Curr Diab Rep (2013) 13:271–278
DOI 10.1007/s11892-012-0357-5

ISSUES IN THE NUTRITIONAL TREATMENT OF TYPE 2 DIABETES AND OBESITY (E MAYER-DAVIS, SECTION EDITOR)

Health Effects of Low-Carbohydrate Diets: Where Should New Research Go?

Judith Wylie-Rosett · Karin Aebersold · Beth Conlon · Carmen R. Isasi · Natania W. Ostrovsky

Published online: 25 December 2012

Abstract There has been considerable debate about the metabolic effects of restricting carbohydrate intake in weight and diabetes management. However, the American Diabetes Association has noted that weight and metabolic improvements can be achieved with low carbohydrate, low fat (implicitly higher carbohydrate), or a Mediterranean style diet (usually an intermediate level of carbohydrate). Our paper addresses variability in the definition for low or restricted carbohydrate, the effects of carbohydrate restriction on diabetes-related health outcomes, strategies for restricting carbohydrate intake, and potential genetic variability in response to dietary carbohydrate restriction. Issues for future research are also addressed.

Keywords Diabetes · Diet · Nutrition · Low carbohydrate · Eating patterns · Available carbohydrate · Genetic variability · Paleolithic diet · Nutrition guidelines · Insulin resistance · Gut hormones · Health effects · Diabetes · Research

Introduction

There has been considerable debate about the effects of restricting carbohydrate intake in weight and diabetes management [1–4]. Carbohydrate intake is the primary determinant of post-prandial glycemia. Evidence-based reviews and recommendations for diabetes management consistently suggest reduced intake of highly processed foods and sugary beverages [5•, 6]. The American Diabetes Association has noted that weight and metabolic improvements can be achieved with low carbohydrate, low fat (implicitly higher carbohydrate), or a Mediterranean style diet (usually an intermediate level of carbohydrate) [7•, 8].

Monitoring carbohydrate intake is used to determine insulin dosage. Weight loss and metabolic improvement have been achieved with widely varying levels of carbohydrate intake. Our paper will address variability in the definition for low or restricted carbohydrate diets, the effects of carbohydrate restriction on diabetes metrics, strategies for restricting carbohydrate intake, and genetic predictors of response to dietary carbohydrate.

J. Wylie-Rosett (✉) · K. Aebersold · B. Conlon · C. R. Isasi · N. W. Ostrovsky
Albert Einstein College of Medicine,
1300 Morris Park Avenue, Bronx, NY 10461, USA
e-mail: judith.wylie-rosett@einstein.yu.edu

Low Carbohydrate Diets: Definition Challenges

The lack of a consistent definition for "low carbohydrate diets" complicates efforts to compare studies throughout the literature [9]. While very low-carbohydrate diets are often defined by the absolute amount of carbohydrate intake, usually less than 70 g per day, other levels of dietary carbohydrate are usually defined based on the proportion of energy intake as illustrated in the Table 1. As the energy level of the diet decreases, the proportion of energy from carbohydrate increases. For example, a diet containing 200 g of carbohydrate might be classified as moderately low for a 2000 calorie intake, moderate-carbohydrate at 1500 calories and high-carbohydrate at 1200 calories.

A recent systemic review of macronutrients in diabetes management noted that the terms "conventional" or "traditional" carbohydrate diet were often used to describe the comparison diet for evaluation of lower carbohydrate diets [5•]. The review found that the terms “diabetic” or “ADA” were frequently used as well. In general, the comparison diets contained 55%–65% of energy from carbohydrate. However, national survey data suggest that people with diabetes consume an eating pattern that contains about 45% of energy

Table 1 Dietary classification based on the amount of carbohydrate*

Description of Amount	Definition	2000 Calorie	1500 Calories	1200 Calories
Very low carbohydrate	21–70 g/d	4%–14%	6%–19%	7%–23%
Moderately low carbohydrate	30%–39.9% of energy	150–200 g/d	113–149 g/d	90–120 g/d
Moderate carbohydrate	40%–65% of energy	200–325 g/d	150–245 g/day	120–195 g/d
High carbohydrate	>65% of energy	>325 g/d	> 245 g/day	>195 g/d

*Classification for the level of dietary carbohydrate based of those used in the Reference 9 meta-analysis.

intake from carbohydrate [10–12]. The assumption that the ADA recommends a specific level of carbohydrate intake is outdated as the current recommendation is for individualizing the macronutrient distribution [7•, 8].

