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Screening for Diabetes and Prediabetes and their Prediction

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Introduction

Despite significant progress, screening for type 2 diabetes mellitus (T2DM) remains controversial, with a lack of uniform recommendation across professional organizations.[1–3] There is a critical need for guidance on how to best use the available evidence, and thus implement an effective screening approach. Screening for prediabetes (i.e. impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]) and T2DM are inseparable, as they are part of a pathophysiologic continuum, are detected by the same tests, and have similar initial therapies (i.e. lifestyle intervention and/or metformin). Trials conducted in various settings and populations have consistently demonstrated the effectiveness of lifestyle modification and/or pharmacotherapy in preventing diabetes after identification of prediabetes.[4] However, most individuals with prediabetes remain asymptomatic, and thus do not receive appropriate care.[5] Indeed, more than 85% of US individuals with prediabetes are unaware of their diagnosis.[6] Consequently, screening for T2DM is a key first step for effective translation of diabetes prevention into practice.

Herein, we offer a summary of the evidence, to enhance clinician compliance with guideline- based diabetes preventive care.

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Rationale for screening

Extent of the problem - burden of hyperglycemia

T2DM is highly prevalent in the US. In 2018, 13% (34.1 million) of US adults had diabetes.[6] Strikingly, 21.4% of US adults with diabetes or 2.8% of all US adults had undiagnosed diabetes.[6] On a global scale, ~9.3% of the population (463 million people) had diabetes in 2019, and the prevalence is projected to rise to 10.9% by 2045.[7]

The risk of death among people with diabetes is twice that of those without diabetes.[8] Diabetes is the seventh cause of death in the US.[6] Globally, diabetes contributed to 11.3% of deaths in 2019 (46.2% of deaths occurred in those younger that 60 years).[9] Among US adults, ~15–81% of those with T2DM have at least one cardiovascular complication.[10] The prevalence of chronic kidney disease (CKD) in patients with T2DM is 43.5%,[11] and diabetes is the most common primary cause of end-stage renal disease (46.7% of cases).[12] Diabetic retinopathy is the leading cause of new cases of blindness among adults aged 20–74 years in developed countries.[13] Peripheral arterial disease, foot ulceration, and amputations are more prevalent among people with diabetes than those without it.[14]

The burden of diabetes is likely to increase over time, given the high prevalence of prediabetes. In 2018, 34.5% of US adults (88 million) had prediabetes.[6] Globally, there are 374 million adults with prediabetes, and nearly 540 million adults will have prediabetes by 2045.[7] Compared to normoglycemia, there is an increased risk of cardiovascular disease (CVD) in those with prediabetes.[15] Microvascular disease may also complicate prediabetes.[4] The financial burden of diabetes is astoundingly high in the US. Diabetes-related costs totaled $327 billion in 2017, which was a 25% increase from 2012.[16] The diabetes-related US medical expenditures in 2017 reached nearly $404 billion, representing a monetary burden averaging $1,240 for each American.[17] Diabetes is associated with a substantially high lifetime medical expenditures, with ~ $124,600 excess lifetime spending when diagnosed at age 40.[18] Globally, diabetes imposes an enormous economic burden with an estimated global cost of US $1.31 trillion, accounting for 1.8% of the world gross domestic product (GDP).[19]

Identifiable preclinical phase

The natural history of dysglycemia is relatively well understood, and includes an asymptomatic phase comprised of two states: (1) prediabetes with an estimated duration of 8.5–10.3 years,[20] and (2) preclinical latent diabetes (after biological onset of the disease) that lasts at least 4–7 years.[21] Prediabetes includes the intermediate states of abnormal glucose regulation (IFG and/or IGT) preceding overt biological diabetes, and is associated with a high risk of progression to diabetes.[43] Latent diabetes refers to the time frame between the biological onset of diabetes and the clinical diagnosis of the disease. The public health burden of latent diabetes is reflected in the substantial proportion of undiagnosed diabetes (21.4% of all diabetes cases in the US population.[7]).

