

Steps Toward the Meaningful Translation of Prevention Strategies for Type 2 Diabetes

As a scientific and medical community, we are clearly in a position to take the next logical steps toward the ultimate goal to reduce progression to type 2 diabetes for our populations at risk. One can argue that we no longer need to debate on the incredible increase in obesity and in new cases of type 2 diabetes occurring worldwide. According to the Centers for Disease Control and Prevention, 35% of U.S. adults aged 20 years or older may have prediabetes. When this statistic is applied to the entire U.S. population in 2010, it would suggest that prediabetic states exist in an estimated 79 million Americans aged 20 years or older (1). In addition, it is well recognized that because of both the associated comorbidities and complications and the costs associated with the care of the disease, diabetes will continue to represent one of the major health issues that we will face in the twenty-first century. Furthermore, there is no argument that the major factors contributing to the development of diabetes consist of lifestyle habits (i.e., physical inactivity and dietary intake) and obesity. It is now well documented that both lifestyle modification and metformin appear to be effective modalities in reducing the cumulative incidence of diabetes for at least 10 years (2–4). As such, evidence to date suggests that we are able to identify individuals in “prediabetic states” and that we can delay the progression to overt diabetes, at least as documented with intervention strategies tested in well-designed clinical trials. Thus, it appears that we are at a stage where we can begin discussions on implementing effective prevention strategies at a population-based level. In this regard, it is very timely that the American Diabetes Association (ADA), as part of its 2012–2015 Strategic Plan, will focus resources in the area of primary prevention. Specifically, the ADA’s strategic plan calls for a specific focus to not only improve outcomes for people with diabetes, but those with prediabetes as well (5).

The ADA’s Strategic Plan, in many ways, relies on and specifically promotes

the effective translation of the clinical research findings from the prevention studies to the community and primary care levels. As specifically outlined (5), the ADA’s plan proposes to monitor progress in the prevention of diabetes by specific metrics, and it is proposed that by the end of 2015, the percentage of Americans with prediabetes who are aware of their condition will double from 7.3 to 15%. In addition, the plan calls for at least a 10% increase in the percentage of people with prediabetes who report engaging in specific preventive behaviors including evidenced-based strategies such as weight control and weight loss, physical activity, and healthy eating (5). To achieve these objectives, the following organizational priorities are quoted directly from the ADA’s Strategic Plan:

- Implement a high-impact national awareness campaign focusing on key prevention messages including targeted, culturally competent outreach to high-risk populations
- Advance rapid adoption of American Diabetes Association standards of care for screening and treatment of prediabetes particularly among primary care providers
- As part of the 2012 revision of national standards for diabetes self-management education, develop standards, review criteria and supporting tools for American Diabetes Association-recognized programs to counsel and support people with prediabetes
- Successfully advocate for funding and accessibility of evidence-based prevention programs and for affordable diabetes screening in those with risk factors

If the goals of the ADA are to be met, there will need to be a paradigm shift in our thinking on how we approach prevention. We will need to emphasize different priorities as required to overcome the obstacles that exist in implementing effective preventive strategies today. To complicate matters further, the goal to

implement preventive strategies will need to be accomplished in an era characterized by continued uncertainty in the direction of health care delivery and in a political environment prone to enacting additional legislation regarding reimbursement of health care services.

One of the most important questions we need to answer is how we effectively translate the findings of the well-designed prevention studies to the primary care level. Clearly, lifestyle modification is the key component to any successful prevention initiative. However, lifestyle modification, although successful particularly at the early time points in promoting weight loss, requires the time and considerable effort of our human health care resources. More importantly, as observed in the highly specialized clinical research centers (and in ones that have documented expertise in the disease state management), success achieved with lifestyle modification does not mean that the intervention and technique used in the prevention studies will be applicable and successful given a different infrastructure as noted for a primary care practice. Even with the substantial resources and considerable effort applied to providing instructions in lifestyle modification, observations suggest that the effectiveness for lifestyle intervention wanes over time. In both of the major prevention studies (the Diabetes Prevention Program [DPP] and the Finnish Diabetes Prevention Study [DPS]) and in subjects with type 2 diabetes, lifestyle intervention, after initial success, was still associated with weight regain over time (2,3,6). The human resources required to implement and sustain lifestyle intervention are not trivial, and the question of cost-effectiveness is of paramount importance. In this issue of *Diabetes Care*, two studies are reported on by the DPP Research Group in follow-up of the DPP and the DPP Outcomes Study (DPPOS) and address some of the relevant issues related to the translation of prevention strategies. Specifically, the article by Bray and colleagues (7) comments on the long-term observations of metformin use as a

preventive strategy, whereas the article by Herman and colleagues (8) provides interesting data on the cost-effectiveness of preventive interventions as observed over a long-term period.

