4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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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 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 but 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. **C**

A successful medical evaluation depends on beneficial interactions and care coordination between the person with diabetes and the care team (1). The Chronic Care Model (2–4) (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 and values of the person with diabetes, elicited by the care team, the person with diabetes, their family or support group, and the health care team together formulate the management plan, which includes lifestyle management (see Section 5,

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

"Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and pharmacotherapy, as appropriate.

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 co-created by the care team and 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 and coping skills for all aspects of diabetes management.

Communication by health care professionals with people with diabetes and their 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 (5–10). 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 (11). The familiar terms noncompliance and nonadherence denote a passive, obedient role for a person with diabetes in "following doctor's orders," which is at odds with the active role people with diabetes take in 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 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 (12–14) and should be a goal of ongoing assessment, education, and treatment planning.

Language has a strong impact on perceptions and behavior. Empowering language can help to inform and motivate, while shame and judgement can be

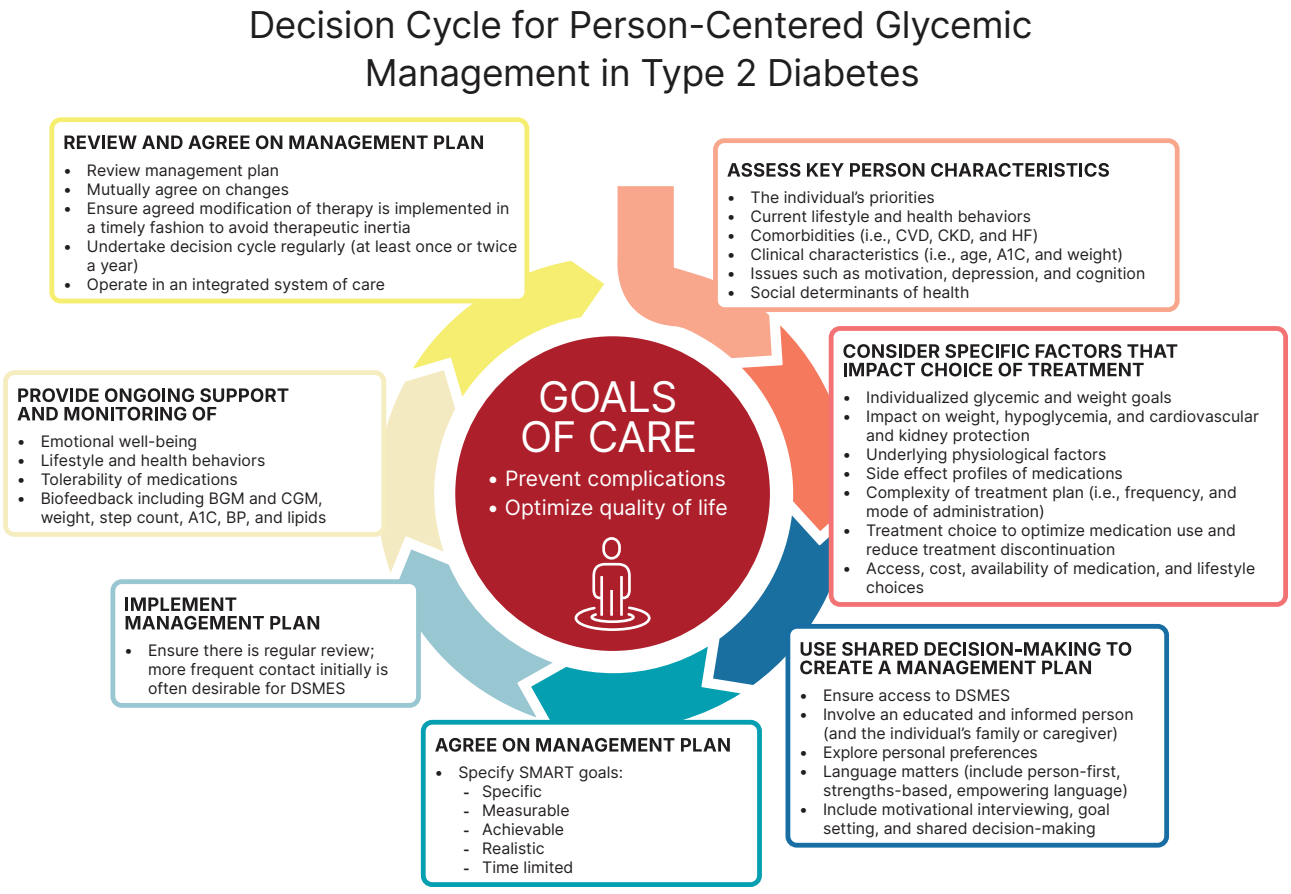

Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure. Adapted from Davies et al. (324).

discouraging. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (ADCES) (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 (15). 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, physiology, or 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 and follow-up, as appropriate, to:

- Confirm the diagnosis and classify diabetes. **A**
- Assess glycemic status and previous treatment. **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 risk factor management in the person with 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 Ongoing management should be guided by the assessment of overall health and functional 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, which comprise 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 also be considered, as this may affect glycemic management. 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 age- and sex-appropriate 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 (CKD) staging (see Section 11, "Chronic Kidney Disease and Risk Management"), presence of retinopathy and 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 medications, and lipid-lowering treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.2**). 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

4.5 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.3**). **A**

Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (16,17). 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 4.3** 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 (18). Here, we discuss the particular importance of specific vaccines.

COVID-19

People with underlying medical conditions, including diabetes, are more likely to become severely ill with coronavirus

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

	Visit		
	Initial	Every follow-up	Annual
Past medical and family history			
Diabetes history			
• Characteristics at onset (e.g., age and symptoms and/or signs)	✓		
• Review of previous treatment plans and response	✓		
• Assess frequency, cause, and severity of past hospitalizations	✓		
Family history			
• Family history of diabetes in a first-degree relative	✓		
• Family history of autoimmune disorders	✓		
Personal history of complications and common comorbidities			
• Common comorbidities (e.g., obesity, OSA, and MASLD)	✓		✓
• High blood pressure or abnormal lipids	✓		✓
• Macrovascular and microvascular complications	✓		✓
• Hypoglycemia: awareness, frequency, causes, and 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, and podiatry)	✓	✓	✓
• Personal history of autoimmune disease	✓		
Surgical and procedure history			
• Surgeries (e.g., metabolic surgery and transplantation)	✓	✓	✓
Interval history			
• Changes in medical or family history since last visit		✓	✓
Behavioral factors			
• Eating patterns and weight history	✓	✓	✓
• Assess familiarity with carbohydrate counting (e.g., type 1 diabetes or type 2 diabetes treated with MDI)	✓		✓
• Physical activity and sleep behaviors; screen for OSA	✓	✓	✓
• 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	✓	✓	✓

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disease 2019 (COVID-19). COVID-19 vaccination using an appropriate number of doses of updated vaccines is recommended for everyone aged 6 months and older in the U.S. (18).

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 of the disease, 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 (19).

Influenza

Influenza is a common, preventable infectious disease associated with high mortality 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 (20). In people with diabetes, the influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (21). 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 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. As of the 2024–2025 season, all influenza vaccines offered in the U.S. are trivalent (22).

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% (23). All people with diabetes should receive one of the CDC-recommended pneumococcal vaccines (24). See details in **Table 4.3**.