The rationale for prediabetes screening includes the significant progression rate to T2DM, effectiveness of interventions for diabetes prevention, and the macrovascular and microvascular complications associated with prediabetes. Prediabetes (IFG and/or IGT) is

associated with a high risk of progression to overt T2DM. A meta-analysis found relative risks for diabetes of 4.32 for IFG defined using the American Diabetes Association (ADA) criteria, 5.47 for IFG defined using the World Health Organization (WHO) criteria, 3.61 for IGT, 6.90 for IFG and IGT, 5.55 for HbA_{1C} >5.7%, and 10.10 for HbA_{1C} >6.0%.[22] Moreover, there have been landmark studies demonstrating the effectiveness of intensive lifestyle modification and drugs for preventing T2DM.[4] Lastly, prediabetes increases the risks of macrovascular and microvascular diseases.[4]

Screening for preclinical diabetes is critical given the complications and morbidities already present at the time of the clinical diagnosis of diabetes. Hyperglycemia-related tissue damage is often already present during the asymptomatic T2DM stage. Indeeed ~50% of people with screen-detected diabetes already have macrovascular (coronary artery disease [CAD])[23] or microvascular complications (retinopathy, nephropathy and neuropathy),[24] at diagnosis. In the Hoorn Screening Study, myocardial infarction (13.3% vs. 3.4%), CAD (39.5% vs. 24.1%), and retinopathy (7.6 % vs. 1.9%) were more frequent in screen-detected patients than in newly conventionally diagnosed patients.[23–25] In the Anglo-Danish-Dutch Study of Intensive Treatment In peOple with screeN detected diabetes in primary care (ADDITION)-Denmark, approximately 6.8% of screen-detected people with diabetes had retinopathy at diagnosis in the ADDITION-Denmark Study.[26]

Testing for hyperglycemia

The approaches to screen for prediabetes or diabetes include risk scoring tools and biochemical tests

Risk scores

Various risk models, consisting of a combination of known risk factors, have been developed to identify people at high risk of T2DM,[27] who account for the majority of people with T2DM. These models involve the use of self-reported questionnaires, health service data or newly collected data (anthropometric, lifestyle or biochemical). Scores based on routinely collected clinical information may be more appropriate for clinical use. Using questionnaires or existing health service data may be more convenient as it allows population stratification prior to blood glucose testing, thus limiting those who undergo blood glucose testing to 20–25% of the overall population. However, such an approach relies on the availability of data on key variables. Clinic-derived risk scores may be conveninent and widely available, they exhibit the best discriminatory accuracy in the populations in which they were developed. The external validation of these risk scores in other populations tend to be moderate to poor.[27]

The extant risk assessment tools for prediabetes are limited by poor metholodogy and lack of data on calibration and external validation, and thus are not yet ready for clinical practice.[28] In the US, the most widely validated and simple to use risk screening tool is the American Diabetes Association (ADA)'s diabetes risk test (https://www.diabetes.org/risk-test),[29] intended to identify asymptomatic adults who need glycemic assessment. However, the US Preventive Services Task Force (USPSTF) does not endorse the use of any specific risk tool.[2] The implementation of risk assessment tools in clinical practice is somewhat

limited.[30] In a report, only 10 of the 65 available non-invasive diabetes risk assessment tools developed worldwide, had been implemented in clinical practice.[30] Barriers to the implementation of these tools include factors related to healthcare providers (perceived lack of accuracy, lack of time and reimbursement support, and interference with physician-patient interaction) and patients (lack of perceived severity of T2DM, fear of complexity of the test, cultural and/or language barriers, uncertainties about next steps after identification of high risk of diabetes, and subsequent fear of the disease, treatment, and cost of care).[30] Strategies are needed to enhance the implementation of diabetes risk scores in daily clinical practice.

Biochemical tests

The advantages and limitations of diabetes screening tests are summarized in Table 1.

