Evidence Tips the Scale Toward Screening for Hyperglycemia

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Screening and early detection for hyperglycemia is a topic of considerable interest, and there is debate as to its overall benefits (1). Policies for screening vary from the position of the American Diabetes Association (2), which recommends glucose testing in all people aged 45 years and over or at high risk for type 2 diabetes, to the position of the U.S. Preventive Services Task Force (USPSTF), which recommends only testing those with sustained hypertension (3). The USPSTF, however, is deliberating its new draft recommendations, which broaden the criteria for type 2 diabetes and prediabetes screening (http://www.uspreventiveservicestaskforce.org/Page/Document/draft-research-plan49/screening-for-abnormal-glucose-and-type-2-diabetes-mellitus). As screening and early detection for hyperglycemia remains a topic of great interest, the article from Herman et al. (4) in this issue of *Diabetes Care* is timely. Specifically, Herman et al. (4) report on the beneficial effect of type 2 diabetes screening on cardiovascular (CVD) morbidity and mortality in the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) trial.

Diabetes is a global problem, affecting 387 million people worldwide (5), that is growing in all countries, in urban and rural areas and projected to affect approximately 600 million individuals by 2035 (5). Type 2 diabetes (accounting for about 95% of all diabetes cases) often exists asymptomatically (6), and approximately 50% of cases globally (varying from 30% to 80% across countries) remain undiagnosed (1). Eighty percent of people with diabetes live in developing countries, and the majority of those affected are aged 40–59 years (5). In addition to the human toll of the disease by way of multiple complications (including premature mortality; heart, kidney, and eye disease; stroke; amputations; physical disability; poorer mental health; and loss of quality of life), diabetes impacts economies of individuals, families, and societies and is estimated to cost the world $612 billion annually (5).

ADDITION-Europe is a randomized controlled trial assessing the effectiveness of intensive treatment compared with routine care on 5-year CVD incidence and mortality in people with screen-detected type 2 diabetes (7). Participants in the study were individuals aged 40–69 years without a previous diagnosis in the U.K., Denmark, and the Netherlands. Study results indicate that after 5.3 years of follow-up, there were no significant differences in the incidence of first CVD event between the intensive-treatment (7.2%) and the routine-care groups (8.5%) (hazard ratio 0.83 [95% CI 0.65–1.05]) (7). There were also no significant differences in all-cause mortality between groups (6.2% and 6.7%, respectively; hazard ratio 0.91 [95% CI 0.69–1.21]) (7).

While the ADDITION-Europe study did not show significant benefits of intensive treatment compared with routine care on CVD incidence or mortality in individuals with screen-detected diabetes, the trial was unable to answer whether there are differences in CVD outcomes in individuals with screen-detected type 2 diabetes compared with those whose diabetes remains undetected and therefore untreated until time of clinical diagnosis. Given that it is not ethically feasible to conduct a trial to directly answer this question in humans, Herman et al. (4) used a validated and well-constructed computer simulation model (Michigan Model for Diabetes) to estimate the risk reductions associated with screening and intensive treatment, screening and routine treatment, and no screening with either a 3- or 6-year delay in routine treatment for the management of type 2 diabetes and the prevention of CVD. Results of the simulation point to substantial benefits of screening and routine care compared with a 3-year delay in diagnosis and treatment after 5 years. Specifically,

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compared with a 3-year delay, screening and routine care was associated with a 3.3% absolute risk reduction (ARR) and a 29% relative risk reduction (RRR) in incidence of CVD outcomes and a 1.2% ARR and a 17% RRR in all-cause mortality (4). These benefits were extended even further when compared with a 6-year delay in treatment and care, which was associated with a 4.9% ARR and a 38% RRR in CVD incidence and a 1.9% ARR and a 24% RRR in all-cause mortality (4).

Although the ADDITION-Europe study and the simulation model were well designed and conducted, a few issues are important to consider. First, the trial was done in populations with somewhat lower type 2 diabetes prevalence (5), and it is not known if similar results would be found in populations whose prevalence (especially that of undiagnosed diabetes) is much higher. Second, an assumption of the study, done in high-income countries, was that routine and follow-up care after diagnosis were good. It is not clear how the results would look in low-income settings that lack good type 2 diabetes care, infrastructure, and resources.