Table 4.1—Continued

	Visit		
	Initial	Every follow-up	Annual
• Review insulin pump settings and use and connected pen and glucose data	✓	✓	✓
Social life assessment			
Social network			
• Identify existing social supports	✓		✓
• Identify surrogate decision maker and advanced care plan	✓		✓
• Identify social determinants of health (e.g., food security, housing stability and homelessness, transportation access, financial security, and community safety)	✓		✓
• Assess daily routine and environment, including school or work schedules and ability to engage in diabetes self-management	✓	✓	✓
Physical examination			
• Height, weight, and BMI; growth and 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, and lipodystrophy)	✓	✓	✓
• Comprehensive foot examination	✓		✓
• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, and toenails)*	✓	✓	✓
• Check pedal pulses and screen for PAD with ABI testing if a PAD diagnosis would change management	✓		✓
• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
• Screen for depression, anxiety, diabetes distress, fear of hypoglycemia, and disordered eating	✓		✓
• Assessment for cognitive performance if indicated†	✓		✓
• Assessment for functional performance if indicated†	✓		✓
• Consider assessment for bone health (e.g., loss of height and kyphosis)	✓		✓
Laboratory evaluation			
• A1C, if the results are not available within the past 3 months	✓	✓	✓
• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides‡	✓		✓^
• Liver function tests (i.e., FIB-4)‡	✓		✓
• Spot urinary albumin-to-creatinine ratio	✓		✓
• Serum creatinine and estimated glomerular filtration rate§	✓		✓
• Thyroid-stimulating hormone in people with type 1 diabetes‡	✓		✓
• Celiac disease in people with type 1 diabetes‖	✓		

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Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a cause of respiratory illness in some individuals, including older adults. People with chronic conditions such as diabetes have a higher risk of severe illness. The U.S. Food and Drug Administration (FDA) approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years. On 26 June 2024, ACIP voted to recommend that all adults aged ≥75 years and adults aged 60–74 years who are at increased risk for severe RSV should receive a single dose of RSV vaccine (25).

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 (26–28). 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

4.6 Screen people with type 1 diabetes for autoimmune thyroid disease soon after diagnosis and thereafter at repeated intervals if clinically indicated. **B**

4.7 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 (29). Other autoimmune conditions associated with type 1 diabetes include autoimmune liver disease, primary adrenal insufficiency (Addison disease), vitiligo, collagen vascular diseases, and myasthenia gravis (30–33). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic

Table 4.1—Continued

	Visit		
	Initial	Every follow-up	Annual
• Vitamin B12 if taking metformin for >5 years	✓		✓
• 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 index; ARBs, angiotensin receptor blockers; CBC, complete blood count; CGM, continuous glucose monitor; FIB-4: fibrosis-4 index; MASLD, metabolic-associated steatotic liver disease; MDI, multiple daily injections; OSA, obstructive sleep apnea; PAD, peripheral arterial disease. *Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations. †At 65 years of age or older. ‡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. §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 11.2**). ||In people with presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease.

disorders such as polyglandular autoimmune syndromes (34). 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) (35,36). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Bone Health

Recommendations

4.8 Assess fracture risk in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities. **A**

4.9 Monitor bone mineral density using dual-energy X-ray absorptiometry in older adults with diabetes (aged ≥65 years) and younger individuals with diabetes and multiple risk factors every 2–3 years (**Table 4.4**). **A**

4.10 Consider the potential adverse impact on skeletal health when selecting pharmacological options to lower glucose levels in people with diabetes. Avoiding medications with a known association with higher fracture risk (e.g., thiazolidinediones and sulfonylureas) is recommended, particularly for those at elevated risk for fractures. **B**

4.11 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. **B**

4.12 Advise people with diabetes on their intake of calcium (1,000–1,200 mg/day) 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**

4.13 Antiresorptive medications and osteoanabolic agents should be recommended for older adults with diabetes who are at higher risk of fracture, including those with low bone mineral density with a T-score ≤−2.0, history of fragility fracture, or elevated Fracture Risk Assessment Tool score (≥3% for hip fracture or ≥20% for major osteoporotic fracture). **B**

Determination of fracture risk traditionally has 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 4.4**). There are factors beyond BMD that contribute to bone strength in people with diabetes.

A low-trauma hip/pelvis, vertebral, or forearm fracture 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 (37,38). Osteoporotic hip fractures are associated with significant morbidity, mortality, and societal costs (39). 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 (40).

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 (41) 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 (42).

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 (43). 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 in young individuals (43). Risk of fracture is increased in people with type 1 diabetes with microvascular complications or neuropathy (41). Moreover, average A1C >7.9% (risk ratio [RR] 3.57 [CI 1.08–11.78]), duration of diabetes >26 years (RR 7.6 [CI 1.67–34.6]), and family history of fractures (RR 2.64 [CI 1.15–6.09]) have been independently associated with high risk of nonvertebral fractures (44).

Type 2 Diabetes. In people with type 2 diabetes, even with normal or higher BMD, hip fracture risk is increased by 1.79 times, and risk throughout life is 40–70%

Table 4.2—Essential components for assessment, planning, and referral

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 11.2**)
• Hypoglycemia risk (see Section 6, "Glycemic Targets and Hypoglycemia Prevention")
• Assessment for retinopathy
• Assessment for neuropathy
• Assessment for MASLD and MASH
Goal setting
• Set A1C, blood glucose, and time in range goals
• Set lipid goal
• If hypertension is present, establish blood pressure goal
• Weight management and physical activity goals
• Diabetes self-management goals
Therapeutic treatment plans
• Lifestyle management (e.g., registered dietitian nutritionist)
• 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 and medical specialists (as needed)
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 and 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

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

higher than in it is in individuals without diabetes (42,45–47). According to a meta-analysis that included 15 studies, people with type 2 diabetes had a 35% higher incidence of vertebral fractures, causing increased risk of mortality (HR 2.11 [95% CI 1.72–2.59]) (48). Fracture risk is also increased in the upper limbs and ankle. However, bone loss is accelerated, and low BMD remains an independent risk factor for fractures (49,50).

Glycemic management significantly impacts fracture risk in people with diabetes. A meta-analysis revealed an 8% increased fracture risk per 1% rise in A1C level (RR 1.08 [95% CI 1.03–1.14]) (51). Poor glycemic management (A1C >9%) over 2 years in individuals with type 2 diabetes correlated with a 29% heightened fracture risk (52). Notably, this risk was higher among White individuals 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]) (51). 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 (53).

Longer disease duration further elevates fracture risk (54); data indicate individuals who have had type 2 diabetes for >10 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 disease (CVD), nephropathy, retinopathy, neuropathy, poor physical function, and frequent falls (55–57).

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 compared with placebo or other glucose-lowering medications (HR 2.23 [95% CI 1.65–3.01]) (58,59). 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 (60). 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 (61).

Screening

Most evidence on screening in individuals at risk for fracture is available from people with type 2 diabetes; fracture risk prediction using BMD in type 1 diabetes has not been extensively studied. Health care professionals should assess fracture history and risk factors in 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, although they present with lower bone strength, impaired bone microarchitecture, and accelerated bone loss (49,62–64). 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 (50). 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 (65). 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 (50). One method to potentially improve fracture risk prediction for people with type 2 diabetes involves using the FRAX "rheumatoid arthritis" input as a proxy for diabetes risk (66,67). Additionally, performance of FRAX can be improved by using *1*) trabecular bone score adjustment, *2*) lowering femoral neck T-score input by 0.5 SD, or *3*) increasing the age by 10 years (66). Growing evidence suggests that fracture risk prediction is enhanced by use of trabecular bone score (65,66), although such studies are not available for

Table 4.3—Highly recommended immunizations for adults with diabetes (from the Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention)

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
COVID-19	All people 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 in the United States (318)
Hepatitis B	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 (19)
Influenza	All people with diabetes advised to receive a trivalent influenza vaccine and 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, 2024–25 Influenza Season (22)
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) (24,319)
	≥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 (24,320)
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		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 (24, 321)
	Adults 19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the Centers for Disease Control and Prevention 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 ≥75 years and those aged ≥60 years and at high risk may receive a single dose of an RSV vaccine		Centers for Disease Control and Prevention, CDC Recommends RSV Vaccine for Older Adults (25)
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 (322)

Continued on p. S67

Table 4.3—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 (323)

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.

individuals with type 1 diabetes and are based on data from the U.S. or Canada.