In contrast to most low carbohydrate diets, which focus on number of g of carbohydrate or the percent of energy from carbohydrate [9], Paleolithic nutrition is based on the principles of evolutionary biology with a focus on the low carbohydrate options available to the hunter-gatherers [13–17]. This dietary approach, which is often referred to as the Paleo diet, targets restriction of grains, dairy products, and all refined food items. Carbohydrate sources that are encouraged include fruits, vegetables, and nuts. The total carbohydrate is approximately 35%–40% of energy intake although no specific amount is considered to be the goal. Paleo nutrition recommendations have been based on epidemiological studies of existing hunter-gatherer populations of today as well as archeological studies [13, 16, 17].

What are the Diabetes-Related Health Effects of Low-Carbohydrate Diets?

The metrics for evaluating the effectiveness of low-carbohydrate diets in the management of diabetes include weight, glycemia, cardiovascular risk indices, and other health indicators.

Weight

In our 2009 review of low-carbohydrate diets in this journal, we noted that low-carbohydrate diets may achieve better early weight loss than comparison diets higher in carbohydrate, but weight loss was comparable for studies that were 1 year or longer [18]. Systematic reviews by the ADA [5•] and by Castaneda-Gonzalez et al [19], which examined clinical trials of low carbohydrate diets in diabetes management, reported no consistent differences in weight loss among the diets being compared. Of the published randomized trials (n = 9 studies) [3, 20–27] which evaluated the effects of low carbohydrate diets in diabetes management, only 3 trials were of 12 month duration or longer [24, 26, 27]. None of these longer term trials reported a significant difference in weight loss in the comparison between low-carbohydrate diet and other dietary strategies.

Our previous review of low-carbohydrate diets [18] in diabetes management reported that weight loss appeared to be better when the analysis was restricted to completers. Without the weight results of study dropouts, who may be close to half of those who were randomized, the findings, would be biased [18]. In a recent preference trial, Hussian et al [28] found a significantly greater 24-week weight loss among participants with diabetes who opted for a low-carbohydrate ketogenic diet than those who opted for a low caloric diet without carbohydrate restriction (12 kg vs 7 kg loss) [28]. However, the participants with diabetes who opted for the low-carbohydrate ketogenic diet were more obese (40.0 vs 36.3 kg/m^2) and younger (39.2 vs 45.2 years) than those opting for the low-caloric diet. Individuals with diabetes who self-select to follow low-carbohydrate diet may achieve a substantial weight loss, but longer-term studies suggest that recommending low-carbohydrate diets to all overweight individuals with diabetes does not yield any greater weight loss benefit than other dietary strategies. Therefore, assessing patient food preferences and appetite appear to be important when considering the potential weight loss effects of carbohydrate restriction in diabetes management [29, 30].

Glycaemia

An evidence-based ADA review [5•] examined research studies that addressed the effects of lowering total carbohydrate intake on glycemic control in patients with diabetes. The clinical trials in the ADA review included a treatment arm classified as very low carbohydrate (n = 7 studies) [3, 22–24, 31–33] and moderately low carbohydrate (n = 4 studies) [34–37]. In general, the lower carbohydrate treatment condition resulted in lower A1c levels and lower doses of antidiabetic medications than the higher carbohydrate comparison diet [5•]. However, the role of weight loss complicated interpretation of these findings, which was noted to be a confounder by the ADA review group [5•]. Meta-analyses by Kodama et al [38] and by Kirk et al [9] which compared low-carbohydrate diets with higher carbohydrate conventional carbohydrate

diets, reported similar conclusions. The effects of carbohydrate restriction on improving glycemic control largely disappeared when the trial was 1 year or longer in duration when results were reported on the basis of intention-to-treat [18, 24]. However, the Esposito et al study [27], which was conducted in individuals with newly diagnosed diabetes, reported improvements in A1c over the 48 month trial. Other studies [23, 24, 26, 28] which instituted a protocol to reduce anti-diabetic medications in the low-carbohydrate study arm, have reported a greater reduction of these medications with carbohydrate restriction.

