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Editorial

Man shall not live by bread alone

Introduction

In a recent issue of *Nutrition*, Feinman et al. [1] proposed carbohydrate restriction as the first approach in diabetes management (before conventional pharmacotherapy). Diabetes is strongly linked with obesity, which is growing in epidemic proportions. Diabetes and obesity triple the risk for associated cardiovascular complications (with even greater effects in women than in men). Feinman et al. supported their recommendation with 12 points. These ideas are put forth in a cogent, comprehensive, and compelling manner. As such, the piece deserves careful consideration and evaluation. In this editorial, we briefly examine each of the 12 points and discuss the merits and caveats of this paradigm in the context of widely advocated low-fat diets. We aim to provide a useful commentary on a thoughtful paradigm that addresses one of the major public health issues in the United States and the developed world.

To provide context for the 12-point analysis, we make general points about the rationale and timeliness of the article by Feinman et al. With the massive and rising epidemic of obesity driving type 2 diabetes and its cardiovascular complications in the United States and the developed world, it is abundantly clear that conventional treatments with acceptable adverse events are simply insufficient to treat and improve, let alone cure, diabetes. This desperate need for alternatives fuels the drive by many patients and some in the health care field to look beyond conventional pharmacologic interventions toward complementary and alternative medicine modalities including lifestyle interventions. Unfortunately, claims of efficacy, effectiveness, and safety of therapies in the domain of complementary and alternative medicine, including nutritional supplements, functional foods, and lifestyle interventions are not rigorously policed by the FDA or equivalent organizations. This leaves the public health at a disadvantage when evaluating such products or schemes. Rigorous scientific paradigms for evaluating functional foods have been proposed [2] but these are not yet widely adopted.

In recent times, the idea that low-fat diets are beneficial for opposing obesity has taken hold in the public and among some health professionals. This has had a feed-forward effect of establishing low-fat diets as a canonical aspect of healthy living, especially among those battling obesity and diabetes. The roots of these low-fat diets are epidemiologic studies from many decades ago [3,4] that strongly influenced colleagues and politicians of a previous era. These underlie commonly held beliefs that high intake of fat leads to fatty depositions in human arteries. As described by Feinman et al., this has had the unintended consequence of increasing intake of refined carbohydrates to replace calories contained in fat. This is harmful for patients with insulin resistance (IR) and impaired β-cell function (i.e., insulin secretion), the sine qua non of type 2 diabetes.

Interestingly, the concept of dietary carbohydrate restriction is not new but has been in existence for millennia. This ranges from relatively recent pop culture ("Sugar is a bad sweet that I made obsolete" —Johnny the Walker, aka John Wowk) back to several millennia ago in the New and Old Testament scripture ("Man shall not live by bread alone," Matthew 4:4; Luke 4:4; Deuteronomy 8:3, "and ye shall eat the fat of the land," Genesis 45:18). With this context in mind, let us examine each of the 12 points raised by Feinman et al.

Analysis

1. *Hyperglycemia is the most salient feature of diabetes. Dietary carbohydrate restriction has the greatest effect on decreasing blood glucose levels.* This is a good point, although a bit overstated in that it ignores therapeutic interventions including insulin and hydration, among others, which have larger acute effects to lower blood glucose in certain clinical contexts of hyperglycemia. Although unquestionably a major feature of diabetes central to its diagnosis, for historical and technical reasons, hyperglycemia is the feature that modern therapeutics and evaluation focuses on most prominently under chronic conditions. For an alternative compelling paradigm, see the piece by JD McGarry in *Science* "What if Minkowski had been ageusic" [5]. This emphasizes the central role of dysregulation of lipid metabolism as a cardinal feature of the pathophysiology of diabetes.

2. *During the epidemics of obesity and type 2 diabetes, caloric increases have been due almost entirely to increased carbohydrate.* The authors make a compelling case for point 2 using data from the National Health and Nutrition Examination Survey. We wish to point out that the data do not parse cleanly differences in caloric density of various food types. But this is a minor caveat in the context of the overall data and not likely to substantially alter the conclusion. Increased sugar intake resulting from Ancel Keys' fat-phobic reasoning has likely contributed to, rather than opposed, abdominal obesity, dyslipidemia, and IR.

Since the 1970s, sugars in food products have increasingly relied on disaccharides, including corn syrup with a high content of fructose content. A recent study compared the effects of hyperalimentation with beverages containing mostly carbohydrates (Coke, containing primarily disaccharides) or a mixture of saturated fatty acids, protein, and lactose (milk). After a 6 mo intervention, obese or overweight individuals randomized to 1 L/d of the soda or milk with similar caloric contents gained

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comparable body weight from excess calories [6]. Strikingly, groups randomized to the soda had a doubling of fat in the liver with significant increases in visceral adiposity, whereas groups randomized to milk did not have increased liver steatosis or visceral adiposity [6]. Results from this trial substantiate arguments by Feinman et al. that choice of nutrients should not favor carbohydrates over saturated fat. The predominant carbohydrate in Coke in this study was the disaccharide sucrose, which is readily converted to monosaccharides glucose and fructose [6]. Unlike glucose, metabolism of fructose to lipids by the liver is not opposed by insulin [7]. Thus, nearly all fructose consumed orally is delivered by the portal vein to the liver where it serves as the substrate for de novo synthesis of lipids [7]. This is one of several reasons that fructose intake promotes liver steatosis and dyslipidemias that result from newly synthesized fatty acids incorporated into very-low-density lipoprotein (VLDL) particles [7]. High intake of fructose for just 7 d increases hepatic lipid content ~80% in humans with a concomitant ~50% to 100% increase in circulating VLDL triacylglycerols (TGs) [8]. With respect to behavior, functional magnetic resonance imaging demonstrates that intake of sugar specifically stimulates reward centers of the human brain in vivo [9]. Moreover, fructose reduces levels of leptin (resulting in decreased satiety) while increasing levels of orexigenic hormones including ghrelin [10,11].