In the study by Bray and colleagues (7), the investigators comment on the long-term safety and tolerability of metformin in prevention and on the importance of adherence to metformin in order to achieve the long-term preventive effect. The use of metformin for prevention is clearly not a new idea. The DPP researchers reported years ago that metformin was shown to reduce the development of diabetes by 31% over an average of 2.8 years of follow-up in the DPP (2). Importantly, the observations from that study as obtained from both the placebo and metformin groups indicated that weight loss was the major contributor and a strong predictor of diabetes prevention. Essentially, weight loss accounted for 64% of the metformin versus placebo effect on diabetes prevention (9). The DPPOS, a long-term follow-up of the DPP, included an open-label extension of metformin treatment in those randomly assigned to metformin in the DPP (4). After a median of 10 years of follow-up since DPP randomization, it was reported that both the lifestyle and metformin intervention groups had significantly less diabetes than the placebo group (4). Interestingly, the lower weight observed from the DPP for the metformin participants appeared to be maintained during the DPPOS period and was reported to average approximately 2.5 kg less (4). As stated, weight loss was observed to be the major predictor of diabetes prevention. Unfortunately, there remain considerable concerns with weight loss maintenance with lifestyle modification alone. Thus, the data providing evidence that metformin is associated with “modest, but durable weight loss” over the 10 years of treatment and appears to be safe and well tolerated cannot be overstated. Using a post hoc analysis, the investigators also demonstrated that one of the most important factors in the weight loss with metformin was indeed related to patient adherence (7).

An interesting comment from the article by Bray and colleagues (7) was that the pattern of weight loss from metformin appears to differ from that seen with caloric restriction alone. Specifically, the authors reviewed the observations that suggest that reductions in body weight occurring with metformin but with minimal change in energy expenditure imply that weight loss may primarily

be in the reduction of adipose tissue as opposed to lean tissue mass (7). In addition, the authors commented that the effect of metformin on energy metabolism at the cellular level may mimic effects seen with exercise, i.e., stimulation of the AMP-activated protein kinase cascade. Collectively, the clinical data suggesting “durable weight loss” combined with the proposed cellular effects on energy metabolism continue to support metformin as a viable strategy for widespread translational efforts in prevention.

Another major question for which additional data are provided in this issue of *Diabetes Care* is the cost-effectiveness of prevention strategies: data previously reported used 3 years of DPP data and suggested that screening for prediabetes in overweight and obese subjects and implementing lifestyle and metformin interventions could be cost-effective (8,10). However, other analyses suggested that costs associated with the specific program used to implement lifestyle modification in the DPP study are too high for health plans or for use as part of a national program. In this case, Eddy et al. (11) suggested that less expensive methods are needed to achieve the degree of weight loss seen in the DPP. In this issue of *Diabetes Care*, Herman and colleagues (8) evaluated the 10-year within-trial cost-effectiveness for both lifestyle and metformin on diabetes prevention. The investigators prospectively collected data on resource utilization, cost, and quality of life, and performed economic analyses from health system and societal perspectives. The authors outlined nicely how preventing or delaying the onset of diabetes would greatly reduce the direct medical costs of diabetes from a health system perspective. These costs were outlined to include support of diabetes education and nutritional counseling, self-monitoring of blood glucose, medications, and recognition and treatment of complications (8). The authors stated that from a societal perspective, delay of diabetes onset would reduce health care-related costs to the individual not reimbursed by the health system (time lost from work and usual activities) and would improve quality of life. With this background, Herman and colleagues (8) reported that their economic analysis of the DPP/DPPOS demonstrated the cost-effectiveness of lifestyle when compared with placebo. Metformin was also reported to be marginally cost saving from health system and societal perspectives. As stated, the analyses on

the economic factors involved in prevention should be very beneficial in discussions with health plans and with policy makers in the coming years (8).

In regards to implementation of any new treatment modality, observations suggest a significant delay from the time the clinical research finding is first reported to the time when the results are translated as an integral part of clinical care. However, with the current worldwide burden of new cases of diabetes and with the associated complications and comorbidities, the need for more rapid clinical translation of prevention strategies is not in question. Each year we seem to accumulate more evidence that prevention over a longer-term period may be feasible, as the data do support efficacy of lifestyle and metformin to delay progression to diabetes to some extent over time. The economic analyses related to the cost-effectiveness of the interventions also provide important food for thought. Nevertheless, other important issues related to prevention have not been adequately addressed. Are we really preventing the disease or, in reality, only delaying the diagnosis for a few years as the data may suggest? At what point in the prediabetic state would we suggest that intervention be initiated? Is there a level for A1C that could serve as a “cut point” that would trigger intervention, or would we rely on fasting or postprandial glucose values? What is the role of the oral glucose tolerance test as an initial diagnostic tool as opposed to its use in monitoring? Thus, the data reported in this issue of *Diabetes Care*, combined with the reports over the past few years, provide additional evidence and, therefore, some guidance on the specifics as required to realistically support large-scale translational efforts.

The newly reported data on both long-term follow-up of subjects in the prevention studies and cost analysis, when combined with the specific focus centered on prevention by organizations such as the ADA, will continue to keep the discussion on prevention moving forward. With the current economic realities facing our nation and with the ever-changing health care delivery landscape, the financial costs of such an initiative will indeed drive the discussion. On the one hand, one can argue that we cannot afford to implement prevention on a national level. On the other hand, we could also argue that we cannot afford not to! Perhaps one day the clinical research findings regarding delaying progression to type 2

