Carbohydrates, Insulin Secretion, and "Precision Nutrition"

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Beyond conventional considerations of adherence, biological factors may influence individual response to weight loss diets. This possibility underlies recent interest in "personalized" or "precision" nutrition, an emerging focus of the National Institutes of Health initiative on precision medicine (1,2). With knowledge of the relevant biology, conceptually, specific diets could be prescribed in ways that would minimize sources of interindividual variability in response and maximize the likelihood of successful weight loss among all individuals.

One biological factor that may influence response to diet is insulin secretion. According to the carbohydrate–insulin model of obesity (CIM) (3), diets with a high glycemic load (GL)—a measure of the extent to which specific foods or diets raise blood glucose in the postprandial period—cause weight gain by increasing the ratio of insulin to glucagon in blood. This highly anabolic hormonal state promotes deposition of metabolic fuels (chiefly glucose and nonesterified fatty acids) into liver, muscle, and adipose, leaving fewer calories available for the brain and fuel-sensing tissues. Consequently, hunger increases and energy expenditure may decrease in the body's attempt to maintain energy homeostasis. A small shift in substrate partitioning through this mechanism, on the order of 10–20 kcal/day, could explain the slow but progressive weight gain typically observed in the development of common forms of obesity. Among numerous specific hypotheses in the CIM, individuals with high endogenous insulin secretion, resulting from genetic or acquired influences, will be especially susceptible to the adverse metabolic effects of a high-GL diet (Fig. 1).

Several lines of evidence support this hypothesis. Sigal et al. (4) examined 107 adults over a mean of 16.7 years after intravenous glucose tolerance tests and found that insulin secretion significantly predicted weight gain. Individuals with high insulin secretion and high insulin sensitivity gained 672 g/year, a rate approximately fourfold greater than those with low insulin secretion and high insulin sensitivity. Astley et al. (5) conducted a bidirectional Mendelian randomization study, employing genetic instruments for insulin secretion based on insulin concentration 30 min into an oral glucose tolerance test (insulin-30) and genetic instruments for BMI. They found that genetically determined insulin-30 strongly predicted higher BMI ($P = 2.2 \times 10^{-21}$), whereas genetically determined BMI did not predict insulin secretion. Chaput et al. (6) followed 276 adults in the Quebec Family Study over 6 years and found evidence for the hypothesized diet–phenotype interaction. Among those in the lowest tertile of dietary fat (thus, the highest GL), insulin-30 explained a large proportion of the heterogeneity in weight gain ($R = 0.51$, $P < 0.0001$), whereas for those in the highest tertile of dietary fat (lowest GL), insulin-30 was unassociated with weight gain. Additional evidence for a diet–phenotype interaction was reported in a laboratory animal study (7) and several (8–12), but not all (13), interventional trials.

In contrast to the numerous studies of adults, few data involving children exist on this research question, a knowledge gap that the study by Halloun et al. (14) in this issue of *Diabetes Care* aims to fill. Halloun et al. examined a cohort of 591 children and adolescents, aged 6–19 years, recruited from 1998 to 2016 in the Yale Childhood Obesity Clinic. Using data from oral glucose tolerance tests collected at baseline, they determined insulin-30, insulinogenic index (another marker of acute insulin response), fasting insulin (a marker of insulin resistance), peak insulin, area-under-the-curve insulin, and low blood glucose at 3 h. They report no association in multivariate models between any of these measures and weight gain as assessed by BMI *z* score over 1.86 ± 1.29 years of follow-up. The authors interpret these results as contrary to the CIM.

The study has several notable strengths, including use of an existing database to facilitate rapid data generation, a relatively large and diverse sample, a high-risk group, and examination of several physiologically relevant measures of insulin dynamics. However, interpretations of these data are limited by three technical and design issues affecting precision.

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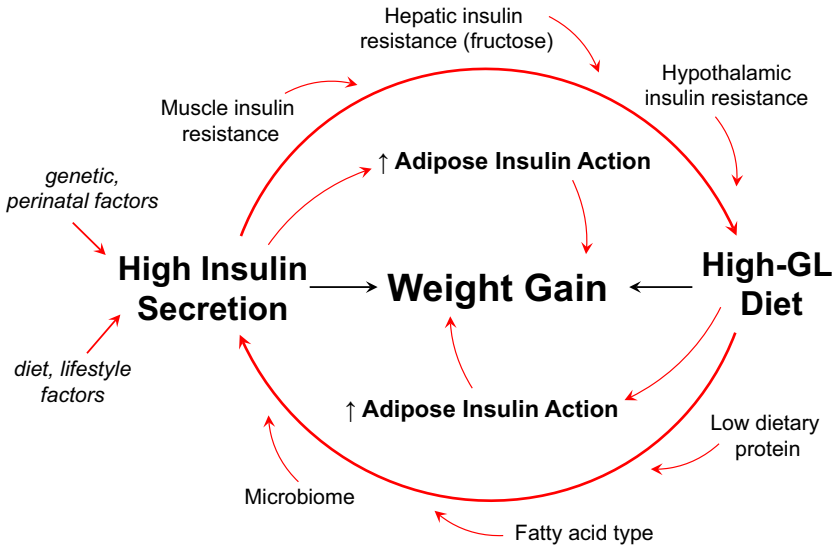

