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### Review Series

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# Carbohydrate restriction for diabetes: rediscovering centuries-old wisdom

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## Introduction

The primary goal of medical nutrition therapy (MNT) for diabetes management is to achieve optimal metabolic control — blood glucose (BG) levels in the normal range, or as near normal as safely possible, and lipid levels in the recommended ranges — to reduce the risk of micro- and macrovascular complications, while preserving normal growth and development in the case of children (1, 2). Increasing recognition of the contribution of postprandial hyperglycemia to elevated glycated hemoglobin (HbA1c) levels and as an independent risk factor for diabetes complications (3) highlights the importance of reducing glycemic excursions (4). As the principal determinant of postprandial glycemia, dietary carbohydrate offers an attractive therapeutic target.

Qualitative aspects of carbohydrate (e.g., fiber) are universally emphasized in nutrition guidelines. However, carbohydrate reduction can decrease postprandial glycemia and insulin requirements more effectively than any other dietary intervention, with additional benefits for reducing cardiometabolic risk factors (5). Nevertheless, concern for hypoglycemia, ketoacidosis, nutritional insufficiency, poor growth in children, and long-term acceptability has limited the adoption of low-carbohydrate diets in diabetes. In this Review, we provide a historical overview of MNT and examine research on carbohydrate-modified diets, with particular emphasis on type 1 diabetes (T1D).

## History of carbohydrate recommendations for diabetes

### The preinsulin era

Before the discovery of insulin, carbohydrate restriction prolonged the lives of people with diabetes. In 1797, Rollo prescribed a diet of moderation, consisting largely of meat and fat, based on observations that plant foods were associated with glucosuria (6). This prescription was widely adopted and empirically optimized over the next century. While Rollo and others promoted fat intake to mitigate nausea and anorexia, diets were often high in protein (e.g., 3 g/kg body weight or ~43% of energy intake [EI], according to a “fair example” described by Woodyatt) (7).

Physiological experimentation and clinical experience subsequently led to variations of the carbohydrate-restricted diet. In the late 19th century, Cantani and Naunyn first described the effects of protein intake on glucose levels and advocated restriction of both carbohydrate and protein to treat glucosuria. With this approach, dietary fat was used to satisfy most energy requirements (8), and, according to a contemporaneous review, up to about 200 g/d was considered well tolerated (9). Based on animal studies and observations that intake of fat and protein exacerbated ketonuria during ketoacidosis, Allen and Joslin introduced prolonged fasting and hypocaloric diets that restricted all macronutrients (10–12). Although effective in treating ketoacidosis, Allen's prescription amounted to a starvation diet that produced severe side effects and fatalities in some cases (13). To prevent inanition, Newburgh and Marsh developed diets with exceptionally high fat content (EI ~5% carbohydrate, 8% protein, and 87% fat) that prolonged life (14) compared with the contemporary high mortality within the first year of diabetes diagnosis (12, 15). Other clinicians reported success with ostensibly higher-carbohydrate diets, such as the “rice cure” or “oatmeal cure,” that still provided lower relative and absolute amounts of glucose and gluconeogenic substrates than

**Conflict of interest:** DSL received royalties for books on obesity and nutrition that recommend a low-glycemic load diet and philanthropic grants from the New Balance Foundation and Arnold Ventures. APK is an inventor on provisional patent applications related to the use of exogenous ketone bodies (US patents 16/768,242, 16/772,490, 16/998,281, and 62/964,952; European patent 18888960.4). JIW received royalties for his role as a section editor for UpToDate.

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were conventionally consumed because of their hypocaloric and protein-restricted nature and the inclusion of fat (7).

Aiming to reconcile nutritional controversies, Woodyatt explored the contributions of endogenous fuels to metabolism in the 1920s, demonstrating that patients with diabetes and obesity did well on calorie-restricted diets, but those with undernutrition experienced loss of lean mass. This catabolic process not only produced inanition, but also released large amounts of amino acids from muscle that fueled gluconeogenesis and ketogenesis, exacerbating glucosuria and acidosis. In further experiments, Woodyatt, among others, found that both glucosuria and acidosis could be prevented by increasing dietary fat to preserve endogenous fat stores (7), and Wilder noted that a certain degree of ketosis was well tolerated (16), laying the foundation for differentiating nutritional ketosis from ketoacidosis (see "Carbohydrate amount" below). With the discovery of insulin in 1921, however, this line of research was largely abandoned.

### Early insulin era

Insulin was initially used as an adjunct to prevailing diets that restricted carbohydrate and promoted a mild energy deficit. By the 1940s, diets with higher carbohydrate content gained favor, with reports of increased energy level, less hunger (potentially related to higher total EI), and better compliance (17). At that time, lacking practical methods for frequent monitoring, BG was measured infrequently and primarily in the fasting state; thus, the impact of high-carbohydrate diets on insulin needs and postprandial glycemia was mostly unrecognized (18, 19). Moreover, studies published during this time, such as by Himsworth (20), suggested a benefit of higher carbohydrate consumption for glucose tolerance and insulin sensitivity in people without diabetes, supporting the notion that additional carbohydrate intake would not increase insulin requirement (18, 19). Possibly owing to a lack of appreciation for the difference between nutritional ketosis and ketoacidosis — and despite earlier findings on this point (16, 21) — many clinicians prioritized reducing ketonuria over the glucosuria that occurred with higher-carbohydrate diets (18). Moreover, some pediatricians specifically aimed for glucosuria and accepted any degree of hyperglycemia to lower the risk of "reactions" (hypoglycemia), provided that the patient felt well and did not lose weight (22).

