3. Prevention or Delay of Diabetes and Associated 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.

For guidelines related to screening for increased risk for type 1 diabetes, prediabetes and type 2 diabetes, and other forms of diabetes, please refer to Section 2, "Diagnosis and Classification of Diabetes." For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14 "Children and Adolescents."

Recommendations

3.1 In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify frequency of testing based on individual risk assessment. **E**

3.2 In people with presymptomatic type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics. **E**

Screening for prediabetes and type 2 diabetes risk through an assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the American Diabetes Association risk test, which can be used by either a layperson or a health care professional (**Fig. 2.2**), is recommended to guide whether to perform a diagnostic test for prediabetes (**Table 2.2**) and type 2 diabetes (**Table 2.1**) (see Section 2, "Diagnosis and Classification of Diabetes"). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost. In addition, substantial time exists before the development of type 2 diabetes and its

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complications during which one can intervene. Once identified, several effective therapeutic approaches exist that can delay type 2 diabetes in those with prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance (IGT) on 75-g oral glucose tolerance test (OGTT), or impaired fasting glucose (IFG). The utility of screening with A1C for prediabetes and diabetes may be limited in the presence of certain hemoglobinopathies and conditions that affect red blood cell turnover (**Table 2.3**). See Section 2, "Diagnosis and Classification of Diabetes," and Section 6, "Glycemic Goals and Hypoglycemia," for additional details on the appropriate use and limitations of A1C testing.

Three distinct stages of type 1 diabetes have been defined, with symptomatic type 1 diabetes being stage 3 (**Table 2.4**). In individuals at risk for developing clinical type 1 diabetes, younger age of seroconversion (particularly under age 3 years), the total number of diabetes-related autoantibodies (1), and the development of autoantibodies against islet antigen 2 (IA-2) have been associated with a more rapid progression to clinical type 1 diabetes. While continuous glucose monitoring can predict progression to overt diabetes in children with autoantibodies (2), OGTT-based metrics appear to be better at predicting progression compared with continuous glucose monitoring (3). The decision to perform an OGTT may depend on such factors as eligibility and interest for stage-specific treatments, participation in clinical research, availability, and the burden of testing. A consensus guidance provides expert recommendations on what should be monitored and how often in people with presymptomatic type 1 diabetes (4).

LIFESTYLE BEHAVIOR CHANGE FOR TYPE 2 DIABETES PREVENTION

Recommendations

3.3 Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity. **A**

3.4 Prescribe an eating pattern known to be effective in preventing type 2 diabetes to individuals with prediabetes. A variety of eating patterns, such as Mediterranean style, intermittent fasting, and low carbohydrate, have shown benefit. **B**

3.5 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payors, and inconsistencies in access should be addressed. **E**

3.6 Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (5), the Finnish Diabetes Prevention Study (DPS) (6), and the Da Qing Diabetes Prevention Study (Da Qing study) (7), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation) (8). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (5). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (9), 43% reduction at 7 years in the Finnish DPS (6), and 34% reduction at 10 years (10) and 27% reduction at 15 years (11) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted to achieve the goals (12). The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and to partake in 150 min of moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, achieving the behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (13).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests higher benefit for prevention of diabetes with at least 7–10% weight loss with lifestyle interventions (13). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the nutrition intervention was on reducing total fat rather than calories. After several weeks, the concepts of calorie balance and the need to restrict calories and fat were introduced (12).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (12).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (12).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions,

motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors (such as how to choose healthy food options when eating out), and guidance on managing psychological, social, and motivational challenges (12).

While the DPP interventions were successful in preventing or delaying the onset of type 2 diabetes, long-term effects on clinically meaningful events (microvascular and macrovascular disease) have not been established (14). However, there is potential benefit without the risk of harm with these interventions.

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total fat and calories (5,12,13). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (15). Based on other trials, a variety of eating patterns (15,16) may also be appropriate for individuals with prediabetes (15), including Mediterranean-style and low-carbohydrate eating plans (17–19). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (20–23). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (22,24,25). As is the case for those with diabetes, individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (26).

Physical Activity

Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in those with prediabetes (5). Similarly, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (27,28). Health care professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (12,29). Breaking up prolonged sedentary time may also be encouraged, as it lowers postprandial glucose levels (30). The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (31).

