

Review



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Restricted-Carbohydrate Diets in Patients with Type 2 Diabetes: A Meta-Analysis

JULIENNE K. KIRK, PharmD; DARBY E. GRAVES, MPH, RD; TIMOTHY E. CRAVEN, MSPH; EDWARD W. LIPKIN, MD, PhD; MARY AUSTIN, MA, RD; KAREN L. MARGOLIS, MD, MPH

ABSTRACT

Many current popular weight-loss diets advocate restricting carbohydrates, but risks and benefits of these diets for patients with diabetes is unclear. We searched for articles published in English between 1980 and April 2006 regarding carbohydrate-restricted diets that included and reported separate results for adult, nonpregnant patients with type 2 diabetes. Articles were limited to studies completed in the United States and Canada. Available data on study design; carbohydrate composition of diet; duration of diet; and the outcomes of weight, lipid levels (total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides), hemoglobin A1c percent and/or fasting glucose were extracted. A total of 56 studies or reviews were evaluated. Thirteen studies met our inclusion criteria. Meta-regression analyses show that hemoglobin A1c, fasting glucose, and some lipid fractions (triglycerides) improved with lower carbohydrate-content diets. Overall effect on weight was equivocal among the studies evaluated in this meta-analysis. Randomized, controlled studies of restricted-carbohydrate diets in patients with diabetes need

to be conducted in order to evaluate the overall sustainability of outcomes and long-term safety.

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Restricted-carbohydrate diets have become popular for weight loss in the general population (1). Because many people with type 2 diabetes are overweight, advice is often sought on carbohydrate-restricted diets. However, the long-term efficacy and safety of restricted-carbohydrate diets has been questioned for people with diabetes, who are already at increased risk for cardiovascular disease (2). Multiple literature reviews on carbohydrate restriction have been published citing isocaloric, non-isocaloric, or ad libitum diets and some evidence suggests that low-carbohydrate diets may be superior to other diets for short-term weight loss (2-10). Variable effects of differing amounts of dietary carbohydrate on metabolic parameters have also been reported (5,7,9). How to best adjust carbohydrate intake to achieve improved metabolic outcomes and lessen cardiovascular risk is confounded by the absence of a standard definition of low-carbohydrate diet.

The American Diabetes Association, in agreement with the guidelines published by the Food and Nutrition Board of the National Academy of Sciences, advocates a diet containing 45% to 65% of total calories from carbohydrate (11). Restricting carbohydrate intake to <130 g/day is not recommended. As a point of reference, 130 g carbohydrate equals 43% of calories in a 1,200-calorie diet, 30% of calories in a 1,700-calorie diet, or 24% of calories in a 2,200-calorie diet. This minimum daily carbohydrate recommendation (130 g) represents a percentage of daily calories that is less than the American Diabetes Association recommendations at all calorie levels of 1,200 calories per day and above. Reasons for this level of carbohydrate intake include the requirement of glucose as a source of energy for the brain and central nervous system, and the need for the water-soluble vitamins, minerals, and dietary fiber that are provided by carbohydrate foods (11,12). In contrast to these recommendations, many diets promote restriction of carbohydrate intake to <130 g/day.

J. K. Kirk is an associate professor and D. E. Graves is a diabetes educator, Department of Family and Community Medicine, and T. E. Craven is a Biostatistician IV, Department of Public Health Sciences, all at Wake Forest University School of Medicine, Winston-Salem, NC. E. W. Lipkin is an associate professor of Medicine, University of Washington, Seattle. M. Austin is principal, The Austin Group, LLC, Shelby Township, MI. K. L. Margolis is a senior clinical investigator, HealthPartners Research Foundation, Minneapolis, MN.

Address correspondence to: Julianne K. Kirk, PharmD, Department of Family and Community Medicine, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157. E-mail: jkirk@wfubmc.edu

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To evaluate the effects of dietary carbohydrate restriction in people with type 2 diabetes to control blood glucose, weight, and blood lipid levels, we performed a meta-analysis of published literature on this strategy. We included studies with a broad range of dietary carbohydrate content, from 4% to 45% of calories from carbohydrates, and assessed the effect of carbohydrate restriction on the outcomes of weight loss, blood levels of triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and total cholesterol, and glycemic control using hemoglobin A1c (HbA1c) and/or fasting glucose.

