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LETTER

Long-term outcomes of dietary carbohydrate restriction for HbA_{1c} reduction in type 2 diabetes mellitus are needed. Reply to Kang J and Ma E [letter]

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To the Editor: We thank Drs Kang and Ma for their interest [1] in our study [2], which gives us the opportunity to further discuss our findings and highlight their novelty and importance.

We completely agree with the notion that randomised trials of diets designed to manage diabetes by substituting carbohydrate with protein and/or fat have not, so far, demonstrated that a particular diet composition is superior to another for improving body weight loss or HbA_{1c} in participants with type 2 diabetes after 1 or 2 years [3, 4]. However, our study is fundamentally different from those studies. We have attempted to address the physiological question of whether the macronutrient composition of the diet in itself, independent of weight loss, can affect glycaemic control in patients with type 2 diabetes. For this reason, we opted for full provision of the experimental diets and made sure all participants lost similar amounts of body weight by tailoring their energy intake. We recognise this design may not be as pragmatic or 'real-world'-like, or even applicable to clinical practice, however, it was necessary for the reasons outlined below.

Larsen et al [3] and Krebs et al [4] prescribed hypocaloric diets of different macronutrient composition for 3 and 12 months, respectively, followed by weight maintenance periods of another 9 and 12 months, respectively. These studies reported no significant differences between diet arms in mean changes in body weight and HbA_{1c}. Interventions that involve any hypocaloric diet prescription, and particularly low carbohydrate diets, are inevitably characterised by variable compliance to the experimental diet—which is often poor [5] and declines over time [6]. Invariably, this leads to very large interindividual variability in the final weight change among participants, regardless of dietary macronutrient composition [6, 7]. The fact that mean weight loss, and the concomitant mean change in HbA_{1c}, are not significantly different between diet groups (partly because of this large variability) in most studies like those by Larsen et al [3] and Krebs et al [4] cannot circumvent the limitation that different amounts of weight loss in each individual will result in different changes in HbA_{1c}. Weight loss correlates fairly linearly with improvements in HbA_{1c} in patients with type 2 diabetes, but this relationship exhibits significant variability between studies and among participants [8], as each individual is likely on a different trajectory, i.e. the changes in HbA_{1c} in response to the same amount of weight loss are different in different individuals. For example, in our study, in which all participants lost close to 6% of their body weight [2], treatment effects on HbA_{1c} ranged from approximately −1 to −18 mmol/mol (Fig. 1). In response to different amounts of weight loss among individuals, as in studies of fixed treatment duration [3, 4], the variability in the HbA_{1c} changes must therefore be significantly greater. Furthermore, the studies

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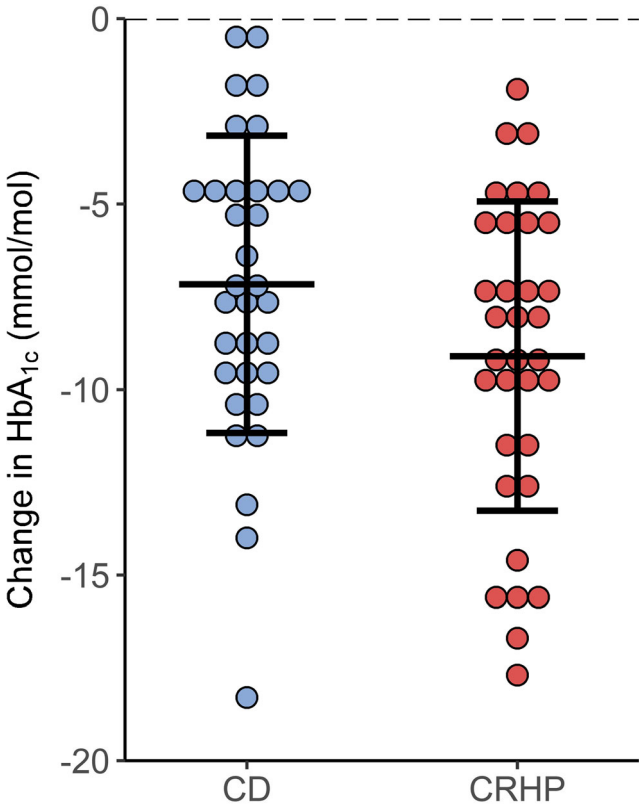

Fig. 1 Change in HbA_{1c} after 6 weeks of matched weight loss by a conventional diabetes (CD) (n = 33) or a carbohydrate-reduced high-protein (CRHP) (n = 34) diet. Solid lines represent mean (± SD) and dots individual data

by Larsen et al [3] and Krebs et al [4] involved periods of weight maintenance (9 and 12 months, respectively), during which some rebound in body weight typically occurs after maximum weight loss has been achieved [9]. Importantly, weight regain also varies between individuals [10] and may cause a rebound in HbA_{1c}, but the trajectories of weight and HbA_{1c} do not always mirror each other after weight loss [11]. We feel all these nuances add considerable 'noise' in the data that eventually makes it impossible to detect an independent effect of diet composition on HbA_{1c}, on top of the effect of concurrent body weight loss.

We aimed for ~6% reduction in body weight because this amount of weight loss is generally considered necessary to obtain clinically significant effects on carbohydrate metabolism in participants with type 2 diabetes [9]. We acknowledge this may not necessarily reflect the amount of weight loss that can be realistically maintained in the long term by many individuals with obesity and type 2 diabetes. Likewise, while we certainly agree with Drs Kang and Ma [1] that our 6-week intervention is not long enough to evaluate the efficacy of an experimental diet on body weight and glycaemic control, our study was not designed to evaluate the real-world effects of diets with different macronutrient composition on body weight and HbA_{1c}. In fact, the seminal studies by Larsen et al [3] and Krebs et al [4] in individuals with type 2 diabetes, or by Sacks et al in people without diabetes [12], published about 10 years ago, already addressed this question. The purpose of our study was to dissect the effects of diet composition from those of weight loss. Certainly, we would have appreciated a longer period of intervention/observation, which was not possible because of study cost and participant burden; although one can always argue about 'how long is long enough'. Finally, although all meals in this study were prepared by our metabolic kitchen, we have previously demonstrated that a similar carbohydrate-reduced high-protein diet, even when prepared by the individuals with type 2 diabetes themselves, does not increase risk of hypoglycaemic events [13]. However, again, this is related to feasibility rather than physiology.

Authors' relationships and activities AA is currently employed by The Novo Nordisk Foundation to establish a National Centre for Healthy Weight and is a member of the advisory board/consultant for Gelesis (USA), Groupe Éthique et Santé (France) and Weight Watchers (USA). AA is co-owner of the University of Copenhagen spin-off Flax-Slim ApS and is co-inventor on a pending provisional patent application for the use of biomarkers to predict responses to weight-loss diets and other related patents and patent applications that are all owned by the University of Copenhagen in accordance with Danish law. AA is co-author of a number of diet and cookery books, including books on personalised diet, but is not an advocate or activist for specific diets and is not strongly committed to any specific diet. The remaining authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement All authors were responsible for drafting the article and critically revising it for important intellectual content before approving the final version for publication.

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