An additional rationale for a higher-carbohydrate diet was its effect on lowering blood cholesterol. By the 1930s, dietary and blood cholesterol had been linked to cardiovascular disease (CVD) in the general population (23), whereas the relationship between glycemia and diabetic complications was not fully accepted until publication of the results of the Diabetes Control and Complications Trial (DCCT) more than a half century later (24). Hence, focus on diabetes research shifted toward lower-fat, high-carbohydrate diets that lowered cholesterol levels (25–27). More broadly, the notion developed that as glucose levels could be controlled by insulin replacement, the nutritional needs of people with diabetes would mirror those of healthy individuals, and subsequent dietary recommendations largely paralleled those for the general population.

Nevertheless, throughout this period, controversy persisted regarding optimal dietary composition. In 1932, Strouse reported increased glucosuria and higher insulin requirements on iso-

caloric high-carbohydrate (65% EI) versus low-carbohydrate (9% EI) diets (28). In the 1960s, Bierman linked higher carbohydrate intake to elevated triglyceride levels in diabetes (29), which Albrink considered a risk factor for micro- and macrovascular complications, even as she questioned the importance of total serum cholesterol (30). In addition, animal studies suggested unique metabolic benefits of carbohydrate restriction. Rodents with experimental diabetes (induced by subtotal pancreatectomy) self-selected a low-carbohydrate diet and had spontaneous resolution of polydipsia, polyphagia, and weight loss (31, 32).

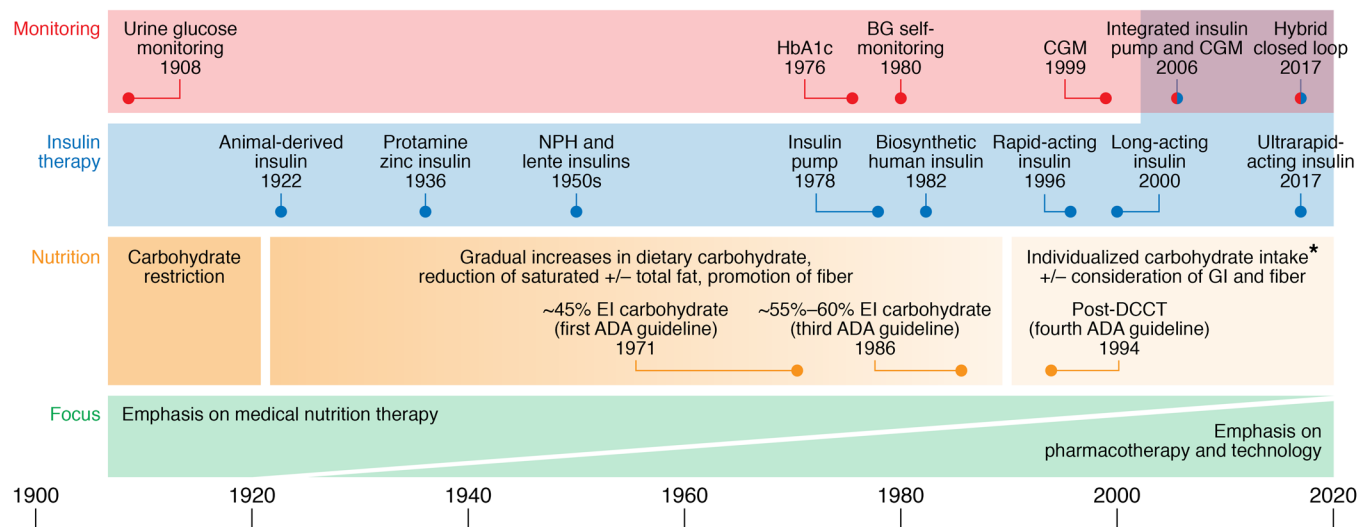
### Evolution of modern ADA dietary guidelines

The first American Diabetes Association (ADA) guidelines in 1971 (33) acknowledged that "there are no controlled prospective studies which provide evidence for choosing the optimal proportion of dietary carbohydrate and fat with regard to long-term complications in any type of diabetic population." Despite these "obvious important knowledge [gaps]," the guidelines suggested that carbohydrate intake of 45% EI, based on population norms, or higher "appears to be acceptable" for the usual patient, while also raising concern for carbohydrate-associated hypertriglyceridemia. With advances in monitoring of glycemia during the decade, the 1979 ADA guidelines (34) revised the goals of dietary management from avoiding "deleterious metabolic derangements" (33) to maintaining "plasma glucose as near to the normal physiologic range as possible."

By that time, most public health nutrition experts had come to advocate a low-fat, high-carbohydrate diet for weight control and chronic disease prevention (35) in the general population, with research on diabetes shifting to qualitative aspects of carbohydrate, such as fiber and, later, glycemic index (GI) (36–38). High carbohydrate intake (50%–60% EI) was recommended, not only for the presumed benefits of high-fiber foods, but also to help limit saturated fat intake. In the 1986 ADA guidelines (39), total fat intake was explicitly restricted to <30% EI, and carbohydrate amount was "liberalized, ideally up to 55–60% of the total calories."

In 1993, the DCCT showed that intensive diabetes management that achieved near-normal glycemic control reduces the risk of microvascular complications. Intensively treated participants in the DCCT received MNT that focused on carbohydrate consistency and adjustment of insulin doses for variations in dietary intake (24, 40, 41). The following year (42), the ADA abandoned specific targets for dietary carbohydrate, recognizing a lack of supporting data, and instead encouraged an individualized approach focused on qualitative dietary aspects. Even so, advice to limit fat intake was maintained, based on recommendations for the general population.