Cardiovascular Risk Indices

Research findings have been mixed with respect to the effects of the amount of dietary carbohydrate on blood lipids. Two studies [39, 40] reported significant reductions in triglyceride level on a carbohydrate restricted diet compared with 50%–55% of energy from carbohydrate. The effects of carbohydrate restriction on LDL and HDL cholesterol appear to be indirect and largely modulated by the fatty acid distribution of fat intake [41]. Nonetheless, carbohydrate restriction under weight-stable conditions has been associated with reduction in total HDL cholesterol ratio, apolipoprotein B, and the mass of small, dense LDL particles. These changes are similar to those achieved with weight loss without restriction of carbohydrate [7•, 8].

The potential impact of dietary fat and fatty acids on lipids needs to be considered when evaluating variability in the level of dietary carbohydrate especially when the dietary comparisons are isocaloric, because changing the amount of carbohydrates is likely to change fat intake as well. In general, replacing saturated fatty acids with mono or polyunsaturated ones achieved a more favorable lipid profile than replacement with refined carbohydrate sources that are low in fiber [41]. Intake of saturated fat would increase if meats and high fat dairy products are used to replace carbohydrate sources such as grains, fruits, and lower fat dairy products [42]. Advocates for carbohydrate restriction suggest that improved glycemic control and reduced insulin fluctuation are primary targets and note carbohydrate-restricted diets are at least as effective for weight loss as low-fat diets [43]. However, in the Diabetes Control and Complication Trial (DCCT) [10], analysis of participants, who were randomly assigned to intensive therapy, found that when dietary intake was higher in total fat and saturated fat and lower in carbohydrate glycemic control was worse, independently of exercise, triglyceride concentration and BMI, which may be associated with insulin resistance [10]. Higher insulin dosage was also associated with higher HbA1c level in the DCCT probably due to increasing insulin dosage in an effort to improve glycemic control. The macronutrient and A1c relationships were no longer significant after adjusting for the baseline degree of glycemic control and concurrent insulin dose suggesting a complex relationship among determinants of glycemia in type 1 diabetes that may differ from type 2 diabetes.

The ADA position suggests that either a low carbohydrate or low fat diet are equally valid approaches [7•, 8] whereas some low carbohydrate advocates have promoted restriction of carbohydrate as the default treatment for diabetes and metabolic syndrome and criticized health agency caution [4, 44]. Feinman and Volek have suggested that substitution of fat for carbohydrate generally improves cardiovascular risk factors [4], but in a 2011 paper in this journal, Feinman [45] stated "pooled data fail to indicate any significant effect of saturated fat on CVD outcome." Examination of novel CVD biomarkers may further complicate the assessment of how low carbohydrate diets affect CVD risk. In 1 study, the C-reactive protein (CRP) decreased in the low-fat arm, and the soluble intercellular adhesion molecule (sICAM) decreased in the low carbohydrate arm [46•]. While both the low-carbohydrate and low-fat diets had beneficial effect, there may be different mechanisms through which weight loss with these diets potentially reduces CVD risk. Evaluation of the effects of carbohydrate restriction on cardiovascular risk factors is complex as the markers of risk may be affected by changes in medication, weight and inherent risk status. Therefore, individualized assessment is warranted to tailor advice to the needs of the diverse population with diabetes.

Other Health Outcomes and Monitoring Issues

The 2012 ADA Standards of Medical Care state their precautionary recommendation as, *"For patients on low-carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in those with nephropathy), and adjust hypoglycemic therapy as needed"*[7•]. The ADA rated the evidence level as "expert opinion" for this recommendation [7•]. However, it should be noted that the ADA standards recommend annual lipid profiles and renal function tests for all adult patients with the following laboratory evaluation (if not performed/available within past year):

- Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
- Liver function tests
- Test for urinary albumin excretion with spot urine albumin-to-creatinine ratio
- Serum creatinine and calculated glomerular filtration rate
- Thyroid-stimulating hormone in type 1 diabetes, dyslipidemia, or women over age 50 years.

While no additional lipid or renal screening tests are needed, adjustment of hypoglycemic therapy (insulin and insulin secretagogues) would be indicated if there is a substantial reduction in carbohydrate intake. The caution with

regard to protein intake is limited to patients who have renal impairment.

Concerns have been raised about the risk of hypokalemia based on a case report [47], which appears to be based on an assumption that restriction of carbohydrate intake would also restrict potassium intake [48]. However, in a randomized clinical trial conducted in patients with type 2 diabetes, the effects of restricting carbohydrate and restricting fat on blood potassium did not differ [48]. The predictors for needing potassium supplementation were baseline blood potassium level and diuretic therapy [48]. In this trial, there was greater early weight loss with carbohydrate restriction, but the 1-year weight loss did not differ [24].