METHODS

Literature Search and Study Selection

We conducted a MEDLINE search in PubMed, Cumulative Index to Nursing and Allied Health, Combined Health Information Database, Cochrane Library, and Web of Science using Medical Subject Heading from 1980 through April 2006. We utilized the medical subject heading term *diabetes mellitus, type 2* and combined it with the medical subject heading term, *dietary carbohydrates*. We retrieved abstracts of English-language studies in people aged 19 years of age and older, comparing restricted-carbohydrate diets in patients with type 2 diabetes. We focused on studies completed in the United States or Canada to be able to make inferences about diets for individuals with types 2 diabetes in North America. Concern about greater differences between the typical North American diet, especially given the interest in low-carbohydrate diets on this continent, and the diet in other countries, such as Japan, Sweden, and Australia, led to exclusion of those studies (13-16). We collected additional references from bibliographies of reviews and original research, along with searching electronic sources. Study designs included inpatient and outpatient trials, with or without concurrent controls; or those using partially or totally regulated food sources (Figure 1).

For the purposes of this meta-analysis, we included studies that contained an amount of carbohydrate up to and including the least that is recommended by the American Diabetes Association (45% of total calories from carbohydrate) in people with type 2 diabetes. We based our definition of restricted carbohydrate on percentage of total calories rather than grams of carbohydrate, in order to provide a uniform standard of comparison. Available data on study design, participant characteristics, carbohydrate composition, duration of diet; and outcomes of weight, and plasma levels of fasting glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were evaluated, if reported.

We included studies that compared a restricted-carbohydrate diet to a nonrestricted-carbohydrate diet in participants with type 2 diabetes and reported one or more of the outcome measures of interest. Studies that included nondiabetic subjects were required to report separate results in the diabetic participants for at least one of the outcomes. We excluded studies of children, type 1 diabetes mellitus, gestational diabetes, or prediabetes. If more than one study was published using data from the same participants, we evaluated the publication that was most comparable to other studies included in this meta-analysis.

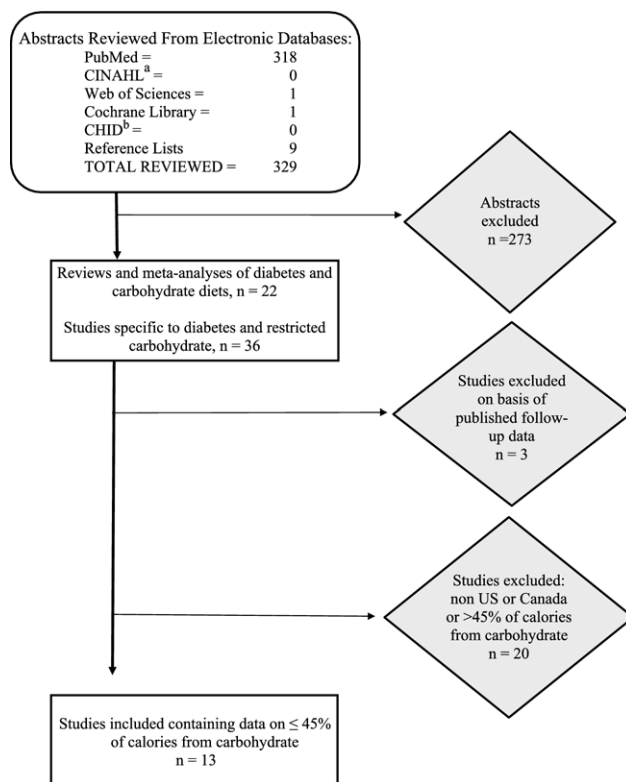


Figure 1. Flow diagram of systematic review of literature. ^aCINAHL=Cumulative Index to Nursing and Allied Health Literature. ^bCHID=Combined Health Information Database.

Data Abstraction

Data were analyzed using SAS software (version 9.1, 2004, SAS Institute Inc, Cary, NC) (17). For each study, information on change in the outcome (post- and prediet phase difference) was collected when available. For cross-over or paired designs, data for each phase were coded separately when baseline values for each phase were reported; otherwise, a single entry contrasting low vs high carbohydrate phases was used. In addition to the seven outcome variables (weight, fasting glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) study-specific data were abstracted for mean age, diet composition (percent of calories from carbohydrates, protein, and fat), duration of each diet phase, and whether participants on insulin were included in the study (Table 1).