The GI (a measure of the glycemic effects of food, as considered below) (38) was first addressed by the ADA in 2002 (43); in 2006 (44), it concluded that use of GI may provide a modest benefit, beyond consideration of carbohydrate amount alone. This latter report cautioned that "foods that contain carbohydrate are important sources of energy, fiber, vitamins, and minerals and are important in dietary palatability" and advised against intakes less than the prevailing recommended daily allowance (130 g/d), while again noting a lack of diabetes-specific data. The 2014 ADA guidelines (45) stated that "there is not an ideal percentage of calories



**Figure 1. Hundred-year timeline of dietary recommendations and technological developments for diabetes.** During the 100 years since the discovery of insulin, the focus of research and clinical care has shifted from nutrition to improving insulin formulations, glucose monitoring, and insulin delivery technology. ADA, American Diabetes Association; BG, blood glucose; CGM, continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; EI, energy intake; GI, glycemic index. \*Other guidelines still maintain high-carbohydrate recommendations.

from carbohydrate, protein, and fat for all people with diabetes,” language that was essentially retained in the 2019 guidelines (46), with the new acknowledgment that for “people with type 2 diabetes or prediabetes, low-carbohydrate eating plans show potential to improve glycemia and lipid outcomes for up to 1 year.” Other influential guidelines, such as those from the International Society for Pediatric and Adolescent Diabetes, continue to promote high intakes of carbohydrate (~45%–50% EI) and specifically caution against low-carbohydrate diets in children and adolescents (47).

#### Trends in glycemic control amid technological developments

In the last 50 years, major pharmacological and technological innovations have been developed to improve glycemic control (Figure 1), including insulin analogs and insulin delivery systems, providing major benefits, but at substantial expense to patients and the health care system.

Self-monitoring of BG allowed patients to make daily therapeutic decisions and to have glycemic targets (48), a prerequisite for intensive insulin therapy with flexible dietary prescriptions (49); however, this method also introduced new challenges. In current “carbohydrate counting” approaches, patients adjust premeal insulin doses to match planned carbohydrate intake (50) and add insulin if BG is above target. Patients must have access to comprehensive nutrition education and the cognitive development and numeracy skills to accurately estimate the carbohydrate content of food (51). Studies have shown wide variations in the ability to accurately count carbohydrates (52–54). Postprandial glycemia and insulin requirements are also affected by carbohydrate quality (i.e., GI) and intake of other macronutrients (55–58), in addition to factors unrelated to diet, such as exercise. Protein contributes to postprandial glycemia and insulin requirements by providing amino acid substrates for gluconeogenesis (59) and by stimulating glucagon secretion (60, 61). Dietary fat delays gastric emptying, blunts the early rise in plasma glucose, and causes dose-depen-

dent late postprandial hyperglycemia (62, 63). Because of the obvious complexity of these interactions, only select individuals are able to master mealtime insulin adjustment to account for variations in the macronutrient composition of usual diets.

Rapid- and ultrarapid-acting insulin analogs, with their earlier onset and shorter duration of action (2) compared with regular insulin, have allowed for more physiological coverage of carbohydrate intake. Despite their rapid absorption, the action of insulin analogs peaks after 90–120 minutes and persists for 5–6 hours (64). In contrast, glucose appearance in blood from a mixed meal typically peaks within 60 minutes and persists only 2–3 hours (65), a mismatch that can be partially addressed by administration of insulin 15–20 minutes before the start of the meal (4, 66). However, glycemic response to high-carbohydrate meals varies substantially among individuals, even with careful control of other dietary factors, and prevention of both early prandial hyperglycemia and late postprandial hypoglycemia remains a major challenge (67).

Continuous glucose monitoring (CGM) systems provide detailed information on glucose patterns and have the additional advantage of showing the direction and rate of change of glucose concentrations (68). CGM can enable patients to observe how food factors affect their postprandial glucose profiles, allowing them to more precisely match insulin delivery to the size and macronutrient content of the meal. Coupling insulin pumps with CGM, hybrid closed-loop (HCL) systems automatically modulate insulin delivery to counteract glycemic trends toward hypo- or hyperglycemia. However, because of the aforementioned mismatch in carbohydrate absorption rate and insulin pharmacodynamics, this approach does not eliminate the need for premeal bolusing.

Together, these developments have translated into greater convenience and flexibility for patients. Epidemiologic and comparative studies have shown clinically meaningful HbA1c reductions of about 1%–2% with intensive insulin therapy (24, 69) (although with substantial variance based on patients’ abilities;

ref. 70), 0.8%–1.3% with combined pump and CGM use (71), and an additional ~0.3% with HCL (72). Nevertheless, glycemic control in the United States remains suboptimal. A recent report from the Type 1 Diabetes Exchange Registry showed that only 17% of children and 20% of adults achieve the glycemic targets of <7.5% and <7%, respectively (71). Furthermore, over the past decade, glycemic control in adolescents has deteriorated (71). Similarly, a substantial proportion of people with type 2 diabetes (T2D) fail to achieve glycemic and metabolic management goals, despite rapidly rising health care expenditures for diabetes (73, 74). Moreover, cardiovascular mortality and all-cause mortality among people with both forms of diabetes remain substantially higher than those in the general population (75, 76).