75-g oral glucose tolerance test (OGTT)—The 75-g OGTT is accepted as the "gold standard" diagnosic test for diabetes and prediabetes. Both the ADA and WHO endorse the 2-hour post-prandial glucose (2hPG) cut-off of 140–199 mg/dL for diagnosing prediabetes and ≥200 mg/dL for diagnosing diabetes.[1,31] OGTT distinguishes between IFG and IGT, which represent distinct phenotypes, with their co-occurrence conferring a greater risk for diabetes than either alone.[32] IGT may be a better predictor of outcomes than FPG or HbA_{1C}. Indeed, 2hPG is an independent predictor of diabetes, CVD, and mortality, above and beyond FPG and HbA_{1C}, and thus could provide enhanced assessment of risk outcomes.[33] OGTT can detect additional cases not captured by other tests; for example in a study OGTT uncovered 5.6% and 20.7% of diabetes and prediabetes, not meeting diagnostic criteria based on HbA_{1C}.[34]

The routine use of OGTT is limited by the need for an overnight fast, a lengthy testing time, higher cost, intra-individual variability, differences in glucose absorption rates, and a relatively low reproducibility.[35] OGTT is almost never performed as the initial screening test for non-pregnant adults.

Random plasma glucose (RPG)—The use of RPG is limited by its low performance. An expert panel has recommended that RPG 130–199 mg/dL (sensitivity of 63% and specificity of 87%) be considered a positive screening test for diabetes, based on validation against OGTT.[36] RPG may be helpful for patients who have a routine chemistry panel drawn for reasons other than diabetes, termed "serendipitous screening." Individuals with glucose levels suggestive of diabetes would then undergo confirmatory tests. RPG would rarely ever serve as the initial screening test in ambulatory patients.

Fasting plasma glucose (FPG)—FPG has modest sensitivity for hyperglycemia screening. The current cut-off of 7.0 mmol/l (126 mg/dL) for diabetes diagnosis exhibits a sensitivity of 56% and specificity of 97.7%, when validated against 75-g OGTT.[37] IFG, defined as 100–125 mg/dL (5.6–6.9 mmol/l) by the ADA, was reduced from 110–125 mg/dL (6.1–6.9 mmol/l) in 2003 in order to optimize the sensitivity and specificity of predicting future diabetes.[38] Even with this lower threshold, FPG alone may detect 27.4% of individuals with prediabetes, compared to 87.1% of cases detected using a complete OGTT.[39]

Glycated hemoglobin (HbA_{1C})—The ADA and WHO endorse HbA_{1C} for diabetes diagnosis.[1,40] As a screening tool, the current cutoff value of 6.5% has a sensitivity of 68.4% and specificity of 95.9% for the diagnosis of diabetesas validated with OGTT data.[37] The convenience of HbA_{1C} over FPG and OGTT should be balanced against its pitfalls,[41] including the genetic, hematologic, and illness-related factors that affect test accuracy, as well as age- and ethnicity-related variations. The use of HbA_{1C} for the defining prediabetes is complicated by varying definitions. ADA defines prediabetes with an HbA_{1C} of 5.7–6.4%.[1] while the International Expert Committee (IEC) utilizes an HbA_{1C} of 6.0–6.4% to define high risk of developing diabetes.[42] The WHO has not endorsed the use of HbA_{1C} for prediabetes diagnosis.[40] A meta-analysis found HbA_{1C} to be neither sensitive nor specific for detecting prediabetes, with a mean sensitivity of 49% and specificity of 79% for prediabetes identification.[43]

Combining FPG and HbA_{1C} testing may be an optimal and accurate approach to identifying diabetes and prediabetes, but is not always the case in clinical practice. Indeed, a community-based study demonstrated that single-sample confirmatory testing for diagnosing diabetes has a high positive predictive value, and thus supports the use of a combination of elevated FPG and HbA_{1C} levels from a single blood sample to identify undiagnosed diabetes.[44]

