CellPress

Spotlight

Getting Personal About Nutrition

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Nutritional guidelines for maintaining healthy blood glucose levels are commonly portrayed as universally applicable. However, a new study now demonstrates that the impact of each food on blood glucose varies dramatically across individuals and largely depends on personal characteristics and gut microbiome properties, laying the foundation for the broad implementation of personalized nutrition.

The prevalence of diabetes among adults in the USA has increased dramatically in recent years, from 3.5% in 1980 to 9% in 2011 (Center for Disease Control). Obesity rates have likewise increased from 13% in 1962 to 36% in 2010 (National Institutes of Health). These epidemics, in turn, have been met with a flood of entrepreneurial diet books and TV shows promoting the latest and greatest food fad, and with a constant flow of overhyped news articles describing new research, vilifying yesterday's nutritional golden boy and exonerating a previously convicted food item (think eggs, coffee, wine, or grains). The resulting public sentiment is epitomized by one Internet commenter who stated recently: 'Every day is April Fool's in nutrition' (http://io9.gizmodo.com/i-fooled-millions-into-thinking-chocolate-helps-weight-1707251800).

However, one feature seems to remain constant in this quagmire: the notion that certain types of food are either universally good (and should therefore be a part of any healthy diet) or universally bad (and should be avoided or consumed in moderation by all). This view underappreciates the potentially substantial metabolic variation in how individuals respond to identical diets; one person's miracle diet may fail miserably for another. For instance, a 2005 clinical trial randomly assigned individuals to one of four contrasting popular diets, and found that although, on average, the participants in each group lost a small amount of weight, the variability in response within each group was high, with some individuals in every diet group gaining weight over the 1-year study [1]. Similar variability has been observed across individuals' blood glucose levels in response to identical single food products; postprandial glucose responses; PPGR-an important risk factor in the development of type 2 diabetes [2].

The variability in people's responses to diet may be attributed to a variety of factors, ranging from genetics and lifestyle, to toxin exposure and other environmental parameters. Indeed, factors beyond diet and exercise are increasingly seen as important contributors to obesity and may influence fat storage and glycemic regulation [3]. One such factor is the gut microbiome, whose composition varies widely across individuals and has been associated with a range of health outcomes, including diabetes, obesity, and other metabolic disorders [4]. Until recently, however, a systematic, large-scale assessment of interpersonal variability in response to food was lacking, and the contribution of various personal and environmental factors to such variability was unclear.

To address this challenge, a recent study by Zeevi *et al.* [5] in *Cell*, set out to characterize interpersonal variability in glycemic responses in unprecedented detail, and to chart its determinants (Figure 1). To the end, the blood glucose levels of 800 individuals were continuously monitored for 7 days, in conjunction with detailed record keeping on diet and lifestyle (including food intake, exercise, and sleep), using a smartphone-adjusted website. Lifestyle and medical background data, blood parameters, anthropometric measures, and stool samples were also collected. Stool samples were used to assay the composition of both species and genes in each individual's gut microbiome. Participants were instructed to follow their usual diet, except for small, standardized meals at the beginning of each day. The process resulted in a large-scale dataset, including approximately 47 000 real-life meals, over 5000 standardized meals, and detailed continuous glucose monitoring data.

Linking blood glucose measurements to dietary logs and nutritional values, the researchers found ramatic variation in glycemic responses to the same food items between individuals (Figure 1A). To explore whether this variation was predictable, they developed a machinelearning algorithm to predict an individual's PPGR to each meal, based on the meal's nutritional content, and on that individual's personal and microbiome data (Figure 1B). They then demonstrated that this algorithm successfully predicted person-specific PPGR to each meal. In fact, the algorithm approached an accuracy level similar to that at which one could predict an individual's response to a meal based on the previous response of that same individual to an identical meal (since a difference in response to the same meal likely represents stochastic variation that cannot be predicted). Importantly, this algorithm performed equally well on an independent 100-person validation cohort.

