PERSPECTIVE

Prevention of Type 2 Diabetes: Risk Status, Clinic, and Community

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Although the idea of preventing type 2 diabetes has been articulated since the discovery of insulin, only in the past decade have clinical trials demonstrated that diabetes can be prevented or delayed. These trials found lifestyle intervention reduces diabetes incidence by over 50% and is more efficacious than metformin. Evidence from prevention trials comes from persons with “pre-diabetes” in which blood glucose levels are elevated but not yet in the diabetes range. In normoglycemic persons, lifestyle or drug intervention has little impact on diabetes incidence. Prevention programs are often conducted outside the clinical sector where participants’ glycemic status is usually unknown; these programs may include many normoglycemic participants, which greatly reduces cost-effectiveness. An economically sustainable system for diabetes prevention will require effective partnerships among the clinical sector, community-based lifestyle programs, and third-party payers to ensure that limited resources for diabetes prevention are focused on persons at high risk of diabetes.

KEY WORDS: diabetes; prevention; glycemic status; cost-effectiveness.

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In 1921, the year insulin was discovered, Elliott Joslin published an impassioned appeal for the prevention of type 2 diabetes. He declared, “*The physician should take pride in the prevention of diabetes in his practice...The physician should consider it as important to prevent his patients acquiring diabetes as he feels it incumbent on himself to vaccinate them against small pox or typhoid fever, or to protect them from exposure to tuberculosis.*”^(1, p. 83). Eighty years later two landmark randomized trials in persons with impaired glucose tolerance were published, the Finnish Diabetes Prevention Study² and the US Diabetes Prevention Program (DPP)³. Both trials demonstrated that the 3-year risk of developing type 2 diabetes was reduced by 58% in those receiving lifestyle interventions; the DPP also found that diabetes risk was reduced by 31% in those who received the drug metformin. The DPP also found that lifestyle intervention, unlike metformin, had similar efficacy in persons with potent diabetes genotypes as in those without the diabetes genes^{4,5}. Furthermore, the lifestyle intervention had consistent effects across

age, gender, and race/ethnicity² and resulted in improvements in cardiovascular risk factors⁶.

Since publication of the Finnish and US studies, as well as a number of other key trials—all of which were performed in persons with impaired glucose tolerance⁷—there have been renewed calls for translation of prevention science into clinical and public health practice, with special emphasis on the high risk, often referred to as “pre-diabetes”⁸. However, based on our experience working with public health programs, as well as the emerging literature on translation of lifestyle programs for diabetes prevention, these efforts may include a high proportion of low-risk, normoglycemic participants. For example, in a recent journal issue reporting on nine studies that attempted to translate the DPP lifestyle intervention into real-world settings, only about 50% of study participants had evidence of pre-diabetes^{9–11}. If limited resources for intensive lifestyle interventions are devoted to large numbers of persons who are unlikely to develop diabetes, we believe it will be difficult to realize the hoped-for health and economic benefits of diabetes prevention.

POTENCY AND PREVALENCE OF PRE-DIABETES

Pre-diabetes refers to blood glucose levels that are elevated, but not in the diabetes range. In the United States pre-diabetes is defined as fasting glucose between 100 and 125 mg/dl (impaired fasting glucose, IFG), or glucose between 140 and 199 mg/dl measured 2 h after a 75-g glucose load (impaired glucose tolerance, IGT)¹². In most other countries, however, IFG is defined as fasting glucose between 110 and 125 mg/dl¹³.

All clinical trials for prevention of type 2 diabetes were carried out in persons with IGT, and one drug trial included persons with IFG⁷. Two trials found that the benefits of lifestyle intervention on diabetes incidence persist 7–20 years after the end of active intervention^{14,15}. Trials in low risk populations without pre-diabetes would require extremely large, long and expensive studies because the annual incidence of diabetes in the normoglycemic population is well below 1%¹⁶. This is in contrast to annual incidences of 5%–10% observed in participants with pre-diabetes in observational cohorts^{17,18}, and in the control arms of the randomized trials^{2,3}. Some may argue that if diabetes prevention is focused on the high risk, the public health impact will be limited because pre-diabetes is rare. However, in a now classic population-based cohort study of 6-year diabetes incidence, persons with pre-diabetes at baseline (defined as IGT or IFG 110–125 mg/dl) accounted for only 16% of the population, but they contributed over 60% of new cases of diabetes that occurred¹⁷. Based on evidence from past efficacy trials showing persons with IGT benefit greatly from structured lifestyle intervention, it is currently estimated

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that nearly 14% of the US adult population, or about 28 million persons, have IGT and should receive intervention¹⁹. Some argue that benefits may extend to the larger population with any form of pre-diabetes (IGT and/or IFG)^{8,19}.

