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Critical Review

Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base

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ABSTRACT

The inability of current recommendations to control the epidemic of diabetes, the specific failure of the prevailing low-fat diets to improve obesity, cardiovascular risk, or general health and the persistent reports of some serious side effects of commonly prescribed diabetic medications, in combination with the continued success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome without significant side effects, point to the need for a reappraisal of dietary guidelines. The benefits of carbohydrate restriction in diabetes are immediate and well documented. Concerns about the efficacy and safety are long term and conjectural rather than data driven. Dietary carbohydrate restriction reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to the reduction or elimination of medication. It has never shown side effects comparable with those seen in many drugs. Here we present 12 points of evidence supporting the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1. They represent the best-documented, least controversial results. The insistence on long-term randomized controlled trials as the only kind of data that will be accepted is without precedent in science. The seriousness of diabetes requires that we evaluate all of the evidence that is available. The 12 points are sufficiently compelling that we feel that the burden of proof rests with those who are opposed.

> "At the end of our clinic day, we go home thinking, "The clinical improvements are so large and obvious, why don't other doctors understand?" Carbohydrate restriction is easily grasped by patients: Because carbohydrates in the diet raise the blood glucose, and as diabetes is defined by high blood glucose, it makes sense to lower the carbohydrate in the diet. By reducing the carbohydrate in the diet, we have been able to taper patients off as much as 150 units of insulin per day in 8 d, with marked improvement in glycemic control—even normalization of glycemic parameters."
>
> —Eric Westman, MD, MHS [1].

Introduction

Reduction in dietary carbohydrate as a therapy for diabetes has a checkered history. Before and, to a large extent, after the discovery of insulin, it was the preferred therapeutic approach [2]. Only total reduction in energy intake was comparable as an effective dietary intervention. The rationale was that both type 1 and type 2 diabetes represent disruptions in carbohydrate metabolism. The most salient feature of both diseases is hyperglycemia and the intuitive idea that reducing carbohydrate would ameliorate this symptom is borne out by experiment with no significant exceptions. Two factors probably contributed to changes in the standard approach. The ascendancy of the low-fat paradigm meant that the fat that would replace the carbohydrate that was removed was now perceived as a greater threat, admittedly long term, than the immediate benefit from improvement in glycemia. The discovery of insulin may have also cast diabetes—at least type 1—as a hormone-deficiency disease where insulin (or more recent drugs) were assumed to be a given and dietary considerations were secondary. For these and other reasons, dietary carbohydrate holds an ambiguous position as a therapy.

Although low-carbohydrate diets are still controversial, they have continued to demonstrate effectiveness with little risk and good compliance. At the same time, the general failure of the low-fat paradigm to meet expectations, coupled with continuing reports of side effects of different drugs, indicates a need for reevaluation of the role for reduction in carbohydrate. The current issue seems to be whether we must wait for a long-term randomized controlled trial (RCT) or whether we should evaluate all the relevant information. Practical considerations make it virtually impossible to fund a large study of nontraditional approaches. In any case, the idea that there is one kind of evidence to evaluate every scientific question is unknown in any science. Here we present 12 points of evidence supporting the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1. They are proposed as the most well-established, least controversial results. It is not known who decides what constitutes evidence-based medicine but we feel that these points are sufficiently strong that the burden of proof rests on critics. The points are, in any case, intended to serve as the basis for improved communication on this topic among researchers in the field, the medical community, and the organizations creating dietary guidelines. The severity of the diabetes epidemic warrants careful and renewed consideration of our assumptions about the diet for diabetes.

Definitions

A lack of agreed on definitions for *low-carbohydrate diet* has been a persistent barrier to communication. We propose the definitions in Table 1 to eliminate ambiguity. Each definition is based on use in multiple publications by those authors who have performed the experimental studies [3–6].

We recognize that levels of carbohydrate tolerance vary between individuals and even in one person over time. For example, a very low-carbohydrate ketogenic diet (VLCKD) is defined as comprised of 20 to 50 g/d carbohydrate, but because of individual variability, ketosis (blood ketone bodies >0.5 mM) may not occur.

12 Points of evidence

Point 1. Hyperglycemia is the most salient feature of diabetes. Dietary carbohydrate restriction has the greatest effect on decreasing blood glucose levels

Both type 1 and type 2 diabetes are defects in the response to food, particularly to carbohydrates. The associated hyperglycemia is both the most characteristic symptom and the cause of downstream sequelae including insulin effects and generation of advanced glycation end products (AGEs). The most

Table 1
Suggested definitions for different Forms of low-carbohydrate diets*

Very low-carbohydrate ketogenic diet (VLCKD)
- Carbohydrate, 20–50 g/d or <10% of the 2000 kcal/d diet, whether or not ketosis occurs. Derived from levels of carbohydrate required to induce ketosis in most people.
- Recommended early phase ("induction") of popular diets such as Atkins Diet or Protein Power.

Low-carbohydrate diet: <130 g/d or <26% total energy
- The ADA definition of 130 g/d as its recommended minimum.

Moderate-Carbohydrate Diet: 26%–45%
- Upper limit, approximate carbohydrate intake before the obesity epidemic (43%).

High-Carbohydrate Diet: >45%
- Recommended target on ADA websites.
- The 2010 Dietary Guidelines for Americans recommends 45%–65% carbohydrate. The average American diet is estimated to be ~49% carbohydrate.
- Carbohydrate Consumption (NHANES)†:
  - Men
    - 1971–1974: 42% (~250 g for 2450 kcal/d)
    - 1999–2000: 49% (~330 g for 2600 kcal/d)
  - Women
    - 1971–1974: 45% (~150 g for 1550 kcal/d)
    - 1999–2000: 52% (~230 g for 1900 kcal/d)

ADA, American Diabetes Association; NHANES, National Health and Nutrition Examination Survey
* Derived from Accurso et al. [3] and references therein.
† NHANES is a series of studies conducted since 1960 that monitors >5000 people.

obvious glycation product, hemoglobin A_{1c} (HbA_{1c}) is widely taken as diagnostic. Glycemic control remains the primary target of therapy in patients with type 1 and type 2 diabetes. It is universally accepted that dietary carbohydrate is the main dietary determinant of blood glucose [7] and restriction shows the greatest reduction in postprandial and overall glucose concentrations as well as HbA_{1c} [3,6,8–14]. Whereas defects in repression of gluconeogenesis and glycogenolysis are the major causes of hyperglycemia [8,15], carbohydrate is by far the greatest dietary contributor to blood sugar rises and, as expected, dietary carbohydrate restriction reliably reduces glucose profile.

Hussain et al. [14], for example, compared a VLCKD with a low-calorie diet over a 24-wk period in 102 diabetic and 261 nondiabetic individuals. As shown in Figure 1, blood glucose dropped more dramatically in the VLCKD group than in those given the low-calorie diet. In the patients with type 2 diabetes, however, after 24 wk, the average blood glucose level was approximately 1 mM lower than in the low-calorie diet group. More significantly, the VLCKD group approached normal blood sugar levels after 24 wk, whereas the low-calorie group's blood glucose concentration leveled out at 16 wk and remained elevated. In the normal patients, blood glucose was already at normal levels, and the VLCKD produced only a small effect.

The second panel in Figure 1 shows the effect of the two diets on HbA_{1c} levels. At 24 wk, patients with diabetes given the VLCKD achieved an HbA_{1c} of 6.2%, whereas the average HbA_{1c} in the low-calorie diet group remained >7.5%.