Benefits of screening for hyperglycemia

Effectiveness of screening

Randomized trials comparing people offered and not offered screening provide the highest level of evidence on the effect of screening for diabetes on morbidity and mortality. The ADDITION-Cambridge trial (with concurrent screening and no-screening groups)found that one-time diabetes screening did not reduce mortality (all-cause, cardiovascular, or other causes) over 9.6 years.[45] A 7-year follow-up study on a sub-sample of the ADDITION-Cambridge (15% from the screening group and 40% from the no-screening group) reported no significant differences in self-reported cardiovascular morbidity.[46] A parallel-group population-based cohort UK (Ely) study found that diabetes screening (versus no screening) did not reduce all-cause mortality,[47] or microvascular and macrovascular complications over 12 years of follow-up.[48] In contrast, the non-randomized ADDITION-Denmark study found that the risk of CVD and mortality were lower in the screening group compared to a retrospectively constructed no-screening control group.[49] In a Swedish population-based cohort study, compared to clinically-detected diabetes those with screen-detected diabetes had lower rates of all-cause mortality, CVD, renal disease and retinopathy.[50] However, the aforementioned results may not be directly applicable to the US environment, as several contextual factors need consideration. The ADDITION-Cambridge study and the Ely studies were conducted in the UK, which has a good primary care infrastructure, and found only 3% with undiagnosed diabetes.[45,47] The US has a less well-organized primary care system, which contributes to more cases of undiagnosed diabetes, as reflected in the high US prevalence of undiagnosed T2DM (21.4%).[6] The majority of participants in ADDITION were White, limiting the translation of findings to other racial/ethnic groups, more present in the US. Tight control of glucose, blood pressure and lipids in screen-detected individuals

can reduce diabetes-related cardiovascular and microvascular complications, as described in the UKPDS and Steno-2 trials.[51,52] In the ADDITION-Europe (England, Denmark and Netherlands) trial, intensive treatment of multiple risk factors after diabetes screening led to small but significant improvements in HbA_{1C}, blood pressure, and cholesterol, with a non-significant reduction in CVD events compared to routine care group,[53] a tendency that persisted at 10-year follow-up.[54] Microvascular outcomes were also not significantly different between the routine care and the intensive management groups in the in ADDITION-Europe study.[55] A simulation study using data from ADDITION-Europe estimated the absolute risk reduction of cardiovascular outcomes associated with screening and routine treatment to be 3.3% and 4.9% in the scenarios of a 3-year and 6-year delay in the diagnosis and treatment of diabetes, with relative risk reductions of 29% and 38% respectively.[56]

There are no clinical trials that directly evaluate the benefits of screening for prediabetes. However, landmark clinical trials have shown that diabetes can be prevented among individuals with prediabetes.[4] In these trials, over a 3 to 6-year period, lifestyle interventions (dietary changes plus increased physical activity) reduced the incidence of diabetes by 28% to 58% compared to the placebo or minimal intervention groups.[4] In the US Diabetes Prevention Program trial (DPP), metformin reduced the incidence of diabetes by 31% among people with prediabetes.[57] There was also a long-term reduction in diabetes incidence at 15-year post-trial follow-up due to lifestyle modification.[58] In the Chinese Da Qing Study, diabetes prevention was associated with a reduction in diabetes incidence during the 6-year trial period,[59] and after 30 years in the post-trial period.[60] The lifestyle modification was also associated with significanlty decreased risks of CVD, cardiovascular deaths, microvascular disease (including a 40% reduction in severe retinopathy), and all-cause mortality after 30 years.[60]

Pyschosocial impact of screening for hyperglycemia

Studies have found limited or no psychological effect of screening on people with newly-detected T2DM. The ADDITION-Cambridge trial demonstrated no adverse psychosocial effect of diabetes screening. On the short- and long-term, the anxiety level, illness perception, and self-rated health of participants invited to screening (with or without diabetes at screening) do not differ from that of those not invited, whether immediately after the test, at 6 weeks, at 3–6 months, or at 12–15 months.[61,62] In those who were tested, the screening outcome (positive or negative for diabetes) was not associated with anxiety or depression at 12 months.[63] Negative screening test results do not promote false reassurance (expressed as lower perceived risk, lower intentions for health-related behavioral change, or higher self-rated health),[64] or negatively affect health behaviors (smoking, alcohol consumption, dietary intake, or physical activity).[46]