Statistical Analysis

Outcome-related data abstracted for each study included sample size, baseline mean, mean change, and standard error of mean change. For studies where standard error of mean was not reported, an upper bound was calculated using the following formula:

$$SEM = \sqrt{\frac{S_1^2}{n} + \frac{S_2^2}{n}}$$

Table 1. Study designs from systematic review including participant characteristics and diet compositions

First author, year (reference)	n	Design	Mean age	Diet phase/group	Weeks duration	% Daily Calories From		
						Carbohydrates	Protein	Fat
Gannon, 2003 (20)	12	RCT ^a , crossover, isocaloric	61	Higher carbohydrate	5	55	15	30
				Lower carbohydrate	5	40	30	30
Gannon, 2004 (21)	8	RCT, crossover, isocaloric	63	Higher carbohydrate	5	55	15	30
				Lower carbohydrate	5	20	30	50
Garg, 1988 (22)	10	RCT, crossover, isocaloric	56	Higher carbohydrate	4	60	15	25
				Lower carbohydrate	4	35	15	50
Garg, 1992 (23)	8	RCT, crossover, isocaloric	63	Higher carbohydrate	3	60	15	25
				Lower carbohydrate	3	35	15	50
Garg, 1994 (24)	42	RCT, crossover, isocaloric	58	Higher carbohydrate	6	55	15	30
				Lower carbohydrate	6	40	15	45
Gerhard, 2004 (25)	11	RCT, crossover	50	Higher carbohydrate	6	65	15	20
				Lower carbohydrate	6	45	15	40
McCargar, 1998 (26)	32	RCT, parallel, isocaloric	57	Higher carbohydrate	4	55	15	30
				Lower carbohydrate	4	33	17	50
Sargrad, 2005 (27)	12	RCT, parallel, isocaloric	48	Higher carbohydrate	8	55	15	30
				Lower carbohydrate	8	40	30	30
Samaha, 2003 (28)	52	RCT, parallel	53	Higher carbohydrate	26	51	16	33
				Lower carbohydrate	26	37	22	41
Gumbiner, 1998 (29)	17	Nonrandomized two-arm trial	53	Higher carbohydrate	6	70	20	10
				Lower carbohydrate	6	9	21	70
Boden, 2005 (30)	10	Single-arm, pre-post	51	Higher carbohydrate	1	40	17	44
				Lower carbohydrate	2	4	28	68
Gutierrez, 1998 (31)	28	Single-arm, pre-post	66	Higher carbohydrate	12	55	20	25
				Lower carbohydrate	8	25	45	30
Yancy, 2005 (32)	21	Single-arm, pre-post	56	Higher carbohydrate	16	40	19	42
				Lower carbohydrate	16	10	28	59

^aRCT=randomized controlled trial.

NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

where S_1 and S_2 are the standard deviations of the pre- and postphase outcomes, respectively (3).

Regression analyses for this meta-analysis were performed using hierarchical linear mixed models that estimated the variance between studies as a random effect and potential study-level predictors as fixed effects (18). Inclusion of “study” as a random effect yielded models that control for correlation between observations within the same study. All regression models included a term for duration of dietary phase to control for differences in that parameter between studies. Regression analyses were weighted using the inverse of the estimated variance of the difference outcomes as weights. Analyses were performed using SAS PROC MIXED (17). Model parameters were estimated via the method of restricted maximum-likelihood. Denominator degrees-of-freedom for statistical tests and confidence intervals were calculated using the method of Berkey and colleagues (19).

RESULTS

Our search resulted in 329 articles; 56 contained information regarding carbohydrate content and type 2 diabetes (Figure 1). Thirteen published studies (Table 1) fulfilled our inclusion criteria (20-32). Some investigators published studies from the same data set, and the most

comparable data set to other studies included in this meta-analysis was utilized (28,29,32-35). A summary description of the designs for all 13 studies included in meta-analyses is presented in Table 1. Mean age of study participants was 57 ± 6 years (range in study-specific mean age was 48 to 66 years). Five studies (39%) included at least some participants on insulin (22,27,28,30,32). Seven studies (54%) were isocaloric by design. Compliance to diets was evaluated by food records (26,27,32), diet recall and interview (20,28,31), laboratory data (20,26) and unused portions of food monitored in the study (22-25,29). Activity modification was not specifically addressed in most of the trials evaluated. However, a large majority outlined that study subjects were instructed to continue their physical activities or exercise level during the study program.

The choice to include all North American studies with at least one dietary phase restricting carbohydrate consumption at or below the recommended American Diabetic Association guidelines resulted in a wide range of carbohydrate intakes. For lower carbohydrate intake phases, the daily calories from carbohydrates averaged $29\% \pm 14\%$ (range=4% to 45%). In higher carbohydrate intake phases, the percent of daily calories from carbohydrates averaged $55\% \pm 8\%$ (range=40% to 70%).