Point 2. During the epidemics of obesity and type 2 diabetes, caloric increases have been due almost entirely to increased carbohydrates

Data from the National Health and Nutrition Examination Surveys (NHANES) [16] indicate a large increase in carbohydrates as the major contributor to caloric excess in the United States from 1974 to 2000 (Fig. 2). From the time of the first NHANES study (1974) to the last (2000), dietary carbohydrate in men rose from 42% to 49% of calories. For women, carbohydrate rose from 45% to 52%. The absolute amount of fat decreased for men during this period and showed only a slight increase for women. The inset to the Figure 2 reveals the rise, during this period, of the incidence of type 2 diabetes to its current near epidemic proportions [17]. More recently, one study [18] analyzed U.S. Department of Agriculture availability data and found that the absolute fat availability had increased slightly, but, as shown in the NHANES data [19], the increase in carbohydrate was the predominant change.

These epidemiologic measurements are supported by biochemical mechanisms. Continued stimulation of insulin production can lead to an anabolic state that favors triglyceride (TG) synthesis over lipolysis and generation of TG-rich lipoproteins [5].

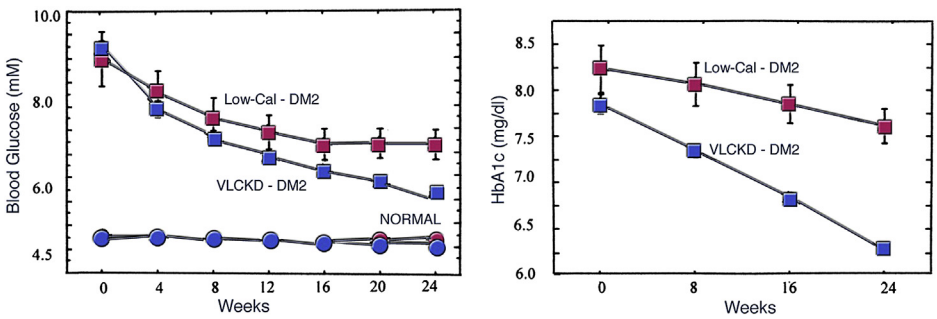

Fig. 1. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Redrawn from [14]. DM2, type 2 diabetes mellitus; VLCKD, very low-carbohydrate ketogenic diet.

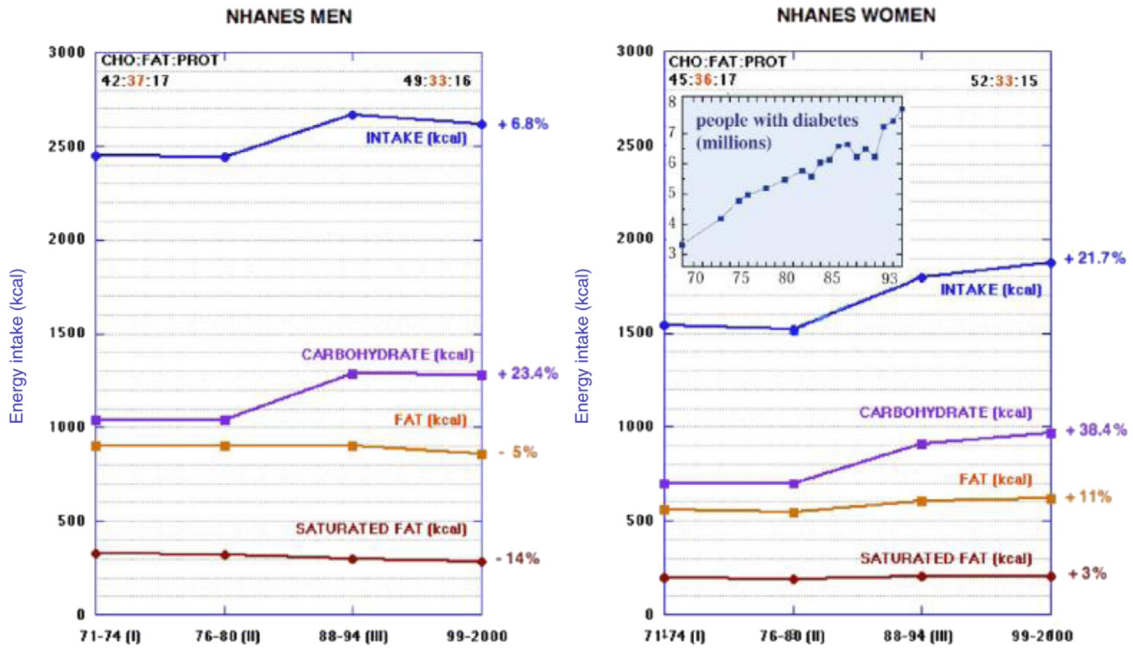

Fig. 2. Macronutrient consumption during the epidemic of obesity and type 2 diabetes. Data from the National Health and Nutrition Examination Survey (NHANES) by year, and from Centers for Disease Control and Prevention [19]. **Inset**: Incidence of diabetes (millions of people with diabetes by indicated year). Data from [17]. CHO, carbohydrate; Prot, protein.

Additionally, accumulation of fat in the liver and, secondarily, in the pancreas, create self-reinforcing cycles that are believed to contribute to the onset of type 2 diabetes. Fatty liver leads to impaired fasting glucose metabolism and increased export of very-low-density lipoprotein (LDL)-TG, which, in turn, increases fat delivery to all tissues, including the insulin-producing pancreatic islets. These liver and pancreas cycles lead to steadily decreasing β-cell function [20]. The hepatic lipogenesis transcriptional program is activated both directly and indirectly by carbohydrate ingestion. Sterol regulatory element-binding protein and carbohydrate-responsive element-binding protein are major transcriptional regulators that are activated by carbohydrate signal to stimulate de novo hepatic lipogenesis. Uncontrolled de novo lipogenesis causes hepatic steatosis, which is closely associated with the onset of obesity, insulin resistance, and type 2 diabetes [13].

Whatever the extent to which the correlation between carbohydrate consumption and diabetes is causal, the lack of association between the levels of dietary fat and diabetes in humans is of real significance. A lack of association is generally considered strong evidence for a lack of causality.

Point 3. Benefits of dietary carbohydrate restriction do not require weight loss

As described in point 1, low-carbohydrate diets generally perform better than explicitly low-calorie diets but because such trials are frequently hypocaloric by design or, by virtue of the spontaneous reduction of intake, it is not always possible to exclude the direct effect of calorie restriction or indirect hormonal effects due to feedback from changes in the adipocytes. This is an important consideration in that it is well established that the symptoms of type 2 diabetes improve with weight loss. Insofar as the American Diabetes Association and other agencies recommend low-carbohydrate diets, it is usually solely for weight loss. Many people with type 2 diabetes, however, are not overweight and, conversely, many overweight people never develop type 2 diabetes. People with type 1 are not generally overweight although, at least anecdotally, the weight gain associated with insulin therapy may be a reason for poor compliance [21,22]. Additionally, several lines of investigation support the idea that weight loss is not required for improvement in glycemic control and other symptoms in diabetes.