The psychological effect of receiving a diagnosis of prediabetes remains unclear. Studies suggest that participation in a diabetes prevention program is not associated with higher levels of anxiety, depression or overall psychological distress than that of the general population,[65,66] but is possibly associated with a better health-related quality of life,[67] and with lower levels of depression.[68]

Cost-effectiveness of screening for hyperglycemia

A limited number of real-life studies have assessed the cost-effectiveness of prediabetes or diabetes screening. A simulation study postulated that diabetes prevention may avoid $124,600 and $91,200 in lifetime medical spending if a new case of diabetes can be prevented at age 40 years and age 50 years respectively.[18] Simulations have shown that diabetes prevention using lifestyle modification and metformin is cost-effective among those with prediabetes (with longer duration of evaluation enhancing cost-effectiveness);[69] which is corroborated by actual cost data from DPP.[70] Futhermore, the non-randomized ADDITION-Denmark showed that the modest cost of a diabetes screening program was offset within 2 years by savings in the healthcare system.[71] Overall, the economic studies of diabetes screening indicate that i) screening for both IGT and diabetes would be cost-effective, ii) universal screening would be less cost-effective than targeted screening of high-risk groups, and iii) the single most important determinant of cost-effectiveness is treatment.[69,72]

Screening intervals

The exact frequency of screening for diabetes is not known. There are no robust real-world data to rely on for the determination of an optimal screening frequency. A US-based simulation including individuals aged 45–74 years found that screening every 3 years yielded a good balance between true positives and false positives.[73] A more recent US-based simulation suggested that targeted screening for undiagnosed T2DM would be most cost-effective if if started in the age range 30–45 years and repeated every 3–5 years.[74] In a UK cohort of diabetes-free individuals aged 40–65 years, 5-year screening interval identified diabetes an average of 3.3 years earlier.[48] In a Japanese cohort of healthy adults, rescreening at intervals shorter than 3 years led to identification of ≤1% of incident diabetes.[75] Based on economic modeling studies and expert opinions, professional organizations have generally favored a 3-year interval.[1,2]

Treatment for screen-detected diabetes or prediabetes

Therapies shown to be effective in preventing complications in people with clinically diagnosed diabetes, particularly macrovascular complications, can be reasonably applied to those with screen-detected disease. These include optimal glycemic control,[52] lipid-lowering therapy for CVD prevention,[76] antihypertensive treatment,[77] and aspirin therapy for CVD prevention when indicated.[78]

Multifactorial intervention have been studied in screen-detected individuals with diabetes. The ADDITION-Europe trial compared routine care of newly screen-detected T2DM to intensive multifactorial treatment to reduce cardiovascular outcomes,[53] using an intervention modeled after the regimen used in the Steno-2 trial. The latter study showed that intensified multifactorial intervention (lifestyle modification and multidrug therapy) to control cardiovascular risk factors was more cost-effective (in reducing macrovascular and microvascular complications, and all-cause mortality) than standard therapy among people with long standing T2DM and microalbuminuria.[51,79] In ADDITION-Europe, intensive multifactorial treatment (targeting several cardiovascular risk factors) of screen-detected

