bone health (90–92) Use of insulin has been shown to double the risk of hip fractures (84), likely because of higher risk of hypoglycemia, longer duration of the disease, and comorbidities.

In conclusion, glucose-lowering medications with good bone safety profiles should be preferred, especially in the elderly, in people with longer duration of disease, or in people with complications. Aggressive therapeutic approaches should be avoided in the frail and in the elderly to prevent hypoglycemic events and falls.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (93). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (94), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. People with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings, coordinated with their primary health care professional, and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus and negative family history) in a middle-aged or older person may precede the diagnosis of pancreatic adenocarcinoma (95). However, in the absence of other symptoms (e.g., weight loss and abdominal pain), routine screening of all such individuals is not currently recommended. Metformin and sulfonylureas may have anticancer properties. Pioglitazone has mixed data, with a previous concern for bladder cancer association. Recommendations cannot be made at this time (96–98).

Cognitive Impairment/Dementia

Recommendation

4.15 In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (99,100). A meta-analysis of prospective observational studies found that individuals with diabetes had a 43% higher risk of all types of dementia, a 43% higher risk of Alzheimer dementia, and a 91% higher risk of vascular dementia compared with individuals without diabetes (101). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (102). See Section 13, "Older Adults," for a more detailed discussion regarding assessment of cognitive impairment.

Diabetes and COVID-19

Recommendations

4.16 Health care professionals should help people with diabetes aim to achieve individualized glycemic goals to reduce the risk of macrovascular and microvascular risk as well as reduce the risk of coronavirus disease 2019 (COVID-19) and its complications. **B**

4.17 As we move into the recovery phase, diabetes health care services and practitioners should address the impact of the COVID-19 pandemic in higher-risk groups, including minority, socioeconomically deprived, and older populations. **B**

4.18 People with diabetes who have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be followed up in the longer term to assess complications and symptoms of long COVID-19. **E**

4.19 New-onset diabetes cases should receive routine clinic follow-up to determine if the condition is transient. **B**

4.20 There is no clear indication to change prescribing of glucose-lowering therapies in people with diabetes infected by SARS-CoV-2. **B**

4.21 People with diabetes should be prioritized and offered SARS-CoV-2 vaccines and vaccine boosters. **B**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the clinical disease COVID-19, was first reported in December 2019 in China and has disproportionately impacted certain groups, including men, older people, racial and ethnic minority populations, and people with certain chronic conditions, including diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases. COVID-19 is now recognized as a complex multisystem disease with sequelae including widespread insulin resistance, endothelial dysfunction, hematological disorders, and hyperimmune responses (103). There is now evidence of not only direct but also indirect adverse effects of COVID-19 in people with diabetes. Many people with multiple long-term conditions have diabetes, which has also been associated with worse outcomes in people with COVID-19 (104). The association with BMI and COVID-19 mortality is U-shaped in both type 1 and type 2 diabetes (105).

COVID-19 has disproportionately affected certain groups, such as older people and those from some ethnic populations who are known to have high prevalence of chronic conditions such as diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases (106). In people with diabetes, higher blood glucose

levels both prior to and during COVID-19 admission have been associated with poor outcomes, including mortality (107). Type 1 diabetes has been associated with higher risk of COVID-19 mortality than type 2 diabetes (108). The largest study of people with diabetes to date, using whole-population data from England with over 3 million people, reported a higher association for mortality in people with type 1 diabetes than type 2 diabetes (105). Male sex, older age, renal impairment, non-Hispanic White race, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19–related mortality in both type 1 and type 2 diabetes (105).

Much of the evidence for recommendations is from a recent systematic review that was commissioned by the World Health Organization on the latest research evidence on the impact of COVID-19 on people with diabetes (108). The review reported that there are no appropriate data to determine whether diabetes is a risk factor for acquiring SARS-CoV-2 infection. Diabetes is a risk factor for severe disease and death from COVID-19.

Reasons for the higher rates of COVID-19 and severity in minority ethnic groups are complex and could be due to higher prevalence of comorbid conditions (e.g., diabetes), differences in exposure risk (e.g., overcrowded living conditions and essential worker jobs), and access to treatment (e.g., health insurance status, specialist services, and medications), which all relate to longstanding structural inequities that vary by ethnicity (109).