To further examine whether these predictions could be used to promote healthy blood glucose levels, Zeevi and colleagues then applied their algorithm to generate comprehensive intervention diets, designed to regulate PPGRs (Figure 1C). They recruited 26 additional subjects and after collecting a week of data using the same format, assigned each participant two diets predicted by the algorithm; one predicted by the

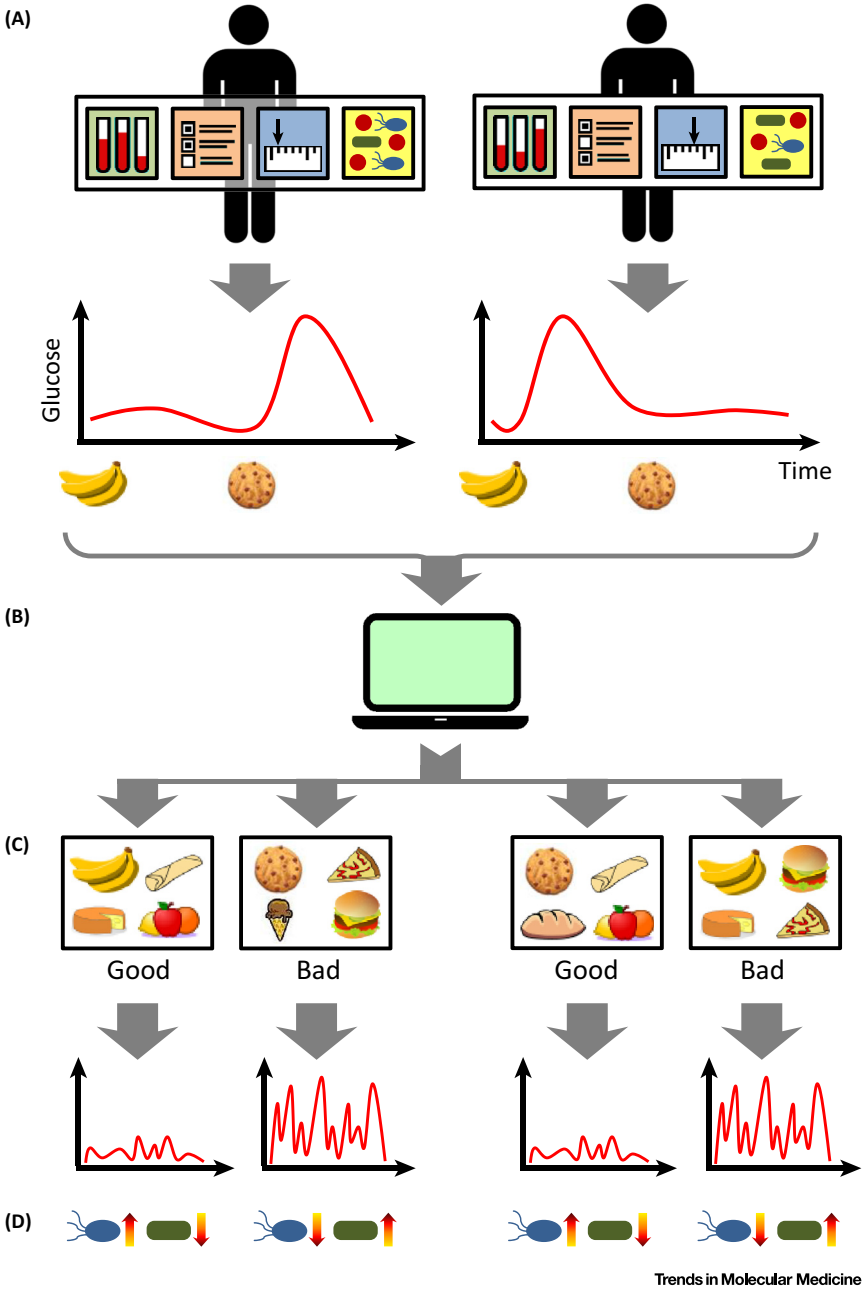

Figure 1. The Impact of Diet on Blood Glucose Is Highly Variable and Predictable. (A) Personal and microbiome are analyzed in response to diet (including clinical and anthropometric measures, lifestyle, medical background, and the composition of species and functional pathways in the gut microbiome) are analyzed in response to diet. These properties markedly affect the glycemic response of each individual to various food items. One person, for example, may have a high postprandial (postmeal) glycemic response to bananas and a low response to cookies, while this ordering may be reversed for another person. (B) Using large-scale data on such personal and microbiome properties, along with continuous glucose monitoring and detailed dietary logs, Zeevi *et al.* [6] developed an algorithm to predict with high accuracy, individual glycemic responses for each meal (computer symbol). (C) With this algorithm, it is possible to generate personalized intervention diets designed to regulate glycemic responses, promoting either low ('good' diet) or high responses ('bad' diet). (D) 'Good' intervention diets can promote microbiome shifts towards a healthier composition, lowering the abundance of specific bacteria previously associated with diabetes and/or obesity ('green' coded), while increasing the abundance of bacteria associated with good health ('blue' coded).

algorithm to promote low PPGRs (the 'good' diet) and one to promote high PPGRs (the 'bad' diet). Interestingly, certain foods (including pizza, hummus, and potatoes), were included in the 'good' diet for some participants but in the 'bad' diet for others. Results showed that PPGRs were indeed significantly lower when participants were eating the 'good' diet (compared with participants' PPGRs when eating the 'bad' diet), and displayed fewer glucose spikes.