individuals with T2DM over 5 years provided a non-significant 17% reduction in a composite cardiovascular primary endpoint favoring intensive treatment compared to routine care, as well as in all individual components (12% reduction in cardiovascular deaths, 30% reduction in non-fatal myocardial infarction, and 21% reduction in revascularization).[53] There were also significant improvements in CVD risk factors (systolic and diastolic blood pressure, and total and LDL cholesterol),[53] the frequency of microvascular complications (retinopathy and neuropathy) was lower for the intensive treatment group, but was not significant.[55] Both the macrovascular and microvascular results may partly be explained by improvements in the quality of diabetes care during the trial period, a phenomenon that can happen in any screening trial. The 10-year follow-up analysis of ADDITION-Europe showed that reductions in cardiovascular risk factors (weight, HbA_{1C}, blood pressure, and cholesterol) were sustained in both groups, but there was a non-significant 13% reduction in the composite cardiovascular primary endpoint, as well as non significant reductions in individual CVD outcomes (including myocardial infarction (28% reduction), stroke (26% reduction) and revascularization (13% reduction]), and in all-cause mortality (10% reduction).[54]

In recent years, the landscape of T2DM therapies has changed with the advent of glucagon-like peptide 1 (GLP-1)-receptors agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors.[80] It is reasonable to think that while the current cardiovascular trials have been conducted in patients with established CVD or at very high-risk for CVD, the cardiovascular benefits would translate to those with screen-detcted diabetes.

As a result of diabetes detection programs, individuals with prediabetes will also be identified. Currently, less than one-third of prediabetic subjects identified in clinical practice in the US currently receive any therapy.[5] Prediabetes individuals can be effectively managed with lifestyle intervention and/or pharmacotherapy, with a stronger evidence for lifestyle intervention.[4] Trials showed that over a 3 to 6-year period, lifestyle interventions (dietary changes plus increased physical activity) reduced the incidence of diabetes by 28% to 58% compared to the placebo or minimal intervention (standard of care) groups.[4] The lifestyle intreventions can be translated into real-life practice with the same level of beneficial effect as in the original trials.[81]

In the trials, the effects of lifestyle modification on the reduction of diabetes incidence persisted for 10- to 30-years after discontinuation of the active intervention, depending on the study.[4] In the Da Qing study, compared to the control group, the lifestyle modification group experienced significant reductions in the riks of CVD events, cardiovascular death, microvascular disease and overall mortality over a 30-year period.[60]

While multiple drugs (metformin, pioglitazone, troglitazone, rosiglitazone, acarbose, orlistat, voglibose, and liraglutide) have been tested for diabetes prevention,[4] most agents carry concerns regarding their costs, side effects, and lack of persistence of effect. Metformin has the best long-term safety profile, tolerability, and efficacy, and is therefore recommended by the ADA for preventing diabetes.[82] Metformin is most effective compared to lifestyle in those with BMI of at least 35 kg/m^2, in younger patients (<60 years of age), and in women with prior gestational diabetes mellitus.[82]

Current screening recommendations in the United States

The available evidence does not support universal diabetes screening. Consequently, most professional organizations advocate a selective and opportunistic approach in high-risk populations (Table 2). These include the American Diabetes Association (ADA),[1] the US Preventive Services Task Force (USPSTF),[1,2] and the Endocrine Society,[3] which recommend diabetes screening at a 3-year interval but yearly among those with prediabetes.[1,23]

The ADA recommends that patients detected with prediabetes be referred to an effective ongoing support program modeled on the DPP intervention. For those with BMI ≥ 35 kg/m^2, aged <60 years, and women with a history of gestational diabetes, metformin should be considered.[1,2]

The USPSTF and ADA recommendations were developed after a rigorous process of systematic review of the available evidence, and thus have a more reliable basis for clinical practice. However, the USPSTF guidelines include a more target population, with studies indicating that implementation of the USPSTF screening recommendations may miss close to half of those with undiagnosed diabetes.[83–85] A modeling study showed that the ADA guidelines would detect 38.9% more cases of prediabetes and 24.3% more cases of T2DM than the USPSTF guidelines. As the most updated USPSTF guidelines have a set of limited criteria and a set of expanded criteria, a cross-sectional analysis found that using the limited criteria resulted in a sensitivity of 47.3% and specificity of 71.4% while the expanded criteria yielded a higher sensitivity of 76.8% with a lower specificity of 33.8%.[86] In comparison, ADA recommendations would capture more individuals with undiagnosed diabetes with a sensitivity of 88.8–97.7% but with less specificity ranging 13.5–39.7%.[87]