There is now overwhelming evidence that approximately 30–40% of people who are infected with COVID-19 get persistent and sometimes relapsing and remitting symptoms 4 weeks after infection, which has been termed postacute sequelae of COVID-19, post-COVID-19 condition, postacute COVID-19 syndrome, or long COVID (110,111). Currently, data on long COVID specifically in people with diabetes are lacking, and people who have been infected with SARS-CoV-2 should be followed up in the longer term.

There have also been recent reports of development of new-onset diabetes in people who have had COVID-19. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known but may include previously undiagnosed diabetes presenting early or later in the disease trajectory, stress hyperglycemia, steroid-induced hyperglycemia, and possibly direct or indirect effects of SARS-CoV-2 on the β-cell (112). One large U.S. retrospective study of over 27 million people reported that COVID-19 was associated with significantly increased risk of new-onset type 1 diabetes and a disproportionately higher risk in ethnic minority populations (113). Another cross-sectional population-based Canadian study observed a slightly higher but nonsignificant increase in diabetes incidence in children during the pandemic, which may have resulted from delays in diagnosis during the pandemic with a catch-up effect (114). There have been several publications on the risk of diabetic ketoacidosis (DKA) during the pandemic. A German diabetes prospective study using registry data of children and adolescents found an increase in type 1 diabetes in the first 3 months of the first wave, and the frequency of DKA at presentation was significantly higher than those for 2019 (44.7% vs. 24.5%, adjusted RR 1.84) and 2018 (vs. 24.1%, adjusted RR 1.85) as well as the proportion with severe DKA (115). A larger study using national data in England during the first two waves found that rates of DKA were higher than those for preceding years across all pandemic periods studied (116). The study reported lower DKA hospital admissions in people with type 1 diabetes but higher rates of DKA in people with type 1 diabetes and those newly diagnosed with diabetes.

There is also evidence of adverse effects of COVID-19 on behavioral health (117) and health-promoting lifestyles during the pandemic. Some small studies in people with diabetes have reported longer-term psychological impact of SARS-CoV-2 infection, including fatigue and risk of suicide (118). Longitudinal follow-up of the Action for Health in Diabetes (Look AHEAD) study of older adults with type 2 diabetes reported a 1.6-fold higher prevalence for depressive symptoms and 1.8-fold higher prevalence for loneliness during the pandemic compared with prepandemic levels (119). Furthermore, many people with diabetes remain fearful of face-to-face contact due to the possible threat from mutant strains of coronavirus (120). Negative emotions due to the pandemic, including lockdowns, have been associated with reduced motivation, physical inactivity, and sedentary behavior (121). Higher levels of pandemic-related distress have been linked to higher A1C (122). Greater pandemic-related life disruptions have been related to higher distress in parents of youth with diabetes, which may have impacted families from racial and ethnic minority groups to a greater degree than non-Hispanic White families (123). On the other hand, for some youth with type 1 diabetes, increased time at home during the early phases of the COVID-19 pandemic provided opportunities for enhanced family support for diabetes self-management and reduced diabetes-related distress (124).

As we recover from the pandemic, it is essential that we prioritize the highest-risk groups for their routine review and assessment as well as management of their behavioral health and risk factors. Diabetes professional bodies in some countries have published guidance on risk stratification and who to prioritize for diabetes review (125,126). Factors to consider for prioritization should include demographics, socioeconomic status, education levels, established complications, comorbidities, and modifiable risk factors, which are associated with high risk of progression of diabetes-related complications.

Several pharmacoepidemiologic studies have examined the association between glucose-lowering medications and risk of COVID-19 and have reported conflicting findings, although most studies showed a lower risk of mortality with metformin and a higher risk in people on insulin. However, the absolute differences in the risks have been small, and these findings could be due to confounding by indication (127). The gold standard for assessing the effects of therapies is by randomized controlled trial (RCT), and only one RCT, the Dapagliflozin in Patients with Cardiometabolic Risk Factors Hospitalized with COVID-19 (DARE-19), a double-blind, placebo-controlled RCT in people with and without type 2 diabetes with at least one cardiovascular risk factor, has been reported (128). In this study, dapagliflozin was well tolerated and resulted in fewer events of organ dysfunction, but results were not statistically significant for the dual primary outcome of prevention (time to new or worsening organ dysfunction or death) and the hierarchical composite outcome of recovery by 30 days.