In people with type 2 diabetes, BMD should be monitored by DXA scan in older adults (aged ≥65 years) in the absence of other comorbidities and in younger individuals (>50 years of age) with bone or diabetes-related risk factors, such as insulin use or diabetes duration >10 years (**Table 4.4**). Reassessment is recommended every 2–3 years (65), depending on the screening evaluation and the presence of additional risk factors, although the evidence on how frequently DXA should be repeated is less robust. According to the European Association for the Study of Obesity (EASO), DXA should be performed every 2 years in subjects undergoing bariatric-metabolic surgery.

DXA-assisted vertebral fracture assessment is a convenient and low-cost method to assess vertebral fractures, although traditional lateral thoracic/lumbar spine X-ray is still considered the gold standard (68). MRI or computed tomography imaging studies performed for other purposes should be analyzed for presence of vertebral fractures as well as chest X-rays in hospitalized individuals. Bone turnover markers are commonly used in clinical practice to monitor bone formation and bone resorption, although they are suppressed in people with diabetes and have not been shown to predict fracture risk (69).

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 (43). 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 (70).

Management

Appropriate glycemic management 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 poor vision, neuropathy, 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 (56,57,71).

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 (72).

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 (73–75).

Intake of calcium should reflect the age-specific recommendations for the general population and should be obtained through diet and/or oral supplements (76).

The optimal level of 25-hydroxyvitamin D is a matter of controversy (77), although serum levels 20–30 ng/mL are generally thought to be sufficient (78).

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 (78). In clinical practice, this dose of supplement may not be sufficient to reach recommended serum levels of vitamin D, particularly in those at risk for vitamin D deficiency, and therefore supplementation should be individualized.

Fractures are important determinants of frailty, a predisability condition that should be mitigated with individualized

Table 4.4—Diagnostic assessment

Individuals who should receive BMD testing
People aged ≥65 years
Postmenopausal women and men aged ≥50 years with history of adult-age fracture or with diabetes–specific risk factors: • Frequent hypoglycemic events • Diabetes duration >10 years • Diabetes medications: insulin, thiazolidinediones, sulfonylureas • A1C >8% • Peripheral or autonomic neuropathy, retinopathy, nephropathy • Frequent falls • Glucocorticoid use

interventions to prevent falls, maintain mobility, and delay disability (72). In many circumstances, conservative management (calcium, vitamin D, and lifestyle measures) are not enough to reduce fracture risk. When pharmacological treatment is needed, treatment initiation 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 antiresorptive and osteoanabolic agents suggest efficacy in type 2 diabetes is similar to that for individuals without diabetes (79–81). Using individual participant data from randomized trials, antiresorptive therapies show similar effects in people with and without type 2 diabetes for vertebral, hip, and nonvertebral fractures (79). 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 zoledronic acid) or denosumab.

Denosumab is preferred in individuals with estimated glomerular filtration rate <30–35 mL/min/1.73 m^2, although the FDA has recently issued a boxed warning for increased risk of severe hypocalcemia in individuals with advanced chronic kidney disease. Self-management abilities of the person with diabetes should be considered in medication selection, recommending strict medication-taking behavior, as there can be rebound bone loss causing multiple vertebral fractures with missed doses of denosumab or delays in care. Bisphosphonate therapy (oral or intravenous) may be more appropriate in individuals with poor medication-taking behavior or gaps in access to medical care.

There are some additional considerations related to medication selection in people with diabetes. Data from a phase 3 trial, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM), and its 10-year extension have shown that people with diabetes treated with denosumab experienced positive effects on fasting glucose (82) and significant improvements in BMD and lower vertebral fracture risk (67). However, according to a post hoc subgroup analysis, a higher risk of nonvertebral fractures was observed in people with diabetes treated with denosumab (67). Romosozumab received FDA approval with a box warning because it may increase risk of myocardial infarction, stroke, or cardiovascular death and should not be prescribed in women who experienced a myocardial infarction or a stroke within the past year (83,84).

Secondary Prevention of Fragility Fractures. The risk of subsequent fracture in individuals with hip or vertebral fracture is 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 the appropriate work-up and therapy to prevent future fractures (85). Individuals on long-term treatment with antiosteoporosis medications, with multiple fragility fractures, or with multiple comorbidities should be referred to a bone metabolic specialist. In these more complicated cases, a bone specialist may choose to initiate an osteoanabolic agent to optimize bone formation and reduce immediate fracture risk (86). It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation (if required) as soon as possible. In the appropriate individual, therapy may even be initiated during an inpatient stay to reduce care delays (85).

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 TZDs are advisable for postmenopausal women or older men with type 2 diabetes due to their safer bone health profiles. While several studies have shown metformin to have a safe profile, special attention should be paid to the wide use of sulfonylureas because of the high risk of hypoglycemic events leading to falls and fractures (87). Dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) 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 (88,89). Tirzepatide may play a positive effect through glucose-dependent insulinotropic polypeptide (GIP) receptor agonism, preventing bone loss associated with weight loss (90), although bone outcomes have not yet been reported in clinical data.

Use of sodium–glucose cotransporter 2 (SGLT2) inhibitors has raised some concerns. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study showed that the proportion of subjects with fracture was higher in the canagliflozin groups than the noncanagliflozin groups (2.7% vs. 1.9%, respectively). 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 (91–94). Although few data are available, use of empagliflozin, ertugliflozin, or dapagliflozin has not been associated with negative effects on bone health (93–95). Use of insulin has been shown to be associated with a doubling of the risk of hip fractures (87), likely because of higher risk of hypoglycemia, longer duration of the disease, and comorbidities that may contribute to diminished bone strength.

In conclusion, glucose-lowering medications with a good bone safety profile are preferred. This is especially true in older adults, in people with longer duration of disease, or in people with complications. Aggressive therapeutic approaches should be avoided in those who are frail and in older adults to prevent hypoglycemic events and falls.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon and rectum, breast,

and bladder (96). 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 (97), 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 (98). Additionally, in a nationwide cancer registry in New Zealand, postpancreatitis diabetes mellitus was associated with significantly higher risk (2.4-fold) of pancreatic cancer compared with pancreatitis after type 2 diabetes (99). However, in the absence of other symptoms (e.g., weight loss and abdominal pain), routine screening for pancreatic cancer is not currently recommended. Metformin and sulfonylureas may have anticancer properties. Data for pioglitazone are mixed, with a previous concern for bladder cancer association. Recommendations cannot be made at this time (100–102). Thus far, the use of GLP-1 RAs has not been shown to be associated with the incidence of thyroid cancer, pancreatic cancer, or any other type of cancer in humans (103).

Cognitive Impairment/Dementia

Recommendation

4.14 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 (104). 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 (104). 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 (105). A new clinical entity of diabetes-related dementia is being recognized as distinct from Alzheimer dementia or vascular dementia. It is characterized by slow progression of dementia, absence of typical neuroimaging findings seen in Alzheimer or vascular dementia, old age, high A1C levels, long duration of diabetes, high frequency of insulin use, frailty, and sarcopenia or dynapenia (106). See Section 13, "Older Adults," for a more detailed discussion regarding assessment of cognitive impairment.

Glycemic Status and Cognition

In individuals with diabetes, higher A1C level is associated with lower cognitive function (107). A meta-analysis of randomized trials found that intensive glycemic management, compared with higher A1C goals, was associated with a slightly lower rate of cognitive decline (108). However, these findings were driven by an older study with an A1C goal of <7.0% in the intensive treatment 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 intensive glycemic management (A1C goal of <6.0–6.5%) resulted in no differences in cognitive outcomes compared with standard control (108–110). Therefore, intensive glycemic management 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 (111), underscoring the importance of supporting diabetes management for individuals experiencing cognitive decline and diminished capacity for self-care. In addition, these individuals have increased difficulty with complex treatment and monitoring plans and are at risk of frailty, hypoglycemia, and disability (112).