Regardless, the analysis by Herman et al. (4) gives support to the benefit of screening for type 2 diabetes in preventing CVD morbidity and mortality. Furthermore, although not addressed by Herman et al., prediabetes and type 2 diabetes are part of a continuum, needing the same screening and diagnostic tests and requiring the same initial treatment (i.e., lifestyle intervention or metformin) (1), and a large body of evidence now exists that identifying people with prediabetes (impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]) and delivering lifestyle, drug, or multicomponent intervention can considerably lower the risk of type 2 diabetes (8) and related complications (9–14). Thus, screening would help promote the implementation of effective prevention for those at high risk for type 2 diabetes (15).

Table 1—Evidence for hyperglycemia screening

Considerable and growing disease burden	• 387 million people living with diabetes worldwide (5) • 28 million people living with diabetes in the U.S. (15) • 316 million people living with IGT worldwide (5) • 86 million people living with prediabetes in the U.S. (21) • Annual diabetes expenditure has reached $612 billion worldwide (5) • Annual diabetes expenditure has reached $176 billion in the U.S. (15)
Detectable early stage of the disease	• 50% (range 30–80%) of diabetes is undiagnosed worldwide (5) • 27% of diabetes is undiagnosed in the U.S. (6) • Diabetes may be present for as long as 9–12 years prior to clinical diagnosis (1) • IFG and IGT are asymptomatic, detectable, intermediate states of hyperglycemia (1) • 90% of prediabetes is undiagnosed in the U.S. (1) • Average duration of prediabetes is 7.8 years in men and 9.8 years in women (22) • Estimated 4.7–12% annual incidence of progression from IGT and/or IFG to type 2 diabetes (23)
Evidence of benefit for early treatment of hyperglycemia	• Reduction in incidence of CVD and mortality (4) • Reduction in the incidence of retinopathy (9) • Reduction in incidence of diabetes among people with IGT (24) • Regression of prediabetes to normoglycemia (10) • Reduction in cardiometabolic risk factors (11) • Reduction in the development of metabolic syndrome (12) • Reduction in the prevalence of urinary incontinence in women (13) • Improvement in quality of life (14) • Evidence for cost-effectiveness of early detection and treatment (16–19) • Limited psychological impact on participants (20)

Another important factor to consider with regard to screening is its cost-effectiveness. A recent systematic review by Waugh et al. (16) examined the cost-effectiveness of screening for both type 2 diabetes and prediabetes. Despite differences in screening interventions, country setting, and target population in the included studies, the results of this review indicated that screening for type 2 diabetes and prediabetes is more cost-effective than no screening, and screening followed by intervention in both type 2 diabetes and IGT has more cost benefit than screening for diabetes alone (16). Furthermore, there is evidence to indicate increased cost benefits for starting screening at an earlier age in high-risk populations (16). An economic model–based evaluation of current screening practices in Bhutan provided evidence that screening for high-risk individuals (those who are overweight, obese, or aged 40 years and older) in primary care centers is economically effective, thereby indicating the value and feasibility of screening in low-resource settings (17). Other studies from the U.S. have indicated that screening for type 2 diabetes is cost-effective from a health systems standpoint (18) and is most effective when initiated between age 30 and 45 years and repeated every 3–5 years (19).

In conclusion, the article by Herman et al. (4) critically adds to the body of evidence for the benefit of early detection and treatment of type 2 diabetes. Furthermore, considerable evidence exists for type 2 diabetes prevention among people with prediabetes, and screening for hyperglycemia is the first step toward delivering interventions to this subpopulation (over 90% of whom remain undetected). Safe and reliable tests are available for hyperglycemia screening (1), and evidence suggests that screening for hyperglycemia is cost-effective and causes little harm (1,20). Of course, follow-up of newly detected prediabetes and type 2 diabetes requires sufficient infrastructure to deliver effective lifestyle intervention and high-quality care. The totality of evidence supporting screening for hyperglycemia is strong (Table 1) and should persuade the USPSTF to adopt its new set of recommendations for type 2 diabetes and prediabetes screening.

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