Increasing concerns about the hepatic abnormalities associated with diabetes and obesity raise questions about how altering dietary composition may affect deposition of fat in the liver of patients with diabetes. A recent isocaloric dietary trial, which was conducted in patients with type 2 diabetes, restricted carbohydrate (40% carbohydrate with 27% of energy from monounsaturated fatty acids) resulted in a significant reduction in hepatic fat measured by proton nuclear magnetic resonance spectroscopy [49]. Whether the reduction in hepatic fat was due to change in carbohydrate or fatty acids is unknown. We found no studies that examined the effects of very low-carbohydrate diets on hepatic fat deposition.

The Paleolithic diet is designed to change intestinal flora, which is the proposed mechanism for health benefits [50]. The plants consumed by early humans contained carbohydrate that was encapsulated within the cells and were extremely high in fiber before the development of plant cultivation [50]. Thus, the pre-agricultural "ancestral foods" would have considerably lower carbohydrate densities than modern foods rich in processed flour and sugar.

It is hypothesized that in parallel with the bacterial effects of sugars on dental and periodontal health, processed carbohydrates produce an inflammatory microbiota via the upper gastrointestinal tract, which with fat are able to affect a "double hit" by increasing systemic absorption of lipopolysaccharide. Therefore, a diet of grain-free whole foods with carbohydrate from cellular tubers, leaves, and fruits is believed to produce a gastrointestinal microbiota consistent with that of our early ancestors and greater sensitivity to endogenous insulin and leptin [15, 50]. However, standardized evaluation of the physio-chemical effects of the Paleo are lacking although there is emerging research addressing how carbohydrate restriction may affect gut microbes in inflammatory bowel disease [50].

Monitoring and Reformulation of Carbohydrate-Containing Foods

Monitoring of carbohydrate intake is widely used to control postprandial glucose excursions by methods that include counting the number of g of carbohydrates using food composition books, exchange lists, and experience-based estimations [8]. While the quantity of carbohydrate consumed is the primary determinant of postprandial blood glucose, the type or source of carbohydrates also influence postprandial glucose response to ingesting carbohydrate [5•, 8]. However, little is known about how monitoring glucose response after meals may function as a feedback loop in decision making with regard to reducing the amount of carbohydrate consumed.

The food industry has modified the formulation of foods to reduce the carbohydrate content. Low-digestible carbohydrates, which include fibers and sugar alcohols, have limited postprandial glucose impact and functional availability [51, 53•]. Fiber or amylose, which are considered resistant starches, are sometimes added to breads, pasta and other starchy or carbohydrate rich foods to create a reduced or low carbohydrate version of typically high carbohydrate foods. The expansion of low carbohydrate products appears to be spawning use of a wide array of fermentable fibers (resistant starch and non-starch polysaccharides) as well as sugar alcohols to reduce carbohydrate availability.

Dietary fiber, which is defined by the Institute of Medicine as the nondigestible (not digested in the human small intestine) sources of carbohydrate and lignin that are intrinsic and intact in plants [52], is sometimes subtracted from the total carbohydrate content of the total fiber if greater than 5 g per serving to yield the available or net carbohydrate. However, the amount of dietary fiber that is subtracted may vary from half to all of the fiber. For example, a slice of bread that contains 15 g of total carbohydrate and 5 g of fiber has 10 g of available (net) carbohydrate when all of the fiber is subtracted. However the available carbohydrate is 12.5 g when half of the fiber is subtracted. While sugar alcohols are absorbable, they are considered to be low-digestible carbohydrates with blunted impact on blood glucose and generally have a lower carbohydrate/caloric level than other sugars [53•]. Therefore, the calculation of carbohydrate in low-carbohydrate diets may reflect estimates of the net carbohydrate based on the use of sugar alcohols to reduce carbohydrates availability. As a result, how the amount of carbohydrate is determined in carbohydrate-restricted diets can vary considerably.