Table 2. Mean change from baseline for hemoglobin A1c, glucose, and weight for restricted-carbohydrate diets

First author, year (reference)	Diet phase ^b	Hemoglobin A1c (%)				Glucose (mg/dL) ^a				Weight (kg)			
		Baseline mean	Mean change	SE ^c change	Change (% baseline)	Baseline mean	Mean change	SE change	Change (% baseline)	Baseline mean	Mean change	SE change	Change (% baseline)
Gannon, 2003 (20)	HC	8.0	-0.3	0.4	-3.8								
	LC	8.1	-0.8	0.2	-9.9								
Gannon, 2004 (21)	HC	9.8	0.0	0.9	0.0	180.0	-21.0	45.7	-11.7				
	LC	9.8	-2.2	0.4	-22.4	167.0	-48.0	11.4	-28.7				
Garg, 1988 (22)	HC												
	LC	7.8	0.3	0.1	2.7	117	-16.0	7.2	-13.7				
Garg, 1992 (23)	HC												
	LC	7.8	-0.7	0.4	-9.0	139.0	-1.8	20.5	-1.3				
Garg, 1994 (24)	HC												
	LC	8.2	-0.3	0.4	-3.7	150.0	-5.0	7.4	-3.3				
Gerhard, 2004 (25)	HC	6.9	-0.2	0.4	-2.9	143.0	-8.0	12.4	-5.6	102.6	-1.5	0.4	-1.5
	LC	6.9	0.0	0.4	0.0	142.0	-2.0	15.2	-1.4	102.8	-0.5	0.3	-0.5
McCarger, 1998 (26)	HC					157.0	-14.0	12.6	-8.9				
	LC					165.0	-29.0	12.7	-17.6				
Sargrad, 2005 (27)	HC	8.2	-1.3	0.6	-15.9	159.0	-28.0	24.3	-17.6				
	LC	7.6	-1.0	1.0	-13.2	150.0	0.0	34.6	0.0				
Samaha, 2003 (28)	HC	7.4	0.0	0.2	0.0	158.0	-5.0	5.0	-3.2	131.8	-1.9	0.5	-1.4
	LC	7.8	-0.6	0.2	-7.7	168.0	-26.0	4.8	-15.5	130.0	-5.8	1.1	-4.5
Gumbiner, 1998 (29)	HC					202.0	-43.0	18.6	-21.3	110.4	-8.3	0.9	-7.5
	LC					227.0	-83.0	27.8	-36.6	101.8	-7.3	0.9	-7.2
Boden, 2005 (30)	HC												
	LC	7.3	-0.5	ND	-6.8	135.0	-22.0	ND	-16.3	114.4	-2.0	ND	-1.8
Gutierrez, 1998 (31)	HC	8.0	0.9	0.3	11.3	185.0	13.0	12.3	7.0	76.6	2.0	4.8	2.6
	LC	9.7	-1.7	0.4	-17.5	259.0	-74.0	13.7	-28.6	77.8	-1.2	4.6	-1.5
Yancy, 2005 (32)	HC												
	LC	7.5	-1.2	0.3	-16.0	164.0	-27.2	12.4	-16.6	131.4	-8.7	2.3	-6.6

^aTo convert mg/dL glucose to mmol/L glucose, multiply mg/dL by 0.0555.

^bPhases are categorized as lower carbohydrate (LC) or higher carbohydrate (HC) content within a specific study and not across studies.

^cSE=standard error.

^dND=data not reported or no outcome measured.

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Meta-regression analyses were performed using the percent reduction in the outcome (postphase mean minus baseline mean, divided by baseline mean, times 100) as the dependent variable. Examination of single-covariate models for each outcome showed little or no significant relationships across studies between mean age of study participants, inclusion of participants on insulin, or diet duration and percent reduction of any of the seven outcomes of interest (weight, glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides); however, because of potential confounding effects of differential durations, phase-specific (lower or higher carbohydrate) diet durations were included as a covariate in all models examining relationships between outcomes and carbohydrate intake.

Glycemia Values

Overall, a greater mean reduction in hyperglycemia was noted in all studies evaluated between the low vs high carbohydrate diets (Table 2). In 9 of 11 studies that evaluated HbA1c, the HbA1c decreased (or was reduced more) on the lower-carbohydrate diet. Figure 2 shows scatter plots of percent change in fasting glucose and HbA1c vs percent of daily caloric intake from carbohydrates, and includes regression lines that show the predicted average reduction in each outcome across the range of carbohydrate intake after controlling for diet-phase duration. Very similar slopes and intercepts were observed be-

tween percent change in both glucose and HbA1c and percent of carbohydrate calories. Diet phases where subjects consumed lower levels of carbohydrate exhibited greater reductions in both outcomes.

Lipid Values

Mean change for lipid values are outlined in Table 3. Across studies evaluated, triglyceride reductions were noted for both lower- and higher-carbohydrate phases. Figure 3 shows scatter plots of percent change in lipid levels vs percent of daily caloric intake from carbohydrates. Regression lines depicting predicted changes in lipid outcomes across ranges of carbohydrate intake (after controlling for diet-phase duration) are also shown. A very strong relationship was observed between reductions in triglyceride levels and lower-carbohydrate diet phases (Figure 3), while no significant relationships were observed for total cholesterol, HDL, or LDL cholesterol. Two studies using a hypocaloric intervention had observed increases of 5% to 10% in LDL cholesterol levels (21,32). Smaller increases in LDL are also noted from Figure 3 in two other studies (20,22).

