

So What Comes First: The Obesity or the Insulin Resistance? And Which Is More Important?

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Unless it is religion, there is no field of human thought in which sentiment and prejudice take the place of sound judgment and logical thinking so completely as in dietetics (1) (p. 191).

Once upon a time, humans were for the most part lean and, apart from susceptibility to infections and trauma, perhaps healthier than today (2). The most long-lived in those populations may also have lived for as long as do modern elderly. All were also less likely to die from the “chronic diseases of lifestyle” (2) that have become increasingly prevalent in the past century.

There are two contrasting explanations for why so many modern humans suffer from that constellation of chronic diseases—obesity, hypertension, type 2 diabetes mellitus, coronary heart disease, dementia, and cancer—that were much less common even as recently as the 1970s (3).

The first implies that our current predicament is largely of our individual making. According to this reasoning, over the past 50 years humans have simply become, well, just progressively lazier and more voracious. The resulting sloth and gluttony means that we now willfully eat too many calories, leading to an obesity pandemic that began in the early 1980s (4).

As our obesity increases, storage of triglyceride in the abdominal organs, especially the liver, causes the key associated complications of obesity—specifically insulin resistance (5), hypertension (6), nonalcoholic fatty liver disease (7), and atherogenic dyslipidemia (8)—all of which explain our current epidemic rates of coronary heart disease (9), dementia (10), and even perhaps cancer (11).

The less-than-subtle inference is that it is our own bad “lifestyle” choices that trigger the corpulence that causes all these chronic medical conditions (“of lifestyle”).

This model fits nicely with a paternalistic model of medicine. When our medical advice and management

fail, ultimately it is the fault of the patient who clearly lacks the appropriate will power to restrict her food intake and to exercise more (12). If only she were to take responsibility for her fat(e) and to follow the advice of our most eminent doctors and scientists, the problem would resolve itself and we could all live happily ever after.

The inconvenient question that is ignored is this: Why did our 2- to 4-million-year-old species suddenly become so indolent and gluttonous only after 1977 when the obesity and diabetes epidemics began to take off (4, 13)? Why did it take millions of years before this catastrophe struck us, appearing apparently from nowhere?

The contrasting model holds that these “diseases of lifestyle” are in fact nothing of the sort. Rather they are diseases of our modern nutrition—“the displacing foods of modern commerce” (14)—that now constitute the majority (approximately 75%) of foods eaten globally.

French gastronome Brillat-Savarin (15) was perhaps the first to suggest that it is an excess of farinaceous (carbohydrate) material in the diet that is the key factor leading to obesity: “The second principal cause of obesity lies in the starches and flours which man uses as the base of his daily nourishment . . . all animals who live on farinaceous foods grow fat whether they will or no; man follows the common rule” (p. 245). Based in part on this ancestral wisdom, the Banting (16)/Harvey (17)/Ebstein (18) (low-carbohydrate) diet, promoted by Sir William Osler, among others (19), became the standard treatment for obesity in Europe and North America in the mid- to late-1800s and remained so through the mid-20th century.

As forensically uncovered by Taubes (20), the idea that some individuals, perhaps as a result of specific hormonal responses to the ingestion of farinaceous foods, might be uniquely predisposed to develop obesity appears for the first time in the scientific writings of leading European clinicians in the early 1900s. German diabetologist Carl von Noorden proposed a link between type 1 diabetes mellitus and obesity.

Comparing the obese to those with type 1 diabetes mellitus, von Noorden wrote: “Obese individuals . . . have already an altered metabolism for sugar but instead of excreting the sugar in the urine, they transfer it to the fat-producing parts of the body, whose tissues are still well prepared to receive it” (20, p. 378). His student Wilhelm Falta

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(21) made the observation, obvious to him but apparently, now as then, to few others, that: “A functionally intact pancreas is necessary for fattening” and that the only method to fatten anyone efficiently was to include “abundant carbohydrates in the diet” (20, p. 378).

Falta continued, “We can conceive that the origin of obesity may receive an impetus through a primarily strengthened function of the insular process” (20, p. 379), which he speculated might involve stimulation of the appetite. In this way carbohydrate ingestion could establish a vicious cycle—an increased carbohydrate intake would “strengthen” the insular apparatus (causing increased insulin secretion—unmeasurable until the 1960s) which would in turn increase the appetite for the ingestion of still more carbohydrates. Taubes relates that by the 1930s insulin therapy was being widely and effectively used to fatten underweight patients.