Figure 1—A diet–phenotype interaction involving insulin secretion in the CIM. Individuals with high endogenous insulin secretion (due to genetic, perinatal, or acquired factors) may have an especially large insulin response to a high-GL diet, increasing insulin action at adipose (relative to muscle, liver, and brain). In addition, high insulin secretion may drive carbohydrate cravings (24,25), leading to a vicious cycle of weight gain. Other aspects of diet may modulate this process by affecting the insulin-to-glucagon ratio (e.g., protein), altering insulin sensitivity in selective tissues (fatty acid type), and driving lipogenesis (fructose) or indirect actions (microbiome). See Ludwig et al. (3) for additional details.

One concern relates to the validity of the independent variables. Quality control studies concurrent with data collection by Halloun et al. emphasize major persistent problems with the insulin assays (15–21). For instance, median insulin values differed by up to twofold in comparisons between assays (15,16), and several types of errors within assays have been reported (17). Of particular concern, these reports found that sources of error are numerous, poorly understood, and not attributable to any single factor. Writing in *Diabetes Care* in 2010, Staten et al. (18) described the measurement of insulin secretion and sensitivity as being in a state of "chaos." Regarding the specific assay used by Halloum et al., a work group convened by the American Diabetes Association in 2009 found that the Millipore assay had bias over much of the measurement range, error related to calibrator concentrations and algorithms, and random error within runs (17). These problems would be compounded over the 18-year timeframe of the current study due to likely changes in specific antibody concentrations and affinities, other reagents, and control samples used for calibration. Errors of this nature would tend to bias results toward the null hypothesis (i.e., no associations). This situation contrasts with prior tests of the CIM, in which insulin measures were likely conducted within a narrow time frame and any assay errors might apply relatively consistently throughout the samples.

A second concern is lack of dietary data to test for effect modification. Study participants received concurrent treatment in clinic, where "The first-line intervention . . . consists of providing advice about discontinuing sugar-laden drinks (eg, fruit juice, soda, lemonade, and ice tea) . . . ." In addition, every 3–4 months, "all adolescents are advised to switch from high-sugar to low-sugar cereal and to eliminate sugar-sweetened beverages . . ." (22). Without dietary assessment, we cannot know how overall GL might have changed in response to these (and perhaps other) recommendations targeting foods that contribute so substantially to the GL of typical diets of children. Any resulting decrease in GL will, per the CIM, diminish the physiological significance of high insulin secretion and consequently reduce the power to see associations with weight gain. Inevitable differences among participants in adherence to clinical recommendations would increase heterogeneity and consequently decrease precision. On this point, a contrast can be made with the clinical trials of insulin-30 (8–13), in which treatment groups received diets of defined, contrasting macronutrient composition and individual dietary intakes were assessed.

A third issue limiting precision is short duration of follow-up compared with prior observational studies (4,6) and the Mendelian randomization study (reflecting accumulated effects from birth) (5). In the Quebec Family Study (6), individuals in the highest tertile of insulin-30 gained ∼0.5 kg/year more than those in the lowest tertile. The difference between groups in Sigal et al. (4) was similar. If real, this effect would have major clinical significance over time (e.g., 20 kg excess weight gain by middle age). However, the analyses of Halloun et al. (14) seem to be underpowered for this effect (∼1 kg during 1.86-year mean follow-up), especially with other sources of imprecision.

Although not conclusive, Halloun et al. (14) make a noteworthy contribution to the field of precision nutrition. As the authors state, additional studies of longer duration will be needed to test the CIM in the pediatric population. These studies should also consider quality control related to the insulin variables, explore alternative BMI metrics (e.g., percent distance from median rather than *z* score) (23), and measure diet to test effect modification by GL.

Duality of Interest. D.S.L. received royalties for books that recommend a low-glycemic load diet, and his spouse owns a nutrition education and consulting business. No other potential conflicts of interest relevant to this article were reported.

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