In Pursuit of a Biomarker of Weight Gain Susceptibility—Is FGF21 a Candidate?

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COMMENTARY

In our westernized obesogenic environment plagued by an overabundance of calorie-dense food and physical inactivity, obesity has become a highly prevalent condition and a major concern to public health. Interestingly, the predisposition for weight gain varies among people despite similar environmental exposures or familial traits (1). While eating less and moving more are obvious remedies for obesity, such therapeutic strategies often fall short of what is expected from affected patients. Many claim that the obesity epidemic should be tackled by prevention, especially if a simple clinical test or established biomarker can identify individuals with a high susceptibility for weight gain.

Individuals who are able to withstand periods of energy excess and resist weight gain are thought to ignite a thermogenic response (an "adaptive" increase in energy expenditure), thus dissipating some of the excess energy consumed as heat rather than storing it as body fat. This hypothesis was first suggested by Neuman in 1902, who coined the term "luxuskonsumption" (2), and was reaffirmed by Stock almost 100 years later (3). In an elegant series of studies using a respiratory chamber, the group from the National Institute of Diabetes and Digestive and Kidney Diseases in Phoenix showed that in response to acute (24-h) fasting or overfeeding, individuals respond differently in decreasing or increasing 24-h energy expenditure, thus identifying individuals with a "thrifty" or "spendthrift" metabolism, respectively (4). Such metabolic phenotypes were associated with variation in weight loss during an 8-week controlled caloric restriction (5) or with spontaneous changes in weight over a 6-month follow-up period (6). However, measuring induction of adaptive thermogenesis in response to fasting or overfeeding requires a room calorimeter, a technology seldom available in research facilities and nonexistent in clinical settings.

In their latest study published in this issue of *Diabetes*, using an acute low-protein overfeeding dietary paradigm, Vinales et al. (7) identify the increase in fibroblast growth factor 21 (FGF21) concentrations as a potential hormonal biomarker of weight gain susceptibility. More specifically, the authors observe that ingestion of a low-protein diet (3% of total intake) that provides twice the amount of energy required for weight maintenance causes almost an average threefold increase in FGF21. Importantly, the increase in FGF21 is positively associated with the increase in 24-h energy expenditure (adaptive thermogenesis) and inversely to the spontaneous weight change (varying from −7.5 to +17.5 kg) over a 6-month follow-up period. In other words, individuals who failed to significantly increase FGF21 in response to acute overfeeding with low protein gain the most weight during the follow-up. Remarkably, the measured increase in FGF21 is robust and not influenced by the remaining diet composition (i.e., high fat or high carbohydrate). The authors therefore propose that the acute response to 24-h overfeeding with a low-protein diet can identify individuals with a "thrifty" metabolism and therefore prone to weight gain versus those with a "spendthrift" metabolism and less likely to gain weight (Fig. 1).

FGF21 is a complex and multifunctional circulatory protein that clearly operates in pathways involved in metabolic regulation throughout the body. Since the impact of FGF21 on energy metabolism is not fully understood (8), it is now imperative to investigate the physiological effects of FGF21 on energy balance. Recent gain- or loss-of-function studies in rodent models have identified compelling roles for FGF21 in the regulation of energy balance, body weight regulation, lipid homeostasis, glucose homeostasis, ketogenesis, lipolysis, and hepatic steatosis (9). However, more than 10 years after the discovery of the importance of FGF21 in weight regulation in rodents, not much progress has been made to test its role in human obesity and whether it represents a potential pharmacological target for weight management.

Longitudinal studies in Pima Indians have clearly shown that weight gain susceptibilty is associated with factors related to energy metabolism, such as low metabolic rate (10), low rates of fat oxidation (11), low levels of spontaneous physical activity (12), and low sympathetic

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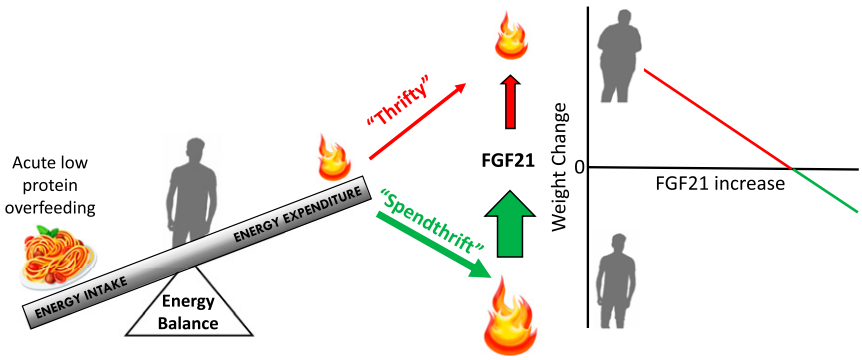

Figure 1—The hypothesized relationship between energy expenditure, FGF21, and body weight regulation. Stimulating energy expenditure with acute low-protein overfeeding can identify individuals who are able to dissipate the excess calories consumed as heat ("spendthrift") versus those who cannot ("thrifty"). The magnitude of the increase in plasma concentration of FGF21 in response to acute low-protein overfeeding is positively associated with the acute change in 24-h energy expenditure. Thrifty individuals have an attenuated increase in FGF21 in response to acute low-protein overfeeding and are more susceptible to weight gain over 6 months.

nervous system activity (13). However, surprisingly, Vinales et al. (7) report that only the acute change in FGF21 was a potential predictor of weight change over 6 months, whereas the acute change in 24-h energy expenditure was not in the present data set. As acknowledged by the authors, the small sample size is a limitation of the current study. Another limitation is the lack of measurement of physical fitness (VO_{2max}), an important physiological trait known to be associated with metabolic flexibility and metabolic health. Finally, it is worth noting that the weight gain in this study was nonhabitual (>5 kg) for some individuals over 6 months. Clearly, this work instigates future explorations into *1*) the use of an acute protein overfeeding paradigm as a "metabolic stress test" for identifying potential biomarkers of weight gain susceptibility and *2*) the potential of FGF21 as a biomarker for predicting weight gain and a therapeutic remedy for obesity in humans. As a next step, it is imperative that a controlled overfeeding study be conducted to investigate the hypothesized greater weight gain in those with lower increase in FGF21 in response to acute low-protein overfeeding. Only such studies will tell us whether FGF21 can be reliably used as a biomarker of weight gain susceptibility in humans.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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