3. *Benefits of dietary carbohydrate restriction do not require weight loss.* This is absolutely true, but it is also true for other interventions that do not induce weight loss. For example, brief, low-impact exercise that has a trivial effect on overall daily calorie consumption has a detectable effect to ameliorate IR and glucose intolerance of overweight and obesity [12]. The same is seen with caloric restriction in general [13]. Finally, this is most impressively demonstrated after Roux-en-Y gastric bypass surgery in patients with diabetes who reduce their insulin requirements dramatically the day after surgery before substantial weight loss has occurred [14].

4. *Although weight loss is not required for benefit, no dietary intervention is better than carbohydrate restriction for weight loss.*

5. *Adherence to low-carbohydrate diets in people with type 2 diabetes is at least as good as adherence to any other dietary interventions and is frequently better.*

6. *Replacement of carbohydrate with protein is generally beneficial.* Points 4 to 6 really belong together as a unit to stress that low-carbohydrate diets are among the best for weight loss in general. This is, in part, because adherence to the diet may be better, and also that subtracting large amounts of carbohydrates necessitates some substitution of other types of calories to maintain a safe weight loss diet (e.g., protein or fat). Although this may be strictly true, the real problem with any dietary regimen is modest success in the short term with absence of long-term success due to recidivism. This is primarily because the physiological feedback systems in place to maintain body weight at a certain set point becomes abnormal upon weight gain and do not return to normal upon weight loss (except for a very small fraction of patients who are living clues to discovering successful dietary interventions). Both obesity and diabetes are consequences of disordered metabolic homeostasis with set points for weight and blood glucose, respectively. In the case of obesity, the set point for weight becomes abnormally high upon weight gain, most likely due to new neuron growth in the hypothalamus [15]. In diabetes, this does not occur. In diabetes, there is IR resulting in abnormal insulin action along with impaired insulin secretion that determines persistent elevated glucose levels. However, the set point for euglycemia does not change in diabetes so that therapies designed to ameliorate IR and impaired insulin secretion do not have to oppose pathophysiological feedback systems attempting to maintain unhealthy set points. In the case of obesity, all known therapies are waging a losing battle against the pathophysiology defending an abnormally high set point for body weight. This abnormal set point persists for decades, if not longer, after weight loss [16,17]. Consistent with points 4 to 6, the Atkins diet (high protein and fat, low carbohydrate) is more effective than a low-fat diet for initial weight loss and for maintaining weight loss up to 2 y with concomitant improvement of blood lipid levels [18].

7. *Dietary total and saturated fat do not correlate with risk for cardiovascular disease (CVD).*

8. *Plasma saturated fatty acids are controlled by dietary carbohydrate more than by dietary lipids.*

In point 7, Feinman et al. presented data that contradict Keys' idea that it is intake of fat, in particular saturated fat, that causes CVD. In point 8, several studies cited argue that the amount of saturated fatty acids in human plasma is primarily controlled by intake of carbohydrates rather than by consumed fatty acids [19].

Cardiovascular complications of obesity and diabetes are responsible for a substantial fraction of morbidity and an overwhelming fraction of mortality in these patients. Moreover, the presence of obesity and diabetes triples the risk for both macro- and microvascular cardiovascular complications. This is due, in part, to endothelial dysfunction and accelerated atherosclerosis. Dyslipidemias are a major contributor to atherosclerosis and there is evidence that consumption of trans-fats may contribute to dyslipidemias and consequent atherosclerosis [20]. Moreover, with the advent of statins to reduce LDL cholesterol (LDL-C), there is absolutely no doubt that high-circulating LDL-C as well as other components of cholesterol contribute casually to endothelial dysfunction and atherosclerosis, especially in patients with diabetes [21].

Feinman et al. discussed the notion that low-carbohydrate diets have not been tested in long-term randomized settings with respect to cardiovascular outcomes. Despite this potential shortcoming, it has hitherto been unheard of in human physiology that a treatment that induces improved risk factors for 2 y [18] suddenly then would revert to induce opposite changes culminating in increased prevalence of disease. To support this point further, it should be noted that low-fat diets have indeed been tested in large American outcome trials. The Women's Health Initiative (WHI) study, which included 48 000 American postmenopausal women reported in 2006 that a low-fat diet has no effect on the reduction of CVD during 8 y [22]. This is despite a mean 2 kg weight loss in a study designed for stability of body weight. In fact, patients in the intervention group with established CVD at baseline experienced a significant 26% increase in cardiovascular events on a low-fat diet (high in fruit, fiber, and vegetables) [22]. Another large trial recently published on lifestyle interventions and CVD is the Look-AHEAD (Action for Health in Diabetes) trial, which included only patients with type 2 diabetes [23]. Although participants combined a low-fat diet with exercise, and the study was designed to induce weight loss and improve fitness (which it did), no trend toward reduction of CVD was observed after a median follow-up of 9.6 y [23].

9. *The best predictor of microvascular and, to a lesser extent, macrovascular complications in patients with type 2 diabetes, is glycemic control.* In patients with diabetes, there is certainly evidence to support this point. It should be noted, however, that many patients have had a myocardial infarction before diagnosis or onset of diabetes. Thus, macrovascular disease sometimes