Siri, What Should I Eat?

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Zeevi et al. report that extensive monitoring of a human cohort for variations in dietary intake, lifestyle, host phenotype, and the gut microbiome has enabled the development of a machine-learning algorithm that accurately predicts the individual glycemic response to meals, providing an important first step toward personalized nutrition.

Nearly 1 in 10 adult Americans now suffers from type 2 diabetes (T2D), placing it among the top ten leading causes of death (National Diabetes Statistics Report, 2014). Insulin resistance and impaired insulin secretion characterize T2D, ultimately leading to persistent dysregulation of plasma glucose. Besides fasting glucose levels, post-meal glucose levels are increasingly recognized as important risk factors for the development of cardiovascular disease and mortality (Cavalot et al., 2011), and the introduction of continuous glucose monitoring has improved glycemic control; for example in type 1 diabetics (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group et al., 2008).

The post-meal rise in plasma glucose levels after ingestion of carbohydrates is reflected by a food's glycemic index (incremental area under the curve of plasma glucose levels relative to a pure glucose load); however, the combination with other macronutrients in a meal adds substantial variation. For example, meals with high fat content may impair glycemic response by delayed gastric emptying. Numerous additional factors, such as anthropometrics, meal times, sleep-wake cycle, physical activity, intestinal disorders, insulin sensitivity/resistance, lifestyle, and the trillions of microbes residing in the gastrointestinal tract (the gut microbiome), among other variables, may all contribute to the high degree of inter-individual variation of glycemic response to a given food (Dodd et al., 2011). In fact, one person may exhibit an exaggerated glucose response to a meal that results in a flat or even negative glucose curve in others. Thus, prediction of individual glucose responses is fraught with issues, and given the substantial health burden of glycemic disorders and associated secondary diseases, improved predictions represent a grand challenge for modern medicine.

In this issue of *Cell*, Zeevi et al. (2015) provide a framework to systematically address this challenge. The authors collected extensive phenotypic data from 800 individuals, which were then used to train a machine-learning algorithm that could accurately predict glycemic response to various meals. Their remote data collection is enabled by a smartphone "app," providing a glimpse into a brave new world wherein our mobile devices, trained with extensive host and microbiome data, provide real-time advice on our dietary consumption and other lifestyle choices (Figure 1).

The resulting algorithm integrates many variables, including well-established contributors to glycemic response, such as carbohydrate intake or anthropometrics, but also various other traits like sleep-wake cycle, physical activity, age, HbA1c, calories, time of meal ingestion, and preceding measurements of glycemic response via continuous glucose monitors. The authors also include data on the gut microbiome, based on prior human studies showing that caloric intake and macro-nutrient composition can rapidly alter gut microbial community structure (e.g., David et al., 2014; Jumpertz et al., 2011) and that the gut microbiome is correlated with glucose regulation (Qin et al., 2012). The algorithm accurately predicts glycemic response in a separate validation cohort and in a follow-up dietary intervention study. Notably, it also yields similar, if not markedly more accurate, predictions of glycemic response compared with an expert nutritionist.

This study provides a generalizable framework for the unbiased development of algorithms that predict other clinically relevant phenotypes. However, in part due to the complexity of the model, many critical questions remain to be addressed. What are the major data-points responsible for the accurate prediction of glycemic response? Could similarly accurate predictions be accomplished by a more limited set of already established determinants of glucose response, such as body composition, caloric and macronutrient content of meals, and age? The authors show that their model out-performs carbohydrate and caloric intake, but how does a model based on a more comprehensive analysis of dietary intake (e.g., including micronutrients) perform? Could this be improved by including information on each carbohydrate's glycemic index and/or susceptibility to host versus microbial digestion? Finally, what contribution did the gut microbiome make to these predictions and to what degree does this represent a causal versus casual link to glucose regulation? The answers to these questions are not just scientifically intriguing but will also be critical to translate these findings into a cost effective strategy for predicting glucose levels in patients.

Figure 1. Computational Models Are Opening the Way toward a More Quantitative and Personalized Approach to Nutrition

Vast datasets on diet, lifestyle, host, and the microbiome can be used to predict the glycemic response to a given food.

Nonetheless, the current study is an important proof-of-principle for the utility of tailoring nutritional and/or pharmaceutical interventions to each individual. Precise predictions of glycemic response could represent a powerful tool to optimize dosing of insulin (or dietary interventions) in type 1 or even type 2 diabetics to avoid hypoglycemic episodes and more efficiently control HbA1c levels. Follow-up studies will be essential to determine whether or not such personalized approaches reduce the risk of secondary disease and death. It will also be important to refine and validate app-based methods to monitor dietary intake and other relevant lifestyle traits in large cohorts. Machine-learning algorithms could be more broadly applicable to pharmacology and toxicology, especially for drugs with a narrow therapeutic window, such as those used for heart failure (Haiser et al., 2013) or cancer (Wallace et al., 2010). Currently, drug dosage can be adjusted based on body surface area and kidney/liver function; however, the more comprehensive approach introduced here could lead to more accurate strategies to improve response rates and reduce the side effects of such therapeutics. Interpreting these models will require inter-disciplinary efforts to establish causal relationships and identify the host and microbial genetic variants that are most relevant and those that can be safely ignored. Finally, it is important to remember that even with a perfect diagnostic tool we would still all be subject to the age-old struggle to maintain this now more personalized "healthy" diet, necessitating a concerted revolution in agriculture, food distribution, and food preparation.

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