A series of well-designed experiments have been carried out that demonstrated improvements in glycemic control and hormonal and lipid parameters under conditions where patients were maintained at constant weight [9-11]. The most effective, 20%, was the lowest level of carbohydrate studied, although still lower might have been more effective. Results from a recent study [9] are shown in Figure 3. Although the experimental protocol, described by the authors as a low-bioavailable glucose (30% of energy) diet, did not conform to the definitions in Table 1, they indicate that improvement in glycemic control is possible without weight loss, even with only slightly lower carbohydrate. Studies in which weight is lost and glycemic control is attained do not show any correlation between the two outcomes (Fig. 4B). Given the difficulties that most people have losing weight, this factor alone provides an obvious advantage to low-carbohydrate diets.

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

The previous point emphasizes that low-carbohydrate diets provide benefit in the absence of weight loss. Nonetheless, such diets consistently outperform low-fat diets for whatever time period they are compared and frequently show dramatically better results. Figure 4 shows two examples in people with diabetes. One study [23] randomly allocated 26 people to either a low-carbohydrate diet (40 g/d carbohydrate) or a “healthy-eating

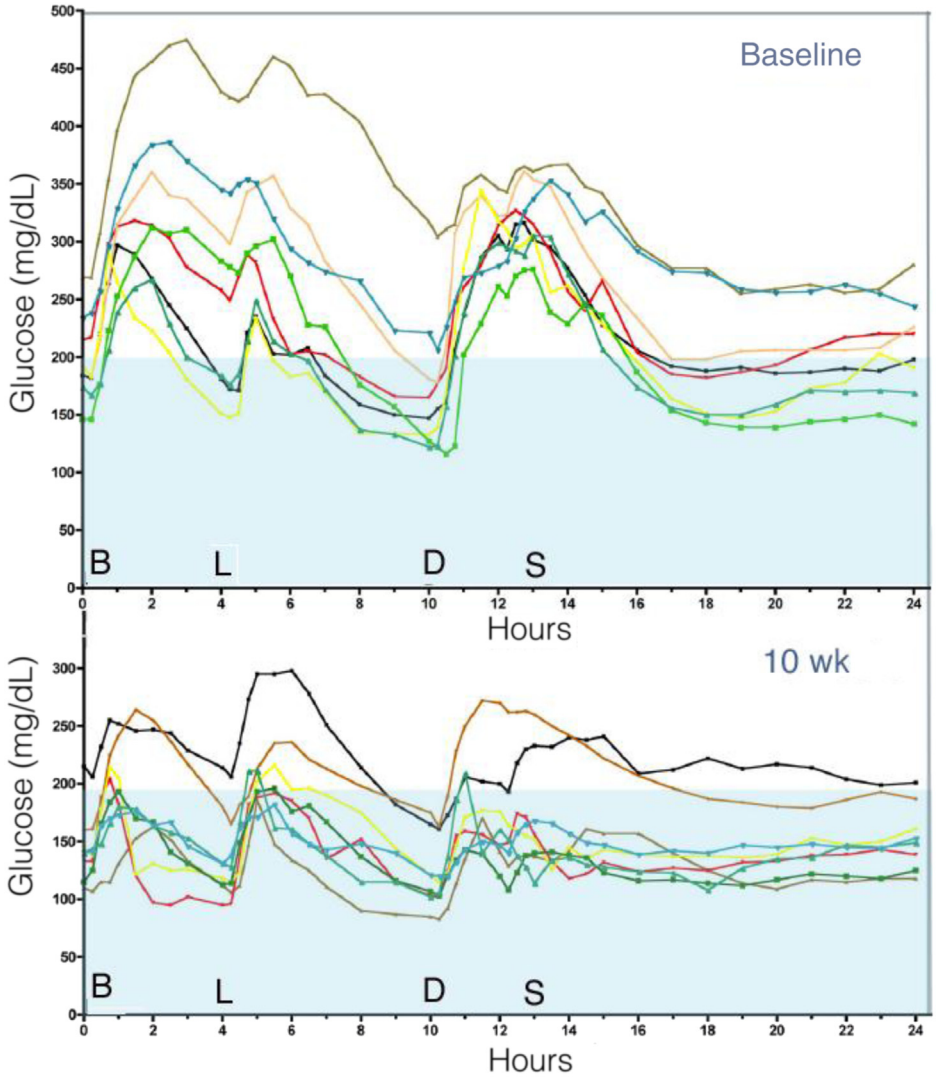

Fig. 3. Twenty-four h glucose responses at baseline and after at 10 wk on a weight-maintaining low-bioavailable glucose diet ($LoBAG_{30}$) for eight individuals. Time of ingestion of breakfast (B), lunch (L), dinner (D), and snack (S) as indicated. Redrawn from reference [9].

diet" following Diabetes UK nutritional recommendations for 3 mo. Thirteen people with type 2 diabetes and 13 controls without diabetes were included. Weight loss was greater in the low-carbohydrate arm (6.9 versus 2.1 kg). Most important, the study reported individual responses, which are shown in Figure 4A. Almost all participants in the low-carbohydrate arm were successful at a loss of 2 kg as an arbitrary cutoff mark, whereas only about half of the "healthy diet" group reached this mark.

Figure 4B compares weight loss on a VLCKD compared with a low-fat diet. Three things are notable in this figure. First, weight loss is better on the VLCKD than the low-fat diet: Inspection of points along the x-axis shows that 70% of the low-fat individuals lost <8 kg (right side of vertical dotted line), whereas 80% of the VLCKD participants lost more than this amount, and along the y-axis, more than one-third of the low-fat individuals increased levels of glycated hemoglobin and only about 10% of the VLCKD did. Finally, as pointed out previously, again by inspection, there is little correlation between the two parameters.

Low-fat diets have in fact, shown very poor results, in the long term, for weight loss in nondiabetic individuals. The Women's Health Initiative (WHI) is the most recent example. In the study [24], diet performance in 48,000 postmenopausal women was compared with usual behavior. The low-fat intervention group was encouraged to consume a 20% fat diet, rich in fruits, vegetables, and grains. Modest weight loss (average 2.2 kg) occurred in the first year. By the end of the intervention, this weight had been regained. The authors made the very modest statement: "A low-fat eating pattern does not result in weight *gain* in postmenopausal women." An editorial response to this study published in *JAMA*, stated: "despite some successes, overall the low-fat dietary approach has been a failure with the US public, which is in desperate need of effective obesity treatment and prevention strategies" [25]. The WHI was also distinguished by a failure to show any benefit in the prevention of diabetes or cardiovascular disease [24,26,27].

