Diet and diabetes revisited, yet again\textsuperscript{1,2}

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Dietary modification has the potential to appreciably reduce the risk of progression of prediabetes to type 2 diabetes (T2D)\textsuperscript{3}, with several high-profile randomized controlled trials (RCTs) conducted in persons of varying ethnicities in different countries that consistently show a halving of risk (1). The benefit appears to persist many years after the conclusion of the interventions (2). Medical nutrition therapy is the mainstay of treatment of T2D. Compliance with dietary advice results in improvement in glycemic control and reduction in cardiovascular risk regardless of duration of disease. A meaningful reduction in glycated hemoglobin after intensified nutrition therapy has been observed in patients with longstanding T2D whose oral hypoglycemic or insulin treatment had been optimized (3). Given that most people at risk of or with T2D are overweight or obese, it is hardly surprising that weight loss (typically ≥5% of initial body weight) has been the most consistent nutrition-related determinant of positive outcomes (4). Reducing excess adiposity is the cornerstone of all nutrition recommendations for prevention and treatment of T2D. Two systematic reviews and meta-analyses published in this issue of the Journal relate to aspects of nutrition for which there is less universal agreement (5, 6).

Livsey et al (6) explored whether there is a dose-response relation between dietary glycemic load (GL) and risk of developing T2D. The meta-analysis, which included 24 prospective cohort studies and 7.5 million person-years of follow-up, showed a relative risk for T2D of 1.45 (95% CI: 1.31, 1.61) for a 100-g increment in GL, a relation apparent at all doses of GL >95 g/2000 kcal. A further additional novel finding was that 97% of the heterogeneity between studies was explained by validity of the dietary instrument, sex (the association between GL and T2D was significant only in women), and ethnicity (the association was stronger in European Americans than in other ethnicities combined). The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined). The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking association was stronger in European Americans than in other ethnicities combined. The sex difference may be explained by sex differences in dietary behavior or standard of recording rather than inherent/genetic differences, and the more striking

Although we acknowledge that the impressive dose-response effect provides strong support for the suggestion that dietary GL is a significant determinant of subsequent risk of developing T2D, we are not convinced that low GL should be a major defining feature of dietary advice aimed to reduce the risk of T2D. The authors acknowledge the imprecision of published glycemic index (GI) data from which dietary GL is calculated. Furthermore, GL was not a feature of the diets that were clearly shown in well-known RCTs (the highest level of evidence in determining dietary recommendations) to reduce risk of progression to T2D. These diets were first and foremost designed to achieve weight loss with an emphasis on reduction in total and saturated fat and generous intakes of fruit, vegetables, whole-grain cereals, and dietary fiber. Undue emphasis on low-GI foods and dietary GL without clear advice on food choices could result in substantial intakes of foods (including functional foods) that are high in sugars (including high-fructose corn syrup) and/or fats and that are energy dense despite having a low GI. Nutritional recommendations for the “prevention” of T2D are most appropriately based on the results of the RCTs. A diet that is based on appropriate food choices is likely to have a GL of <100 g/2000 kcal without specific advice in this regard.

Ajala et al (5) have made a brave attempt to answer a rather more difficult question: whether any particular dietary pattern or macronutrient distribution is most suitable for inducing weight loss and improving glycemic control and lipid profile in people with T2D. They chose to examine the merits of low-carbohydrate, low-GI, high-fiber, high-protein, Mediterranean, vegetarian, and vegan diets and included in their review RCTs lasting for ≥6 mo in which one or more of these dietary approaches was compared with a control diet, the composition of which was not specified. On the basis of their review and meta-analysis, the authors conclude that the low-carbohydrate, low-GI, Mediterranean, and high-protein diets are effective in improving various markers of cardiovascular risk in people with diabetes and suggest that there may be a range of beneficial dietary options for those with T2D. How valid and novel are these conclusions?