## Revisiting carbohydrate recommendations

### Rationale

Dietary carbohydrate, as the only macronutrient directly digested into glucose, is the main determinant of postprandial glycemia and insulin requirements (77–79). For most processed grains and other foods high in glycemic load (GL; the multiplicative product of GI and amount of digestible carbohydrate consumed), the digestion rate is exceptionally fast, increasing immediate insulin demand (80–82) and exacerbating the aforementioned mismatch between insulin kinetics and glucose appearance. Beyond glycemic control, a high-GL diet may also increase risk for cardiometabolic complications of diabetes (83–85), exacerbated by higher associated insulin requirements. Insulin resistance and hyperinsulinemia are well-recognized features common to both T2D and the metabolic syndrome (including central adiposity, hypertriglyceridemia, low HDL-cholesterol, hypertension, fatty liver, coagulopathy, and chronic inflammation) (86). Hyperinsulinemia is also characteristic of T1D, in part because the peripheral route of insulin administration (versus portal secretion) requires higher-than-normal systemic concentrations to control hepatic glucose output. Peripheral hyperinsulinemia increases anabolic activity of adipose tissue, potentially contributing to the higher incidence of overweight (71, 87) and metabolic syndrome in T1D (88–90). Although intensive insulin management on a conventional diet reduces postprandial hyperglycemia, weight gain frequently occurs (91–94) and is related to decreased glucosuria, increased calorie intake from treatment of more frequent hypoglycemia, and metabolic effects of hyperinsulinemia. Hence, measures to slow the rate (with a focus on carbohydrate quality) or total amount (low-carbohydrate diet) of glucose absorption from a meal may not only improve management of glycemia, but also reduce cardiometabolic risk. A reduction in GL may also help prevent T2D, in light of strong positive associations observed between high-GL foods (sugary beverages, processed grains, potatoes) (95–97) or an overall high-GL diet (98) and incidence of T2D in prospective studies.

### Carbohydrate quality

Independent of amount consumed, qualitative aspects of carbohydrate may influence glycemic control, metabolic responses, and CVD risk factors. Both soluble and insoluble fiber may affect the glycemic response to a meal, the former by increasing intraluminal viscosity in the small intestine and slowing carbohydrate

absorption and the latter primarily through mechanical effects that slow digestion of intact foods (e.g., with whole-kernel but not highly refined grains). Dietary fiber may also promote insulin sensitivity through effects on the gut microbiome, production of short-chain fatty acids, and other actions (99). In a meta-analysis of 42 intervention trials and two prospective studies, high-fiber versus control diets slightly reduced HbA1c (mean difference –0.18%) in patients with diabetes and showed small benefits for other measures of glycemia, serum lipids, body weight, and C-reactive protein levels (100). With regard to T1D, some studies have shown improvement in glycemic control (101–103), cholesterol levels (101), and inflammation (104), and reduction in all-cause mortality and CVD (105), whereas others did not observe benefits for metabolic control (106–108), insulin requirement (106), inflammation, or arterial stiffness (108). Large variations in the amount of fiber across studies and the challenges in isolating this factor from other dietary components have confounded interpretation of the findings.

The GI was introduced by Jenkins et al. in 1981 (38), and GL was subsequently introduced to reflect the glycemic response to a food, meal, or diet as commonly consumed (109). Low-GI/GL diets have shown modest benefits for HbA1c levels in diabetes, typically in the range of about 0.5% (110–112). In T1D, improvements in glycemic control, reduced rates of hypoglycemia, and decreased insulin requirements have been observed (102, 113–115). Additional benefits include improved quality of life (115), reduced lipid levels (114), and weight loss (116). Other studies failed to show any benefits from a low-GI diet (117). Study limitations include small sample sizes, variable study duration (range 12 days to 12 weeks for randomized controlled trials), dietary heterogeneity, and low intervention intensity, as discussed below.

### Carbohydrate amount

With the possible exception of nursing infants, humans at all stages of life can survive with virtually no dietary carbohydrate, as evidenced by hunter-gatherer populations living at high latitudes that had little access to plant foods (the only significant source of carbohydrate, other than breast milk) throughout most of the year. Therefore, for the purposes of this Review, the question arises of what level of carbohydrate intake is optimal for glycemic control and prevention of complications in people with diabetes.

Diets focused on carbohydrate amount can be characterized with reference to prevailing intakes as high-carbohydrate ( $\geq 45\%$  EI, “standard”) and reduced-carbohydrate ( $< 45\%$  EI). Reduced-carbohydrate diets can be further categorized as moderate-carbohydrate (MC; 26%–44% EI), low-carbohydrate (LC; 10%–25% EI), very-low-carbohydrate (VLC;  $< 10\%$  EI), and ketogenic, according to the relative or absolute amount of digestible carbohydrate consumed, as summarized in Table 1 (5, 118). While these definitions are somewhat arbitrary, the term ketogenic refers to a physiologically distinctive state. With restriction of digestible carbohydrate intake to a critical threshold (typically  $\leq 30$ –50 g/d) and concurrent limitation of protein, the resulting high serum glucagon/insulin ratio increases rates of lipolysis and hepatic ketogenesis (119), producing concentrations of  $\beta$ -hydroxybutyrate (BOHB) typically between 0.5 and 5.0 mmol/L. This state of “nutritional ketosis” (120, 121) contrasts

**Table 1. Classification of reduced-carbohydrate diets**

| Carbohydrate amount     | Diet name                       | Defining features/Comments  |
|-------------------------|---------------------------------|---|
| ≥45% EI; ≥225 g/d       | High-carbohydrate               | Prevailing dietary pattern in the US; consistent with recent recommendations for people with diabetes and USDA recommendations for general public   |
| 26%–44% EI; 131–224 g/d | Moderate-carbohydrate           | Moderate reduction of grains, starchy vegetables, added sugar<br>Unlimited legumes, whole fruits<br>Unlimited non-starchy vegetables                |
| 10%–25% EI; 51–130 g/d  | Low-carbohydrate                | Substantial reduction of grains, starchy vegetables, added sugar<br>Moderate reduction of legumes, whole fruits<br>Unlimited non-starchy vegetables |
| <10% EI; ≤50 g/d        | Very-low-carbohydrate           | Elimination of grains, starchy vegetables, added sugar<br>Substantial reduction of legumes, whole fruits<br>Unlimited non-starchy vegetables        |
|                         | Very-low-carbohydrate ketogenic | As above, with protein intake typically limited to ≤20% of EI<br>Serum BOHB characteristically 0.5–5.0 mmol/L                                       |