It should also be emphasized that popular implementations of low-carbohydrate diets like the Atkins diet [28,29] or Protein Power [30] put no formal limit on caloric consumption on the assumption that the greater satiety of protein and fat will provide control of intake. As a result, it has been traditional to carry out comparisons in which low-carbohydrate diets are ad libitum, whereas the control diets, usually low-fat, are explicitly

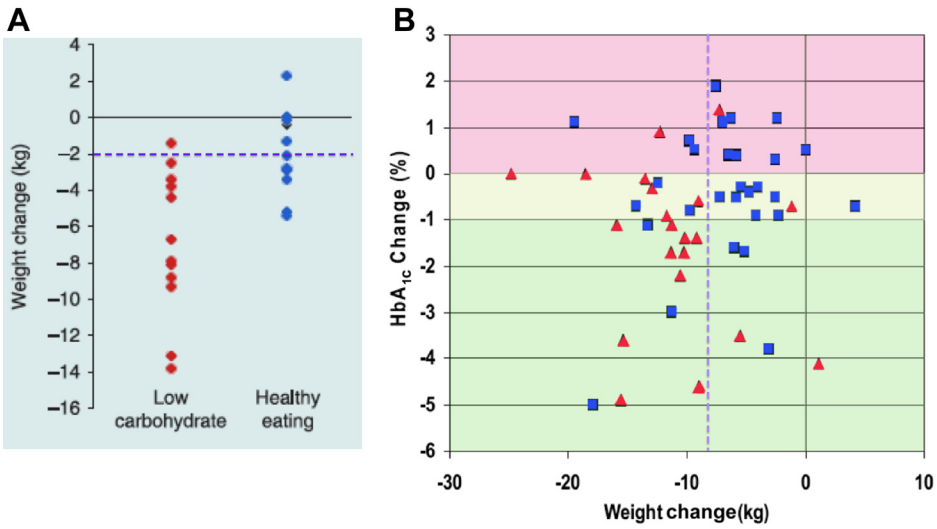

Fig. 4. Effect of diet on weight loss in people with type 2 diabetes. (A) Data from Dyson et al. [23] comparing a low-carbohydrate diet with the "healthy-eating diet" of the Diabetes UK agency. (B) Comparison of weight loss and changes in glycated hemoglobin. Very low-carbohydrate ketogenic diet (red triangles) is compared with a low-glycemic index diet (blue squares). Data from [6].

restricted in calories [31,32]. That the low-carbohydrate diets usually do better under these conditions supports the idea of implicit control of total intake and has to be considered a clear benefit for this approach to weight loss.

Point 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 significantly better.

Adherence to low-carbohydrate diets, as formally measured in clinical trials, is usually equal to or better than other diets containing the same number of calories and is comparable with that for many pharmacologic interventions. A comparison of the number of completers of carbohydrate-restricted vs fat-restricted diets in 19 studies (Fig. 5) showed similar behaviors for the two regimes. If anything, adherence was better on the low-carbohydrate arms [33]. Comparable responses have been reported elsewhere [34]. Positive results are usually attributed to the effect of carbohydrate restriction on satiety and appetite suppression due to behavioral effects or hormones. In a study of The Active Low-Carber Forum, an online discussion group with >150,000 members, a common assertion was that a low-carbohydrate regimen provides the greatest degree of satisfaction [35]. Protein and fat are known to induce satiety and to reduce hunger-inducing blood sugar swings, likely via modulation of insulin-mediated and signaling pathways that send orexigenic signals to the brain. Additionally, patients who are on insulin or insulin secretagogues are able to reduce their doses on carbohydrate-restricted diets and find they are less likely to need to "feed" their insulin. As noted previously, in many studies, the low-carbohydrate group is allowed unlimited access to food as long as carbohydrate is reduced, whereas the low-fat control is explicitly constrained to reduction in calories, an obvious benefit for compliance. In this sense, compliance is tied to the features of the diet but encouragement by peers and health providers is a major factor.

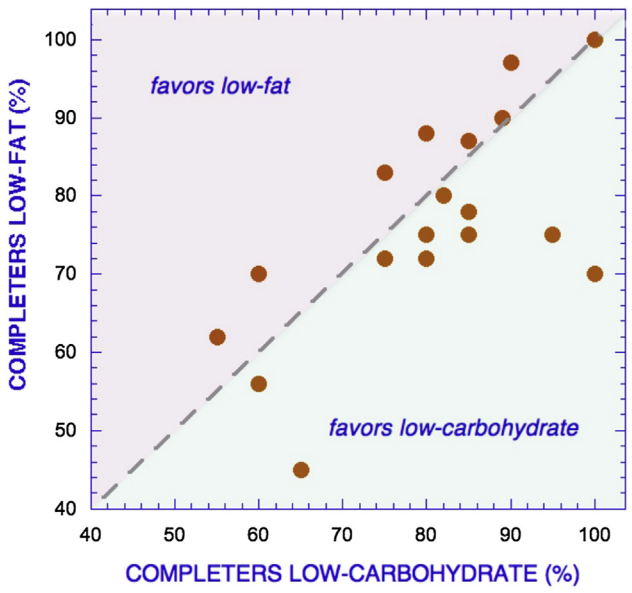

Fig. 5. Comparison of percent completion of diet studies. Each point represents a comparison from one of 19 studies. Low-carbohydrate values on the horizontal axis. Low-fat values on vertical axis. Data from [33] which contains references to individual studies.

Point 6. Replacement of carbohydrate with protein is generally beneficial

In practice, reduced-carbohydrate diets are not generally high-protein diets except in comparison with low levels recommended in high-carbohydrate diets. It is also generally recommended that carbohydrate is replaced by fat. However, a large number of RCTs have compared higher-protein, lower-carbohydrate diets (HPLCDs) with low-fat diets, and a number of systematic reviews and meta-analyses have assessed efficacy and short-term safety. These analyses have found that HPLCDs have a more favorable effect on weight loss, body composition, resting metabolic rate, and cardiovascular risk than fat-reduced diets. One meta-analysis included 23 RCTs involving 1141 obese nondiabetic participants who were reported in the literature to be on a "low-carb" diet, regardless of the actual diet

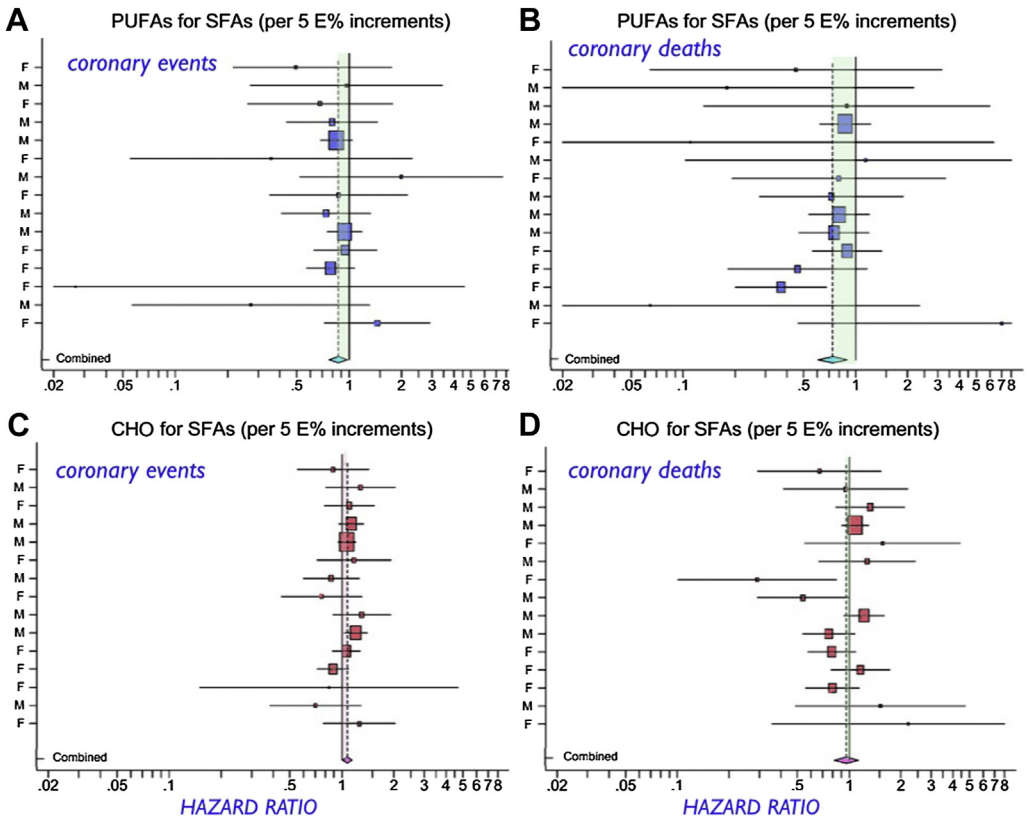

Fig. 6. Hazard ratios and 95% confidence intervals for coronary events and deaths in the different studies in a meta-analysis. Each line indicates a different cohort study with either men (M) or women (W). Individual studies are indicated in the original meta-analysis [53]. Red is increased risk by substitution for SFAs. Green indicates lower risk if SFA is substituted by indicated nutrient. Figure modified from [53]. Used with permission. CHO, carbohydrate; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