It is therefore important that people with diabetes have regular SARS-CoV-2 vaccines (see IMMUNIZATIONS, above, for detailed information on COVID-19 vaccines).

It is unclear currently how often people with diabetes will require booster vaccines. Although limited data are available on COVID-19 vaccination attitudes or uptake in people with diabetes in the U.S. (129), diabetes health care professionals may be in a position to address questions and concerns among people with diabetes and encourage vaccination.

Disability

Recommendation

4.22 An assessment of disability should be performed at each visit for people with diabetes. If a disability is impacting functional ability or capacity to manage their diabetes, a referral should be made to an appropriate health care professional specializing in disability (e.g., physical medicine and rehabilitation specialist, physical therapist, occupational therapist, speech-language pathologist). **E**

A disability is defined as a physical or mental impairment that substantially limits one or more major life activities of an individual (130,131). Activities of daily living (ADLs) and instrumental activities of daily living (IADLs) comprise basic and complex life care tasks, respectively. The capacity to accomplish such tasks serves as an important measure of function. Diabetes is associated with a strong increase in the risk of physical disability, with estimates of the association between diabetes and disability representing up to a 50–80% increased risk of disability for people with diabetes compared with people without diabetes (132). Reviews have shown that lower-body functional limitation was the most prevalent disability (47–84%) among people with diabetes (133,134). In a systematic review and meta-analysis, the presence of diabetes increased the risk of mobility disability (15 studies; odds ratio [OR] 1.71 [95% CI 1.53–1.91]; RR 1.51 [95% CI 1.38–1.64], of IADL disability (10 studies; OR 1.65 [95% CI 1.55–1.74]), and of ADL disability (16 studies; OR 1.82 [95% CI 1.63–2.04]; RR 1.82 [95% CI 1.40–2.36]) (132). Diabetic peripheral neuropathy is a common complication of both type 1 and 2 diabetes and may cause impaired postural balance and gait kinematics (135), leading to functional disability. Furthermore, diabetic peripheral neuropathy may progress to cause debilitating neuropathic pain and nontraumatic lower-limb amputation, which has a devastating effect on quality of life (136). In addition to complications of diabetes from microvascular conditions such as diabetic kidney disease, retinopathy, and peripheral neuropathy, it is important to recognize the disabilities caused by macrovascular complications of diabetes. These macrovascular complications, which include coronary heart disease, stroke, and peripheral arterial disease, can lead to further impairments (133).

An assessment of disability should be performed at each visit and a referral made to an appropriate health care professional specializing in disability (e.g., physical medicine and rehabilitation physician, physical therapist, occupational therapist, or speech-language pathologist). Customized rehabilitation interventions for individuals with a disability from diabetes can recover function, allowing for safe physical activity (137), and improve quality of life (138). Additionally, frailty is commonly associated with diabetes, with progression to disability, morbidity, and mortality in older adults. People with diabetes as well as frailty or disability may contend with comorbid conditions such as hypoglycemia, sarcopenia, falls, and cognitive dysfunction. A thorough medical evaluation is imperative to identify the best approaches to preventative and therapeutic interventions with respect to frailty and diabetes management (139).

Moreover, when treating people with an acquired disability from diabetes, it is vital to consider social determinants of health, race/ethnicity, and socioeconomic status (140). Rates of diabetes-related major amputations have been found to be higher in individuals who are from racial and ethnic minority groups (141), live in rural areas, and are from the lowest socioeconomic regions (142). Addressing the complex challenges faced by individuals with acquired disabilities from diabetes requires a multifaceted approach involving solutions from both within and outside the health care system. By focusing on social determinants of health, health care professionals can develop targeted interventions and establish support systems that cater to the specific needs of this population.

Hepatitis C

Infection with hepatitis C virus (HCV) is associated with a higher prevalence of type 2 diabetes, which is present in up to one-third of individuals with chronic HCV infection. HCV may impair glucose metabolism by several mechanisms, including directly via viral proteins and indirectly by altering proinflammatory cytokine levels (143). The use of newer direct-acting antiviral drugs produces a sustained virological response (cure) in nearly all cases and has been reported to improve glucose metabolism in individuals with diabetes (144). A meta-analysis of mostly observational studies found a mean reduction in A1C levels of 0.45% (95% CI −0.60 to −0.30) and reduced requirement for glucose-lowering medication use following successful eradication of HCV infection (145).