Sleep Characteristics Associated With Increased Risk of Type 2 Diabetes

Sleep occupies approximately one-third of the day for most people and modulates a variety of metabolic, endocrine, and cardiovascular processes (32). The latest ADA-EASD consensus report on management of hyperglycemia highlights sleep as a central component in the management of prediabetes and type 2 diabetes, placing it, for the first time, on the same level as other lifestyle behaviors (e.g., physical activity and nutrition) (33). Sleep can be characterized using three key constructs: quantity, quality, and timing (i.e., chronotype). There is now established evidence for a U-shaped association between sleep duration and type 2 diabetes incidence, with the nadir typically occurring at 7 h per day, with short (typically defined as <6 h) and long (typically defined as >9 h) sleep duration having up to a 50% increase in the risk of type 2 diabetes, including progression from prediabetes (33). Sleep quality has recently been defined as "an individual's self-satisfaction with all aspects of the sleep experience" (34,35). Poor sleep quality was associated with a 40–84% increased risk of developing type 2 diabetes in a meta-analysis (36). Chronotype preference has been linked with many chronic diseases, including type 2 diabetes. For example, for those with a preference for evenings (i.e., going to bed late and getting up late), there was a 2.5-fold higher odds ratio for type 2 diabetes than for those with a preference for mornings (i.e., going to bed early and getting up early), independent of sleep duration and sleep sufficiency (37).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payors ensued (38–42). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (43,44).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes-prevention). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/risktest/). During the first 4 years of implementation of the CDC's National DPP, 36% achieved the 5% weight loss goal (45). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP (46). To expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI

>25 kg/m^2 (or BMI >23 kg/m^2 if self-identified as Asian) and glycemic testing consistent with prediabetes in the last year. Medicaid DPP is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payors, lower retention rates have been reported for younger adults and racial and ethnic minoritized populations (47). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP-like interventions has been shown to be effective and cost-effective (48,49) (see Section 1, "Improving Care and Promoting Health in Populations," for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage by third-party payors remains limited. Counseling by a registered dietitian/nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (15,50–52). Individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (26,50). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia (23,26). Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (51,53). Other health care professionals, such as pharmacists and diabetes care and education specialists, may also be considered for diabetes prevention efforts (53,54).

Technology-assisted programs may effectively deliver a DPP-like intervention (55–58). A digital diabetes prevention program improved cardiovascular risk at 4 months but not at 12 months (59). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for individuals with low income and/or in rural locations; however, not all technology-assisted programs are effective (55,60–62). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based interventions; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Health care professionals should consider referring adults with prediabetes to certified technology-assisted programs.

PHARMACOLOGIC INTERVENTIONS TO DELAY TYPE 2 DIABETES

Recommendations

3.7 Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus. **A**

3.8 Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 level in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in nutrition and physical activity may not be sufficient on their own and can be difficult to maintain long term (10), some people at high risk of type 2 diabetes may benefit from additional support and pharmacotherapeutic options. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, incretin receptor agonists (e.g., liraglutide and semaglutide), thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations (63–68), whereas diabetes prevention was not seen with nateglinide (69).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (13). In individuals with previous history of GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (70). Several medications evaluated for weight loss (e.g., orlistat, phentermine and topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of type 2 diabetes in those with prediabetes (68,71–73).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan or testosterone (74,75) but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (75–78). Vitamin D therapy has recently been advocated by the U.S. Endocrine Society to prevent progression of high-risk prediabetes to type 2 diabetes in adults (79). Three randomized controlled trials have been designed and conducted to test whether vitamin D therapy in combination with lifestyle modification reduces the risk of developing diabetes in adults with high-risk prediabetes (i.e., IGT or meeting two or three ADA prediabetes glycemic criteria [fasting glucose, A1C, 2-h glucose after a 75-g OGTT]): the Tromsø study in Norway, with 511 participants; the Vitamin D and Type 2 Diabetes (D2d) study in the U.S., with 2,423 participants; and the Diabetes Prevention with Active Vitamin D (DPVD) study in Japan, with 1,256 participants (80–82). Although vitamin D therapy modestly reduced the risk of developing diabetes compared with the placebo to a nearly identical degree in all three trials, none of the results of the individual studies were statistically significant (reportedly due to insufficient power). Subsequently, several meta-analyses related to these (and other smaller) studies have suggested a modest potential benefit in specific populations (83,84). However, there are several concerns and uncertainties regarding recommending widespread vitamin D therapy for adults with high-risk prediabetes. *1*) The recommended vitamin D dose is unclear. The included trials used varying dosages of vitamin D that were higher than the recommended daily allowance for this population (i.e., 600 IU/day for those aged 18–70 years