Weight Change

A similar figure depicting weight change and its duration-adjusted regression line vs percent of daily caloric intake from carbohydrates is shown in Figure 4 for six

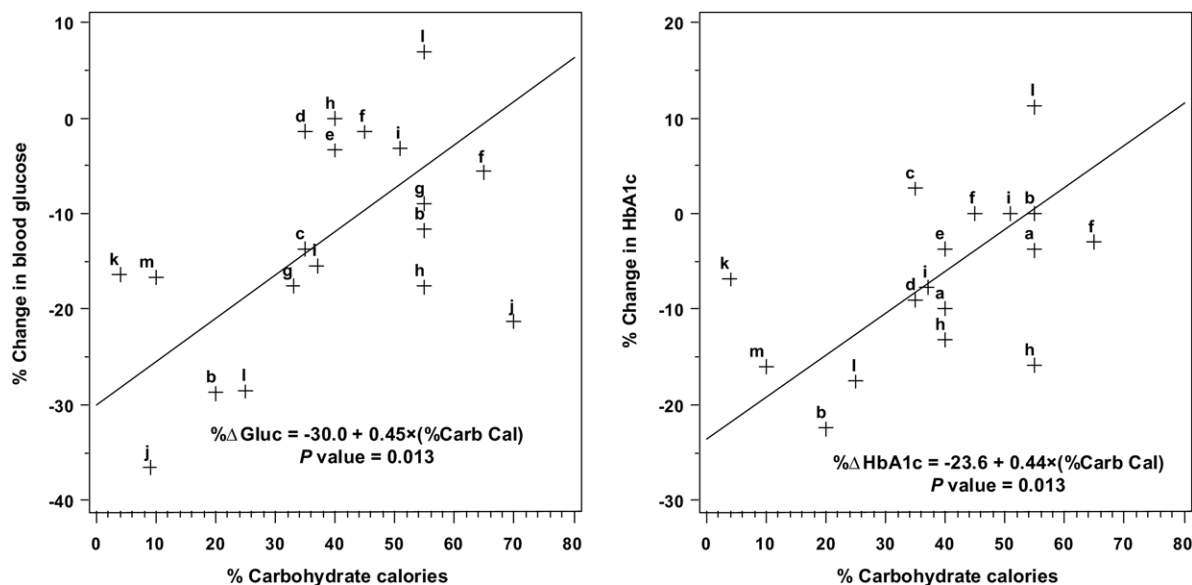


Figure 2. Scatter plots of percent change in blood glucose and hemoglobin A1c (HbA1c) vs percent daily caloric intake from carbohydrates. The lowercase letters correspond to the following studies (first author, year [reference number]): a=Gannon, 2003 (20); b=Gannon, 2004 (21); c=Garg, 1988 (22); d=Garg, 1992 (23); e=Garg, 1994 (24); f=Gerhard, 2004 (25); g=McCargar, 1998 (26); h=Sargrad, 2005 (27); i=Samaha, 2003 (28); j=Gumbiner, 1998 (29); k=Boden, 2005 (30); l=Gutierrez, 1998 (31); m=Yancy, 2005 (32). (Information from this figure is available online at www.adajournal.org as part of a PowerPoint presentation.)

studies that reported weight change. Seven studies were isocaloric (Table 1) and there was no weight loss by design, thus these studies were omitted from Figure 4. No significant relation was observed between carbohydrate content of the diet and weight.

In order to examine weight change as a potential mediator of the effects of carbohydrate intake on glycemia and lipids, a second set of regression analyses for each change outcome (excluding weight) were performed that included weight change, diet-phase duration, and percent carbohydrate calories as independent variables. Studies that were isocaloric by design were included in the analysis by assuming zero weight change for them. Inclusion of weight change attenuated the regression coefficients for percent carbohydrate calories vs both glucose and HbA1c; however, the regression coefficient for carbohydrate intake to predict percent change in blood glucose remained statistically significant. A 10% increase in carbohydrate caloric intake was associated with a $3.2\% \pm 1.2\%$ increase in glucose change ($P=0.047$). Including weight change did not substantially alter the previously observed strong relationship of percent carbohydrate calories with triglycerides. A 10% increase in carbohydrate intake was associated with a $7.6\% \pm 0.6\%$ increase in triglyceride change ($P=0.001$).