Hyperglycemia

In individuals with diabetes, higher A1C level is associated with lower cognitive function (43,146). A meta-analysis of randomized trials found that tight glycemic control, compared with higher A1C goals, was associated with a slightly lower rate of cognitive decline (147). However, these findings were driven by an older study with an A1C goal of <7.0% in the tight-control arm. Analyses within the ACCORD, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies found that tight glycemic control (targeting A1C <6.0–6.5%) resulted in no differences in cognitive outcomes compared with standard control (147–149). Therefore, intensive glycemic control should not be advised for the improvement of cognitive function in individuals with type 2 diabetes. Additionally, people with type 2 diabetes and dementia are at heightened risk for experiencing hyperglycemic crises (diabetic ketoacidosis and hyperglycemic hyperosmolar state) compared with people without dementia (150), underscoring the importance of supporting diabetes management for individuals experiencing cognitive decline and diminished capacity for self-care.

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. Multiple observational studies of adults with diabetes have found an association

between severe hypoglycemic episodes and cognitive decline or incident dementia (151–155). Decreased cognitive function also increases the risk for severe hypoglycemia, likely through impaired ability to recognize and respond appropriately to hypoglycemic symptoms (152,156,157). Tailoring glycemic therapy and/or liberalizing A1C goals may prevent hypoglycemia in individuals with cognitive dysfunction. See Section 13, "Older Adults," for more detailed discussion of hypoglycemia in older people with type 1 and type 2 diabetes.

Low Testosterone in Men

Recommendation

4.23 In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity or erectile dysfunction, consider screening with a morning serum testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (158,159). Testosterone replacement in men with symptomatic hypogonadism may have benefits, including improved sexual function, well-being, muscle mass and strength, and bone density (160). In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay (161). In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations (161). Please see the Endocrine Society clinical practice guideline for detailed recommendations (161). Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the individual. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men (161). Erectile dysfunction is common in people with diabetes and warrants evaluation (162).

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Screening

Recommendations

4.24a Adults with type 2 diabetes or prediabetes, particularly those with obesity or cardiometabolic risk factors or established cardiovascular disease, should be screened/risk stratified for clinically significant liver fibrosis (defined as moderate fibrosis to cirrhosis) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), even if they have normal liver enzymes. **B**

4.24b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease. **B**

4.25 Adults with type 2 diabetes or prediabetes with an indeterminate or high FIB-4 should have additional risk stratification by liver stiffness measurement with transient elastography or the blood biomarker enhanced liver fibrosis (ELF). **B**

4.26 Adults with type 2 diabetes or prediabetes with indeterminate results or at high risk for significant liver fibrosis (i.e., by FIB-4, liver stiffness measurement, or ELF) should be referred to a gastroenterologist or hepatologist for further workup. Interprofessional care is recommended for long-term management. **B**

Nonalcoholic fatty liver disease (NAFLD) includes a broad spectrum of disease, ranging from macrovesicular hepatic steatosis (with or without mild inflammation) to nonalcoholic steatohepatitis (NASH) to cirrhosis. This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding evaluation) or other secondary causes of hepatic steatosis (163).

Diabetes is a major risk factor for developing NASH, disease progression, and worse liver outcomes (164). Recent studies in adults in the U.S. estimated that NAFLD is prevalent in >70% of people with type 2 diabetes (165–167). This is consistent with studies from other countries (168). NASH is defined histologically as having ≥5% hepatic steatosis and is associated with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (163). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with NAFLD (169) and appears to be a driver for the development of fibrosis. Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis. In the U.S., between 12 and 20% of people with type 2 diabetes have clinically significant fibrosis (≥F2) (165, 166,169), with similar prevalence worldwide (164,168). NASH is a leading cause of hepatocellular carcinoma (HCC) (170, 171) and of liver transplantation in the U.S., with transplant waiting lists being overrepresented by people with type 2 diabetes (172). Clinicians underestimate its prevalence and do not consistently implement appropriate screening strategies, thus missing the diagnosis of the potentially progressive form of NAFLD in high-risk groups, such as those having obesity or type 2 diabetes. This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with proven efficacy in NASH (173,174).