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe or repeated episodes of hypoglycemia. Multiple observational studies of adults with diabetes have found an association between severe hypoglycemic episodes and cognitive decline or incident dementia (113–116). Decreased cognitive function also increases the risk for severe hypoglycemia, likely through impaired ability to recognize and respond appropriately to hypoglycemic symptoms (113,117,118). Additionally, long-term follow-up of Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) showed recurrent severe hypoglycemia was associated with the highest risk of long-term psychomotor and mental function decline (119). Simplifying or deintensifying 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.

Dental Care

Recommendations

4.15 People with diabetes should be referred for a dental exam at least once per year. **E**

4.16 Coordinate efforts between the medical and dental teams to appropriately adjust glucose-lowering medication and treatment plans prior to and in the post–dental procedure period as needed. **B**

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 (120–122). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, and periodontal treatment using subgingival instrumentation may improve glycemic outcomes (123,124). In a randomized controlled trial (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 (125).

Dental health professionals should be included in the diabetes care team (126). Early detection of oral health problems by clinicians may be helpful to promote prompt referral to dental care and mitigate the expensive and extensive procedures needed to treat advanced oral disease (127,128). Clinical assessment of people with diabetes should include a dental history, and dental professionals should be informed about key aspects of the person's health and diabetes treatment plan, including glycemic goals, medications, and comorbid conditions (127,128). It is important for dental professionals to know when people with diabetes have high A1C levels, as this population may have lower oral healing capacity (129,130). Hepatic, renal, and pulmonary conditions should also be known by dental professionals to assist in appropriate dosing of antibiotics and other medications. Coordination between dental professionals and the diabetes care team will be especially important for people treated with insulin, sulfonylureas, or meglitinides who are at risk of hypoglycemia during dental procedures, especially if fasting. The risk of hypoglycemia can be mitigated by coordination between the dentist and treating clinician prior to the procedure to make a hypoglycemia prevention plan, which may include medication adjustment, blood glucose monitoring before and during the procedure, and treatment of hypoglycemia if appropriate. Therefore, dental professionals caring for people with diabetes should have access to blood glucose monitors during procedures as well as carbohydrates and glucagon to treat any hypoglycemia that occurs.

Disability

Recommendation

4.17 Assess for disability at the initial visit and for decline in function at each subsequent visit in 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, or speech-language pathologist). **C**

A disability is defined as a physical or mental impairment that substantially limits one or more major life activities of an individual (131,132). 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 an increase in the risk of work and physical disability, with estimates of 50–80% increased risk of disability for people with diabetes compared with people without diabetes (133). Reviews have shown that lower-body functional limitation was the most prevalent disability (47–84%) among people with diabetes (134,135). 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]) (133). The mechanisms underlying disability are multifactorial and include obesity, coronary artery disease, stroke, lower extremity complications, and physiological factors such as hyperglycemia, sarcopenia, inflammation, and insulin resistance (136).

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and 2 diabetes and may cause impaired postural balance and gait kinematics (137), leading to functional disability. DPN can be found in up to half of people with type 1 or type 2 diabetes, resulting in physical disability, and neuropathic pain, resulting in a diminished quality of life (138). Glycemic management prevents DPN development in type 1 diabetes; in contrast, glycemic management has modest or no benefit in individuals with type 2 diabetes, possibly due to the combined effect of coexisting comorbidities (138). People with lower-extremity involvement due to DPN have 3 times more risk of restricted mobility, resulting in people with DPN experiencing more physical dysfunctions and impairments than people who have diabetes but not neuropathy (139). Furthermore, DPN may progress to nontraumatic lower-limb amputation, which significantly impacts quality of life (140).

In addition to complications of diabetes from microvascular conditions such as CKD, retinopathy, autonomic neuropathy, 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 (134).

An assessment of disability should be performed as necessary with referrals made to appropriate health care professionals specializing in disability (e.g., physical medicine and rehabilitation physician, physical therapist, occupational therapist, or speech-language pathologist) (133,141,142). Customized rehabilitation interventions for individuals with a disability from diabetes can recover function, allowing for safe physical activity (143), and improve quality of life (144). 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 for frailty and diabetes management (145).

To assess the impact of diabetes on an individual's daily functioning, clinicians should consider evaluating their ability to perform ADLs and IADLs, ensuring they can manage basic self-care and more complex tasks necessary for specific living situations, services, and supports. A psychosocial assessment should be conducted to screen for behavioral health conditions like depression and anxiety and to understand the individual's social support and coping mechanisms. Functional capacity evaluations, involving tests for physical endurance and strength, are used to gauge the ability of the person with diabetes to work and carry out daily activities. Additionally, standardized disability questionnaires and scales, such as the Diabetes Distress Scale (DDS) and the World Health Organization Disability Assessment Schedule (WHODAS 2.0), are employed to measure the emotional burden of diabetes and overall disability (146,147). These suggested structured assessments are particularly relevant if individuals have fallen, had emergency department visits, missed appointments, made significant errors in the treatment plan, or exhibit apathy and depressed mood.

Moreover, when treating people with an acquired disability from diabetes, it is vital to consider social determinants of health, race and ethnicity, and socioeconomic status (148). Rates of diabetes-related major amputations are higher in individuals who are from racial and ethnic minoritized groups (149), live in rural areas, and are from regions with the lowest socioeconomic levels (150). 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 appropriate interventions, provide advocacy, and establish support systems that cater to the specific needs of this population. See Section 1, "Improving Care and Promoting Health in Populations."

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 (151). 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 (152). 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 (153).

Low Testosterone in Men

Recommendation

4.18 In men with diabetes or prediabetes, inquire about sexual health (e.g., low libido and erectile dysfunction [ED]). If symptoms and/or signs of hypogonadism are detected (e.g., low libido, ED, and depression), screen with a morning serum total testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes than in age-matched men without diabetes, but obesity is a major confounder (154,155). Testosterone replacement in men with symptomatic hypogonadism may have benefits, including improved sexual function, well-being, muscle mass and strength, and bone density (156). 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 (157). 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 (157). 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 all men with hypogonadism (157). Furthermore, erectile dysfunction (ED) is also common in people with diabetes (158), and it is reasonable to measure and correct testosterone levels close to the lower limit to address the desire component that contributes to erectile difficulties (159) (see ERECTILE DYSFUNCTION, below, for more information on evaluation and further discussion).

Erectile Dysfunction

Recommendation

4.19 In men with diabetes or prediabetes, screen for ED, particularly in those with high cardiovascular risk, retinopathy, cardiovascular disease, chronic kidney disease, peripheral or autonomic neuropathy, longer duration of diabetes, depression, and hypogonadism, and in those who are not meeting glycemic goals. **B**

The most common sexual dysfunction in men is ED, with an estimated prevalence of 52.5% in men with diabetes (160). The best predictors of ED are age (>40 years), CVD, diabetes, hypertension, obesity, dyslipidemia, metabolic syndrome, hypogonadism, smoking, depression, and use of medications such as antidepressants and opioids (161,162). Because diabetes, poor nutrition, obesity, lack of exercise, and CVD are often interrelated, it may be challenging to identify the primary risk factor (159), although the most likely primary underlying risk factor is vascular disease (159).

