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EDITORIAL

Personalized nutrition by prediction of glycaemic responses: fact or fantasy?

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Zeevi *et al.*[1] conclude there is high interpersonal variability in postprandial glycaemic responses (PPGRs), that personal and microbiome features enable accurate glucose response prediction that is superior to common practice and that short-term personalized dietary interventions successfully lower post-meal glucose. This seems to suggest that we have to toss out everything we thought we knew about dietary interventions to improve glycaemic control because it doesn't apply to everyone. However, the sophisticated methodology, vast amount of data collected and complex figures (some with >20 panels) conceal important flaws in the rationale for the study, and in the presentation and interpretation of the results, which undermine the stated conclusions.

FLAWED RATIONALE

The Introduction states that '... in order to achieve normal glucose levels it is imperative to make food choices that induce normal postprandial (post-meal) glycemic responses…'. The definition of 'normal' PPGR is unclear. Nevertheless, a person with fasting hyperglycaemia cannot have a normal PPGR regardless of what they eat, and a diet that elicits a low PPGR acutely may not necessarily promote low PPGR in the long term. The authors claim that no method exists for predicting PPGR and that glycaemic index (GI) has limited applicability in assessing PPGR elicited by 'real-life meals consisting of arbitrary food combinations and varying quantities'. However, in support of this they cite only one paper, which did not study 'real-life meals consisting of arbitrary food combinations and varying quantities' and whose conclusions we have refuted.[2] Recent evidence suggests that PPGRs can be predicted, for example, we showed that individual incremental areas under the glucose response curve (iAUC) elicited by self-selected breakfast meals consumed by 57 free-living abdominally obese adults was predicted ($r=0.748$) by the GI and carbohydrate content of the meal consumed and each participant's iAUC after 75 g oral glucose.[3]

Perhaps the most important problem, however, is the authors' imprecise use of the terms 'variability' and 'PPGR'. Variation in PPGR includes inter-individual (between-individual) and intra-individual (within-individual) variation. Zeevi *et al.* focus on the former and ignore the latter. The term 'PPGR' is generally used to refer to absolute glycaemic response (e.g., iAUC); however, Zeevi at al. use it to mean both absolute and relative glycemic response, things which are not the same. Normalizing an individual's iAUC after a food to that after glucose removes or at least greatly reduces inter-individual variation.[4,5] Assuming the authors would not deliberately obfuscate the distinction between absolute and relative responses, either they are unaware of it or are carelessly imprecise in their use of terminology. This is important because the clinical utility of absolute and relative glycaemic response differs: absolute response is a diagnostic test to identify people with hyperglycaemia, whereas knowledge of relative glycaemic response assists in the dietary management of hyperglycaemia. Zeevi *et al*'s. finding of high inter-individual variation in iAUC is trivial in that it is not novel; however, it would be important if their results demonstrated inter-individual variation in relative glycaemic response.

DO THE RESULTS DEMONSTRATE HIGH INTER-INDIVIDUAL VARIATION IN RELATIVE GLYCAEMIC RESPONSE?

Subjects consumed 50 g carbohydrate from glucose (G), bread (B) or bread plus 30 g butter (BB) on two occasions and Zeevi *et al.* calculated iAUC over 2 h using continuous glucose monitoring (CGM). Clearly the resulting iAUCs are highly variable; the question is whether this variation is due to intra- or inter-individual variation. If the former, then, on average (given enough replicates) different individuals' PPGR respond similarly to the same nutritional intervention; if the latter they do not. Zeevi *et al.* claim their results demonstrate inter-individual variation in relative response based on the facts that different meals elicited the highest glycemic response in different people and that there was a large range of normalized glycaemic responses.

Based on their GI values, B is expected to elicit an iAUC 29% less than G, BB ~25% less than B in normal subjects,[6,7] and, therefore, BB ~47% less than G. Within-individual variation of iAUC measured by CGM has been estimated be ~45%.[8] When expressed relative to G, individual differences in iAUC between G and B (e.g., $G_x - B_x$ for subject x) are normally distributed with a mean of 29%, and a s.d. of s (in this case $s=45\%/\sqrt{2}\approx32\%$, because each subject tested B and G twice). The area under the normal curve from minus infinity to 0 represents the proportion differences <0 (i.e. $B_x>G_x$). With a s.d. of 32%, it would be expected that $B>G$ in 26% of subjects, $BB>G$ in 15% of subjects and $BB>B$ in 30% of subjects. Based on Figure 2d, Zeevi *et al.*[1] found that $B>G$ in ~40% of subjects, $BB>G$ in ~24% and $BB>B$ in ~30%, values similar to those expected by chance. Somewhat more subjects had $B>G$ and $BB>G$ than expected, and this could be explained if the method Zeevi *et al.* used to calculate AUC was not the method used for GI, which is not unlikely. In an interlaboratory study, the protocol stipulated that iAUC should be calculated using the method Zeevi *et al.* claim to use;[9] however, >50% of the 28 labs involved reported incorrect iAUC values.[10] Calculation of net incremental AUC yields higher GI values and is associated with somewhat higher intra-individual variation;[11] this would reduce the expected differences between B and G and BB and G and, thus, increase the expected proportion of differences where $B>G$ and $BB>G$. Regardless, the results in Figure 2d can largely, if not entirely, be explained by intra-individual variation and do not provide evidence for large inter-individual variation in relative glycaemic response.