and 800 IU for those older than 70 years). Due to this variability, it is not possible to recommend a specific vitamin D dosage for diabetes prevention. *2*) The benefit-to-risk ratio of vitamin D therapy for high-risk prediabetes remains uncertain. Although there was no evidence of safety concerns with vitamin D therapy in study participants with prediabetes, the numbers of adults included in these studies are small compared with the potentially many millions of adults with prediabetes in the U.S. and globally who may have risk of adverse events if treated with unspecified doses of vitamin D without monitoring blood 25-hydroxy vitamin D levels. In light of these and other issues, further research is warranted to better define the population characteristics and determine the dose and clinical pathway of vitamin D therapy for diabetes prevention.

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for prevention of type 2 diabetes. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost and burden of administration. Additionally, pharmacologic interventions must be long-term because of the waning of effect after stopping the medication.

Metformin

Metformin has the most safety data as a pharmacologic therapy for diabetes prevention (85). Metformin was overall less effective than lifestyle modification in the DPP, though group differences attenuated over time in the DPPOS (11), and metformin may be cost-saving over a 10-year period (40). In the DPP, metformin was as effective as lifestyle modification in participants with BMI $\geq$35 kg/m^2 and in younger participants aged 25–44 years (5). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (86). Both interventions remained highly effective during a 10-year follow-up period (87). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose ($\geq$110 mg/dL [$\geq$6 mmol/L] vs. 95–109 mg/dL [5.3–5.9 mmol/L]), those with a higher A1C (6.0–6.4% [42–46 mmol/mol] vs. <6.0% [<42 mmol/mol]), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that may benefit the most from metformin (88). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; however, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (89). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., younger individuals, those with history of GDM, or those with BMI $\geq$35 kg/m^2).

Decreased vitamin B12 levels are a known consequence of long-term treatment with metformin (90). Periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency, especially in those receiving a higher dose (e.g. $\geq$1,500 mg/day) (91) or longer treatment duration and in those with existing risk factors. Vitamin B12 serum levels should be tested if deficiency is suspected, such as in people with anemia or peripheral neuropathy (90,92) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details). The effect of metformin on vitamin B12 increases with time (93), with a higher risk for vitamin B12 deficiency (<200 pg/mL [<150 pmol/L]) noted at 4–5 years of treatment. A person who has been taking metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan dietary pattern, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually (94).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.9 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.10 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be avoided or discontinued for this adverse effect. **B**

3.11 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fractures. **A** Lower doses may mitigate the risk of adverse effects but may be less effective. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (95), and are at increased risk for cardiovascular disease (96,97). Evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (98,99), and individuals should be monitored for diabetes development and receive evidence-based lifestyle behavior change for diabetes prevention as described in this section. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (100,101). The lifestyle intervention in the Da Qing study was associated with lowering cardiovascular disease and mortality at 23 and 30 years of observational follow-up (7,9). Treatment goals and therapies for hypertension and dyslipidemia in the primary and secondary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular disease risk factors (102). Statin use increases risk of diabetes (103–105). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [HR] [95% CI] for incident diabetes 1.36 [1.17–1.58]) (104). In trials of primary and secondary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (106,107), suggesting a highly favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins due to concerns

of diabetes risk is not recommended in this population.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, "Cardiovascular Disease and Risk Management," for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance (as defined by a HOMA of insulin resistance index of ≥3.0), evaluated pioglitazone (goal dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower in the pioglitazone group than in the placebo group; weight gain, edema, and fractures were higher in the pioglitazone treatment group (108–110). Lower doses may mitigate the adverse effects but may also be less effective (111).