DISCUSSION

This meta-analysis indicates that lower-carbohydrate diets can be beneficial in treating type 2 diabetes, not only because of improved glycemic control, but also because of potential salutary changes in the lipid profile. Improvements in fasting glucose, HbA1c, and triglycerides appear to result from even moderate decreases in carbohydrate

intake. For example, based on the meta-analysis regression model for triglycerides, a decrease in carbohydrate intake from 65% to 35% shows an expected decrease of approximately 23% in triglyceride level.

The scatter plot of percent change in body weight does not show statistically significant differences in the lower-carbohydrate diet phases (Figure 4). This is not surprising, given that the studies evaluated were not consistent in design or distribution of nutrients (Table 1). Some studies promoted weight stability throughout the trial period (20-24), while others induced weight loss through intentional calorie restriction in at least one arm of the study (28,29). Some studies showed similar weight change regardless of the diet or type of nutrient restriction (26,27). Hypocaloric diets, regardless of nutrient composition, resulted in weight loss. Regression models for glycemia and lipid outcomes suggested that weight loss does not mediate all of the change in glucose and triglycerides. Regression models controlling for weight during the diet phase showed substantial effects of percent carbohydrate calories for both glucose and triglyceride. Regression models also suggest that controlling for weight during the diet phase substantially decreases the impact of carbohydrate restriction on raising HDL and lowering triglyceride.

Seven studies that examined HbA1c found a difference in outcomes that was statistically significant in the low-carbohydrate group (20,21,27,28,30-32). Some studies of short duration also showed changes in HbA1c. Because HbA1c represents average blood glucose over a period of approximately 3 months, it takes a substantial and immediate drop in blood glucose level to change HbA1c over 2 weeks.

Table 3. Effects of restricted carbohydrate diets on lipid components in patients with type 2 diabetes

Report Detailed and/or Summarized Report		Total Cholesterol (mg/dL) ^a				Low-Density Lipoprotein Cholesterol (mg/dL) ^a				High-Density Lipoprotein Cholesterol (mg/dL) ^a				Triglycerides (mg/dL) ^b				
First author, year (reference)	Diet phase ^c	n	Baseline mean	Mean change	SE ^d change	Change (% baseline)	Baseline mean	Mean change	SE change	Change (% baseline)	Baseline mean	Mean change	SE change	Change (% baseline)	Baseline mean	Mean change	SE change	Change (% baseline)
Gannon, 2003 (20)	HC				ND ^e				ND				ND					ND
	LC	12	181.0	-10.0	19.3	-5.5	100.0	1.0	17.1	1.0	38.0	1.0	4.1	2.6	199.0	-35.0	14.2	-17.6
Gannon, 2004 (21)	HC	8	195.0	-11.0	23.9	-5.6	105.0	-3.0	11.1	-2.9	38.0	-1.0	3.0	-2.6	264.0	-38.0	67.9	-14.4
	LC	8	188.0	-11.0	18.0	-5.9	105.0	5.0	13.2	4.8	37.0	-1.0	4.0	-2.7	246.0	-97.0	42.0	-39.4
Garg, 1988 (22)	HC				ND				ND				ND					ND
	LC	10	205.0	-9.0	4.0	-4.4	131.0	3.0	11.2	2.3	30.0	4.0	1.1	13.3	218.0	-55.0	17.4	-25.2
Garg, 1992 (23)	HC				ND				ND				ND					ND
	LC	8	198.0	-9.0	5.2	-4.5	116.0	0.0	18.8	0.0	26.3	3.1	1.0	11.8	288.0	-62.0	13.8	-21.5
Garg, 1994 (24)	HC				ND				ND				ND					ND
	LC	40	196.0	-4.0	7.8	-2.0	130.0	0.0	6.3	0.0	35.4	1.6	2.2	4.5	194.0	-39.0	15.2	-20.1
Gerhard, 2004 (25)	HC	11	188.0	-18.0	17.1	-9.6	108.0	-11.0	11.5	-10.2	42.0	-3.0	3.4	-7.1	208.0	-27.0	57.1	-13.0
	LC	11	187.0	-19.0	15.6	-10.2	106.0	-8.0	10.4	-7.5	44.0	-2.0	3.6	-4.5	194.0	-45.0	47.9	-23.2
McCarger, 1998 (26)	HC	16	196.0	-19.0	13.2	-9.7			ND		53.0	-11.0	7.8	-20.8				ND
	LC	16	203.0	-8.0	13.0	-3.9			ND		58.0	-11.6	6.3	-20.0				ND
Sargrad, 2005 (27)	HC	6	196.0	-31.0	24.6	-15.8	109.0	-13.9	20.4	-12.8	38.3	-1.9	5.5	-5.0	562.0	-174	150.6	-31.0
	LC	6	181.0	-31.0	24.6	-17.1	87.0	-12.4	10.2	-14.3	52.2	-3.1	10.7	-5.9	478.0	-176	258.0	-36.8
Gumbiner, 1998 (29)	HC	8	174.0	-15.0	12.0	-8.6	97.0	-10.0	12.0	-10.3	38.7	-5.8	1.7	-15.0	195.0	-22.0	31.0	-11.3
	LC	9	205.0	-48.0	15.0	-23.4	120.0	-17.0	12.0	-14.2	38.7	1.5	12.0	3.9	248.0	-146	31.0	-58.9
Boden, 2005 (30)	HC				ND				ND				ND					ND
	LC	10	180.0	-17.0	ND	-9.4	101.0	-2.0	15.7	-2.0	45.0	-1.0	6.1	-2.2	163.0	-58.0	ND	-35.6
Yancy, 2005 (32)	HC				ND				ND				ND					ND
	LC	20	178.0	-2.7	6.9	-1.5	97.0	10.0	5.7	10.3	35.6	2.7	1.5	7.6	238.0	-99.2	25.8	-41.7