Calculations based on a 2000-kcal/d diet. BOHB,  $\beta$ -hydroxybutyrate; EI, energy intake; USDA, US Department of Agriculture.

with the uncontrolled ketone production characteristic of diabetic ketoacidosis most commonly due to insulin deficiency, in which BOHB typically exceeds 5 mmol/L, and clinical derangements (e.g., dehydration, weight loss, nausea, altered mental state) may occur (Supplemental Table 1; supplemental material available online with this article; <https://doi.org/10.1172/JCI142246DS1>). In nutritional ketosis, ketone bodies constitute a primary fuel for the brain, decreasing dependency on glucose, with other potential metabolic benefits (e.g., related to chronic inflammation, oxidative stress, myocardial energy metabolism) (35, 122–124).

**Carbohydrate reduction in T1D.** The impact of macronutrients on glycemic control in T1D has been extensively studied among populations consuming high-carbohydrate diets. Therefore, we explored this relationship in a systematic search of studies focused on reduced-carbohydrate diets (<45% EI, ≥2 months), as detailed in Table 2. We identified 24 articles in heterogeneous settings, including 4 randomized controlled trials (RCTs), 5 uncontrolled interventional studies, 3 observational studies, and 12 case reports or series.

While glycemic control on MC diets was similar to that of the general population with T1D, all LC and VLC studies reported mean HbA1c of less than 7.5%. Moreover, in studies of VLC, HbA1c was in the normal range and insulin doses were low, with the exception of one case report. CGM showed remarkably stable glycemic profiles. For instance, among 316 respondents in an online community of children and adults with documented T1D following a VLC diet for at least 3 months, mean HbA1c was 5.67%, daily insulin dose was 0.4 U/kg/d, mean CGM glucose was 104 mg/dL, and mean CGM glucose standard deviation was 36 mg/dL (125). Likewise, short-term RCTs comparing LC (126, 127) or VLC (128) with HC diets showed reductions in HbA1c (126), insulin doses (126–128), glycemic variability, and time spent in hypoglycemia (127, 128). When reported, severe hypoglycemia and diabetic ketoacidosis were infrequent or reduced compared with the prediet period (125, 129–132). Lipid levels varied, with generally favorable triglyceride/HDL-cholesterol ratio but elevated LDL-cholesterol in several case reports.

As noted in a recent meta-analysis (133), inferences regarding the efficacy of a reduced-carbohydrate diet in T1D are limited by small study size, short duration, dietary assessment methodology (e.g., self-report), and selection bias. Nevertheless, mirroring trends in the general population, popular interest in carbohydrate reduction for diabetes management has surged recently (134, 135), with several books focused on or including sections on VLC diets for T1D management (136–140).

#### *Carbohydrate reduction in T2D.*

In the absence of well-controlled and -powered interventions in T1D, clinical trials of reduced-carbohydrate diets in T2D may be informative, as both types

of diabetes share key pathophysiological features (i.e., glucose intolerance and peripheral hyperinsulinemia) and comorbidities. Meta-analyses of trials comparing reduced-carbohydrate versus higher-carbohydrate diets or standard of care report modestly lower HbA1c (~0.5%) (141–147) and reduced usage of glucose-lowering medications (142, 144, 145, 147), suggesting a clinical benefit greater than that reflected by HbA1c alone. As in studies in T1D, the reduced-carbohydrate diets produced favorable changes in triglycerides and HDL-cholesterol (141–146); effects on LDL-cholesterol were inconsistent, with no marked increase seen in any meta-analysis. Effects were also reported in studies without substantial weight loss (143–147), suggesting the potential of a weight-independent benefit of carbohydrate reduction. However, dietary adherence and glycemic effects diminish over time (148), and the efficacy of carbohydrate restriction for hard clinical outcomes — micro- and macrovascular disease, organ failure, or premature death — has not been established.

The generally moderate magnitude of benefits observed in these and other diet studies should be interpreted in light of fundamental design limitations common to most of these trials. Recognizing the difficulty of maintaining major dietary change over the long term for most people (149, 150), trials focused on the potential efficacy of novel diets — and especially a reduced-carbohydrate diet in the modern food environment — should use high-intensity interventions to facilitate behavioral change and differentiation between dietary groups, potentially incorporating food provision, individual counseling from a behavior modification specialist, cooking classes, daily internet support, and more. However, most published trials have depended on low-intensity interventions, typically consisting of nutritional education and group dietary counseling. Indeed, as shown by van Wyk et al. (148), dietary adherence is often low, with little difference in carbohydrate intake between treatment groups in many long-term behavioral trials.