Metabolic dysfunction–associated steatotic liver disease (MASLD) has been proposed to replace the term nonalcoholic fatty liver disease (NAFLD) to identify steatotic liver disease in the presence of at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of steatosis (175). A separate category outside of MASLD, named metabolic dysfunction and alcoholic liver disease (MetALD), was created for circumstances in which alcohol intake is greater than that allowed for NAFLD but less than that attributed to alcoholic liver disease. The new definition of NAFLD aims to remove potential stigma from the term "fatty" when referring to steatosis and to provide a positive diagnosis by means of having a cardiometabolic risk factor as a surrogate for insulin resistance, the metabolic dysfunction believed to be driving the development of steatosis. While the definition may not conflict with the past definition of NAFLD for people with prediabetes or type 2

diabetes (who already have, by definition, one cardiometabolic risk factor), limitations include the need for better validation, as cardiometabolic risk factors may carry different weights and thus some may also have lower specificity as surrogates for insulin resistance (e.g., hypertension). In addition, some people may have insulin resistance and steatosis without cardiometabolic risk factors, something more common in young adults in primary care clinics or even in some lean people with steatohepatitis. Finally, some people with type 2 diabetes or other forms of diabetes may have steatosis with predominantly insulin secretion deficiency, making diabetes a more questionable surrogate for insulin resistance.

The goal of screening for NAFLD is to identify people at risk for adverse health outcomes associated with NASH, such as cirrhosis, HCC, and death from liver disease. This risk is higher in people who have central obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for >6 months) (176,177). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of NASH progression and cirrhosis (178,179), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established.

Individuals with clinically significant fibrosis (≥F2), especially those with type 2 diabetes, have a greater risk of cirrhosis with liver decompensation, HCC, liver transplantation, and all-cause mortality (180–183). Increased mortality associated with NAFLD is attributable not only to cirrhosis and HCC but also to extrahepatic cancer (171), type 2 diabetes (184), and cardiovascular disease (185,186). The estimated relative impact depends on length of follow-up and population studied, among other factors. Emerging evidence suggests that NAFLD increases the risk of chronic kidney disease, particularly when liver fibrosis is present (187,188), although the association of NAFLD with diabetic retinopathy is less clear (189). Early diagnosis is essential to prevent future cirrhosis and complications.

A recent meta-analysis reported a prevalence of NAFLD of 22% in people with type 1 diabetes (190). This risk may be linked to the fact that about one-third of people with type 1 diabetes in the U.S. have obesity (191). However, there is large variability in NAFLD prevalence across studies, and most measured liver fat by ultrasound. In one of the few studies using the gold-standard MRI technique to quantify liver fat, the prevalence of steatosis in a population with type 1 diabetes with low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (192). The prevalence of fibrosis was not established in that study. Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for NAFLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

There is consensus that the fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or with type 2 diabetes in primary care and diabetes clinical settings (168,174,176,177,193–195). See the proposed diagnostic algorithm by an expert group that included ADA representatives in **Fig. 4.2** (174). A screening strategy based on elevated plasma aminotransferases >40 units/L would miss most individuals with NASH in these settings, as clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (165–167,169,196,197). The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals (198), as higher levels are associated with increased liver-related mortality, even in the absence of identifiable risk factors. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). A value of <1.3 is considered low risk of having advanced fibrosis (F3–F4) and for developing adverse liver outcomes, while >2.67 is considered as having a high probability of advanced fibrosis (F3–F4) and increased risk of adverse liver outcomes. FIB-4 predicts changes over time in hepatic fibrosis (199,200) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (201). FIB-4 has reasonable specificity but low sensitivity, hence a negative result rules out fibrosis while a positive result requires confirmatory testing (200,202–205). It has a reasonable specificity and negative predictive value to rule out advanced fibrosis but lacks adequate sensitivity and positive predictive value to establish presence of advanced fibrosis in many cases, which is the reason why people with diabetes often fall in the "indeterminate" (or intermediate) risk group for advanced fibrosis and adverse liver outcomes (when FIB-4 is between 1.3 and 2.67). However, its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). Performance is better in a population with higher prevalence of significant fibrosis (i.e., hepatology clinics) compared with primary care settings. FIB-4 has not been well validated in pediatric populations and does not perform as well in those aged <35 years. In people with diabetes ≥65 years of age, higher cutoffs for FIB-4 have been recommended (1.9–2.0 rather than >1.3) (206,207).