Men with diabetes are at increased risk for both CVD and ED, and ED is a predictor of cardiovascular events in men with diabetes (163,164) as well as in men without diabetes. The significant factors associated with ED in men with diabetes are age, peripheral or autonomic neuropathy, presence of microvascular disease including retinopathy, CVD, duration of diabetes, poor glycemic management, hypogonadism, and diuretic therapy (165). Physical activity may be protective. Men with diabetes and ED report a significant decline in quality-of-life measures and an increase in depressive symptoms (166), and depression is a well-recognized risk factor for ED. Given the bidirectional relationship between ED and depression, treatment of either one can result in improvement in the other condition. CKD is also a risk factor for CVD and ED, with prevalence rates of ED >75% in men on hemodialysis (167).

Awareness and identification of these characteristics, factors, and behaviors can guide clinicians in early screening, treatment, prevention, and counseling in all men with diabetes and particularly those at higher risk for ED (165). Given the evidence that ED is strongly associated with diabetes and CVD, men with ED should be evaluated and managed for cardiovascular and endocrine risk factors. Glycemic assessment in men not previously diagnosed with diabetes, lipid profile, and morning total testosterone should be considered mandatory in all men newly presenting with ED (168).

In a recent meta-analysis, testosterone was superior to placebo in improving erectile function in men with testosterone deficiency; however, the magnitude of the effect was lower in the presence of diabetes and obesity (169).

Meta-analyses show that all phosphodiesterase type 5 inhibitors (PDE5Is) are superior to placebo in treating ED, lower dosages had effects comparable with those of higher dosages, and various PDE5Is show comparable efficacy (159). PDE5Is are associated with an increased risk of headaches, flushing, and dyspepsia (159). First-line therapy for ED in men with diabetes is PDE5Is, but men with diabetes may be less responsive than men without diabetes (160). Strategies to improve response to PDE5Is include daily therapy and

optimization of comorbidities. In men with diabetes not responding to PDEIs, other potentially effective treatments may include intracavernosal injections, intraurethral prostaglandin, vacuum erection devices, and penile prosthetic surgery (160).

Female Sexual Dysfunction

Recommendations

4.20 In women with diabetes or prediabetes, inquire about sexual health by screening for desire (libido), arousal, and orgasm difficulties, particularly in those who experience depression and/or anxiety and those with recurrent urinary tract infections. **B**

4.21 In postmenopausal women with diabetes or prediabetes, screen for symptoms and/or signs of genitourinary syndrome of menopause, including vaginal dryness and dyspareunia. **B**

Female sexual dysfunction (FSD) is common in women with diabetes. In an epidemiologic cross-sectional study of community-residing middle-aged and older adults (57–85 years), women with diagnosed diabetes were less likely than men with diagnosed diabetes (adjusted OR 0.28 [95% CI 0.16–0.49]) and women without diabetes (0.63 [0.45–0.87]) to be sexually active (170). Older women with diabetes are as likely as men to have sexual problems but are significantly less likely to have discussed sex with a physician (170).

While studies showing the association between diabetes and FSD are less conclusive than those in men, most have reported a higher prevalence of FSD in women with diabetes compared with women without diabetes (171). A meta-analysis found that sexual dysfunctions are more common in women with type 1 and type 2 diabetes (OR 2.27 and 2.49, respectively) than in women without diabetes (172).

Reviews report a wide range of prevalence rates of sexual dysfunctions in women with diabetes. In women with type 1 diabetes, 16–85% (vs. 0–66% in women without diabetes) report problems with desire, 11–76% (vs. 0–41%) report problems with arousal, and 9–66% (vs. 0–39%) report problems with orgasm; 9–57% (vs. 0–28%) report problems with lubrication, and 7–61% (vs. 5–39%) report problems with pain. In women with type 2 diabetes, 70–82% (vs. 10–66% in women without diabetes) report problems with desire, 54–68% (vs. 3–41%) report problems with arousal, and 33–84% (vs. 2–39%) report problems with orgasm; 33–66% (vs. 4–28%) report problems with lubrication, and 33–46% (vs. 8–39%) report problems with pain (173).

The Diabetes MILES (Management and Impact for Long-term Empowerment and Success) study examined the prevalence of sexual dysfunction in sexually active women with type 1 or type 2 diabetes and the associations between sexual dysfunction and clinical and psychological variables. Overall, 33% of women reported sexual dysfunction (type 1, 36.0%; type 2, 26.2%). The prevalence of specific FSDs according to diabetes type was decreased desire (type 1, 22%; type 2, 15%), decreased arousal (type 1, 9%; type 2, 11%), lubrication problems (type 1, 19%; type 2, 14%), and orgasmic dysfunction (type 1, 16%; type 2, 15%) (173).

Medical comorbidities that are risk factors for FSD include hypertension, obesity, metabolic syndrome, smoking, and hyperlipidemia. Clinical factors for consideration include longer duration of diabetic retinopathy and neuropathy and individuals not meeting glycemic goals. The prevalence of FSD in women with end-stage kidney disease is 74% (174).

In women with diabetes, social and psychological components play a major role in FSD. Depression, anxiety, and emotional adjustments to diabetes have been found to be associated with sexual dysfunctions in women with diabetes. A study from Norway reported that women with type 1 diabetes with scores on the Female Sexual Function Index (FSFI) (a validated instrument) indicating sexual dysfunction were more likely than women without sexual dysfunction to have diabetes distress, depression, and menopausal symptoms. They were also older and more likely to be single and postmenopausal (175). Another study also showed that women with sexual dysfunction were significantly more likely to report impaired well-being, have elevated diabetes distress, have poor adjustment to diabetes, and have more moderate to severe anxiety than women without sexual dysfunctions (173).

In a qualitative study exploring the experiences of sexual health and sexual challenges, women with type 1 diabetes reported that diabetes affected their relationship, including sex life, and had an impact on their partner. Challenges included reduced sexual desire, decline in frequency, less spontaneous desire resulting in lack of initiation, and physical challenges such as pain, vaginal dryness, and impaired sensitivity. Several women explained that vaginal dryness was an obstacle during sexual intercourse, leading to pain or even refraining from sexual activity. Sexual challenges were perceived to become a source of disappointment to the partners and consequential guilt for the women. Women also reported fear of hypoglycemia during sex, and some reported trying to maintain mild hyperglycemia. Technology devices, such as glucose monitors and insulin pumps, could be perceived as both a physical and mental obstacle during sexual activity (176).

Women with type 2 (25%) or type 1 (17%) diabetes would like their health care professional to initiate a discussion on how diabetes is affecting their sex life (177). Women with type 1 diabetes almost unanimously endorsed that sexual health should be addressed, that they would find it a relief that they were not alone, that they should be provided with information when they are young, and that it would be difficult to address the topic themselves (176). Unfortunately, many health care professionals do not actively discuss sexual functioning in consultations, meaning that when the topic is discussed it is mostly the person with diabetes who initiates the conversation (170). This leads to a marked underdiagnosis and undertreatment of sexual dysfunctions in people with diabetes.

While no specific guidelines are available for the treatment of FSD in this population, women with type 1 or type 2 diabetes should be encouraged to engage in lifestyle interventions and, in the absence of contraindications, may benefit from already-approved treatments for FSD (178). The Look AHEAD (Action for Health in Diabetes) study on intervention demonstrated statistical improvements in the FSFI total score and all domains of sexual dysfunction (179). Lifestyle factors that enhance desire and sexual function include nutrition (such as the Mediterranean eating pattern), exercise (such as walking), and smoking cessation. Other interventions include improving glycemic management and prevention of diabetes complications; diagnosis and treatment of menopausal symptoms with hormonal therapies; addressing vaginal dryness and dyspareunia as well as urinary tract and mycotic genital infections; screening and addressing depression, anxiety, diabetes distress, and

related psychosocial issues; and considering FDA-approved centrally acting medications for hypoactive sexual desire disorder, including flibanserin and bremelanotide.