^aTo convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
^bTo convert mg/dL triglycerides to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.6. Triglycerides of 159 mg/dL=1.80 mmol/L.
^cPhases are categorized as low-carbohydrate (LC) or high-carbohydrate (HC) content within a specific study and not across studies (Samaha, 2003 and Gutierrez, 1998 did not report lipid data).
^dSE=standard error.
^eND=data not reported or no outcome measured.
 NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

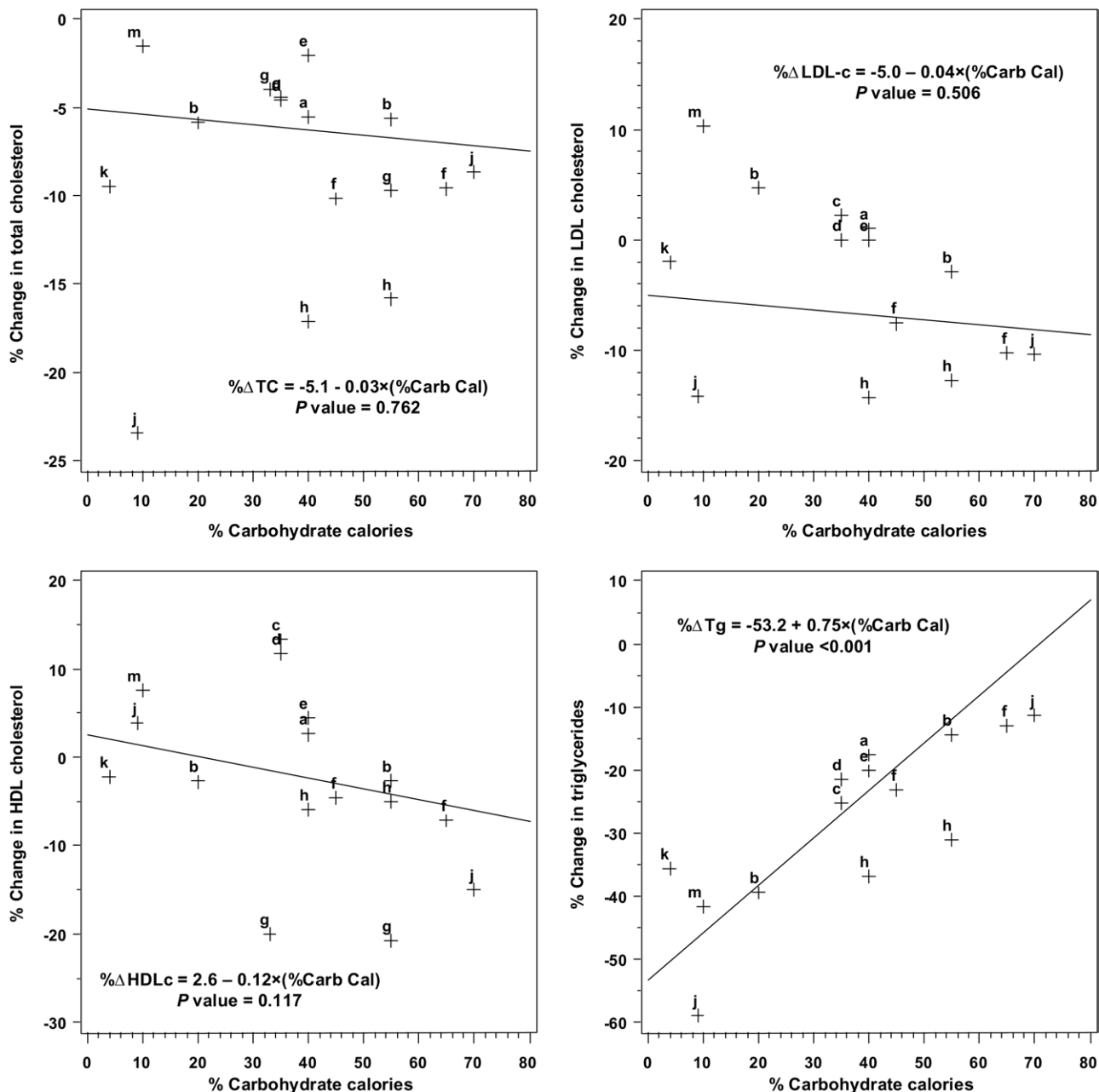


Figure 3. Scatter plots of percent change in lipid levels vs percent daily caloric intake from carbohydrates. LDL=low-density lipoprotein; HDL=high-density lipoprotein. The lowercase letters correspond to the following studies (first author, year [reference number]): a=Gannon, 2003 (20); b=Gannon, 2004 (21); c=Garg, 1988 (22); d=Garg, 1992 (23); e=Garg, 1994 (24); f=Gerhard, 2004 (25); g=McCargar, 1998 (26); h=Sargrad, 2005 (27); i=Samaha, 2003 (28); j=Gumbiner, 1998 (29); k=Boden, 2005 (30); l=Gutierrez, 1998 (31); m=Yancy, 2005 (32). (Information from this figure is available online at www.adajournal.org as part of a PowerPoint presentation.)

Restricted-carbohydrate diets consistently appear to have overall beneficial effects on triglyceride and HDL-cholesterol levels in nondiabetic populations (1,28,36,37). Results of this meta-analysis show that the effect on triglycerides is found in individuals with type 2 diabetes as well. Active weight loss can cause a decrease in plasma triglyceride and cholesterol levels and may not reflect steady-state values, thus confounding interpretation of