In people with an indeterminate or high FIB-4, additional risk stratification is required with a liver stiffness measurement (LSM) by transient elastography (**Fig. 4.2**) or, if unavailable, by commercial blood fibrosis biomarkers such as the enhanced liver fibrosis (ELF) test (208) or others. Use of a second nonproprietary diagnostic panel is not recommended (i.e., NAFLD fibrosis score and others), as they generally do not perform better than FIB-4 (167,202). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in NAFLD (176,177,209). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) (210–212) and indicates low risk for clinically significant fibrosis. Given the lack of widespread availability of LSM, the ELF test is a good alternative. Individuals with ELF <7.7 are considered at low risk for adverse outcomes. Such individuals with diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years, although the precise time interval remains to be established. If the LSM is >12 kPa, the risk for advanced fibrosis is high and people with diabetes should be referred to the hepatologist (168). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals (204,209,213–215) (**Fig. 4.2**).

Specialists may order additional tests for fibrosis risk stratification (175–177,

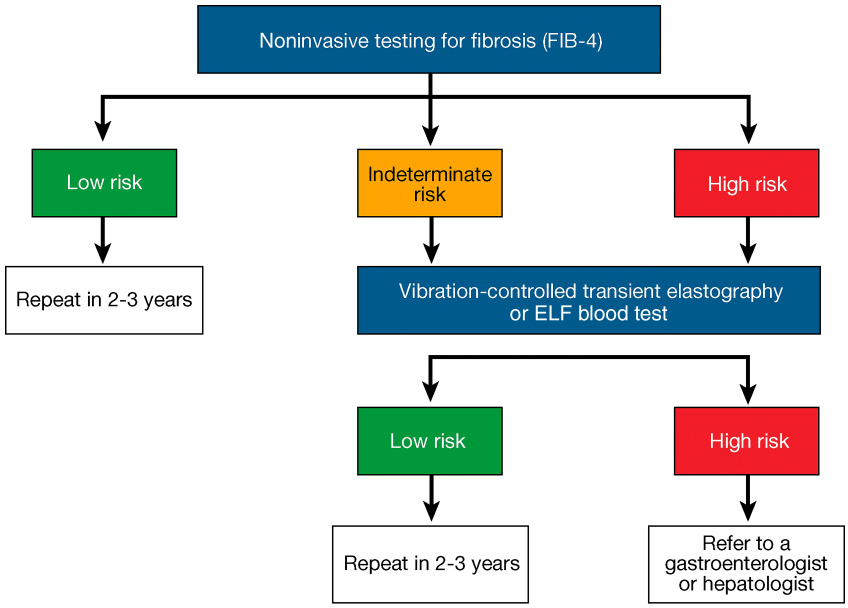

Figure 4.2—A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index. Adapted from Kanwal et al. (174).

195,209), with magnetic resonance elastography (MRE) having the best overall performance (particularly for early fibrosis stages). However, the accessibility and costs associated with MRE are barriers to its use. While liver biopsy remains the gold standard for the diagnosis of NASH, its indication is reserved to the discretion of the specialist within an interprofessional team approach due to high costs and potential for morbidity associated with this procedure.

In 2020, an expert panel convened by the American Gastroenterological Association that included representatives of the ADA reviewed the published literature on the burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD (175). See **Fig. 4.2**, which is adapted from this special report (174). A Clinical Care Pathway summarized the diagnosis and management of NAFLD in a subsequent publication (177). Consensus has emerged to start screening with FIB-4 followed by LSM or ELF and patented biomarkers as needed for the noninvasive fibrosis risk stratification of individuals with NAFLD in primary care and diabetes clinics (167,174,176,177,193–195,216).

After initial risk stratification (i.e., FIB-4, LSM, and/or patented biomarkers), people with diabetes at indeterminate or high risk of fibrosis should be referred, based on practice setting, to a gastroenterologist or hepatologist for further workup within the framework of an interprofessional team (163,176,177,216,217).