The findings of one recent, nonrandomized trial suggest that carbohydrate restriction may be sustainable and efficacious when combined with high-intensity individual support (151). Among

**Table 2. Reports on reduced-carbohydrate diets in people with T1D**

| Reference   | Design | Setting   | <i>n</i><br>(Ped <i>n</i> ) | Diet time,<br>months | HbA1c,<br>% | Insulin,<br>IU/kg | Trig,<br>mg/dL | TC,<br>mg/dL | LDLc,<br>mg/dL | HDLc,<br>mg/dL |    |
|---|--------|---|-----------------------------|----------------------|-------------|-------------------|----------------|--------------|----------------|----------------|----|
| <b>Moderate-carbohydrate diet (131–224 g/d; ~26% to &lt;45% EI)</b> |        |   |                             |                      |             |                   |                |              |                |                |    |
| Donaghue 2000 (180)   | RCT    | Control group (intervention group had CHO >45%)           | 11 (11)                     | 3                    | 9.3         | 0.9               | 71             | 155          | 93             | 50             |    |
| Soedamah-Muthu 2013 (181)   | O      | Cohort study; stable CHO over 7 years                     | 1102                        | 84                   | 8.2         | 0.68              | 85             | 205          | 124            | 63             |    |
| Strychar 2009 (182)   | RCT    | Equicaloric lower-CHO diet arm                            | 15                          | 6                    | 7.1         | –                 | 58             | 164          | 89             | 63             |    |
| Chantelau 1987 (183)  | UI     | Intensified insulin regimen with liberalized diet         | 48                          | 3                    | 8.3         | 0.68              | 11             | 18           | –              | 5              |    |
| Knight 2016 (184)   | UI     | Liberalized diet with intensive insulin therapy           | 46                          | 12                   | 7.8         | –                 | –              | –            | –              | –              |    |
| Chantelau 1982 (185)  | UI     | Liberalized diet  | 10                          | 4–6                  | 7.3         | –                 | 102            | 204          | –              | 59             |    |
| <b>Low-carbohydrate diet (51–130 g/d; ~10%–25% EI)</b>              |        |   |                             |                      |             |                   |                |              |                |                |    |
| Krebs 2016 (126)  | RCT    | Parallel, LC vs. HC                                       | 5                           | 3                    | 7.2         | 0.57              | 71             | 178          | 108            | 58             |    |
| Schmidt 2019 (127)  | RCT    | Crossover, LC vs. HC                                      | 13                          | 3                    | 7.4         | 0.45              | 53             | 190          | 97             | 79             |    |
| Nielsen 2005 (186)  | UI     | LC diet education   | 22                          | 12                   | 6.4         | 0.4               | 53             | 217          | –              | 54             |    |
| Nielsen 2012 (187)  | UI     | LC diet education ( <i>n</i> = 48), 48% report adherence  | 23                          | 48                   | 6.4         | –                 | –              | 217          | –              | 70             |    |
| <b>Very-low-carbohydrate diet (≤50 g/d; ~ &lt;10% EI)</b>           |        |   |                             |                      |             |                   |                |              |                |                |    |
| Bouillet 2019 (188)   | C      | Self-selected diet; prolonged remission                   | 1                           | 1                    | 48          | 5.5               | 0              | 75           | 132            | 51             | 47 |
|   |        |   | 2                           | 1                    | 15          | 5.6               | 0              | –            | –              | –              | –  |
|   |        |   | 3                           | 1                    | 48          | 4.6               | 0.17           | 67           | 301            | 209            | 79 |
| McClellan 2019 (189)  | C      | Self-selected diet  | 1 (1)                       | 48                   | 5.2         | 0.55              | –              | –            | –              | –              |    |
| Eiswirth 2018 (130)   | C      | Self-selected diet  | 1                           | 5                    | 5.3         | –                 | –              | 155          | 81             | –              |    |
| Lennerz 2018 (125)  | O      | Self-selected diet; survey of online community            | 316 (131)                   | 26                   | 5.7         | 0.4               | 74             | 234          | 147            | 74             |    |
| Vernon 2003 (190)   | C      | Chart review, self-selected diet                          | 1                           | 3                    | 5.3         | –                 | 47             | 165          | 93             | 62             |    |
| O'Neill 2003 (191)  | C      | Chart review, self-selected diet                          | 10 (1)                      | 8–61                 | 5.5         | –                 | 64             | 199          | 112            | 71             |    |
| Nolan 2019 (131)  | C      | Self-selected diet, athlete                               | 1                           | 48                   | 5.0         | –                 | 168            | 368          | 228            | 104            |    |
| de Souza Bosco Paiva 2019 (192)                                     | C      | Self-selected diet  | 1 (1)                       | 3                    | 4.8         | 0.06              | –              | –            | –              | –              |    |
| Leow 2018 (193)   | O      | Self-selected diet  | 11                          | 31                   | 5.3         | 0.26              | 97             | 306          | 213            | 77             |    |
| Dressler 2010 (129)   | C      | Ketogenic diet for epilepsy                               | 1 (1)                       | 13                   | 6.2         | 0.45              | 175            | 182          | 106            | 124            |    |
| Bernstein 1980 (194)  | C      | Self-selected diet  | 1                           | ≥60                  | 4.0         | 0.4               | 69             | 187          | –              | 86             |    |
| Henwood 2006 (195)  | C      | Ketogenic diet for seizure disorder                       | 1 (1)                       | 10                   | 5.1         | –                 | –              | –            | –              | –              |    |
| Tóth 2014 (132)   | C      | Remission phase, adoption of “paleolithic ketogenic” diet | 1                           | 2.5                  | 5.5         | 0                 | 111            | 301          | 224            | 55             |    |
| Tóth 2015 (196)   | C      | Remission phase, adoption of “paleolithic ketogenic” diet | 1 (1)                       | 14                   | 5.6         | 0                 | 124            | 224          | 129            | 69             |    |