composition or degree of carbohydrate restriction [36]. Within-group changes, as opposed to comparisons with low-fat or other control diets, were measured. The lower carbohydrate diets were associated with significant decreases in body weight, body mass index, TG levels, and blood pressure; additionally, they showed improvement in several other metabolic and lipid indicators.

A meta-regression of RCTs was used to determine the comparative effects of protein and carbohydrate during energy restriction [37]. The study examined 87 trials with 165 intervention groups, comparing diets providing at least 1000 kcal/d (4200 kJ/d). Diets that provided <35% to 41% of energy from carbohydrate were associated with a 1.7 kg greater weight loss, a 0.7 kg greater loss of fat-free mass, and a 2 kg greater loss of fat mass than diets with a higher percentage of energy from carbohydrate. In studies lasting >12 wk, the effects were increased to 6.6 kg weight loss and 5.6 kg greater fat loss. Protein intakes >1.05 g/kg were associated with 0.60 kg additional fat-free mass retention compared with diets with protein intakes <1.05 g/kg. In studies with duration >12 wk, this difference increased to 1.2 kg. It has been concluded that HPLCDs favorably affect body mass and composition independent of energy intake which, in part, supports the proposed metabolic advantage of these diets [38,39].

Point 7. Dietary total and saturated fat do not correlate with risk for cardiovascular disease

Several large and expensive clinical studies have been carried out since the so-called diet–heart hypothesis was framed in the middle of the 20th century [40,41]. From the original Framingham study [42] to the WHI [26], as well as more than a dozen additional studies, have failed to show an association between dietary lipids and risk for cardiovascular disease (CVD). There is now a large volume of literature of both scientific papers [43–47] and popular books [48–51] documenting the failure of attempts to support the diet–heart hypothesis. Few rebuttals have been offered [52]. The very strong recommendations from health agencies predicted that none of these trials should fail. In fact, almost all of them have failed.

Three additional recent meta-analyses should help settle the question of a causal link between dietary lipid and CVD [53–55]. Follow-up results were pooled from 11 major cohort studies that followed the replacement of saturated fatty acids (SFAs) with either polyunsaturated fatty acids (PUFA; Fig. 6A, B) or carbohydrate [53].

The effect of replacing 5% of energy intake from SFA is shown in Figure 6 [53]. Conclusions from the individual primary studies are compelling. Almost all of the studies show no effect of replacement of SFA with either carbohydrate or PUFA. The statistical rule is that if the 95% confidence interval (CI) crosses 1, there is no difference. The shaded areas in Figure 6, meant to represent the differences between the pooled data, are very small. More important, in our view, the statistical analysis is inappropriate. Meta-analyses are appropriate for small underpowered studies where there is a chance that combining them may point to some unappreciated correlation. Figure 6, however, collates large-scale, well-controlled studies that individually showed no effect. It is questionable whether any statistical method will allow one to average studies that have not shown a statistical association and come up with a meaningful correlation.

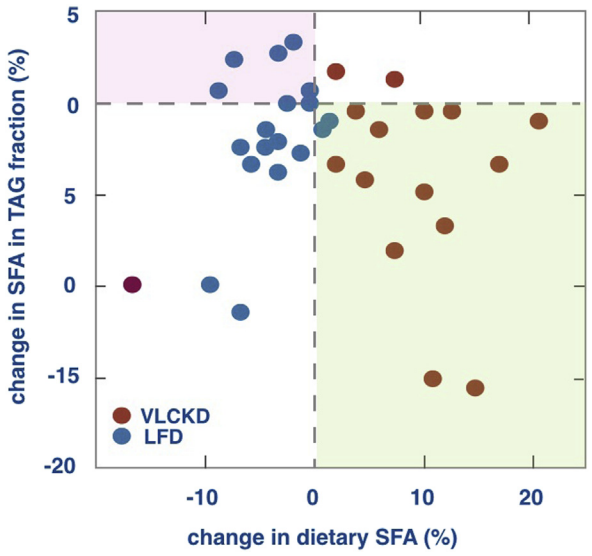

Fig. 7. Lack of association between dietary and plasma TG SFAs. In the green area, an increase in dietary SFA is associated with a reduction in SFA in the TG fraction in plasma. In the pink area, SFA inncreases even though dietary SFA is reduced. Data from [61]. LFD, low-fat diet; SFA, saturated fatty acid; TG, triglyceride; VLCKD, very low-carbohydrate ketogenic diet.

Even taking previous conclusions [53] at face value, the calculated hazard ratios increased when SFAs were replaced with carbohydrate and the study reported a "modest significant direct association between carbohydrates and coronary events." A similar analysis concluded that "replacing SFA with CHO [carbohydrate] has no benefits" [54], and others similarly concluded, "A meta-analysis of prospective epidemiologic studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD" [43,44]

In the end, the fact that so few individual studies found any effect is what is striking. None of the 15 studies on replacing saturated fat with carbohydrate showed any effect on coronary events and only two found a statistical effect on coronary deaths. Indeed, one of the few studies widely quoted as showing an effect of SFA is the Finnish Mental Hospital Study whose scientific limitations have been extensively analyzed [56], including the observation that many changes could be attributed to differences in antipsychotic medications. Looking at the studies in Jakobsen's analysis (Fig. 6), and the fact that some of these studies date from >20 y ago, it seems reasonable to conclude that if there is any risk in replacing carbohydrate with SFAs, it is still conjectural and long term and should not override the established and immediate benefit of the replacement.

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

Despite the failure to establish real risk in point 8, a significant barrier to implementation of carbohydrate restriction as a therapy in diabetes remains the traditional fear of the effect on blood lipids and, for example, the tendency of dietary SFA to raise blood total cholesterol [52,57]. The rationale for this concern followed from the idea that because dietary SFA raised cholesterol and plasma cholesterol was correlated with CVD [58], it was assumed that dietary SFA would cause heart disease. The fallacy is that the data were statistical and, to show cause, one had to show that the people whose cholesterol was raised by SFA were the same people whose cholesterol predicted CVD. In other words, it is necessary to show a direct effect of dietary SFA on CVD. The previous point emphasized that this has been impossible to do. Dietary SFA does not correlate with CVD. On the other hand, it is increasingly understood that plasma SFAs are associated with increased risk for CVD and insulin resistance [59]. in humans, plasma SFAs do not correlate with dietary saturated fat but, rather, are more dependent on dietary carbohydrates [5,60–62]. Elevated SFAs arise from increased production of TG-containing lipoproteins, reduced clearance, and the effect of dietary carbohydrate on de novo fatty acid synthesis. In one study 40 patients diagnosed with metabolic syndrome were treated with either a low-fat diet or a VLCKD. The VLCKD group showed reduced plasma SFA levels compared with the low-fat group, despite having consumed a threefold higher intake of dietary saturated fat compared with the low-fat group. Figure 7 shows that a low-carbohydrate diet was more likely to reduce SFA in plasma TG fraction than a low-fat diet. It should be mentioned, however, that an increase in dietary saturated fat is not a necessary feature of a carbohydrate-restricted diet.