Fibers commonly used in low carbohydrate food products include acacia gum, beta-glucan, cellulose, chitin/chitosan, corn bran, corn fiber, inulin, oat bran/oat fiber, pea fiber, pectin, polydextrose, psyllium, rice bran, soy fibers, wheat bran, and wheat fiber. All of these fibers are unique in their functional capability for treatment of a number of diseases. The effects of fiber on the absorption and metabolism of carbohydrate is likely to vary based on structure (monomeric composition, chain length, type of binding, branching, and side chains) [53•]. The viscosity hypothesis

suggests that fibers, such as b-glucans and arabinoxylans, form a viscous solution in the stomach that delays gastric emptying and physically inhibits the absorption of carbohydrate. Viscosity is affected by the molecular weight of the fiber, the food processing method(s), and the combination of foods and drinks consumed. Specific types of dietary fibers vary in composition. For example, arabinoxylans vary in their arabinose: xylose ratio and resistant starches can vary in their amylose: amylopectin ratio, which may influence their metabolic effects.

Little is known about how carbohydrate restriction may affect the beneficial gut microbes, which may reduce the risk of autoimmune diseases such as type 1 diabetes, and alter the level of gut hormones associated with obesity and type 2 diabetes [54]. The high fermentable soluble diet may improve glucose tolerance of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) [54]. More recent research has addressed the endocrine effects of fibers that undergo fermentation in the colon. Secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which occurs after food ingestion, is stimulated by intake of resistant starch (RS), an amylose rich fermentable fiber. How secretion of GLP-1 and PYY are related to the blunted glycemic response and release short-chain fatty effects of resistant starch has been examined in Sprague-Dawley rats [54]. Resistant starch appears to stimulate GLP-1 and PYY secretion in a sustained day-long manner, independent of meal effect, or changes in glycemic response. Fermentation and the liberation of short chain fatty acids in the lower gut was associated with increased proglucagon and PYY gene expression. The primary mechanism for increased endogenous secretions of total GLP-1 and PYY may be fermentation rather than carbohydrate availability. Therefore, restriction of carbohydrate per se would not be expected to affect secretion of these gut hormones.

Genetic Variability in Response to Dietary Carbohydrate

Increased research regarding the role of gene-environment interactions in the development of diabetes and obesity has been accompanied with interest in the potential for genetic variability in response to carbohydrate restriction. The "Carnivore Connection" hypothesis is based on the premise that the genetic determinants of insulin resistance evolved in response to a scarcity of dietary carbohydrate during the ice age when early humans, whose diet had been largely from berries and other fairly readily available plant sources, were exposed to low plant: animal subsistence ratios [55]. As an adaptation to the lack of carbohydrate in the food supply, selection of genes for insulin resistance provided a survival advantage. This is so because habitual consumption of a low-carbohydrate, high-protein diet appears to increase insulin resistance with a concomitant rise in hepatic glucose production (mediated through an increased carbon flux through the gluconeogenic pathway) and a decrease in peripheral glucose utilization [56].

At the beginning of the Agricultural Revolution the availability of cereals for some populations would theoretically reduce genetic selection for insulin resistance. The "Carnivore Connection" is used to explain the high prevalence of intrinsic insulin resistance and type 2 diabetes in populations that transition rapidly from traditional diets with a low-glycemic impact to high-carbohydrate intake with more processing [57]. The hypothesis shares many of the evolutionary assumptions underlying the Paleolithic dietary principles. However, it differs from the thrifty genotype theory proposed by Neel [57], which focuses on the evolutionary role of energy restriction as a cause of insulin resistance rather than restriction of carbohydrate per se. However, as new genes are associated with the risk of type 2 diabetes, there has been no clear signature of positive selection around these genomic regions [58].

Genetic regulation of response to carbohydrate has been evaluated in mice [59]. A high fat diet containing 60% of energy from fat and 26.5% carbohydrate was used to induce hepatic insulin resistance, which was accompanied by accumulation of fat in wild type mice [59]. However, induction of insulin resistance appeared to be dependent on CB1 cannabinoid receptor activity with the (CB1-/CB1-) knockout mice having a lack of response to the high fat (low carbohydrate) similar to that of lean, insulin sensitive animals with normal livers. Differences in the expression of the cannabinoid receptor gene in humans may account for variability in response to carbohydrate restriction.