DIABETES PREVENTION IN PERSONS AT LOW RISK

Evidence for diabetes prevention in persons from the general population, including those with normoglycemia, is not encouraging. In the MRFIT trial the 6-year incidence of diabetes in men receiving dietary counseling was compared with that of men given usual care²⁰. In non-smokers, 60 percent of whom had normal fasting glucose, there was a statistically significant but small reduction in diabetes incidence of 18%. There was no effect on diabetes incidence in men who smoked. It is unlikely that this weak reduction in diabetes incidence was the result of poor weight loss. The non-smokers who received counseling maintained a 6-year weight loss of 4.6 lbs (−2.4%) compared to weight loss in usual care of −0.2 lbs (−0.1%). This weight loss is comparable to that achieved by persons with IGT in the Finnish and DaQing prevention trials in which 7-year and 20-year diabetes incidence was reduced by 36% and 43%, respectively^{14,15}.

The XENDOS study²¹, a 4-year randomized controlled trial for prevention of type 2 diabetes using the weight loss drug orlistat, included participants with IGT and with normal glucose tolerance. In participants with IGT the incidence of diabetes was reduced statistically significantly by 45%, but in those with normal glucose tolerance there was no effect on diabetes incidence. Weight loss, however, was virtually identical in those with IGT (−5.7 kg) and with normal glucose tolerance (−5.8 kg). A more recent smaller 3-year randomized trial of orlistat²² was carried out in participants who were predominantly normoglycemic, and although this trial found a statistically significant reduction in diabetes incidence, the reduction represented a difference of only nine cases.

Seidel et al.²³ conducted an innovative 6-month, one-arm lifestyle intervention trial to reduce cardiovascular risk factors in an obese urban population. The intervention was a shortened version of the very effective Diabetes Prevention Program core curriculum modified for group sessions. Fifty-nine percent of participants, however, had normal fasting glucose. Mean weight loss was not reported, but 41% of participants had lost ≥5% of body weight at the 6-month follow-up. Surprisingly, the proportion of participants with IFG increased statistically significantly from 41% to 61%. Others have also noted declines in insulin sensitivity following diet-induced weight loss in obese, but metabolically healthy persons²⁴.

RESOURCE IMPLICATIONS OF INTERVENING IN THE LOW RISK

Risk status plays a key role when making economic decisions on how best to improve health. Cohen et al. point out that, "In general, whether a particular preventive measure represents good value or poor value depends on factors such as the population targeted, with measures targeting higher-risk populations typically being the most efficient" (²⁵, p. 662). The majority of adults who are currently normoglycemic have a

low likelihood of developing diabetes, and the benefits of intervention for them remain unproven. In contrast, people with pre-diabetes have a very high likelihood of developing diabetes, and the evidence that intervention will benefit this group is well established. Although primary prevention of type 2 diabetes is not a new intervention concept, evidence-based prevention programs have not been established, and it is likely that their value will be scrutinized and judged in stricter terms than currently accepted and reimbursable interventions.

The two most rigorous studies modeling the long-term economic value of diabetes prevention based their results on data derived exclusively from interventions in persons with pre-diabetes^{26,27}. Even so, neither study suggested that prevention of type 2 diabetes will automatically result in cost savings. One of the studies observed that even if intervening in health plans' pre-diabetic patients raises all patients' costs by only \$2.30 per month, this would increase total US health care costs about 1 percentage point as we struggle to keep annual increases in costs to single digits (²⁷, p. 261). By investing diabetes prevention resources in low risk persons we risk not only raising health care costs even more dramatically, but also inadvertently denying these limited resources to higher risk persons who will benefit greatly, but remain unidentified.

BARRIERS TO IDENTIFICATION OF PERSONS WITH PRE-DIABETES

The largest community-based translation study published to date reported achieving weight loss goals nearly identical to those of the DPP¹⁰. During the 16-week intervention, weight loss was 6.7%, and 45% of the 293 participants lost 7% or more of their body weight. Comparable figures in the DPP were a mean weight loss of 7% with 50% of participants losing 7% or more of their body weight. Yet because of difficulty in obtaining information on participant's glycemic status only 52% of participants in this successful translation study had evidence of pre-diabetes. However, it is estimated that over a 3-year period 70% of primary care patients will have blood glucose measurements recorded in their medical record²⁸. Nevertheless, there is very limited reimbursement for clinicians to identify and counsel patients with pre-diabetes. In addition, most clinical settings are not designed to provide lifestyle programs of the intensity and duration required for prevention of type 2 diabetes. Many clinicians also find it quite challenging to provide good care for patients who have established diabetes.

Because of these factors the clinical sector may fear that attempts to address pre-diabetes will overwhelm the clinical system. Therefore, efforts to establish diabetes prevention programs often take place outside the clinical sector, using community-based organizations to deliver lifestyle intervention²⁹. Clinical settings in which glucose testing occurs, however, do not routinely communicate patients' glycemic status to non-clinical providers, making identification of persons with pre-diabetes by community-based programs very challenging. For persons without access to regular health care the likelihood of receiving glucose testing, as well as communication of test results outside the clinical sector, is extremely low.