Overall, targeted screening in individuals aged 45 years and older with additional risk factors as recommended by the ADA and USPSTF have been shown to be cost-effective.[88]

A special consideration is needed for ethnic/racial minorities, in whom the prevalence of diabetes and its related complications are higher than among whites. Indeed, in 2017–2018, diabetes frequency was highest among American Indian/Alaska Natives (14.7%), followed by people of Hispanic origin (12.5%), non-Hispanic blacks (11.7%), non-Hispanic Asians (9.2%), and lowest in non-Hispanic whites (7.5%).[6] Non-Hispanic blacks have the highest rates of diabetes-related end-stage renal disease, and hospitalizations for lower extremity amputations and stroke.[6] The 2015 USPSTF recommendations included an expanded criteria, recommending that the following racial/ethnic groups - African Americans, American Indians or Alaskan Natives, Asian Americans, Hispanics or Latinos, or Native Hawaiians or Pacific Islanders - be considered for screening at a younger age or at a lower BMI than the traditional target population.[2] A study of the 2015 USPSTFcriteria showed that the use of the limited screening criteria (without consideration of race/ethnicity as a separate risk factor) has a limited sensitivity for detecting dysglycemia in all minority groups.[86] This was more so among Asians, who are known to have an increased risk for developing diabetes at a lower BMI cut-off.[89] In amother study, racial/ethnic minorities detected with dysglycemia using USPSTF screening criteria were younger and/or had a

more normal weight compared to whites.[90] Lastly, the 2015 USPSTF systematic review of the evidence identifieed a significant research gap in evaluating the risks and benefits of screening on racial/ethnic minorities.[91]

Conclusion

Screening for for diabetes or prediabetes is dictated by the burden of the conditions, the recognizable pre-diabetic and prolonged latent diabetic phases, and the availability of reliable, high-performance and widely acceptable detection tests. Screening for diabetes or prediabetes does not appear to have adverse psychosocial consequences. There are accepted and cost-effective treatments (lifetsyle modification and metformin) for diabetes prevention, but the effect of these therapies on cardiovascular outcomes remains to be unequivocally proven. There is an incremental benefit of intensive multifactorial therapy over current standards in people with screen-detected diabetes. Economic models support targeted screening for both prediabetes and diabetes. Overall, there is adequate evidence to justify the implementation of opportunistic screening for undiagnosed diabetes and prediabetes among asymptomatic high-risk individuals preferably using the ADA or USPSTF criteria, with a re-screening interval of 3 years.

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Key Points

- Clinic-based opportunistic screening for prediabetes and diabetes among high risk individuals is feasible using fasting plasma glucose and/or HbA_{1C}.
- The management of screen-detected diabetes can be optimized using a multifactorial intervention that targerts cardiovascular risk factors above and beyond glycemia.
- Prediabetes is primarily managed by lifestyle modification, but a select group of prediabetic individuals are eligible for initial metformin therapy
- Screening for prediabetes and diabetes conducted at a 3-year interval is potentially cost-effective.

Synopsis

Overt type 2 diabetes (T2DM) is preceded by prediabetes and latent diabetes (lasts 9–12 years). Key dysglycemia screening tests are fasting plasma glucose, and hemoglobin A_{1C}. Screen-detected T2DM would benefit from a multifactorial management of cardiovascular risk beyond glycemia. Prediabetes is best addressed by lifestyle modification, with the goal of preventing T2DM. While there is no trial evidence of prediabetes/T2DM screening effectiveness, simulations suggest that clinic-based opportunistic screening of high risk individuals is cost-effective. The most rigorous extant recommendations are those of the American Diabetes Association (ADA) and US Preventive Services Task Force (USPSTF), which advise opportunistic 3-yearly screening.