In human studies [60, 61], obese individuals who were homozygous for the transcription factor 7-like 2 *TCF7L2 rs7903146* T-risk allele, had a better metabolic response to a low fat (20%–25% of energy)-higher carbohydrate (60%–65% of energy) diet than to a higher fat and lower carbohydrate diet (40%–45% of energy from each). The *TCF7L2* variant risk for developing type 2 diabetes [62] has been associated with greater glucose response to a high glycemic load from the diet but not total carbohydrate intake. Other research has suggested that *TCF7L2 rs7903146* carriers may not be less responsive to the potential protective effects of a higher fiber intake on incident diabetes than non-risk allele carriers [63]. These findings suggest that the extent to which dietary carbohydrate increases insulin demand might enhance the risk of T2D associated with *TCF7L2* variants, but in the research little is known about the interaction of low carbohydrate diets and genetics per se.

Where Should New Research Go?

Challenges in evaluating the evidence regarding the effects of carbohydrate intake on metabolic parameters in diabetes management include variability in study methodology eg, adherence measurement with regard to carbohydrate intake, small study samples for intervention trials, low retention rates, and confounding by weight loss. The intention-to-treat analysis has been criticized by advocates who focus on the best case scenario results using data from the completers – highly adherent individuals who "stick to the low-carbohydrate intervention plan." [64]. This approach may yield insights about mechanism of action within the low carbohydrate treatment but does not address predictors of response in the general population.

Examination of how economic, cultural, and clinical variables are related to adherence and study outcomes may yield valuable insights. New research needs to address the impacts of lowering carbohydrate on a wide range of biomarkers including lipids, insulin resistance, liver metabolism, gut hormones, inflammation, and glycemia. The clinical significance of biomarkers is an important area to address the long-term outcomes. The availability of carbohydrate can be affected by the co-ingestion of fiber. The research needs to include properties of such a fermentation which affects gut hormone secretion and their wide-spread metabolic effects. As research generates new information about the effects of carbohydrate and fiber, the food industry will generate new research to reformulate and create new food products and nutraceuticals. As genomic research advances, more research that examines genetic variability in response to dietary carbohydrate will provide insights for tailoring nutrition advice. While prior research has explored the mechanisms underlying the relationship between nutrition and glycemia, future studies are likely to focus on individualizing nutritional intake recommendations by examining how nutrition relates to genetic polymorphism and the endocrine functions of gut hormones such as GLP-1 and PYY with regard to glycemia and other cardiovascular parameters.

Conclusions

Widely varying levels of carbohydrate intake have been effective for the target outcomes of improved glycemic control and reduced CVD risk among individuals with diabetes [5•]. However, genetic and other factors may influence response in individuals at risk for or with diabetes.

Acknowledgments This work was supported in part by 5R18DK075981, the Diabetes Research and Training Center P60 DK020541, and Clinical and Translational Science Award UL1 RR025750.

Disclosure Conflicts of interest: J. Wylie-Rosett: provided research advice to the American Potato Research Council; has received grant support from NIDDK, Kraft-Provident, and the Robert C and Veronica Atkins Foundation; has received honoraria from the State of Montana, Nutrition Society Cardiovascular Nurses; has received book royalties from the American Diabetes Association; and has received travel/accommodations expenses covered or reimbursed from the State of Montana, Nutrition Society, Cardiovascular Nurses Association; K. Aebersold: none; B. Conlon: none; C.R. Isasi: none; N.W. Ostrovsky: none.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Brehm BJ, D'Alessio DA. Weight loss and metabolic benefits with diets of varying fat and carbohydrate content: separating the wheat from the chaff. Nature clinical practice Endocrinol Metab. 2008;4:140–6.
2. Spence M, McKinley MC, Hunter SJ. Session 4: CVD, diabetes and cancer: diet, insulin resistance and diabetes: the right (pro)portions. The Proceedings of the Nutrition Society. 2010;69:61–9.
3. Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. Diabetic Med. 2007;24:1430–5.
4. Feinman RD, Volek JS. Carbohydrate restriction as the default treatment for type 2 diabetes and metabolic syndrome. Scand Cardiovasc J. 2008;42:256–63.
5. • Wheeler ML, Dunbar SA, Jaacks LM, Karmally W, Mayer-Davis EJ, Wylie-Rosett J, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature. Diabetes Care. 2012;35:434–45. *This systematic review examines the effects of altering macronutrient distribution in diabetes management. The effects of carbohydrate restriction are addressed.*
6. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care. 2002;25:148–98.
7. • American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2012;35 Suppl 1:S11–63. *The Standards assess the evidence and provide guidelines regarding carbohydrate restriction in the management of diabetes.*
8. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, et al. American Diabetes Association; nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2008;31 Suppl 1:S61–78.
9. Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 2008;108:91–100.
10. Delahanty LM, Nathan DM, Lachin JM, Hu FB, Cleary PA, Ziegler GK, et al. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. Am J Clin Nutr. 2009;89:518–24.
11. Vitolins MZ, Anderson AM, Delahanty L, Raynor H, Miller GD, Mobley C, et al. Action for Health in Diabetes (Look AHEAD) trial: baseline evaluation of selected nutrients and food group intake. J Am Diet Assoc. 2009;109:1367–75.

