A "Spoonful of Sugar" and the Realities of Diabetes Prevention!

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Given the remarkable progress made to date in regard to unraveling the pathophysiology and natural history of type 2 diabetes, identifying at-risk individuals, and evaluating effective clinical interventions for diabetes prevention, it would be very logical to think that assembling the required resources and implementing the "real-world" translation of findings to prevent type 2 diabetes would be only a matter of time. There is no debate on the need for widespread dissemination of effective interventions to delay onset of type 2 diabetes. First and foremost, there is an incredible amount of data defining the factors contributing to the development of diabetes (e.g., physical inactivity, dietary intake, and obesity). Second, we are all aware of the complications and the financial and emotional costs of the disease. Third, we recognize the global burden of the diabetes epidemic given the prevalence and incidence rates of obesity, prediabetes, and type 2 diabetes reported for each region of the world. And finally, it is no longer questioned that clinical interventions that consist of both lifestyle modification and metformin appear to be effective modalities in reducing the cumulative incidence of diabetes for at least 10 years (1–3). So, is there really any further debate needed regarding this topic? As outlined in this issue of the journal, the answer may not be so clear. Given the importance of this topic, our editorial team has featured articles focused on diabetes prevention in this issue of *Diabetes Care*—the topics range from discussion of genetic risk and progression to diabetes to policy development (4–8).

In this issue, Sullivan and colleagues, reporting on behalf of the Diabetes Prevention Program (DPP) Research Group, examined the utility of genetic risk scores (GRS) (as developed from a composite of single nucleotide polymorphisms at loci associated with type 2 diabetes) in predicting progression to diabetes and response to intervention in women with and without gestational diabetes mellitus (GDM) (4). Previously, the DPP Research Group reported that a prior analysis suggested that risk reduction for progression to diabetes in response to metformin was greater among women with GDM compared with women without GDM. Thus, the investigators hypothesized that genetic variability may be contributing to the observation and, if proven, would be an important finding. The data suggested the GRS predicted the presence of GDM, as it was higher in women with as opposed to without GDM. However, the GRS did not appear to be associated with progression to diabetes in high-risk women either with or without a GDM history in any of the study arms. The reasons for this observation are not precisely known, but the authors did state that the possible limitations of the study were small sample size and perhaps the long diabetes-free interval since the index pregnancy case, suggesting the DPP excluded women with GDM who had the highest risk for diabetes progression.

Another topic featured in this issue and of importance to prevention of type 2 diabetes concerns pharmacologic therapies as a viable intervention. In both of the major prevention studies (DPP and the Finnish Diabetes Prevention Study [DPS]) and in subjects with type 2 diabetes, lifestyle intervention has been shown as the cornerstone of therapy. Unfortunately, after initial success, lifestyle intervention appears to be associated with weight regain over time (1–3,9). Thus, consideration of pharmacotherapies to delay progression to type 2 diabetes has been an area of great interest. A major question has been whether these therapies can be cost-effective and whether the benefit outweighs the risk of therapy. We do have some information in this regard, at least for metformin, as in a prior report in *Diabetes Care*, the DPP Research Group provided a report on the long-term safety and tolerability and the long-term preventive effect of metformin (10). Importantly, the observations from that study demonstrated that weight loss was the major contributor and a strong predictor of diabetes

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prevention in both the placebo and metformin groups. In this issue, Garvey and colleagues (5) essentially confirm this observation by demonstrating that it is primarily the weight loss that is responsible for the delay in diabetes development. They provide a report on the effect of treatment with a combination of agents phentermine (PHEN) and topiramate extended release (TPM ER) in subjects classified as having prediabetes or metabolic syndrome (MetS) at baseline. The subjects were evaluated over 108 weeks on the progression to type 2 diabetes and/or cardiometabolic disease. Specifically, the study reported was a subanalysis of the SEQUEL study, a 52-week blinded extension study of the CONQUER trial, a phase 3, randomized, placebo-controlled, double-blind study assessing the effect of PHEN and TPM ER to induce weight loss in overweight/obese subjects when compared with lifestyle alone. At baseline, 475 subjects met the criteria for prediabetes and/or MetS. Subjects were randomized to placebo or to PHEN 7.5 mg/TPM ER 46 mg or PHEN 15 mg/TPM ER 92 mg. After 108 weeks, subjects with prediabetes and/or MetS randomized to placebo or 7.5/46 mg and 15/92 mg PHEN/TPM ER interventions experienced mean percent weight loss of 2.5%, 10.9%, and 12.1%, respectively. This weight loss resulted in reductions of 70.5% and 78.7% in the annualized incidence rate of type 2 diabetes for those receiving 7.5/46 mg and 15/92 mg PHEN/TPM ER, respectively. The reduction in progression to diabetes was clearly related to degree of weight loss. The authors report that the pharmacotherapy was well tolerated over the course of study. The importance of this study is twofold: *1*) it reinforces that the major contributor to achieving a delay in diabetes progression is weight loss rather than any specific agent as the "ability to prevent type 2 diabetes was greatly dependent on the magnitude of weight loss, independent of randomization group" (5), and *2*) it provides additional clinical research evidence of the value of a pharmacotherapy option for prevention of type 2 diabetes. Additional studies are needed that will allow for greater numbers of subjects to be evaluated so as to validate the effectiveness in real-world situations and to confirm the tolerability. But, the study clearly adds to the growing body of evidence demonstrating the value of pharmacotherapy to achieve weight loss as required for diabetes prevention.

