Primary Prevention of Type 2 Diabetes: There Are No Simple Solutions!

William T. Cefalu

The marked increase in new cases of type 2 diabetes observed throughout the world and the associated comorbidities represent one of the major health issues we will face in the 21st century. It is also understood that environmental factors such as lifestyle habits (i.e., physical inactivity and dietary intake) and obesity act as initiating factors for progression to type 2 diabetes. A number of studies have confirmed that intensive lifestyle modification is effective in the prevention of diabetes in individuals with impaired glucose tolerance (1,2). Although it is well established that caloric restriction and exercise greatly promote weight loss and improve insulin resistance for those at risk for developing type 2 diabetes, the success of lifestyle intervention over a long-term period is poor. Therefore, strategies to improve risk factors related to progression to type 2 diabetes, i.e., insulin resistance, by pharmacologic or nutritional supplementation represent a very attractive approach. In this regard, pharmacologic agents have shown efficacy in diabetes prevention, but adverse events need to be considered before routine use is recommended (3,4). In addition, other novel risk factors, e.g., homocysteinemia, have been associated with the development of type 2 diabetes, and cellular mechanisms have been postulated that provide an understanding for this effect (5). Until recently, however, there have been no prospective studies to evaluate whether nutritional interventions aimed at effectively treating homocysteinemia will reduce the chances for diabetes development. Nevertheless, the recently reported observations from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), presented in this issue of *Diabetes*, provide new information regarding treating this risk factor and diabetes progression (6). Specifically, the results from the study of Song et al. (6) suggest that a simple attempt to supplement the diet with folic acid and B vitamins in individuals at high risk for development of type 2 diabetes does not attenuate progression to type 2 diabetes (6).

WAFACS was a randomized double-blind placebo-controlled trial that evaluated the effects of a combination pill of folic acid and vitamins B6 and B12 in the secondary prevention of vascular events among high-risk women with prior cardiovascular disease or at least three cardiovascular disease risk factors. The study began in 1998 when the vitamin B supplementation component was added to the Women's Antioxidant Cardiovascular Study (WACS), which was an ongoing study evaluating three antioxidant vitamins, i.e., vitamins C, E, and β-carotene. Specifically, after excluding women who had diabetes, 4,252 women were evaluated at baseline. The hypothesis for WAFACS was that elevated homocysteine levels may contribute to development of insulin resistance and type 2 diabetes and, by effectively treating the levels, the risk for type 2 diabetes would be lowered. Specifically, it was hypothesized that B vitamins may modulate the progression to type 2 diabetes by improving the contributing metabolic parameters implicated in the development and progression to type 2 diabetes such as oxidative damage, inflammation, and endothelial dysfunction (6). Thus, following baseline evaluations, subjects were randomized to the combination pill (2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12) or a matching placebo. Study medications and end point ascertainment were continued in a blinded fashion for a follow-up duration of 7.3 years. At the end of the study, homocysteine levels were reported to be significantly reduced in the active treatment group by 18.5% (group difference 2.27 μmol/l) as compared with that for the placebo group (geometric group mean level 12.28 μmol/l). During the mean follow-up period, 504 women were diagnosed as having type 2 diabetes: 245 incident cases (11.5%) in the active treatment group and 259 (12.2%) in the placebo group. The key finding from the study was that supplementation of folic acid/B vitamins in a high-risk patient population did not attenuate progression to type 2 diabetes.

The strengths of WAFACS included that it was a randomized placebo-controlled trial in a large number of subjects, i.e., over 2,000 subjects in each arm of study. The observation period of over 7 years was significant. The determination of onset of the diabetic state appeared to be well validated and assessed. The limitations of the study outlined by the authors did include the declining compliance over the course of study, but evaluation restricted to women who were compliant did not change the results. In addition, the intervention with a combination pill did not allow assessment or evaluation of individual components. Finally, homocysteine levels were not measured in all subjects. Yet, with the stated limitations, WAFACS was carefully conducted and appropriately evaluated and, as such, did provide novel and important clinical observations.

The observation from WAFACS does not support recommendations for folic acid/B vitamins for diabetes prevention. These data are very clinically relevant given the observations suggesting that elevated levels of homocysteine were independently associated with increased diabetes risk and also suggesting that lowering homocysteine may prevent or reduce risk (5). Clearly, the question addressed by the investigators was relevant and the trial

From the Joint Diabetes, Endocrinology, and Metabolism Program, Louisiana State University Health Sciences Center School of Medicine, New Orleans, Louisiana, and Pennington Biomedical Research Center, Baton Rouge, Lousiana.

Corresponding author: William T. Cefalu, cefaluwt@pbrc.edu.

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needed to be conducted to answer the question. However, given these findings, can we really be surprised by the outcome? Did we really expect such a simple solution to diabetes progression would be in the form of dietary supplementation with inexpensive and readily available nutrients? If anything, this study highlights the current reality that we are facing in that there are no simple or easy solutions to diabetes prevention!

What we do definitively know is that the most effective strategy for diabetes prevention involves lifestyle modifications to favorably impact energy balance, i.e., reduce caloric (energy) intake and increase energy expenditure with enhanced physical activity (1,2). Thus, the real challenge we must address is how to successfully implement and maintain the strategy, i.e., lifestyle modification, in the vast majority of those at high risk for diabetes. What means can be put in place to ensure that the results from landmark studies such as the Diabetes Prevention Program are commonly seen in clinical practice? Clearly, as a society and as a medical community, we need to adopt a different mind-set if we hope to stem the tide of the diabetes epidemic. With regard to being a priority in clinical practice, we need to stress a strategy that provides appropriate resources and fair compensation to providers, nutritionists, educators, etc., so that they can spend the required time necessary to counsel patients to achieve goals directed at diabetes prevention. Such a strategy will not be inexpensive nor easy! However, given that health care costs attributed to overweight/obesity are projected to double every decade and to represent one in every six USD spent on health care in 2030 (7) as well as with the complications and mortality attributed to type 2 diabetes, the real question we must ask is whether we can really afford not to address this situation.

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