Metabolic Dysfunction–Associated Steatotic Liver Disease and Metabolic Dysfunction–Associated Steatohepatitis

Screening

Recommendations

4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their risk of having or developing cirrhosis related to metabolic dysfunction–associated steatohepatitis (MASH) 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**

4.22b 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**

4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or, if unavailable, the enhanced liver fibrosis (ELF) test. **B**

4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. **B**

Metabolic dysfunction–associated steatotic liver disease (MASLD) has replaced the term nonalcoholic fatty liver disease (NAFLD) to identify steatotic liver disease. The definition includes the presence of steatotic liver disease and at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of steatosis (180). 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 (181). It is estimated that in adults in the U.S., the prevalence of MASLD is >70% of people with type 2 diabetes (182–184). This is consistent with studies from other countries (185,186). The new definition of MASLD aims to remove potential stigma from the term "fatty" when referring to steatosis, highlights the role of prediabetes and type 2 diabetes in MASLD, and provides a positive diagnosis by using cardiometabolic risk factors as surrogates for insulin resistance, the main driver for the development of steatosis. The new definition correlates well with the past definition of MASLD for people with prediabetes or type 2 diabetes (who already have, by definition, one cardiometabolic risk factor) (187,188). A separate category outside of MASLD, named metabolic dysfunction and alcoholic liver disease, was created for circumstances in which alcohol intake is greater than that allowed for MASLD but less than that attributed to alcoholic liver disease. More research is needed to better characterize the predictive value for metabolic dysfunction–associated steatohepatitis (MASH) of different cardiometabolic risk factors and the natural history of metabolic dysfunction and alcoholic liver disease or steatosis in young adults without cardiometabolic risk factors.

Diabetes is a major risk factor for developing MASH (formerly nonalcoholic steatohepatitis, or NASH) and worse liver outcomes (185,186). MASH is defined histologically as having ≥5% hepatic steatosis with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (181). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with MASLD (189,190). 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 "at-risk" MASH (i.e., steatohepatitis with clinically significant fibrosis [≥F2] and at risk for cirrhosis) (182,183,189). A similar or higher prevalence has been observed worldwide (185,186,190). People with type 2 diabetes and at-risk MASH are at an increased risk of future cirrhosis, hepatocellular carcinoma (HCC) (191,192), and liver transplantation (193). The prevalence of MASLD in people with type 1 diabetes is ∼20% and is driven by obesity, which is becoming more common in this population (194), with a large variability across studies using different steatosis measurement methods (195). The prevalence of liver steatosis in a population with type 1 diabetes by MRI (i.e., the gold standard) with low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (196). The prevalence of clinically significant fibrosis (≥F2) is estimated to be ∼5% (197), which is much lower than the prevalence in type 2 diabetes (182,183,189). Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for MASLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

Clinicians underestimate the prevalence of at-risk MASH and do not consistently implement appropriate screening strategies in people with prediabetes or type 2 diabetes, thus missing a chance to establish an early diagnosis (198). This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with potential efficacy in MASH (199,200). The goal of screening for MASLD is to identify people with at-risk MASH to prevent future cirrhosis, HCC, liver transplantation, and all-cause mortality (201–204). 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) (205,206). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of MASH progression and cirrhosis (207,208), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established. Individuals with MASLD also are at a greater risk of developing extrahepatic cancer (192), type 2 diabetes (209), and CVD (210,211). Emerging evidence suggests that MASLD increases the risk of CKD in people with type 2 diabetes, particularly when liver fibrosis is present (212,213), although the association of MASLD with diabetic retinopathy is less clear (214).

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 for at-risk MASH in

primary care and diabetes clinical settings (186,200,205,206,215–217). The diagnostic algorithm for the screening and liver fibrosis risk stratification of people with prediabetes or type 2 diabetes is shown in **Fig. 4.2**. A screening strategy relying on elevated plasma aminotransferases >40 units/L would miss most individuals with MASH in these settings, as at-risk MASH with clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (182–184,189,218,219). 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 (220), as higher levels are associated with increased liver-related mortality. 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 ≥1.3 is considered as having a higher probability of at-risk MASH clinically significant fibrosis (≥F2) and increased risk of adverse liver outcomes. A value of >2.67 confers a high risk of having advanced fibrosis (F3–F4), and referral to the liver specialist is warranted without additional testing. FIB-4 predicts changes over time in hepatic fibrosis (221,222) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (223). FIB-4 has reasonable specificity but low sensitivity, hence a negative result rules out fibrosis while a positive result requires confirmatory testing (222,224,225). Its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). FIB-4 has not been validated in pediatric populations or in adults 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) (226).

In people with a FIB-4 ≥1.3, there is need for additional risk stratification with a liver stiffness measurement (LSM) by transient elastography (**Fig. 4.2**). Use of a second nonproprietary diagnostic panel is not recommended (e.g., MASLD fibrosis score and others), as they generally do not perform better than FIB-4 (181,184,224). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in MASLD (205,206,227). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) (228–230) and indicates lower risk for clinically significant fibrosis. Such individuals with prediabetes or type 2 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 ≥8.0 kPa, the risk for advanced fibrosis (≥F3–F4) is higher and such individuals should be referred to the hepatologist (181,189,205,206) within the framework of an interprofessional team (231–233). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals (227,234–237) (**Fig. 4.2**). Given the lack of widespread availability of LSM, the ELF test is a good alternative (238). Individuals with ELF <9.8 are considered at low risk for adverse liver outcomes. Individuals with ELF ≥9.8 are considered at high risk of having MASH with advanced liver fibrosis (≥F3–F4) and