A further ambiguity in the literature arises from extrapolation of rodent data. In some mouse models, dietary saturated fat is correlated with plasma saturated fat but this result is not seen in

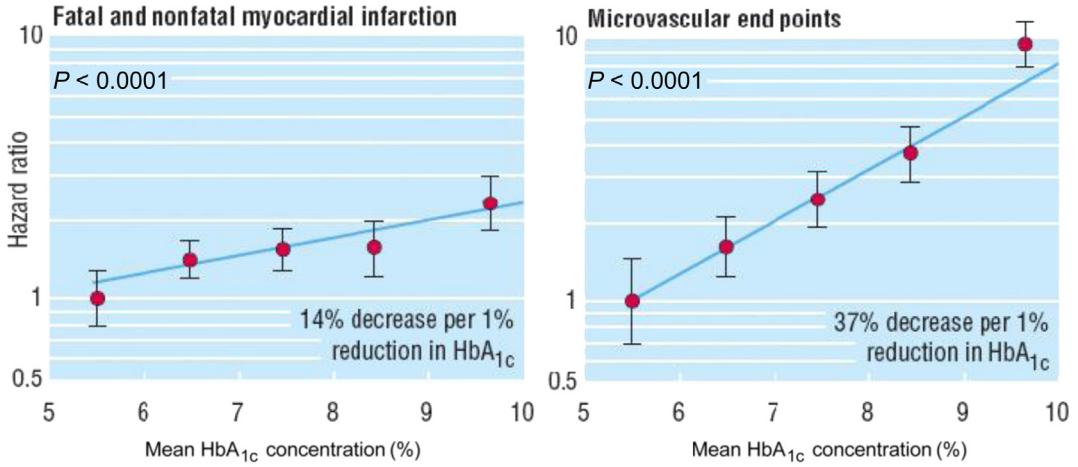

Fig. 8. Dependence of risk for myocardial infarction and microvascular end points on hemoglobin A_{1c}. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high- and low-density lipoprotein cholesterol, and triglycerides. Modified from [65–67]. Used with permission. Hemoglobin (Hb).

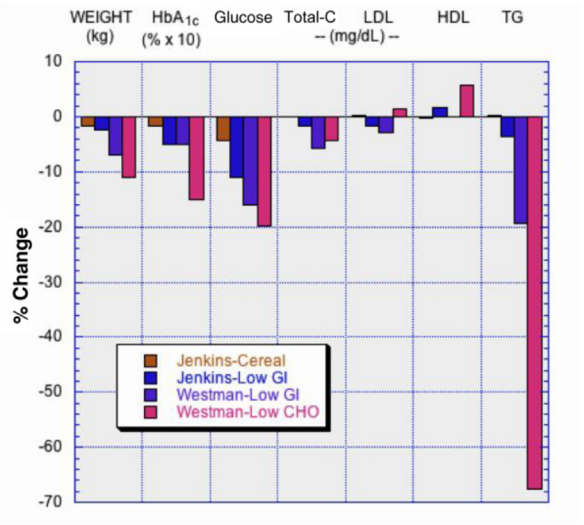

Fig. 9. Comparison of low-glycemic index diet with high-cereal diet, and of low-glycemic index diet with low-carbohydrate diet. Data from [6,70]. Redrawn from [75]. CHO, carbohydrate; GI, glycemic index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; Total-C, total cholesterol.

humans [63]. Some, although not all, studies in rodents consistently show negative effects of high-fat diets on obesity and insulin resistance, in some cases, even in the absence of carbohydrate [64]. These outcomes are not seen in humans and one should be circumspect about generalizing results to a human population. Among other species differences, some common mouse lines are more resistant to nutritional ketosis.

Point 9. The best predictor of microvascular and, to a lesser extent, macrovascular complications in patients with type 2 diabetes, is glycemic control (HbA_{1c})

The results in point 7, that dietary SFA does not correlate with CVD, did not specifically include individuals with diabetes. It is known that patients with both type 1 and type 2 diabetes are at increased risk for CVD. The United Kingdom Prospective Diabetes Study (UKPDS), described next, addresses the question of the relation between diabetes and CVD.

The UKPDS studied the incidence of macrovascular or macrovascular complications in a population of 5102 patients with newly diagnosed type 2 diabetes in 23 centers in the United Kingdom between 1977 and 1991 [65–67]. The study found that the key controlling variable was HbA_{1c}. As HbA_{1c} increased, there was a corresponding increase in fatal and nonfatal myocardial infarction (MI) events. There was a 14% decrease in MI for every 1% reduction in HbA_{1c}. The right panel in Figure 8 shows results for microvascular end points. There was a dramatic 37% decrease in these end points for microvascular risk for each 1% reduction in HbA_{1c}. It is important to consider that the authors found that no specific thresholds of glycemia were found. Risk appeared to increase for any HbA_{1c} above normal, taken in this study as 6%. Other studies had similarly failed to identify any threshold effect of plasma glucose effects on cardiovascular outcome [68]. The results are critical as a clear demonstration that the increased risk for CVD in people with diabetes is the diabetes itself as indicated by HbA_{1c}. Point 1 emphasized that HbA_{1c} is reliably reduced by low-carbohydrate diets. The alternative, cited by the authors, of "adding insulin to improve the relatively modest reduction in glycaemia achieved with oral hypoglycaemic treatments can be constrained by reluctance from patients and providers because, in part, of side effects such as weight gain."

Point 10. Dietary carbohydrate restriction is the most effective method (other than starvation) of reducing serum TGs and increasing high-density lipoprotein

Carbohydrate restriction is the single most effective intervention for reducing all of the features of metabolic syndrome [5,62,69]. Figure 9 shows the results from a study comparing a low glycemic index (low-GI diet) with a standard high-cereal diet in 210 people with type 2 diabetes [70]. Results show a 1.7 mg/dL increase in high-density lipoprotein (HDL) levels for the low-GI diet compared with a 0.2 mg/dL decrease for the high-cereal diet. Coincidentally, at almost the same time, another study [6] carried out a comparison, under very similar conditions, of a low-GI diet with a VLCKD (<20 g/d carbohydrate). The difference in outcomes between these two groups is striking. Figure 9 shows the results of a study in 84 obese type 2 diabetics in comparison with the results from a high-cereal/low-GI study that stands as the single most telling indication of the potential for carbohydrate restriction in diabetes. The low-carbohydrate diet (reddish bar) shows the greatest decrease in TG, as well as decrease in weight, HbA_{1c} and glucose and a greater increase in HDL.