Yet, perhaps the most intriguing finding of this study was the observation that the 'good' intervention diet not only resulted in healthier PPGRs, but also promoted gut microbiome shifts toward compositions previously associated with health (although this was not always the case) (Figure 1D). Clearly, the impact of a specific microbiome composition on health is in many cases mediated by the microbiome metabolism of dietary compounds, which can subsequently modulate immune and/or metabolic pathways [6]. The composition of the microbiome itself can in turn be modulated by a range of diet components, selecting for certain microbial species and hindering the growth of others [7]. Nevertheless, there is no *a priori* reason to assume that these two processes, namely, the impact of microbiome metabolism on health and diet-induced shifts in microbiome composition, act in concert. In theory, a diet that beneficially impacts one aspect of health (such as short-term PPGR) via the gut microbiome's metabolic activity, may still promote the long-term growth of bacteria with negative health effects. The observation above therefore implies that microbiome activity and selection are in fact strongly and positively intertwined and, that the effect of the microbiome on health may be amplified by a concordant selection towards microbiome compositions that reinforce the same effect (be it beneficial or harmful). Moreover, this observation suggests that diet may be an important trigger, determining whether these two processes – microbiome

metabolism of diet and diet-induced microbiome shifts – ultimately spiral towards a healthy or unhealthy outcome for the host.

Undoubtedly, tailoring medical and nutritional decisions based on detailed personal information is a promising opportunity. The study by Zeevi *et al.* therefore represents an exciting first step towards translating such high-dimensional personal health data into actionable personalized recommendations with clinical relevance. With the rise in accuracy and popularity of health and lifestyle monitoring technologies and the drop in DNA sequencing costs, generating the type of data used by this predictive model is becoming increasingly easier and more accessible. Similar machinelearning approaches could be applied to other health conditions and medical recommendations, for instance, to tailor drug dosages. In addition, while this study set out to highlight the need for personalized nutrition, this type of analysis can nonetheless inform global diet recommendations by suggesting the extent to which a specific food's impact on health varies or holds universally across the population.

It is important to note, however, that, while this study underscores the potential promise of personalized nutrition, it also reveals how much remains unknown, particularly with respect to the complex interactions between diet and the microbiome. For example, it is not yet clear which spatial and temporal scales and which taxonomic resolution matter for an accurate prediction of the microbiome impact on health [8,9]. Moreover, the extent to which such personalized interventions prevent disease, promote long-term wellness, and are able to generate a stable microbiome composition, remains to be determined. Most importantly, this predictive algorithm, though powerful, is a black box that reveals complex statistical associations, but not the mechanisms underlying such associations. A better systems-level understanding of the mechanisms by which the gut microbiome functions, metabolizes the host diet, and ultimately contributes to host health will be essential for the development of microbiome-based therapies [10].

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Spotlight

Vessel Normalization in the Spot-LIGHT of Cancer Treatment

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Targeting the aberrant, nonfunctional tumor vasculature is one of the most promising approaches of new anticancer therapies. Here, we discuss a recent publication and a novel mechanism by which tumor-associated macrophages can actively induce vessel normalization and junction stability, and improve the distribution of therapeutic drugs into a tumor.

The Tumor Vasculature as a Potential Target for Cancer Therapy

Although great achievements in cancer treatment have been made in recent years, many tumor types are still associated with a poor prognosis and have little hope for a cure. This underscores the importance of identifying new targets and developing alternative therapeutic strategies against neoplastic malignancies.

Given the large number of accumulated mutations and the fast development of escape mechanisms within cancer cells, it is expected that targeting tumor stromal cells for clinical applications could result in more durable therapeutic outcomes. The most prominent achievements in this field are therapies that target the aberrant tumor vasculature. The original aim of anti-angiogenic drugs was to starve cancer cells to death via complete inhibition of tumor angiogenesis, thereby keeping tumor growth below a certain threshold. However, this concept was challenged when it became clear that tumors could adapt and evade such adverse growth conditions. As a result, patients on anti-angiogenic regimens might survive longer than those treated with chemotherapy alone, but eventually experience disease progression after only a few months, depending on the cancer type and the stage of malignancy [1,2].

In light of these findings, a recent strategy has been to block excess angiogenic stimuli in specific tumors, down to a level where the tumor vasculature might acquire features reminiscent of functional and quiescent blood vessels in normal organs. This newer concept of vessel normalization bears the potential promise of