Management

Recommendations

4.27 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, with nonalcoholic fatty liver disease (NAFLD) should be recommended lifestyle changes that promote weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits **B** and histological improvement. **C**

4.28 For adults with type 2 diabetes, particularly with overweight or obesity, with NAFLD, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated benefits in nonalcoholic steatohepatitis (NASH) as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.29 Pioglitazone or GLP-1 receptor agonists are the preferred agents for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven NASH or those at high risk with clinically significant liver fibrosis using noninvasive tests. **A**

4.30a In adults with type 2 diabetes and NAFLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 receptor agonists may be continued as clinically indicated, but these therapies lack evidence of benefit in NASH. **B**

4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. **C**

4.31a Adults with type 2 diabetes and NAFLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. **B**

4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from NAFLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. **B** Statin therapy should be used with caution and close monitoring in people with decompensated cirrhosis, given limited safety and efficacy data. **B**

4.32a Consider metabolic surgery in appropriate candidates as an option to treat NASH in adults with type 2 diabetes **B** and to improve cardiovascular outcomes. **B**

4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from NAFLD **B** and is not recommended in decompensated cirrhosis. **B**

While steatohepatitis and cirrhosis occur in lean people with diabetes and are believed to be linked to genetic predisposition, insulin resistance, and environmental factors (218–220), there is ample evidence to implicate excess visceral and overall adiposity in people with overweight and obesity in the pathogenesis of the disease (221,222). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (223). Therefore, clinicians should enact evidence-based interventions (as discussed in Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") to promote healthy lifestyle change and weight loss for people with overweight or obesity and NAFLD. A minimum weight loss goal of 5%, preferably ≥10% (224, 225), is needed to improve liver histology, with fibrosis requiring the larger weight reduction to promote change (225–227). Individualized, structured weight loss and exercise programs offer greater benefit

than standard counseling in people with NAFLD (218,228).

Dietary recommendations to induce an energy deficit are not different from those for people with diabetes with obesity without NAFLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean diet has the best evidence for improving liver and cardiometabolic health (176,193,194, 228–232). Both aerobic and resistance training improve NAFLD in proportion to treatment engagement and intensity of the program (233–235).

Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment for people with type 2 diabetes and NASH is centered on the dual purpose of treating hyperglycemia and obesity, especially if clinically significant fibrosis ($\geq$F2) is present. The rationale for the treatment of people with type 2 diabetes is based on their high prevalence of NASH with significant fibrosis (10–15% of people with type 2 diabetes) (165–169), their higher risk of disease progression and liver-related mortality (164,183,236), and the lack of pharmacological treatments once cirrhosis is established (237). Therefore, early diagnosis and treatment of NAFLD offers the best opportunity for cirrhosis prevention. Pioglitazone and some glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been shown to be effective to treat steatohepatitis (176, 177,238–240) and may slow fibrosis progression (241–243) and decrease cardiovascular disease (177,239), which is the number one cause of death in people with type 2 diabetes and NAFLD (185).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes or type 2 diabetes (244,245) and even without diabetes (246–248). Fibrosis also improved in some trials (245,247). A meta-analysis (241) concluded that pioglitazone treatment results in resolution of NASH and may improve fibrosis. Pioglitazone may halt the accelerated pace of fibrosis progression observed in people with type 2 diabetes (242) and is overall cost-effective for the treatment of NASH (249,250). Vitamin E may be beneficial for the treatment of NASH in people without diabetes (246). However, in people with type 2 diabetes, vitamin E monotherapy was found to be negative in a small RCT (242), and it did not seem to enhance pioglitazone's efficacy when used in combination as reported in an earlier trial in this population (245). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean of 1–2%; 45 mg/day, 3–5%), increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial (163,176,177,239,240).