Total and/or LDL cholesterol are the most commonly assessed lipid markers for CVD risk despite the general recognition that they are not good predictors. Several other parameters have been shown to provide stronger evidence of risk and these tend to be reliably improved by dietary carbohydrate restriction. These include apolipoprotein (apo) B [71], ratio of total cholesterol to HDL, higher populations of the smaller dense LDL known as pattern B [72,73], as well as the ratio of apoB to apoA1. The ratio of TG to HDL, which is also improved more by carbohydrate restriction is taken as a correlate of the smaller dense LDL, which is not routinely measured [74].

Despite their routine measurement, a number of studies have failed to support any connection between LDL cholesterol lowering and improved mortality. During the first 14 y of the Framingham study, for every 1 mg/dL per year drop in cholesterol levels there was a 14% increase in cardiovascular death and an 11% increase in overall mortality [68]. Similar increase in mortality following a drop in cholesterol was seen in other studies [76,77].

In our view, Figure 9 in combination with Figure 3 tells the whole story on dietary interventions in type 2 diabetes. The important point is that there is nothing in these studies that suggests that there is any long-term harm as long as the protocol is followed. One cannot start from the possibility of risk. In short-term comparisons, it is the diet that does poorly that is of concern in the long run. As in point 5, adherence is at least as good on a low-carbohydrate regimen as any other dietary protocol or even some pharmacologic interventions. Common sense dictates that the two most important factors in adherence are efficacy—people will stay on a diet that works—and encouragement from the health provider. The first of these is a feature of the diet. The second, again, is up to the health provider.

Point 11. Patients with type 2 diabetes on carbohydrate-restricted diets reduce and frequently eliminate medication. People with type 1 usually require lower insulin

Dietary carbohydrate restriction, because of its increased effectiveness in glycemic control, frequently leads to reduction and often complete elimination of medication in type 2 diabetes.

Similarly, patients with type 1 typically require less medication on low-carbohydrate diets [78,79]. In both cases, carbohydrate restriction reduces the number and severity of hyperglycemic and hypoglycemic episodes. For people with type 1 diabetes, decreasing the amount of carbohydrates in a meal reduces error in determining insulin needs to match it.

Reduction of medication concomitant with reduction in symptoms is considered a sign of efficacy in most therapeutic contexts. Table 2 shows results from a study that demonstrated reductions in medication in patients on a VLCKD (20–50 g/d carbohydrate) compared with a moderate carbohydrate diet that was explicitly lower in calories [80]. In the study, of 11 patients on medication in the VLCKD arm who finished the study, 5 reduced or discontinued one medication and 2 discontinued all medications. Of the 13 patients on the moderate carbohydrate diet, only 1 discontinued a sole medication. Similarly, another study found that 17 of 21 patients with type 2 diabetes reduced or discontinued diabetes medication upon carbohydrate restriction [81]. This result is a general feature of carbohydrate restriction in type 2 diabetes [82–84].

Point 12. Intensive glucose lowering by dietary carbohydrate restriction has no side effects comparable to the effects of intensive pharmacologic treatment

The ACCORD (Action to Control Cardiovascular Disease in Diabetes) trial was halted because of deaths from CVD [85]. After 3.5 y of follow-up, there were 257 deaths in the intensive-therapy group compared with 203 in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01–1.46; $P = 0.04$). Hypoglycemia requiring assistance and weight gain >10 kg were more frequent in the intensive-therapy group ($P < 0.001$). The results were interpreted as showing "a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes." Results were reported as such in the popular media. Logically, however, it is not the target but the method of trying to attain it. Intensive use of medications in high-risk patients is a more reasonable explanation. There are numerous concerns about diabetes medications [85].

That the goal of lowering blood glucose has no inherent harm to offset benefit can be seen in the data for a subset of participants in the ACCORD trial who had lower HbA_{1c} values (Table 3). These patients did not show the same risk as those with higher values.

Risks from several medications prescribed for diabetes have been identified. Rosiglitazone is the subject of continuing debate. It has been suggested that the agent posed a significant risk for MI and a risk for death from CVD, the latter of "borderline significance." The original result has been disputed [86–89] and the fate of the drug is unknown, but no such ambiguity attaches to dietary carbohydrate restriction.

Discussion

The need for a reappraisal of dietary recommendations stems from the following:

1. General failure to halt the epidemic of diabetes under current guidelines.
2. The specific failure of low-fat diets to improve obesity, cardiovascular risk, or general health (points 1 and 4).
3. Constant reports of side effects of commonly prescribed diabetic medications, some quite serious (points 12).
4. Most importantly, the continued success of low-carbohydrate diets to meet the challenges of improvement in the features of diabetes and metabolic syndrome in the absence of side effects.

Table 2
Comparison of Effects of Diet on Medication Use at Baseline and at 3 mo Among Participants Assigned to Either of the Indicated Diets*

Low-carbohydrate ketogenic diet (not calorie restricted)		
1	Glimepiride, Actos, Exenatide, Metformin	Dropped out of study
2	Metformin 500 mg bid	No change
3	Metformin 850 mg bid	No change
4	Metformin 1000 mg bid	No change
5	Metformin 2000 mg	No change
6	Metformin 500 mg	Metformin discontinued
7	Glyburide 2.5 mg bid, Metformin 1000 mg bid	Glyburide and metformin discontinued
8	Glipizide 2.5 mg, Metformin 1000 mg bid	Glipizide discontinued
9	Glipizide 5 mg, Metformin 1000 mg bid	Glipizide discontinued
10	Glyburide 2.5 mg bid, Metformin 500 mg	Glyburide discontinued
11	Januvia 50 mg, Metformin 1000 mg bid	Januvia discontinued
12	Glyburide 2.5 mg, Januvia 100 mg, Metformin 1000 mg bid	Glyburide and januvia discontinued
Moderate-carbohydrate calorie restricted		
1	Metformin 500 mg	No change
2	Metformin 500 mg	No change
3	Metformin 500 mg bid	No change
4	Metformin 500 mg bid	No change
5	Metformin 500 mg bid	No change
6	Metformin 1000 mg bid	No change
7	Metformin 1000 mg bid	No change
8	Glipizide 10 mg, metformin 1000 mg bid	No change
9	Glimepiride 8 mg, januvia 1000 mg bid, metformin 50 mg bid	No change
10	Glipizide 2.5 mg bid, metformin 1000 mg bid	No change
11	Glipizide 5 mg, Metformin 2000 mg, Januvia 50 mg	No change
12	Metformin 850 mg tid	Metformin lowered to 500 mg bid
13	Glipizide 5 mg, Metformin 500 mg bid, Acarbose 50 mg tid	Glipizide discontinued

* Data from [80].

The benefits of carbohydrate restriction are immediate and well documented. Concerns about the efficacy and safety of carbohydrate restriction are long term and conjectural rather than data driven. Most objections stem from the proposed dangers of total or saturated fat embodied in the so-called diet–heart hypothesis. At this point, the diet–heart hypothesis has had a record of very limited clinical or experimental success to support its position. The issue has become the subject of strong reaction in both the scientific literature and the popular press [48,50,51,90] (point 8).