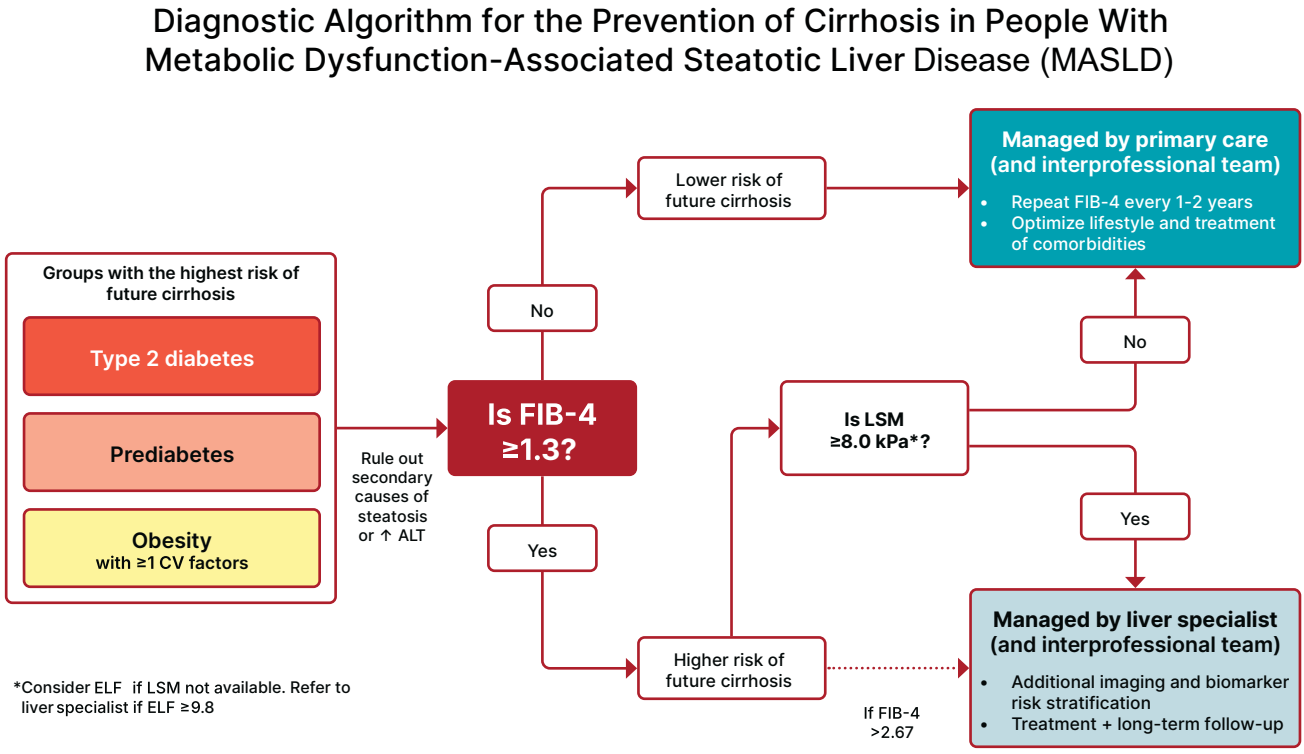


Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

therefore are at risk for adverse liver outcomes (181,217). They should be referred to a gastroenterologist or hepatologist. The optimal cutoff for clinical use of ELF in primary care and endocrinology settings is evolving (239–242). An ELF <9.8 suggests an individual is at low risk of advanced liver fibrosis and may be followed in the nonspecialty clinic with repeat testing in ≥2 years but may need repeat testing more often if ELF is between 9.2 and 9.7.

Specialists may order additional tests for fibrosis risk stratification in MASH (180,205,206,217), including magnetic resonance elastography (MRE) (best overall performance, particularly for early fibrosis stages) or multiparametric iron-corrected T1 MRI (cT1) (243) and patented blood-based fibrosis biomarkers. While liver biopsy remains the gold standard for the diagnosis of MASH, 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.

Management

Recommendations

4.25 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, who have metabolic dysfunction–associated steatotic liver disease (MASLD) should be recommended lifestyle changes using an interprofessional approach that promotes weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits **B** and histological improvement. **C**

4.26 In adults with type 2 diabetes, MASLD, and overweight or obesity, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA for the treatment of obesity with potential benefits in MASH as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.27a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management because of potential beneficial effects on MASH. **B**

4.27b Combination therapy with pioglitazone plus GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) because of potential beneficial effects on MASH.**B**

4.28 For consideration of treatment with a thyroid hormone receptor-β agonist in adults with type 2 diabetes or prediabetes with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology, or by a validated imaging-based or blood-based test, refer to a gastroenterologist or hepatologist with expertise in MASLD management. **A**

4.29 Treatment initiation and monitoring should be individualized and within the context of an interprofessional team that includes a gastroenterologist or hepatologist, consideration of individual preferences, and a careful shared-decision cost-benefit discussion. **B**

4.30a In adults with type 2 diabetes and MASLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 RAs may be continued as clinically indicated, but these therapies lack evidence of benefit in MASH. **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 MASLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. **B**

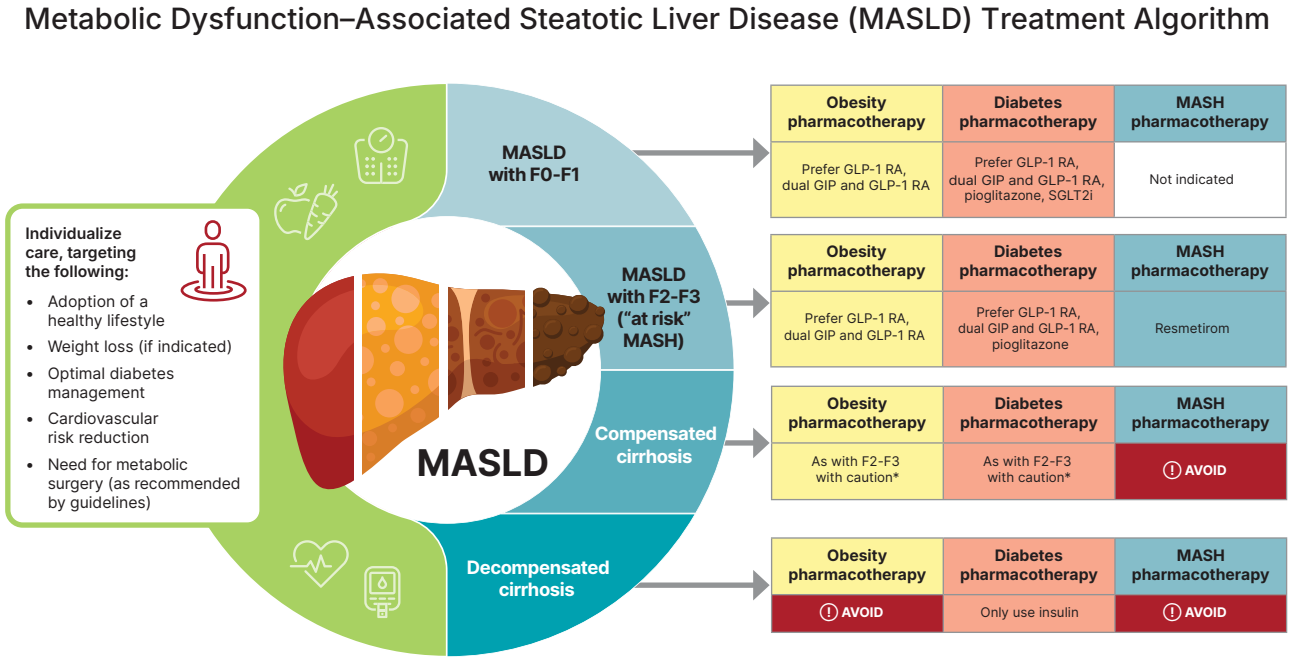
4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from MASLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. **B** In people with decompensated cirrhosis, statin therapy should be used with caution, and close monitoring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

4.32a Consider metabolic surgery in appropriate candidates as an option to treat MASH 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 MASLD **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 (244,245), ample evidence implicates excess visceral fat and overall adiposity in people with overweight and obesity in the pathogenesis of the disease (246,247). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (248). 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 MASLD. There is consensus that a minimum weight loss goal of 5%, preferably ≥10%, is needed to improve liver histology (181,205,206,217), with fibrosis requiring the larger weight reduction to promote change (249,250). However, there is significant individual variability in histological outcomes with weight loss. Individualized, structured weight loss and exercise programs offer greater benefit than standard counseling in people with MASLD (251).

Dietary recommendations to induce an energy deficit are not different from those for people with diabetes with obesity without MASLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean eating pattern has the best evidence for improving liver and cardiometabolic health (205,215–217,251). Both aerobic and resistance training improve MASLD in proportion to treatment engagement and intensity of the program (252). 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").