12. Oza-Frank R, Cheng YJ, Narayan KM, Gregg EW. Trends in nutrient intake among adults with diabetes in the United States: 1988–2004. J Am Diet Assoc. 2009;109:1173–8.
13. Konner M, Eaton SB. Paleolithic nutrition: twenty-five years later. Nutr Clin Pract. 2010;25:594–602.
14. Eaton SB, Konner MJ. Stone age nutrition: implications for today. ASDC. 1986;53:300–3.
15. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med. 31 1985;312:283–9.
16. Eaton SB, Eaton 3rd SB. Paleolithic vs modern diets–selected pathophysiological implications. Eur J Nutr. 2000;39:67–70.
17. Eaton SB, Eaton 3rd SB, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. Eur J Clin Nutr. 1997;51:207–16.
18. Wylie-Rosett J, Davis NJ. Low-carbohydrate diets: an update on current research. Curr Diabetes Rep. 2009;9:396–404.
19. Castaneda-Gonzalez LM, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. Nutricion Hospitalaria. 2011;26:1270–6.
20. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003;348:2074–81.
21. Nielsen JV, Joensson E. Low-carbohydrate diet in type 2 diabetes. Stable improvement of bodyweight and glycemic control during 22 months follow-up. Nutr Metab. 2006;3:22.
22. Daly ME, Paisey R, Paisey R, Millward BA, Eccles C, Williams K, et al. Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes–a randomized controlled trial. Diabetic Med. 2006;23:15–20.
23. Westman EC, Yancy Jr WS, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet vs a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab. 2008;5:36.
24. Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, Stein D, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet vs a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care. 2009;32:1147–52.
25. McLaughlin T, Carter S, Lamendola C, Abbasi F, Schaaf P, Basina M, et al. Clinical efficacy of two hypocaloric diets that vary in overweight patients with type 2 diabetes: comparison of moderate fat vs carbohydrate reductions. Diabetes Care. 2007;30:1877–9.
26. Guldbrand H, Dizdar B, Bunjaku B, Lindstrom T, Bachrach-Lindstrom M, Fredrikson M, et al. In type 2 diabetes, randomization to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012;55:2118–27.
27. Esposito K, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med. 2009;151:306–14.
28. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie vs low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012;28:1016–21.
29. Martin CK, Rosenbaum D, Han H, et al. Change in food cravings, food preferences, and appetite during a low-carbohydrate and low-fat diet. Obesity. 2011;19:1963–70.
30. Borradaile KE, Halpern SD, Wyatt HR, Klein S, Hill JO, Bailer B, et al. Relationship between treatment preference and weight loss in the context of a randomized controlled trial. Obesity. 2012;20:1218–22.
31. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med. 2005;142:403–11.
32. Yancy Jr WS, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. Nutr Metab. 2005;2:34.
33. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. The effects of low-carbohydrate vs conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med. 2004;140:778–85.
34. Haimoto H, Sasakabe T, Wakai K, Umegaki H. Effects of a low-carbohydrate diet on glycemic control in outpatients with severe type 2 diabetes. Nutr Metab. 2009;6:21.
35. Miyashita Y, Koide N, Ohtsuka M, Ozaki H, Itoh Y, Oyama T, et al. Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. Diabetes Res Clin Pract. 2004;65:235–41.
36. Jonsson T, Granfeldt Y, Ahren B, Branell UC, Palsson G, Hansson A, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. Cardiovasc Diabetol. 2009;8:35.
37. Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87:114–25.
38. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M, et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 2009;32:959–65.
39. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr. 2003;78:734–41.
40. Rodriguez-Villar C, Perez-Heras A, Mercade I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. Diabetic Med. 2004;21:142–9.
41. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. Curr Atheroscler Rep. 2010;12:384–90.
42. Alminger M, Eklund-Jonsson C. Whole-grain cereal products based on a high-fibre barley or oat genotype lower post-prandial glucose and insulin responses in healthy humans. Eur J Nutr. 2008;47:294–300.
43. Accurso A, Bernstein RK, Dahlqvist A, Draznin B, Feinman RD, Fine EJ, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. Nutr Metab. 2008;5:9.
44. Feinman RD, Volek JS. Low carbohydrate diets improve atherogenic dyslipidemia even in the absence of weight loss. Nutr Metab. 2006;3:24.
45. Feinman RD. Fad diets in the treatment of diabetes. Curr Diabetes Rep. 2011;11:128–35.
46. • Davis NJ, Crandall JP, Gajavelli S, Berman JW, Tomuta N, Wylie-Rosett J, et al. Differential effects of low-carbohydrate and low-fat diets on inflammation and endothelial function in diabetes. J Diabetes Complications. 2011;25:371–6. *This paper reports the findings of a randomized trial that compared low fat and low carbohydrate diets focusing on endothelial function and inflammation.*
47. Stevens A, Robinson DP, Turpin J, Groshong T, Tobias JD. Sudden cardiac death of an adolescent during dieting. South Med J. 2002;95:1047–9.
48. Davis NJ, Cohen HW, Wylie-Rosett J, Stein D. Serum potassium changes with initiating low-carbohydrate compared with a low-fat weight loss diet in type 2 diabetes. South Med J. 2008;101:46–9.