Additional articles on prevention featured in this issue relate to the most relevant question of how we effectively translate the findings of the well-designed prevention studies to real-world settings. Can we expect that the success and results observed from studies conducted by the highly specialized academic centers be easily translated to clinical practice? As outlined above, lifestyle modification is the cornerstone to any effective prevention initiative, but implementing and maintaining lifestyle modification at the primary care level requires the time of the health care team, resources, and expertise. Even with the substantial resources and considerable effort applied to providing instructions in lifestyle modification from the research studies to date, observations suggest that the effectiveness of lifestyle intervention wanes over time. So, real-world assessment and outcomes are needed.

As a first step in commenting on real-world translation, Dunkley and colleagues (6) summarize the evidence on effectiveness of translational diabetes prevention programs. As was a stated intention of their study, the authors sought to "examine whether closer adherence to guideline recommendations for diabetes prevention improves the effectiveness of real-world interventions." Thus, they provided a systematic review of studies considering the effectiveness of translational interventions for prevention of type 2 diabetes in high-risk populations. The authors conclude that there is evidence suggesting diabetes prevention programs are effective, but effectiveness varies substantially between programs. They also concluded that "adherence to international guidelines on intervention content and delivery explained much of the variance in effectiveness." Thus, it was the opinion of the authors that diabetes prevention programs could be more effective if guideline adherence was maximized. As outlined by the authors, questions do remain on the best ways to maximize cost-effectiveness and how to maintain long-term compliance of lifestyle modification.

Dunbar and colleagues (7) provide an interesting report on the collaboration and interaction needed at multiple levels to achieve real-world effectiveness for diabetes prevention. Specifically, they report on the Australian lifestyle intervention program Life!. As stated by the authors, the Life! program represents only the second reported, large-scale diabetes prevention program that has reported results, the other being the FIN-D2D study. They also mentioned a recently started U.S. National Diabetes Prevention Program. The article is of interest as the authors reported that their program "demonstrated higher effectiveness than FIN-D2D" and this increased effectiveness was "probably due to the program's systems design with performance measurement." In this regard, the authors provide significant commentary on the policy formation that facilitated its implementation along with an outline of the collaboration between senior policy officials and the research and practice experts. This collaboration was felt to lead to the successful statewide establishment of the program and its intervention and key outcomes.

Despite the promise of diabetes prevention as outlined in studies mentioned above, the article from Drs. Kahn and Davidson provides a somewhat more sobering view of the issue (8). Specifically, Drs. Kahn and Davidson do not dispute the evidence to date demonstrating that lifestyle modification programs focused on weight loss can delay the onset of type 2 diabetes in subjects at high risk of developing the disease. They agree that the goal of diabetes prevention is extremely important, but it is their opinion that "too much information is missing to implement nationwide, community-based diabetes prevention programs, as has been suggested." They make their case that we still need realistic cost-effectiveness studies and that more evidence is needed on specific lifestyle or pharmacologic interventions on outcomes for extended periods. They conclude their article by providing consideration for a different suggested paradigm for prevention. Specifically, they state: "Finally, it may be more beneficial to achieve diabetes prevention by attacking the problem through national policies that reduce our overall

consumption of food. In the long run, a societal solution (not a medical one) to the obesity/diabetes epidemic may end up being the best option."

Finally, given the central role obesity plays in contributing to the development of diabetes, we feature a debate on dietary factors related to this condition. Specifically, we present one of the more intriguing point-counterpoint narratives that our journal has ever published and that is focused on dietary sugar and the crisis in the epidemic of obesity and diabetes. The debate clearly centers on the controversy in regards to sugar-sweetened drinks and the increased dietary intake of glucose and high-fructose corn syrup as a major contributor of obesity and metabolic syndrome. In the point narrative, Drs. Bray and Popkin report that "consumption of soft drinks has increased fivefold since 1950" and that "consumption of sugar-sweetened beverages (SSBs) is related to the risk of diabetes, the metabolic syndrome, and cardiovascular disease" (11). It was of interest that they state that drinking as little as two 16-ounce SSBs per day for a duration of 6 months, an amount that may be commonly consumed among many individuals, induced features of the metabolic syndrome and fatty liver. Thus, from their report, SSBs may be considered a culprit in the epidemic of obesity and the metabolic syndrome. In the counterpoint narrative, Drs. Kahn and Sievenpiper (12) suggest that "there is no direct evidence that sugar itself, in liquid or solid form, causes an increase in appetite, decreases satiety, or causes diabetes." Thus, they state "if there are any adverse effects of sugar, they are due entirely to the calories it provides, and it is therefore indistinguishable from any other caloric food." For the point-counterpoint debate, both author groups clearly defend their positions, and in this regard, it is obvious we have more work to do to fully understand this area of research.

Based on progress to date and knowledge gained, diabetes prevention in real-world settings should be our major focus. By featuring the articles in this issue of *Diabetes Care,* we felt it was our duty as the editorial team to keep the discussion moving forward on this issue. Clearly, the task at hand is difficult, but one our medical community and society cannot afford to ignore. As also outlined, different approaches and collaboration are needed at all levels to successfully implement the programs. We all hope that in the not-too-distant future effective interventions to prevent diabetes in high-risk patients will be routinely integrated in our communities and health care systems as a result of effective collaboration among health care providers, policymakers, payers, and patients themselves. In addition, perhaps at that time, we will also have clarity regarding additional factors in our diet that may be contributors. So, given the knowledge we have on obesity as the key player in the global epidemic of diabetes in general, and given the debate on the issue related to increased dietary sugar consumption in particular, we may have to reconsider the lyrics from the song from Walt Disney's *Mary Poppins*, which states a "spoonful of sugar helps the medicine go down!"

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