PERSON-CENTERED CARE GOALS

Recommendations

3.12 In adults with overweight or obesity at high risk of type 2 diabetes, care goals should include weight loss and maintenance, minimizing the progression of hyperglycemia, and attention to cardiovascular risk. **B**

3.13 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, and cardiovascular risk reduction) should be considered to support person-centered care goals. **B**

3.14 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.1–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C ≥6.0% [≥42 mmol/mol]), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk-to-benefit ratio should be considered in screening, intervention, and monitoring to lower the risk of type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (112,113). Prediabetes is associated with increased cardiovascular disease and mortality (97), which emphasizes the importance of attending to cardiovascular risk in this population. However, the new diagnosis of prediabetes in older adults (aged >70 years) is less relevant for progression to diabetes, because regression to normoglycemia or death was more frequent than progression to diabetes in the Atherosclerosis Risk in Communities (ARIC) study (113).

In the DPP, which enrolled high-risk individuals with IGT, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo group was 11 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 29% (5). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases per 100 person-years) included BMI ≥35 kg/m^2, higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.0–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], A1C ≥6.0% [≥42 mmol/mol]), or a history of GDM (5,86,87). In contrast, in the community-based ARIC study, observational follow-up of adults with mean age 75 years with laboratory evidence of prediabetes (based on A1C 5.7–6.4% [39–47 mmol/mol] and/or fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L]), but not meeting specific BMI criteria, found lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes and 8% of those with IFG (113).

Thus, it is important to individualize the risk-to-benefit ratio of intervention and consider person-centered goals. Risk models have generally found a higher benefit of the intervention in those at highest risk (13). Diabetes prevention trials and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight or obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit seen with greater weight loss (13,114). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (11). Achieving normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications irrespective of the treatment arm (115). Observational follow-up of the Da Qing study also showed that regression from IGT to normal glucose tolerance or remaining with IGT rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (116).

Pharmacotherapy for weight management and cardiovascular risk reduction (see Section 10, "Cardiovascular Disease and Risk Management," for more details) can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

PREVENTION OR DELAY OF SYMPTOMATIC TYPE 1 DIABETES

Lifestyle and Type 1 Diabetes Progression

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand, including less physical activity (117), higher glycemic index (118), and total sugar intake (119), are associated with progression to clinical diabetes. Similar associations have not been seen in the development of autoantibodies. In The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study, daily minutes spent in moderate to vigorous physical activity were associated with a reduced risk of progression to type 1 diabetes in children 5–15 years of age with multiple islet autoantibodies (HR 0.92 [95% CI 0.86–0.99] per 10-min increase; $P = 0.021$) (117). In the Diabetes Autoimmunity Study in the Young (DAISY), in children with islet autoantibodies, progression to type 1 diabetes was associated with higher glycemic index (HR 2.20 [95% CI 1.17–4.15]) and total sugar intake (HR 1.75 [95% CI 1.07–2.85]) (118,119). In nonobese diabetic mice, an animal model for the development of type 1 diabetes, sustained high-glucose drinking significantly aggravated islet inflammation and accelerated the onset of type 1 diabetes (120). Lifestyle interventions focusing on such factors in those with

stage 1 or stage 2 type 1 diabetes have not yet been reported.

Pharmacologic Interventions to Delay Symptomatic Type 1 Diabetes

Recommendation

3.15 Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be discussed with selected individuals aged ≥8 years with stage 2 type 1 diabetes. Treatment should be in a setting with appropriately trained personnel. **B**

Teplizumab, a CD3-directed humanized monoclonal antibody engineered to have decreased Fc receptor binding, has been approved to delay the onset of stage 3 type 1 diabetes in people 8 years of age and older with stage 2 type 1 diabetes based in part on the results of a single trial in relatives of people with type 1 diabetes (121). In this study, 44 individuals were randomized to a 14-day course of teplizumab and 32 to placebo. The median time to stage 3 type 1 diabetes diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group. Type 1 diabetes was diagnosed in 19 (43%) participants who received teplizumab and 23 (72%) participants who received placebo (HR 0.41 [95% CI 0.22–0.78]). In prespecified analyses, the presence of HLA-DR4, absence of HLA-DR3, and absence of anti-zinc transporter 8 antibody predicted response to teplizumab (HR 0.20 [95% CI 09.0.45], 0.18 [0.07–0.45], and 0.07 [0.02–0.26], respectively). The most common adverse reactions were transient lymphopenia (73%) followed by rash (36%).

Numerous clinical studies are being conducted to test methods for preventing or delaying the onset of stage 3 type 1 diabetes in those with evidence of autoimmunity without symptoms or for delaying loss of insulin secretory capacity after onset of stage 3, some with promising results (see ClinicalTrials.gov and TrialNet.org).

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