To examine the relationship between dietary carbohydrate amount and glycemic control among reduced-carbohydrate diets, we conducted a PubMed search on May 1, 2020, with the query “(diabetes[title/abstract] OR diabetic[title/abstract]) AND (ketogenic[Title/abstract] OR carbohydrate[Title/abstract]) AND insulin NOT type 2 NOT animal,” limited to English language and human articles. A total of 1358 publications were identified, independently reviewed, and cross-referenced by authors, from which 24 studies were selected based on these criteria: (a) included a group with T1D; (b) carbohydrate <45% EI; and (c) reported HbA1c ≥2 months on the diet. One case series confounded by insulin omission and other issues was excluded (169). For studies with multiple groups, only those meeting inclusion criteria were included. C, case report or series; CHO, carbohydrate. HC, high-carbohydrate; HDLc, HDL-cholesterol; LC, low-carbohydrate; LDLc, LDL-cholesterol; *n*, number of eligible participants; O, observational; Ped *n*, number of pediatric participants; RCT, randomized controlled trial; TC, total cholesterol; Trig, triglycerides; UI, uncontrolled intervention; “–”, not reported.

262 adults with T2D prescribed a ketogenic diet and provided with a novel “continuous care intervention” (e.g., Web-based resources, tracking tools, telemedicine support), 74% completed the 2-year follow-up period. Among them, mean weight loss was 11.9 kg, mean HbA1c decreased by 0.9%, and use of glucose-lowering medications (other than metformin) decreased by more than 50%. “Diabetes reversal,” defined as HbA1c <6.5%, without glucose-lowering medications other than metformin, occurred in 53.5% of participants. A usual-care comparison group showed no improvements in outcomes. A second recent trial compared a less

restrictive LC diet (with 90 g/d carbohydrate) versus a conventional low-fat (≤30% EI) diet in 85 patients with poorly controlled T2D (152). After 18 months, the LC group maintained good dietary adherence and had lower HbA1c, weight, waist circumference, and blood pressure. Carotid intima-media thickness was nonsignificantly (*P* = 0.08) improved in the LC group. High-quality RCTs will be needed to assess the generalizability of these findings.

Meta-analyses do not suggest special safety concerns for carbohydrate-restricted diets in T2D (141–147), although long-term and well-powered trials will also be needed to address this ques-

tion. For individuals taking insulin or drugs that increase insulin action, medical supervision is needed to guide dose adjustment to prevent hypoglycemia. Since carbohydrate-restricted diets are not inherently high in protein, impairment of renal function would not necessarily preclude their use.

#### **Safety concerns about very-low-carbohydrate diets for T1D**

Despite more than a century of clinical experience with low-carbohydrate diets, considerable controversy persists regarding the safety of VLC diets for the public in general and people with diabetes in particular (134). Specific concerns in T1D relate to risk for hypoglycemia and ketoacidosis; general concerns include cardiovascular risk, nutrient deficiencies, and poor growth in children.

**Hypoglycemia.** While hypoglycemia may occur without appropriate insulin dose reduction, a VLC diet may lower the risk for this complication through reduction in prandial insulin requirements, thus ameliorating the difficulty of controlling early postprandial hyperglycemia without causing late postprandial hypoglycemia. In support of this possibility, two RCTs found less time spent in hypoglycemia below 54 mg/dL on carbohydrate-reduced versus high-carbohydrate diets (127, 128). Severe hypoglycemic events were not noted in any of the reviewed case reports, and the online survey cited above (125) reported few such events among respondents after adoption of a VLC diet relative to their prediet period and compared with rates in the general T1D population (153, 154). Another potential advantage of a VLC diet is the neuroprotection conferred by nutritional ketosis for not only symptomatic hypoglycemia, but also long-term brain health (122, 155–158). Landmark experiments by Cahill (159) and others (156) show that, with adaptation to ketosis following a prolonged fast, research participants without diabetes injected with insulin to produce severe hypoglycemia (mean BG <40 mg/dL, and, in one case, 9 mg/dL) experienced no symptoms and showed no evidence of a counter-regulatory hormonal response. However, no high-quality longer-term prospective data are available to assess this risk in the context of nutritional ketosis and diabetes management.

**Ketoacidosis.** Concern has been expressed that severe ketoacidosis might develop more easily from the baseline nutritional ketosis associated with a VLC diet or that the transition from physiological to pathological ketosis might be hard to recognize. However, the amount of insulin (endogenously secreted or exogenously administered) necessary to maintain normal BG is almost always sufficient to prevent a pathological rise in ketoacids by suppressing excessive lipolysis and ketogenesis. In fact, people on a VLC diet, by virtue of having more normal and less variable glycemic patterns, can use relatively small increases in BG (e.g., to 180 mg/dL) as an early indication of physiological stress and possible under-insulinization and an early warning sign of impending pathological increase in ketoacid concentrations. Ketoacidosis was not noted in any of the reviewed case reports, and the online survey found low rates of hospitalization for ketoacidosis in individuals after adoption of a VLC diet relative to their prediet period (125) and to rates in the general T1D population (153, 154).

The possibility of euglycemic ketoacidosis remains a theoretical concern, with rare case reports among patients with T1D (160) when vomiting occurs or patients are unable to tolerate food intake, and in the general public (161, 162) following a VLC diet.

Although it has not been described in people with T1D in conjunction with a VLC diet, the occurrence of this complication with use of sodium-glucose cotransporter-2 (SGLT2) inhibitors — a class of drugs that, analogous to a VLC diet, decreases insulin requirements and shifts metabolism from carbohydrate to fat (163, 164) — emphasizes the need for vigilance.

