RESPONSE TO 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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We thank Dr. Garvey for his letter (1) in response to our 2015 Diabetes Care Editors’ Expert Forum on the prevention of type 2 diabetes (2). We appreciate his comments regarding the importance of the topic and the need for effective preventive strategies. Dr. Garvey also pointed out two shortcomings in our paper that we would like to address.

Dr. Garvey first stated that “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” (1). He further stated, “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) [3], which was not referenced in the forum” (1). We fully agree that weight loss in the range of 10% does appear to be maximally effective and can indeed reduce progression to type 2 diabetes. However, our goal in this Expert Forum was to specifically target studies whose primary aim was primary prevention of type 2 diabetes. For instance, the study evaluating phentermine/topiramate ER trials (4) was not primarily a type 2 diabetes prevention trial but rather reported type 2 diabetes incidence as a “subanalysis of a phase 3, randomized, placebo-controlled, double-blind study of overweight/obese subjects (BMI ≥27 to ≤37.5 kg/m2) with two or more comorbidities.” Thus, although we appreciate Dr. Garvey’s point and do not dispute the evidence he presented for weight loss per se driving diabetes remission, our intent was to feature studies with a main goal of primary prevention of type 2 diabetes. In addition, although it is clear that weight reduction in obese subjects with prediabetes and metabolic syndrome reduces the risk of type 2 diabetes, this is not true in Asian populations with normal BMI and impaired glucose tolerance (IGT). Both Indian and Chinese prevention trials have shown that we can achieve significant reduction in the incidence of type 2 diabetes without weight loss by lifestyle management.

The second shortcoming Dr. Garvey suggested was our “focus only on prediabetes as a condition conferring high diabetes risk and to ignore metabolic syndrome.” Again, for this Expert Forum, we tried to identify those cohorts within the broader category of “prediabetes” for which there were specific reported interventions. Clearly, the most consistently studied group of individuals with prediabetes has been those with IGT. We recognize that the “prediabetic” state encompasses impaired fasting glucose (IFG), IGT, and combined IFG/IGT. These three subcategories may represent somewhat different pathophysilogies, and individuals in all three—with or without metabolic syndrome—have been shown to have increased diabetes risk (5). Furthermore, it is understood that individuals at the lower end of the glycemic range in all three groups are at lower risk for progressing to diabetes than those at

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**References**

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4. Danish Diabetes Institute, Danman, Kuwait
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the higher end. Although we are not ignoring the fact that other components of metabolic syndrome are also associated with an increased risk of type 2 diabetes, there are many other factors that increase risk in people with prediabetes. In addition, very few studies have evaluated the primary prevention potential specifically in people with metabolic syndrome.

We do not disagree with Dr. Garvey's statements; rather, we want to clarify that our approach was primarily to focus on major primary prevention programs. We agree that heightened awareness and further evaluation are required for individuals in all three subgroups of prediabetes (IFG, IGT, and combined IFG/IGT) and especially for those in each subgroup who are at the higher end of the glycemic range and thus at higher risk. We also recognize Dr. Garvey's work on weight loss and diabetes prevention and agree that weight loss in obese people may be the most important factor in type 2 diabetes prevention.

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References
1. Garvey WT. 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. Diabetes Care 2016;39:1186–1201 (Letter). Diabetes Care 2017;40:e21–e22. DOI: 10.2337/dc16-0022
2. Cefalu WT, Buse JB, Tuominen J, 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. Diabetes Care 2016;39:1186–1201
3. Garvey WT, Mechanick JI, Brett EM, et al.; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22:842–884
4. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care 2014;37:912–921
5. Cefalu WT. “Prediabetes”: are there problems with this label? No, we need heightened awareness of this condition! Diabetes Care 2016;39:1472–1477