



COMMENT ON CEFALU ET AL.

Update and Next Steps for Real-World Translation of Interventions for Type 2 Diabetes Prevention: Reflections From a *Diabetes Care* Editors' Expert Forum.

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The 2016 *Diabetes Care* Editors' Expert Forum on the prevention of type 2 diabetes is both welcome and timely (1). Prevention of type 2 diabetes is not a routine therapeutic goal in clinical practice despite the 1) increasing prevalence of type 2 diabetes, 2) large numbers of at-risk individuals with prediabetes and/or metabolic syndrome, and 3) presence of interventions for effective disease prevention. The only way to stem the rising rates of type 2 diabetes is prevention, and the authors have reviewed copious evidence demonstrating that lifestyle therapy and medications approved for diabetes can effectively delay or prevent progression to type 2 diabetes. Unfortunately, there are no medications approved by the U.S. Food and Drug Administration for type 2 diabetes prevention. The value of this forum is to call attention to this important clinical need and to consider approaches for a more concerted effort toward diabetes prevention.

The forum, however, has two shortcomings. First, there was a relative lack of emphasis on medication-assisted weight loss as a primary treatment approach, whereas conventional diabetes medications were afforded greater discussion. All five medications approved for chronic management of obesity are highly effective for treating type 2 diabetes, and published clinical trials for three of these medications also demonstrate high efficacy for type 2 diabetes prevention, namely, orlistat, liraglutide 3 mg, and phentermine/topiramate

extended release (ER) (2), which was not referenced in the forum. In the Diabetes Prevention Program (DPP) and phentermine/topiramate ER trials (3), 10% weight loss led to a ~80% reduction in type 2 diabetes rates; greater weight loss, for example after bariatric surgery, does not lead to any further reduction in diabetes rates (4). Therefore, weight loss therapy targeting 10% weight loss is maximally effective and can be achieved in many patients using structured lifestyle interventions in conjunction with weight loss medications. Medicine-assisted weight loss additionally results in substantial lowering of blood pressure and improvements in lipids. Thus, a comprehensive approach to weight loss therapy using evidence-based combinations of structured lifestyle interventions and weight loss medications, as described in the American Association of Clinical Endocrinologists clinical practice guidelines for obesity (2), is highly effective in preventing type 2 diabetes in high-risk patients with prediabetes and metabolic syndrome.

The second shortcoming is to focus only on prediabetes as a condition conferring high diabetes risk and to ignore metabolic syndrome. Of course, patients with impaired fasting glucose may satisfy criteria for both; however, 23% of U.S. adults meet criteria only for metabolic syndrome and have normal glucose tolerance (5) yet will have similar rates of conversion to type 2 diabetes as observed in patients with

prediabetes (3). Further, the authors considered as problematic that the large numbers of patients with prediabetes will reduce the feasibility for broad application of intensive or expensive interventions. In this regard, approaches for risk stratification can identify patients at high disease risk and allow for targeting of interventions to optimize benefit/risk ratio and cost-effectiveness. Evaluating patients for metabolic syndrome traits can help with risk stratification. For example, cardiometabolic disease staging in multiple cohorts of overweight/obese subjects identifies a progressive 40-fold increase in risk of future diabetes comparing patients with none, one, or two traits; metabolic syndrome alone; and combined metabolic syndrome plus prediabetes (6). The presence or absence of Metabolic Syndrome traits, and the number of these traits, are used to stratify patients for increasing risk of developing type 2 diabetes. A family history of type 2 diabetes and previous gestational diabetes mellitus also confers a greater risk for future type 2 diabetes. Thus, clinicians or health care systems can use readily available clinical information to identify and target patients with overweight or obesity who are in higher risk strata for type 2 diabetes as candidates for weight loss therapy.

In summary, prediabetes and metabolic syndrome are manifestations of a cardiometabolic disease process that is deserving of treatment to prevent progression to type 2 diabetes. In patients

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who are overweight or obese, medication-assisted weight loss achieving a ~5%–10% decrease in body weight is highly effective. Risk stratification can be used to target more aggressive interventions to those at higher risk in order to optimize the benefit/risk ratio. Finally, any bias in favor of diabetes medications over medication-assisted weight loss for type 2 diabetes prevention is not based on data.

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