**Cardiovascular disease risk.** Carbohydrate-reduced diets may increase total and LDL-cholesterol in the general population, mediated in part by higher intake of saturated fats. These elevations have been inconsistently observed in people with T1D or T2D. For individuals who do experience an increase, improvements in triglycerides and HDL-cholesterol may attenuate or counterbalance the adverse effects of high LDL-cholesterol, although this possibility remains speculative. Moreover, a VLC diet may selectively enrich large, buoyant LDL particle subspecies that have a weaker association with CVD than smaller dense LDL particles (165). In analyses of adolescents and young adults who participated in the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study — a longitudinal, observational study using the DCCT cohort to determine the long-term effects of glycemic levels on micro- and macrovascular outcomes — HbA1c was the strongest modifiable predictor of cardiovascular events, followed by triglycerides; LDL-cholesterol had weaker associations (166). This observation is consistent with the 2014 ADA and American Heart Association consensus statement that reported a weaker association of CVD events with LDL-cholesterol elevation than with poor glycemic control or other risk factors (167). Furthermore, high LDL-cholesterol can be more effectively treated with drugs, and with fewer adverse effects, than metabolic syndrome components for which carbohydrate restriction may be especially effective.

**Nutritional insufficiency.** Like other restrictive diets, VLC diets have been linked to various nutrient deficiencies (134, 168, 169). These observations highlight the importance of ensuring proper formulation and professional oversight in prescribing carbohydrate reduction for diabetes. Even with a daily limit of 50 g carbohydrate, a VLC diet can include regular consumption of dairy products, nuts, seeds, non-starchy vegetables, and limited amounts of low-sugar fruits (e.g., berries). On diets with less severe carbohydrate restriction, moderate amounts of legumes and grains can also be incorporated.

**Growth.** Poor growth has been reported among children with epilepsy treated with a ketogenic diet. However, the macronutrient composition used for refractory epilepsy may be more extreme (sometimes with fat >80% EI) than would be used in other clinical settings, and these children may have other complicating medical issues or drug treatments that affect growth (124, 170, 171). Growth delay has also been reported in children with T1D following a VLC diet (169); however, with possible concurrent insulin omission and other confounding factors, a causal relationship cannot be readily established from the limited available data. In the online survey (125), a modest decrease in height percentile since diagnosis was reported in 34 children, but the magnitude of the growth deceleration was similar to that observed in large diabetes registries and potentially related to metabolic stress surrounding diagnosis and implementation of treatment (172–174). Prospective studies are needed to address this concern.



*Other concerns.* Restrictive dieting, which is associated with eating disorders in the general population, may be of special concern for people with T1D, who are at increased risk for disordered eating (175). Adherence is also a concern. While VLC diets are popular and people who chose them report high satisfaction with their diet (125), studies on carbohydrate restriction report high rates of attrition (148). This may relate to the inherent challenges of behavior change and, as noted above, the low intervention intensity characteristic of most diet trials. In fact, restrictive diets have a long history of success for numerous specific conditions — such as celiac disease, phenylketonuria, and severe food allergies — when they provide symptom relief or other tangible benefits. With widespread usage of CGM, patients with diabetes may observe a marked reduction in postprandial hyperglycemia on a carbohydrate-restricted diet, providing not only immediate positive feedback, but also the hope of preventing much-feared diabetes complications. Furthermore, benefits might be achievable with flexible approaches, such as combining moderate carbohydrate reduction (e.g., 25% EI) with a focus on reducing GI, allowing for daily consumption of nontropical fruits, legumes, and modest portions of whole-kernel grains.

### Economic considerations

The total annual economic costs of diabetes in the United States were estimated at \$327 billion in 2017, including approximately \$15 billion for insulin. Of major concern, the cost of insulin analogs has increased enormously, with some patients now paying in excess of \$800 per month (176, 177). By reducing both the need for expensive, rapid-acting insulin analogs (to better match glucose absorption rates on a high-carbohydrate diet) and the total daily insulin dose required, a VLC diet might substantially lower out-of-pocket costs to patients with both types of diabetes. If carbohydrate restriction were to help prevent or treat T2D, the incidence of which has greatly increased in recent decades (178), the medical cost savings could be much greater.

### Conclusion

Reduced-carbohydrate diets have been used to treat diabetes for more than a century. After the discovery of insulin, high-carbohydrate

diets became the mainstay of MNT for diabetes, not because of demonstrated superiority for long-term outcomes, but because insulin could ameliorate the acute metabolic effects of carbohydrate consumption. Additional impetus for use of a high-carbohydrate diet in diabetes arose from concern for ketoacidosis in an era when the distinction between nutritional ketosis and ketoacidosis was not well understood. Moreover, the lack of practical methods for frequent BG monitoring delayed recognition of the ubiquity of postprandial hyperglycemia. Subsequently, a high-carbohydrate, low-fat diet was promoted to reduce serum cholesterol, even as evidence for an adverse effect on the development of metabolic syndrome accrued. Despite major pharmacological and technological developments, outcomes of management of T1D remain suboptimal, and the prevalence of T2D has greatly increased, placing many people at risk for micro- and macrovascular complications.

With new understanding of the importance of controlling postprandial hyperglycemia, mitigating glycemic variability, and ameliorating metabolic syndrome, carbohydrate restriction has gained renewed attention. Preliminary research suggests that this dietary approach might transform clinical management and perhaps normalize HbA1c for many people with diabetes, at substantially reduced treatment costs. High-quality RCTs, with intensive support for behavior changes, will be needed to address this possibility and assess long-term safety and sustainability (Supplemental Table 2). With total medical costs of diabetes in the United States approaching \$1 billion a day (179), this research must assume high priority.

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