Clinics Care Points

- Undiagnosed type 2 diabetes and prediabetes are frequent and generally asymptomatic disorders, and thus can be detected early.
- Opportunistic screening for undiagnosed type 2 diabetes or prediabetes in the clinical setting, can be done among high-risk individual, at a 3-year frequency, and using fasting plasma glucose and/or glycosylated hemoglobin.
- Screen-detected type 2 diabetes is treated using a multifactorial approach (lifestyle modification and drugs) targeting glycemia and other cardiovascular risk factors.
- Prediabetes is best addressed using lifestyle modification, and metformin in select number of cases.

Table 1.

Practical advantages and limitations of biochemical screening tests for diabetes

Test	Advantages	Limitations
Random blood glucose	Easy to obtain; no fasting required; inexpensive	Prompt processing (<2 hours) needed, thus the high risk of errors; measurement can be affected by numerous factors (short-term lifestyle changes, time since prior meal, etc.)
Fasting plasma glucose	Relatively cheap and simple; single plasma glucose level measured; highly correlated with presence of complications	Patient needs to fast overnight (at least 8 hours), potential for processing error; measurement can be affected by short term lifestyle changes, risks of phlebotomy
75g-oral glucose tolerance test	Gold standard for the diagnosis of diabetes; most sensitive test for impaired glucose tolerance	Requires 8-hour fast, lengthy and requires commitment of nurse staff, overall test-retest reproducibility lower than with other tests
Glycated hemoglobin (HbA_{1C})	Stable long-term glycemic marker; no fasting required; not affected by short-term lifestyle changes; requires venous blood or a point of care testing capillary sample, lower intraindividual variability (<2%) than fasting plasma glucose	Value may vary with assay method used; Potential errors related to non-glycemic factors as hemoglobinopathies and anemia; insensitive for detection of impaired glucose tolerance; costly in comparison to glucose testing; limited availability in some areas of the world

Table 2.

Diabetes and prediabetes screening recommendations from major professional organizations in the United States

Organization	American Diabetes Association (ADA).	US Preventive Services Task Force (USPSTF)	Endocrine Society
Screening Criteria	**1** Overweight or obese adults (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) with ≥ 1 risk factor: • 1st degree relative with diabetes • High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) • History of CVD • Hypertension • HDL-cholesterol <35 mg/dL and/or triglyceride >250 mg/dL • PCOS • Physical inactivity • Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans) **2** Patients with prediabetes **3** Women with prior diagnosis of GDM **4** For all other patients, testing should begin at age 45 years	**1** Adults aged 40 to 70 who are overweight or obese **2** Consider screening earlier in persons with ≥ 1 risk factor: • Family history of diabetes • History of GDM or PCOS • Racial/ethnic groups (African Americans, American Indians or Alaskan Natives, Asian Americans, Hispanics or Latinos, or Native Hawaiins or Pacific Islanders)	**1** Adults aged 40–75 years, screen for all 5 components of metabolic risk: • Elevated blood pressure • Increased waist circumference • Elevated fasting triglycerides • Low HDL-cholesterol • Elevated glycemia
Screening Tests	**1** Fasting plasma glucose **2** 75-g OGTT **3** Hemoglobin A_{1c}	**1** Fasting plasma glucose **2** 75-g OGTT **3** Hemoglobin A_{1c}	**1** Fasting plasma glucose **2** 75-g OGTT **3** Hemoglobin A_{1c}
Re-screening Intervals	**1** Patients with prediabetes should be tested annually.	Every 3 years	**1** Patientswith prediabetes should be tested at least annually

Organization	American Diabetes Association (ADA).		US Preventive Services Task Force (USPSTF)	Endocrine Society	
	2	Women with prior diagnosis of GDM should have lifelong testing at least every 3 years		**2**	If do not yet have atherosclerotic CVD or T2DM and already have ≥ 1 risk factor, screen every 3 years
	3	For all other patients, re-screen at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.			

BMI: body mass index, CVD: cardiovascular disease, GDM: gestational diabetes, HDL: high density lipoprotein, OGTT: oral glucose tolerance test