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Variation and the spice of life

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If variety is the spice of life, it is also simultaneously the goal and bane of science. The scientific method seeks to limit methodologic variation to better identify biological variation. And it is only once we have identified true biological variation that we can attempt to explain what lies behind it. For Darwin, variation in nature implied evolution. For the medical doctor, variation, be it in clinical or biochemical values, implies disease.

All methods of measurement, of whatever hue, are subject to variation; that variation is encapsulated in the concept of precision. The more background noise there is surrounding a given assay, the less the chance of repeatability of that assay. The less the variation, the more likely it is that an assay result is repeatable and the conclusions drawn from it are valid. These days we demand assays with a degree of repeatability that ensures reliability. But, given that even the most precise assay is subject to noise and error, the question arises as to what is an acceptable degree of repeatability. Laboratories use complex systems pioneered by Westgard et al. (1) that include estimates of total analytic bias, but for conventional use the College of American Pathologists has variable criteria to target. For example, the criterion for acceptable performance of glycated hemoglobin (HbA1c) testing in a proficiency testing survey was a variability of $\leq$7.0% (2). For capillary blood glucose measurement, the equivalent acceptable level of variability is $<$15% for measurements $>$5.6 mmol/L (100 mg/dL). It follows that the level at which an assay is acceptable is itself subject to error depending in part on the analyte and the analytic capability of the assay itself, so that the assay of HbA1c is more accurate than that for blood glucose. For a dynamic test, the error is further compounded by biological error.

Human variation is in part genetic and in part nongenetic. If we take the example of physiologic response to the ingestion of glucose, twin studies have found a potent role for genetics in controlling insulin secretion and insulin action, whereas hepatic glucose production is predominantly determined by nongenetic factors (3). These results imply that human responses to diet can vary, and that variation, when measured as glucose and insulin responses, will reflect both the food composition and the individual's genetic composition.

In an important study published in this issue of the Journal, Matthan et al. (4) considered the controversial subject of the utility of glycemic index (GI) values for chronic disease risk management through dietary advice. Specifically, they determined the reliability of GI value determinations and potential sources of variability among healthy adults. This was a substantial and carefully conducted study in an important area with immediate clinical relevance. Serum glucose and insulin were monitored for 5 h postingestion, and GI values calculated by using different AUC methods. They found that intra- and interindividual CVs were 20% and 25%, respectively, for a GI with a substantial range (2–77%).

The authors then sought to identify biological factors that could account for such variation. They found that the insulin index and HbA1c values explained 15% and 16% of the variability, with 5 other factors contributing between 5% and 11% of that variability. But there was no single dominant biological factor, which could be used to adjust the final GI result. Because there is such substantial variation between individuals and for any given individual, it seems likely that the genetic structure of an individual and genetic variation within the study group contributed substantially to the index.

There was, intriguingly, a positive relation between postprandial glycemic response with HbA1c and C-reactive protein concentrations, which suggests that metabolic and inflammatory statuses are significant contributors to the variability in GI response even in normoglycemic individuals. These results further limit the utility of GI in diabetic subjects in whom both HbA1c and C-reactive protein are typically abnormal.

Diabetes diets have been plagued by uncertainty, fashion, and error. Over the past 40 y, low-fiber diets were in vogue; these morphed into high-fiber diets and low-carbohydrate diets, which were followed by high-carbohydrate diets and low-fat, then high-fat diets. The introduction of the concept of low-GI diets came as a welcome break from this cycle. But the increasing use of continuous glucose monitors has highlighted some of the shortfalls in our GI advice, not least the lack of consistency when responding to a standard meal—typically, breakfast (the one meal we never seek to vary).

The broad recommendation of the American Diabetes Association is that the quantity of carbohydrates consumed should be the most important element to be first considered by a patient presented with a meal. The total carbohydrate content is a strong

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First published online September 14, 2016; doi: 10.3945/ajcn.116.143313.

predictor of the blood glucose response and a better predictor than the GI. Nevertheless, the current recommendation is that the GI is helpful and has a role, at least in "fine tuning" the response to a meal. The present study pushes GI off the main table in our management of diabetes. If it were a biochemical assay it would be kicked into the long grass. Some physicians, including ourselves, will still find it has a role. But in the context of the dietary management of diabetes, especially for type 1 diabetes, here is an instance where quantity trumps quality.

Both of the authors contributed equally to this editorial and reviewed the final draft together. Neither of the authors had a conflict of interest.

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