49. Bozzetto L, Prinster A, Annuzzi G, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. Diabetes Care. 2012;35:1429–35.
50. Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes Metab Syndr Obesity. 2012;5:175–89.
51. Grabitske HA, Slavin JL. Gastrointestinal effects of low-digestible carbohydrates. Crit Rev Food Sci Nutr. 2009;49:327–60.
52. Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: The National Academies Press; 2005.
53. • Gemen R, de Vries JF, Slavin JL. Relationship between molecular structure of cereal dietary fiber and health effects: focus on glucose/insulin response and gut health. Nutr Rev. 2011;69:22–33. *This paper addressed the role of fiber as a constituent of carbohydrate in relation to glucose, insulin, and gut response.*
54. Zhou J, Martin RJ, Tulley RT, Raggio AM, McCutcheon KL, Shen L, et al. Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. Am J Physiol. 2008;295:E1160–6.
55. Brand-Miller JC, Griffin HJ, Colagiuri S. The carnivore connection hypothesis: revisited. J Obes. 2012;2012:258624.
56. Rossetti L, Rothman DL, DeFronzo RA, Shulman GI. Effect of dietary protein on in vivo insulin action and liver glycogen repletion. Am J Physiol. 1989;257(2 Pt 1):E212–9.
57. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? 1962. Bull WHO. 1999;77:694–703;discussion 692–3.
58. Neel JV. The "thrifty genotype" in 1998. Nutr Rev. 1999;57(5 Pt 2): S2–9.
59. Liu J, Zhou L, Xiong K, Godlewski G, Mukhopadhyay B, Tam J, et al. Hepatic cannabinoid receptor-1 mediates diet-induced insulin resistance via inhibition of insulin signaling and clearance in mice. Gastroenterology. 2012;142:1218–28:e1211.
60. Florez JC. The new type 2 diabetes gene TCF7L2. Curr Opin Clinl Nutr Metab Care. 2007;10:391–6.
61. Grau K, Cauchi S, Holst C, Astrup A, Martinez JA, Saris WH, et al. TCF7L2 rs7903146-macronutrient interaction in obese individuals' responses to a 10-wk randomized hypoenergetic diet. Am J Clin Nutr. 2010;91:472–9.
62. Cornelis MC, Qi L, Kraft P, Hu FB. TCF7L2, dietary carbohydrate, and risk of type 2 diabetes in US women. Am J Clin Nutr. 2009;89:1256–62.
63. Hindy G, Sonestedt E, Ericson U, Jing XJ, Zhou Y, Hansson O, et al. Role of TCF7L2 risk variant and dietary fibre intake on incident type 2 diabetes. Diabetologia. 2012;55:2646–54.
64. Feinman RD. Intention-to-treat. What is the question? Nutr Metab. 2009;6:1.