As Taubes describes, there are several reasons why von Noorden’s alternate (“diabetogenous obesity”) theory for obesity went missing after World War II. In its place arose an Anglo-American theory projecting obesity more as a condition of personal responsibility, one caused by ingesting too many calories and performing too little exercise (22), the since-labeled calories in calories out (CICO) or energy balance model of obesity.

But what of the presence of an “altered metabolism for sugar” in the obese as speculated by von Noorden? Could this be the state of insulin resistance? And what if van Noorden was correct so that this altered metabolic state of insulin resistance is not caused by obesity but is itself the biological driver of obesity (and the other so-called “diseases of lifestyle”) in those eating high-carbohydrate diets?

Gerald Reaven, Stanford University endocrinologist, is considered the Father of (the study of) insulin resistance (23). In research conducted over the past 40 years, he has proposed that insulin resistance (24) is the common metabolic state driving atherogenic dyslipidemia (25), obesity (26, 27), type 2 diabetes mellitus (28), hypertension (29, 30), and coronary artery disease (29, 31). Others might also argue that dementia (32, 33) and perhaps even cancer (34, 35) may fit into this basket of common diseases. If true, then it is the insulin resistance and not the obesity that drives these conditions. Furthermore, at least some of the metabolic markers of these abnormalities can be “reversed” by a diet in which the intake of carbohydrate, including especially sugar, is restricted (36–38).

The reason why we must, as a matter of priority, resolve this difference is because the management of these chronic diseases of “lifestyle” will differ depending on the theory being advanced. According to the CICO model, the nature of the food eaten is of little consequence. The only variable in food that can influence body weight is calorie content or perhaps caloric density. Rather the fo-

cus of treatment must be to teach patients to use their conscious controls to develop a calorie deficit by eating less and exercising more.

On the other hand, if obesity and its “related” conditions truly result from eating too much farinaceous foods—sugar, starches, and grains—particularly in those with an inherited predisposition to develop insulin resistance, then the treatment is quite different. The cornerstone of treatment would be variants of the Banting/Harvey/Ebstein low-carbohydrate diet as promoted by Sir William Osler with a much lesser emphasis on physical activity (39).

Which brings us finally to the study of Christina Astley, Jennifer Todd, and colleagues published in this issue of *Clinical Chemistry* (40). They wished to use genetic markers to distinguish between these competing theories for the development of obesity—the “diabetogenous” model of von Noorden in which insulin drives weight gain in susceptible persons with insulin resistance when exposed to high-carbohydrate diets (what the present authors term the carbohydrate-insulin model of obesity) vs the CICO model in which the insulin resistance is the result rather than the cause of the obesity.

For their study, the authors used bidirectional Mendelian randomization analysis of genome-wide association studies to search for relationships between measured body mass index (BMI)—their marker of obesity—and genetic predictors of BMI or of measured insulin secretion in response to carbohydrate ingestion. The most significant associational relationship uncovered by the authors was between BMI and genetically determined measured insulin secretion in response to glucose ingestion. In contrast, higher genetically determined BMI was unassociated with measured insulin secretion. They therefore concluded that their data “provide evidence for a causal relationship of glucose-stimulated insulin secretion on body weight, consistent with the Carbohydrate-Insulin Model of obesity (CIMO).”

In a discipline split unequally between the vast majority believing in the CICO, with just a small but increasingly vocal minority promoting the CIMO, this paper of Christina Astley and her colleagues will no doubt ignite more fire and brimstone in what Steffanson (1), almost a century ago when this conflict was still young, recognized as the scientific discipline in which “sentiment and prejudice” so completely dominate “sound judgment and logical thinking.” The strength of the study is that this technique is less susceptible to confounding and reverse causation, the Achilles heel of other association studies.

But the reality is that a single study can seldom provide the definitive solution to a contested topic. The study of Astley and her colleagues reminds us that we must always consider the totality of the evidence and sound science requires that we always consider multiple

hypotheses. These authors have used a novel method to provide another piece of the jigsaw puzzle—information that must be incorporated into our thinking and not rejected on the grounds that it conflicts with a rigid intellectual position based more on sentiment and religious devotion than on hard science.

Only by considering all the evidence, from Brillat-Savarin via Banting, Ebstein, and Osler, to von Noorden and Reaven and on to Astley and her colleagues, are we ever likely to come to the correct conclusion. And sometimes we need to understand how our personal experiences determine our biases, even if we believe we are rigorously disinterested scientists.

My medical experience determining my own bias is as someone with severe insulin resistance and type 2 diabetes mellitus, not reversible by significant weight loss, but controlled by severe carbohydrate restriction (41).

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