It is well established that weight loss, by any method, is beneficial for individuals with diabetes. The advantages to a low-carbohydrate approach are that, because of greater satiety,

Table 3
Difference in Event Incidence (%) Hazard Ratio for Subsets of Patients in the ACCORD Trial with Lower HbA_{1c} Values or Who Had Not Had a Previous Event (grey highlight)*

	Event incidence (%)	HR	Statistically significant
Previous cardiac event			
Yes	10.9	1.1	No
No	5	0.8	Yes
Baseline HbA_{1c}			
≤8%	5.8	0.7	Yes
>8%	8.%	1.05	No

ACCORD, Action to Control Cardiovascular Disease in Diabetes; Hb, hemoglobin; HR, hazard ratio

* Data from reference [85].

explicit calorie reduction on the part of the patient may not be required. There may be de facto reduction in calories without the need for replacement. The extent to which there is replacement, either fat or protein may be beneficial (points 4 and 6) although, in practice, fat is recommended unless there is already lower protein. Concerns about high protein in carbohydrate restriction have been raised but, except for those people with existing kidney disease, none has ever been demonstrated [91]. Protein also tends to a stable self-limiting part of the diet. Perhaps most important, if carbohydrate is low, glycemic control and other physiologic parameters are improved even if weight loss is not accomplished (point 3).

Finally, it should be recognized that the use of low-carbohydrate diets is not a recent experiment and may well approximate the diet used by much of humanity for tens of thousands of years before the rise of agriculture. Current knowledge dictates that carbohydrate restriction should be a default treatment for type 2 diabetes and a default adjunct therapy for type 1. Given the superior outcomes of carbohydrate-restricted diets, patients should not be discouraged from adhering to them as is frequently observed. They should, in fact, be encouraged to follow this approach.

The 12 points of evidence represent the best investigated and least conjectural ideas on diabetes. It is unlikely that one dietary strategy, any more than one kind of pharmacologic treatment will be best for all individuals. Patients can refuse medication or opt out of surgery, but they cannot *not* be on a diet and low-carbohydrate is the reasonable place to start. We recognize that there are many complications and issues that are still not understood, however, we have tried to isolate the factors that have the fewest contradictions.

This review emphasized the most obvious principles. An anonymous reviewer, however, raised two important if more conjectural points. We were asked "To specify role of starch versus mono- and disaccharides in carbohydrate-semi-restricted diet (optimal proportions)." and "In discussion to draw more attention to the possible disadvantages of low-carbohydrate diet in people with diabetes."

Role of starch versus mono- and disaccharides

Replacement of carbohydrate with fat or, in some cases, with protein, is beneficial in both types of diabetes leading to better glycemic control, weight loss, cardiovascular risk markers, and reduction in medication. This is what we know. That is what is established in well-controlled experiments in individuals with diabetes (points 1, 3, and 10). The evidence does not contain strong data on which carbohydrates should be removed (or even what the effect of different fats of protein might be). On first principle, glucose is of greatest importance in diabetes. The sudden interest in fructose and sucrose as unique types of carbohydrate has made the discussion quite controversial. Both the scientific [92,93] and popular literature [94] have been unrestrained in attributing harm to fructose. Generally, fructose is known to have unique effects compared with glucose, although most of these are seen on a high-carbohydrate diet [95] and there may be little difference as carbohydrate is lowered. It is likely that on a low-carbohydrate diet, most fructose that is consumed will be converted to glucose. We have provided a perspective on the metabolism of fructose [96] where we emphasize its integration into general carbohydrate metabolism. The fact that up to 60% of ingested fructose can be converted to glucose makes the analysis of which sugar does what very difficult.

The definitive experiment, testing whether removing fructose is preferable to removing glucose in the implementation of a low-carbohydrate diet has never been performed. This is presumably due to the poor acceptance of low-carbohydrate diets in general [4]. One study showed that glycemic response was lower after ingestion of a low-starch meal with 43% total carbohydrate and high levels of fruit compared with a high-starch, high-carbohydrate meal or a 40% carbohydrate "typical American meal" [97]. There was also, as expected, a lower 24-h integrated serum insulin response. The results demonstrate the value of specifically removing starch, although it was not determined whether removing sugar would be equally effective or better. As above, this group has also shown good results simply by reducing glucose (point 3).

Because of the limited insulin effect, it was once thought that fructose might be an acceptable source of carbohydrate, but this turned out to be questionable and may actually have a deleterious effects if administered intravenously alone. Analysis of the hepatic metabolism shows that the liver expects the two sugars to appear together [96], fructose (e.g., increases glucokinase activity).

The reviewer's original question is framed in terms of "carbohydrate-semi-restricted diet (optimal proportions)." It is unlikely that there is a general answer. As a guide for the patient with diabetes, the prescription of many agencies to "eat to the meter" seems like a good one.

Possible disadvantages of low-carbohydrate diet in people with diabetes

To assess the disadvantages of carbohydrate restriction for individuals with diabetes, one has to ask what the standard is and where it came from. The idea that there is an effective diet of known macronutrient composition, one tested in long-term, or even short-term trials, that is beneficial in treating diabetes is implied by the question. To our knowledge, no such diet exists. The more dietary carbohydrate, the more medication will be required (point 11). The disadvantage to a low-carbohydrate diet, as in any intervention, will rest with individual choices. Low-carbohydrate diets generally have better compliance (point 5) but individuals vary in tastes and assessment of risk–benefit perceptions.

The flipside of the benefit from reduced medication (point 11) presents a real potential disadvantage. Because of the effectiveness of carbohydrate restriction on glycemic control, there is a danger of hypoglycemia for those patients on glucose-lowering medication. It is recommended that medication be reduced in advance of initiating a low-carbohydrate diet. Personal communications suggest that there are a variety of strategies for reducing insulin or other drugs. Whether the patient (or the physician) knows this is potentially serious question. Instructions for the study in reference [80], for example, provide the following guide:

"Metformin was continued for the duration of the study unless the participant or his/her doctor requested it be lowered, at which point the dose was cut in half or discontinued completely. Sulfonylurea doses were reduced in half if the entry HbA1c was $<$7.5% or discontinued if the participant was on a minimum dose. Sulfonylurea was discontinued if predinner glucose levels went below 110 mg/dL despite prior dose reduction; thiazolidinediones were continued for participants with starting with a HbA1 c above 7% and discontinued for those with starting HbA1 c below 7%."

Conclusion and recommendations

What evidence would be required to change the current recommendations for dietary treatment in diabetes? Evidence-based medicine tends to emphasize RCTs as a gold standard. Such absolute requirements, however, are unknown in any scientific discipline. As in a court of law, science admits whatever evidence is relevant [98]. Following the legal analogy, one has to ask: Who decides on the admissibility of the evidence? The parody by Smith and Pell [99] has been described as both funny and profound in illustrating how there is not a single type of experiment that fits every scientific question. Given the current state of research funding and the palpable bias against low-carbohydrate approaches [4], it is unlikely that an RCT can be performed that will satisfy everybody. The seriousness of diabetes suggests that we have enough evidence of different types to reevaluate our current recommendations for treatment.

This review has described 12 points of evidence based on published clinical and experimental studies and the experience of the authors. The points are supported by established principles in biochemistry and physiology and emphasize that the benefits are immediate and documented while the concerns about risk are conjectural and long term.

We would recommend that government or private health agencies hold open hearings on these issues in which researchers in carbohydrate restriction can make their case. We think that traditional features of the analysis of evidence such as vigorous cross-examination should be part of the process. We suggest that open discussion with all sides contributing will be valuable. The seriousness of diabetes suggests that a bench decree will be inappropriate.

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