Zeevi *et al.* found that: '…high variability was also observed with the PPGR of each participant was normalized to his/her own PPGR to glucose….'. PPGR are normalized by calculating $100\times F/G$ where F and G are the iAUCs after the food and glucose, respectively. However, both F and G vary independently to an extent determined by the magnitude of intra-individual variation estimated here to be $CV=45\%/\sqrt{2}\approx31.8\%$. It is a mathematical property of ratios that high independent variation of the numerator and denominator results in non-normally distributed ratios that are skewed to the right, similar to that shown by Zeevi *et al.* in Supplementary Figures S3I–S3K. High intra-individual

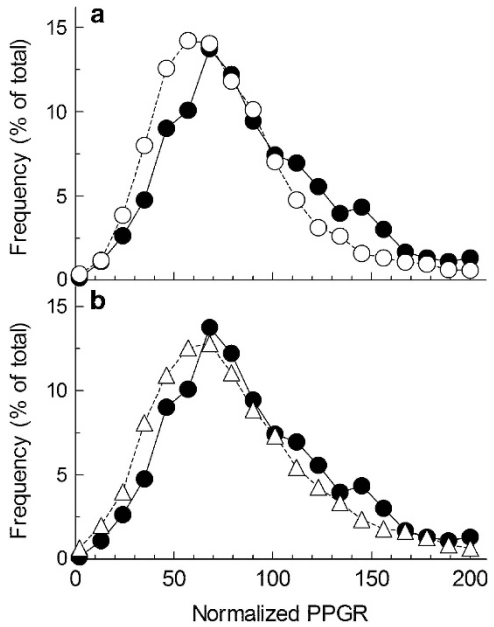

Figure 1. Distribution of glycaemic response elicited by bread normalized to glucose observed by Zeevi *et al.*[1] compared to expected distributions with inter-individual variation = 0 and high intra-individual variation. Filled circles: distribution reported by Zeevi *et al.* in their Supplementary Figure S3I. (**a**) Open circles: distribution of $100 \times F/G$ calculated from 7000 normally distributed random values for F with a mean of 71 and s.d. of 22.6 and 7000 normally distributed random values of *G* with a mean of 100 and s.d. of 31.8. (**b**) Open triangles: distribution of $100 \times F/G$ calculated from 7000 normally distributed random values for F with a mean of 75 and s.d. of 26.5 and 7000 normally distributed random values of *G* with a mean of 100 and s.d. of 35.4.

variation in iAUC leads to even higher variation in relative glycaemic response. Assuming that mean iAUC for $G = 100$, mean iAUC for $F = 71$, and intra-individual CV = 31.8%, 68% of values for *G* will be between 68 and 132 and 68% of values for *F* will be between 39 and 103; thus, normalized responses within this range will vary from 30 ($100 \times 39/132$) to 151 ($100 \times 103/68$). To estimate the expected distribution of normalized PPGR responses I created 2 sets of 7000 normally distributed random numbers with means of 100 and 71 (inter-individual variation = 0) and SDs of 31.8 and 22.6 (intra-individual CV = 31.8%), representing PPGRs for glucose and bread, respectively. The distribution of the resulting values of $100 \times F/G$ is similar to that shown by Zeevi *et al.* for bread, with the latter being somewhat more skewed to the right (Figure 1a). This might be expected if Zeevi *et al.* really calculated net incremental AUC instead of iAUC. If, as expected for netAUC,[11] intra-individual CV is increased from 45 to 50% and the GI of bread increased from 71 to 75, the fit of the expected distribution fits that from Zeevi *et al.* better (Figure 1b). Nevertheless, either way, the majority of the variation in normalized iAUC values as shown by Zeevi *et al.* can be accounted for by intra-individual variation and does not represent of large inter-individual variation.

IS PERSONALIZED PREDICTION SUPERIOR TO NORMAL PRACTICE?

Zeevi *et al.* conclude that personalized prediction is superior to normal practice based on the finding that the prediction model predicted iAUC better ($r = 0.70$) than normal practice; however, 'normal practice' included only consideration of carbohydrate intake ($r = 0.38$) or calorie intake ($r = 0.33$). The latter are trivial and irrelevant comparisons because carbohydrate or calorie intake is not used to diagnose hyperglycaemia. In clinical practice hyperglycaemia is diagnosed by measures of fasting glucose, HbA_{1c} and/or a 75 g oral glucose tolerance test. Zeevi *et al.* did not show how their model compares to these methods and whether the improved performance, if any, is worth the additional time and cost required to collect the food diary, anthropometrics, questionnaires, additional blood tests and faecal sample necessary to use their model.

What Zeevi *et al.* did show is that using their prediction model to reduce PPGR was no better than advice to eliminate those foods that, based on CGM profiles, elicited high PPGR (termed expert-based); the mean reduction in PPGR using the prediction model, 46%, was similar to that for expert-based advice, 44%, and the individual variation in % response of PPGR to the prediction model, s.d. = 28%, was somewhat higher than for expert advice, 23%. Zeevi *et al.* did not compare their model to dietary advice such as reducing carbohydrate intake or reducing diet GI, manoeuvres known to be effective in reducing PPGR.[12,13] In addition, Zeevi *et al.* did not indicate the composition of their 'bad' and 'good' diets, something that would normally be expected when reporting the results of any nutritional intervention.

CONCLUSION

Zeevi *et al.* contribute some interesting and novel findings; however, their results do not demonstrate high interpersonal variation in relative glycaemic responses, do not show that their model is superior to current methods of detecting hyperglycaemia, and do not show that personalized nutrition advice is superior to standard dietary advice to manage high post-prandial glucose responses.

CONFLICT OF INTEREST

I received no payment for writing this article. I receive payment as Medical Director, scientist and part-owner of Glycemic Index Laboratories, Inc. (GI Labs), a contract research organization, and part-owner of Glycaemic Index Testing, Inc., which provides services to GI Labs. My wife receives payment as Chief Financial Officer and part-owner of these corporations. Neither my wife nor I nor either of our companies has any financial interest in any food company, food product or food ingredient (with the possible exception of their inclusion in large mutual funds).

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