The authors acknowledge the potential confounding and heterogeneity that result from appreciable differences in macronutrient composition of the control diets, the fact that the

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\textsuperscript{3} Abbreviations used: EASD, European Association for the Study of Diabetes; GI, glycemic index; GL, glycemic load; RCT, randomized controlled trial; T2D, type 2 diabetes.

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intervention diets in each group were not identical, the varying duration of the interventions, and the variable quality of the trials. Indeed, one might question whether a meta-analysis of such widely different studies is justified given that meta-analyses are intended for the aggregation of like studies (7). For example, when considering the trials that examined the effects of a low-carbohydrate dietary pattern, the carbohydrate intakes in the interventions ranged from 20 g/d to 45% of energy intake, and the “control” groups included conventional, low-fat, low-GI, and Mediterranean patterns. Given that in many of these studies there is no evidence that the control group was given advice regarding the nature of carbohydrate [essential advice to avoid deterioration of metabolic control on a high-carbohydrate diet (8)], it is hardly surprising that an overall benefit of the low-carbohydrate pattern has emerged. Such heterogeneity might have been managed by subgroup analysis or by the use of a random-effects analysis as Ajala et al have done. We recalculated the data for the low-carbohydrate diet comparisons by using a random-effects model and found the beneficial effect of this dietary pattern to be of more marginal significance (effect size: $-0.28; 95\% CI: -0.56, 0.00; P = 0.05$).

Compliance or lack thereof is a critical issue not considered in any detail by the authors who opted to include only those studies in which the intervention was continued for $\geq 6$ mo. In the single “negative” RCT presented, which examined the effects of a high-fiber diet, Milne et al (9) found that neither of the dietary groups complied with the recommended macronutrient intake over the 18-mo intervention. Thus, if examining proof-of-concept rather than whether people can comply with a particular diet over a prolonged period is of interest, it may be more appropriate to also consider RCTs of shorter duration. Many such studies have shown the improvement in glycemic control, especially when legumes, vegetables, and fruit high in soluble forms of dietary fiber predominate (8).

Ajala et al suggest that there is insufficient evidence to justify the recommendations of, among others, organizations such as the American Diabetes Association (10) and the European Association for the Study of Diabetes (EASD) (8). The former are based on the American Diabetes Association’s evidence grading, and the latter used the Scottish Intercollegiate Guidelines Network system. Both sets of recommendations, which have been updated regularly [Ajala et al did not quote the most recent version (8) of the European recommendations], emphasize the need to take individual dietary preferences into account, and the European recommendations, in particular, emphasize the acceptability of a range of dietary patterns, including the Mediterranean diet, which, in the Ajala et al meta-analysis, was associated with the greatest improvement in glycemic control. Indeed, in all 3 studies included in the analysis, the macronutrient composition of the intervention was well within the range recommended by the EASD. Of the diets favored in the Ajala et al review, only the very-low-carbohydrate diet is not recommended in the official recommendations, principally because there is no long-term confirmation of both safety and efficacy. The same reservations apply to diets in which a particularly high protein intake is recommended (11). Finally, note that a fairly recent RCT that examined the effects of an intervention diet on the basis of EASD recommendations found an improvement in glycemic control similar to the weight mean difference reported by Ajala et al for the comparison of the Mediterranean diet with other diets (3).

Thus, despite our concerns with regard to some aspects of the methodology, accuracy, and interpretation of the Ajala et al study, it is reassuring to note that the conclusions are largely compatible with the US and European nutrition recommendations that have been in place for a number of years. Further debate with regard to the optimal macronutrient composition of preventive and therapeutic dietary prescriptions for T2D is likely. In particular, there is likely to be discussion around whether lower intakes of carbohydrate and higher intakes of protein than are currently recommended are also acceptable. However, even more important in the attempts to stem the tide of the diabetes epidemic and better manage those who have already developed diabetes are some more innovative approaches to encourage long-term compliance with one of the several acceptable dietary patterns. In addition to appropriate food choices, portion size needs to reflect energy requirements to ensure appropriate energy balance. We suspect that this is unlikely to be achieved without also a population-based approach to healthier eating.

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REFERENCES