*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Given the high prevalence of at-risk MASH (~12–20%) (182–184,186,189), higher risk of disease progression and liver-related mortality (185,204,253), and the lack of pharmacological treatments once cirrhosis is established (254,255), optimizing the pharmacological management of hyperglycemia and obesity in people with type 2 diabetes and MASH could serve the dual purpose of addressing these comorbidities while treating the liver disease (**Fig. 4.3**). Therefore, early diagnosis and treatment of MASLD offers the best opportunity for cirrhosis prevention. In phase 2 clinical trials, pioglitazone and some GLP-1 RAs have been shown to be potentially effective to treat steatohepatitis (205,256–259) and to slow fibrosis progression (260–262). They may also decrease CVD (257), which is the number one cause of death in people with type 2 diabetes and MASLD (210). Evidence from phase 3 clinical trials still are not fully published (e.g., a phase 3 study on semaglutide, The Effect of Semaglutide in Subjects With Non-cirrhotic Non- alcoholic Steatohepatitis [ESSENSE] trial, is predicted to be published in 2025) (263), and no glucose-lowering or weight management medication is FDA approved for the treatment of MASH. The recommendation to treat hyperglycemia with GLP-1 RAs and/or pioglitazone in people with type 2 diabetes and MASLD is based on consistent histological benefit for steatohepatitis in several phase 2 RCTs with GLP-1 RAs and with pioglitazone (264–268) compared with no benefit with metformin or other glucose-lowering medications in MASH (181,205,206).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes or type 2 diabetes (261,264,265) and even in individuals without diabetes (266–268) (**Fig. 4.3**). Fibrosis also improved in some trials (265,267). A meta-analysis (260) concluded that pioglitazone treatment results in resolution of MASH and may improve fibrosis. Furthermore, combination therapy with pioglitazone plus a GLP-1 RA has been reported safe and effective for the treatment of hyperglycemia in adults with type 2 diabetes (269–272) as well as in reducing hepatic steatosis (269,271), suggesting additive benefit in individuals with MASLD. It is important to note that these studies are based on phase 2 clinical trials and await further phase 3 evidence. However, these plans are attractive because they offer potential benefit compared with lack of histological benefit (or clinical trial data) from other oral glucose-lowering therapies in MASLD. In the context of treating hyperglycemia in people with type 2 diabetes with MASLD, where the low cost of pioglitazone and any liver improvement would be an added benefit to glycemic management, these plans would be potentially cost-effective for the treatment of MASLD (273,274). Vitamin E may be beneficial for the treatment of MASH in people without diabetes (266). However, in people with type 2 diabetes, vitamin E monotherapy was found to be ineffective in a small RCT (261), and it did not seem to enhance pioglitazone's efficacy when used in combination, as reported in an earlier trial in this population (265). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean weight gain of 1–2%; 45 mg/day, mean weight gain of 3–5%), which can be blunted or reversed if combined with SGLT2 inhibitors or GLP-1 RAs (257,271,272,275). Pioglitazone 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 (181,205,206,257,258).

GLP-1 RAs are effective at inducing weight loss and ameliorating elevated

plasma aminotransferases and steatosis (256) (**Fig. 4.3**). However, there are few phase 2 RCTs of GLP-1 RAs in individuals with MASH proven by biopsy. A small RCT reported that liraglutide improved some features of MASH and may delay fibrosis progression (276). Subcutaneous semaglutide treatment in 320 people with MASH (62% having type 2 diabetes) led to resolution of steatohepatitis without worsening of fibrosis in 59% of individuals at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (262). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people but, over 72 weeks, slowed the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide is a dual GIP and GLP-1 RA known to reduce liver steatosis in MASLD (277), and a phase 2 paired-biopsy study of 190 adults with overweight or obesity with MASH (50–60% of whom had type 2 diabetes) recently reported that doses of 5, 10, and 15 mg/day resulted in resolution of steatohepatitis without worsening of fibrosis in 44%, 56%, and 62% of participants, respectively, compared with 10% of participants receiving placebo ($P < 0.001$ for all three comparisons) (278). Improvement of at least one fibrosis stage without worsening of MASH occurred in 55%, 51%, and 61% of participants, respectively, compared with 30% of participants receiving placebo. Survodutide is a dual GLP-1 and glucagon RA that is in development, and a phase 2 paired-biopsy trial recently reported benefit in MASH (279). In summary, GLP-1–based therapies and/or pioglitazone is recommended to treat type 2 diabetes in adults with MASH based on histological benefit for steatohepatitis in several phase 2 RCTs (278,279) compared with no benefit with metformin or other glucose-lowering or weight loss medications. Within the context of their approved indication (e.g., obesity or type 2 diabetes), these medications are cost-effective to treat the comorbidity, while potentially improving MASH, which becomes an added benefit.

SGLT2 inhibitors (280–282) and insulin (258) 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 MASLD for glycemic management, 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).

Resmetirom is a thyroid hormone receptor-β agonist approved by the FDA for the treatment of adults with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology or a validated imaging- or blood-based test. In a phase 3 RCT, resmetirom for 52 weeks in 966 adults at the highest dose of 100 mg (or placebo) met the primary end point of MASH resolution without worsening of fibrosis in 29.9% of participants compared with 9.7% on placebo ($P < 0.001$) (283). Fibrosis improved in up to 25.9% and 14.2%, respectively ($P < 0.001$). Nausea, vomiting, and diarrhea occurred more often with resmetirom. The gastrointestinal side effects are dose dependent and improve with continued treatment. Resmetirom decreased free thyroxine (T4) levels by ∼20% and increased sex hormone-binding protein levels two- to threefold. Although a recent review of the data concluded that there is little concern about these changes, long-term postmarketing data must be collected (284,285). Guidance by the American Association for the Study of Liver Diseases (AASLD) about optimal individual identification for treatment, safety, and long-term monitoring has recently been published (286). This is especially relevant because hypothyroidism and hypogonadism are more prevalent in people with MASLD than in the general population (181,205), and clinicians should monitor all individuals with MASLD for symptoms of endocrine deficiency and manage according to clinical practice guidelines. Per its label, candidates for resmetirom treatment are those with MASLD and moderate (F2) to advanced (F3) liver fibrosis but not with cirrhosis or other active liver disease (i.e., alcohol-related liver disease, autoimmune hepatitis, or primary biliary cholangitis) or unmanaged hypothyroidism or hyperthyroidism. Given complexities associated with selection of an individual for therapy, drug cost, and treatment monitoring, therapy should be individualized and initiated by a hepatologist or gastroenterologist with expertise in MASH within an interprofessional team.

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 dual GIP and GLP-1 RAs) (255), although a recent 48-week study suggested that GLP-1 RAs are safe in individuals with MASH and compensated cirrhosis (287).

Metabolic surgery leading to sustained weight loss and improvement of type 2 diabetes can improve MASH and cardiometabolic health, altering the natural history of the disease (288). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis, 50–75% of people have improvement in inflammation and hepatocyte ballooning (necrosis), and 30–40% of people have improvement in fibrosis (289,290). It may also reduce the risk of HCC (290). It is important to note that currently metabolic surgery is not indicated solely for treatment of MASH. Given that many individuals with MASH have metabolic risks (type 2 diabetes and obesity) that are indications for metabolic surgery, the improvement in liver health is expected, but surgical indication should follow current practice guidelines. 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 (181,205,206).

Adults with type 2 diabetes and MASLD are at an increased risk of CVD and require comprehensive management of cardiovascular risk factors (181,205,206). 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 MASH, including in the presence of compensated cirrhosis (Child-Pugh class A or B cirrhosis) from MASLD. Some studies

even suggest that statin use in people with chronic liver disease may reduce episodes of hepatic decompensation and/or overall mortality (291,292). Statin therapy is not recommended in decompensated cirrhosis given limited safety and efficacy data (181,205,206).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for CVD, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (293) (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% (294,295). In participants with obesity enrolled in the Look AHEAD trial, the prevalence exceeded 80% (296). Obstructive sleep apnea should be evaluated in individuals with suggestive symptoms (e.g., excessive daytime sleepiness, snoring, and witnessed apnea) (297). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. Recently, two phase 3 randomized trials found that among adults with obesity and moderate-to-severe obstructive sleep apnea but without diabetes, treatment with the dual GIP and GLP-1 RA tirzepatide substantially reduced sleep apnea severity (298). More research is needed to determine the effects of GLP-1 and dual GIP and GLP-1 RAs on sleep apnea in people with diabetes.

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 (299). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (300).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of individuals after an episode of acute pancreatitis (301); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (302). 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 (303–306).

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 (307–311). Both personal factors for the individual 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.

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 (312). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress with cochlear microangiopathy and auditory neuropathy (313). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes as in those without, after adjusting for age and other risk factors for hearing impairment (314). 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 glycemia has not been consistently observed (315). In the 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 (316). Impairment in smell, but not taste, has also been reported in individuals with diabetes (317).

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