GLP-1 RAs are effective at inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis (238). However, there are only two RCTs of GLP-1 RAs in biopsy-proven individuals with NASH. A small RCT reported that liraglutide improved some features of NASH and, of particular relevance, delayed the progression of fibrosis (251). More recently, once-daily subcutaneous semaglutide in 320 people with biopsy-proven NASH (62% having type 2 diabetes) reported resolution of steatohepatitis in 59% at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (243). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people (70% of whom had F2 or F3 at baseline), but it significantly slowed over 72 weeks the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide (252), sodium–glucose cotransporter inhibitors (253–255), and insulin (240) reduce hepatic steatosis, but their effects on steatohepatitis remain unknown. The use of glucose-lowering agents other than pioglitazone or GLP-1 RAs may be continued in individuals with type 2 diabetes and NAFLD for glycemic control, as clinically indicated. However, these agents have either failed to improve steatohepatitis in paired-biopsy studies (metformin) or have no RCTs with liver histological end points (i.e., sulfonylureas, glitinides, dipeptidyl peptidase 4 inhibitors, or acarbose).

Insulin is the preferred glucose-lowering agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis given the lack of robust evidence about the safety and efficacy of oral agents and noninsulin injectables (i.e., GLP-1 RAs and GLP-1/GIP RAs) (256), although a recent 48-week study suggested that GLP-1 RAs are safe in individuals with NASH and compensated cirrhosis (257).

Metabolic surgery improves NASH and cardiometabolic health, altering the natural history of the disease (258). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis, 50–75% in inflammation and hepatocyte ballooning (necrosis), and 30–40% in fibrosis (259, 260). It may also reduce the risk of HCC (260). Metabolic surgery should be used with caution in individuals with compensated cirrhosis (i.e., asymptomatic stage of cirrhosis without associated liver complications), but with experienced surgeons the risk of hepatic decompensation is similar to that for individuals with less advanced liver disease. Because of the paucity of safety and outcome data, metabolic surgery is not recommended in individuals with decompensated cirrhosis (i.e., cirrhosis stage with complications such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice) who also have a much higher risk of postoperative development of these liver-related complications (163,176,177).

A number of studies now recognize that adults with type 2 diabetes and NAFLD are at an increased risk of cardiovascular disease and require comprehensive management of cardiovascular risk factors (163,176,177). Within an interprofessional approach, statin therapy should be initiated or continued for cardiovascular risk reduction as clinically indicated. Overall, its use appears to be safe in adults with type 2 diabetes and NASH, including in the presence of compensated cirrhosis (Child-Pugh class A or B cirrhosis) from NAFLD. Some studies even suggest that their use in people with chronic liver disease may reduce episodes of hepatic decompensation and/or overall mortality (261,262). Statin therapy is not recommended in decompensated cirrhosis given limited safety and efficacy data (163,176,177).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity

(263) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (264,265). In participants with obesity enrolled in the Look AHEAD trial, the prevalence exceeded 80% (266). Individuals with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, and witnessed apnea) should be considered for screening (267). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. The evidence for a treatment effect on glycemic control is mixed (268).

Pancreatitis

Diabetes is linked to diseases of the exocrine pancreas, such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of individuals with diabetes may have some degree of impaired exocrine pancreas function (269). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (270).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of individuals after an episode of acute pancreatitis (271); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (272). Studies of individuals treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established (273–275).

Islet autotransplantation should be considered for individuals requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of individuals undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a decade after the surgery in some individuals (276–280). Both person with diabetes and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels (281–283). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (284,285). In an RCT, intensive periodontal treatment was associated with better glycemic outcomes (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (286).

Sensory Impairment

Hearing impairment, both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people (287). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress to cochlear microangiopathy and auditory neuropathy (288). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes than in those without, after adjusting for age and other risk factors for hearing impairment (289). Low HDL cholesterol, coronary heart disease, peripheral neuropathy, and general poor health have been reported as risk factors for hearing impairment for people with diabetes, but an association of hearing loss with blood glucose levels has not been consistently observed (290). In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, increases in the time-weighted mean A1C was associated with increased risk of hearing impairment when tested after long-term (>20 years) follow-up, with every 10% increase in A1C leading to 19% high-frequency impairment (291). Impairment in smell, but not taste, has also been reported in individuals with diabetes (292).

Statins

Systematic reviews of observational studies and randomized trials have found no adverse effects of statins on cognition (293). The FDA postmarketing surveillance databases have also revealed a low reporting rate for cognitive function–related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (293). Therefore, fear of cognitive decline should not be a barrier to statin use in people with diabetes when indicated.

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