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Invited Commentary

# The Carbohydrate-Insulin Model of Obesity Is Difficult to Reconcile With Current Evidence

Kevin D. Hall, PhD; Stephan J. Guyenet, PhD; Rudolph L. Leibel, MD

**Ludwig and Ebbeling**[1] compare 2 mechanistic models of obesity, the so-called conventional model (CM) and the carbohydrate-insulin model (CIM). The CM considers energy intake and expenditure to be functionally independent processes receiving no feedback from circulating fuels or endocrine signals. Food intake and physical activity are portrayed to be under conscious control, albeit subject to environmental influences. Thus, preventing and treating obesity simply requires the willpower to eat less and move more.

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However, this CM of obesity is a strawman that is inconsistent with the current state of obesity science because it omits the known neuroendocrine mechanisms that regulate energy homeostasis.[2] Weight loss and obesity prevention are not simply a matter of willpower, and any accurate model of obesity must include the known physiological processes that resist weight loss and promote weight gain.

The CIM proposed by Ludwig and Ebbeling[1] postulates that carbohydrate intake is the primary cause of common human obesity, and insulin its primary effector. Elevated insulin levels are hypothesized to trap metabolic fuels inside adipocytes, decrease levels of circulating fuels, and thereby reduce energy availability to the body's other tissues. This reduction in metabolic fuels leads to adaptive increases in energy intake, decreases in energy expenditure, weight gain, and obesity. In this regard, the CIM recapitulates so-called pull models of obesity in which expanding adipose tissue is the cause rather than the consequence of excessive calorie intake (the push model). In other words, the CIM puts the adipocyte in the mechanistic driver's seat.

If the CIM were correct, then common variation in genes related to insulin signaling and adipocyte function should account for much of the population variability in obesity which is a highly heritable condition. Whereas genetic variants associated with body fat distribution (eg, waist-to-hip ratio) are often involved in insulin signaling and adipocyte biology,[3] genetic variants associated with total adiposity are primarily related to central nervous system development and function.[4] It therefore seems unlikely that insulin signaling in adipocytes is the primary locus of control in common obesity pathogenesis, although it may be an important determinant of body fat distribution.

In discussing predictions of the CIM that are contravened by existing evidence, Ludwig and Ebbeling[1] argue that experiments whose results are in apparent contradiction of the CIM are flawed because the measurements were conducted at the wrong time, or that unobserved variables would support CIM predictions if they were available.

For example, a central tenet of the CIM is that low energy availability of circulating fuels is the proximal cause of increased energy intake leading to obesity. However, individuals with obesity have normal or elevated levels of circulating fuels, including free fatty acids (FFA) and glucose, and their adipose tissue releases more total FFA and glycerol. Furthermore, the energy availability calculations used by Ludwig and Ebbeling did not include plasma triglycerides,[5] which are a major contributor to circulating chemical energy, are typically increased by higher carbohydrate diets, and are often elevated in obesity. Ludwig and Ebbeling suggest that the CIM-predicted reduction in circulating fuels would have been observed if studies had been conducted during the so-called "dynamic phase of obesity development,"[1] but there is little evidence for this phenomenon in humans. Although diets higher in refined carbohydrates may result in lower glucose and FFA in the late postprandial period, the role of these fuels in the physiological regulation of human eating behavior is controversial. Indeed, diets varying widely in glycemic index and load do not reliably result in differences in hunger during either the early or late postprandial period.[5] Nevertheless, hypoglycemia can be a powerful stimulus for food intake in the context of aberrent or exogenous insulin delivery.

If decreased circulating fuels caused the development of common human obesity as described by the CIM, then experimentally decreasing circulating fuels should result in increased energy intake, decreased energy expenditure, and body fat accumulation. The drug acipimox reduces FFA levels by mimicking the effect of insulin to inhibit adipocyte lipolysis. In a 6-month trial, acipimox induced a persistent 38% reduction of plasma FFA levels in adults with obesity but did not impact energy or macronutrient intake, resting energy expenditure, or body composition.[6] Thus, a key prediction of the CIM was not experimentally supported.

Feeding isocaloric diets of divergent fat and carbohydrate content are a means of creating metabolic and endocrine environments that test the CIM. Such studies show that reduction of dietary carbohydrate leads to rapid and sustained decreases in insulin secretion. The CIM predicts that reduced insulin preferentially mobilizes body fat and thereby increases circulating fuel levels and increases energy expenditure. Although the decline of insulin does increase circulating FFA levels and fat oxidation, these changes do not consistently increase energy expenditure or promote body fat loss. Rather, the increased fat oxidation observed with isocaloric low-carbohydrate, high-fat diets approximately parallels the increase in fat intake, resulting in little net difference in body fat.

Ludwig and Ebbeling[1] explain these findings by suggesting that longer-term adaptations to low-carbohydrate, high-fat diets are required for CIM predictions to manifest. They point to starvation studies showing progressively increased circulating ketones as evidence for long-term adaptations that increase fat oxidation and promote body fat loss. However, rates of lipolysis and adipocyte hepatic ketogenesis reach maxima within 1 week of starvation; subsequent increases in circulating ketones occur because of decreased utilization and reduced energy expenditure. Thus, elevation of circulating ketones over several weeks of fasting does not imply that energy expenditure and fat loss will increase over time on a high-fat, low-carbohydrate diet. Although we cannot rule out the possibility of a long-term delay between the observed rapid changes in insulin secretion and subsequent changes in energy expenditure and adiposity, it is unclear how the CIM explains such delayed effects when it rests on an insulin-signaling mechanism with relatively fast kinetics.

The medical literature is replete with diet trials showing clinically insignificant differences in mean long-term weight losses between randomized diet groups.[7] Carbohydrate-restricted diets are at least as effective as other diets. But if the CIM were the primary driver of common obesity, then low-carbohydrate diets should be substantially more efficacious and result in considerably more long-term weight loss than is typically observed.

Proponents of the CIM have suggested that individuals with greater postmeal insulin secretion constitute a subgroup that experiences superior results on a low-carbohydrate diet. A recent 12-month randomized clinical trial assessed the predictive value of baseline glucose-stimulated insulin secretion on the weight-loss response to low-fat vs low-carbohydrate diets in overweight adults.[8] Unlike previous studies, the interaction between insulin secretion and diet effectiveness was a preregistered primary outcome. Despite large and sustained between-group differences in dietary glycemic load (>200% at 3 and 6 months, and 72% at 12 months), weight loss did not differ significantly between diets, and baseline insulin secretion had no predictive value regarding weight loss. There may be unidentified factors accounting for individual variability in the weight loss response to different diets, but insulin secretion may not be one of those factors. Knowledge of such factors could enable rational, personalized weight-loss diet prescriptions.

Although refined carbohydrate may contribute to the development of obesity, and carbohydrate restriction can result in body fat loss, the CIM is not necessarily the underlying mechanism. Ludwig and Ebbeling[1] argue that the CIM is a comprehensive paradigm for explaining how all pathways to obesity converge on direct or insulin-mediated action on adipocytes. We believe that obesity is an etiologically more heterogeneous disorder that includes combinations of genetic, metabolic, hormonal, psychological, behavioral, environmental, economic, and societal factors. Although it is plausible that variables related to insulin signaling could be involved in obesity pathogenesis, the hypothesis that carbohydrate-stimulated insulin secretion is the primary cause of common obesity via direct effects on adipocytes is difficult to reconcile with current evidence.

ARTICLE INFORMATION

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