Currently accepted diagnostic tests for pre-diabetes require an overnight fast, blood draws, and are not easily administered

and evaluated by non-clinical staff in the community setting. To compensate for this, community-based programs often use relatively informal "paper and pencil" tests to identify the high risk. These tests are based on characteristics such as body weight, age, ethnicity, and family history. However, the tests are intended for use in screening, rather than diagnosis, of pre-diabetes and those who test positive even with formally developed screening instruments often include a majority who are normoglycemic³⁰.

There is also the perception that lifestyle programs for weight loss and physical activity are beneficial for everyone regardless of their diabetes risk, and identification of risk status is therefore unnecessary. This view fails to appreciate the economic implications of expanding relatively resource-intensive lifestyle programs to much wider segments of the US population. Others believe that broader policy interventions that do not target individuals, but instead target factors such as food pricing and the physical environment, will be more effective in preventing type 2 diabetes. Although philosophically appealing, this view currently has little conclusive scientific support^{31,32}, nor will such long-term approaches provide needed preventive services to current generations of persons at high risk of developing diabetes in the near future.

WHAT IS NEEDED TO IMPROVE IDENTIFICATION AND PREVENTION IN THE HIGH RISK?

A reliable diagnostic test for pre-diabetes administered outside the clinical sector would greatly help maximize the benefit of diabetes prevention and reduce economic costs. Two recent efforts using "risk scores" based on personal characteristics, and limited clinical information not requiring measures of blood glucose, hold significant promise for identifying those at high risk^{33,34}. Similar to findings based on blood glucose, well-developed risk scores can identify a minority of the population that account for a majority of new cases of diabetes³³. The HbA1c test, which does not require fasting, is also receiving attention as a possible alternative to the fasting and 2-h blood glucose diagnostic tests³⁵. This is a promising development, but work remains before this test becomes accepted within the clinical sector as a diagnostic test; no doubt, further challenges remain before a convenient HbA1c test (e.g., dried blood spot or point of care testing) can be accepted for use outside the clinical setting.

Although we strongly support efforts outside the clinical sector to provide lifestyle intervention to persons with pre-diabetes, four factors underscore the importance of keeping the clinical sector actively involved in diabetes prevention. First, the most accurate information on persons' glycemic status currently resides within the clinical sector, and this is unlikely to change within the foreseeable future. Second, regardless of the diagnostic test or setting for identification of persons with pre-diabetes, substantial numbers of persons with undetected diabetes may be identified¹⁹; these persons need access to the clinical sector in order to receive diabetes treatment and follow-up. Third, because persons with pre-diabetes are at such elevated risk of developing type 2 diabetes, lifestyle alone may not be adequate for some persons with pre-diabetes, and pharmacotherapy (i.e., metformin) may be

additionally required⁸. Fourth, clinicians can play a key role in creating broader acceptance and population demand for diabetes prevention. However, until appropriate reimbursement mechanisms are developed, clinicians will be unable to spend even the modest amount of time required to counsel high risk patients about the importance of diabetes prevention and to refer them to effective lifestyle programs in their community. The current practice of referring patients with musculoskeletal injuries to physical therapy providers, or referral for patients with diabetes to diabetes educators, offers some precedent, but reimbursement schemes for these practices are well established.

There is now significant movement in Europe toward large-scale diabetes prevention efforts involving both the community and primary care³⁶⁻³⁸. One can only speculate about why progress in the US has been slow, but a combination of factors including concerns about clinician workload, a bias toward requiring prevention activities to be cost-saving rather than cost-effective, little precedent for effective clinical-community partnerships, and uncertainty about the direction of health care reform likely account for the lack of progress. There is now increasing evidence, however, that structured lifestyle intervention programs conducted in US communities, and outside the walls of the clinical sector, can closely approximate the weight losses achieved during active intervention in the highly efficacious DPP diabetes prevention trial^{10,29}, and at substantially lower cost³⁹. However, no organized effort, even on a pilot demonstration basis, currently exists to design, develop, and evaluate the impact of practical referral mechanisms between primary care and community-based lifestyle programs for diabetes prevention. Such an effort is sorely needed and will require systematic cooperation among clinical care systems, community-based lifestyle programs, and third-party payers.

We believe that a reduction in the health and economic burden of diabetes will not be achieved until the large population of adults with pre-diabetes is identified and given access to effective lifestyle intervention at reasonable cost. A sustainable reduction in diabetes incidence will require effective partnerships supported by third-party payers, with good communication and clearly defined roles between the clinical sector and community-based lifestyle programs to ensure that limited resources for diabetes prevention are focused on persons at high risk of diabetes.

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