the results. The effects of acutely raising HDL with low-carbohydrate diets may reflect a change in HDL subfractions that occurs with intake of saturated fats, which is thought to be more atherogenic (38). Although LDL cholesterol levels did not increase in this meta-analysis, it is unknown whether the most atherogenic of lipoprotein particles (eg, small, dense LDL) and progression of atherosclerosis are affected by low-carbohydrate diets.

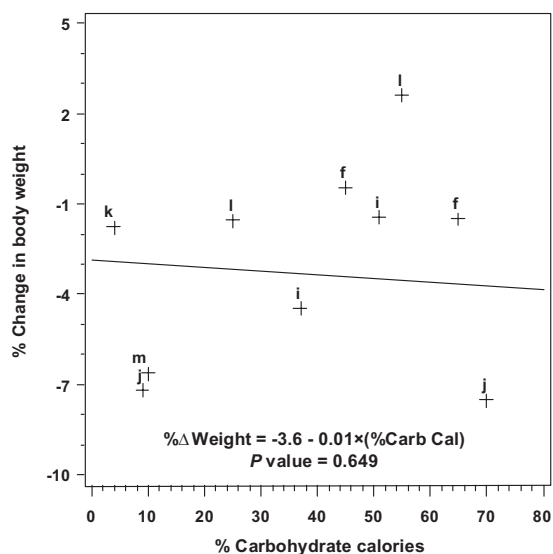


Figure 4. Scatter plots of percent change body weight vs percent daily caloric intake from carbohydrates. The lowercase letters correspond to the following studies (first author, year [reference number]): a=Gannon, 2003 (20); b=Gannon, 2004 (21); c=Garg, 1988 (22); d=Garg, 1992 (23); e=Garg, 1994 (24); f=Gerhard, 2004 (25); g=McCargar, 1998 (26); h=Sargrad, 2005 (27); i=Samaha, 2003 (28); j=Gumbiner, 1998 (29); k=Boden, 2005 (30); l=Gutierrez, 1998 (31); m=Yancy, 2005 (32). (Information from this figure is available online at www.adajournal.org as part of a PowerPoint presentation.)

There are several limitations to this meta-analysis. Foremost is the limited duration of included studies, most relatively short-term (<120 days). The small number of studies (n=13) available for inclusion in the analysis limited the number of covariates that could be introduced simultaneously in regression analyses. Study designs were heterogeneous and varied in participant setting, from inpatient feeding studies to outpatient self-selected diets. Specifically, there was a mixture of crossover, parallel, single-arm, and two-arm designs that were evaluated. Also, criteria for patient inclusion with regard to diabetes medications were mixed, ranging from drug naïve to stable doses of insulin or oral hypoglycemic agents throughout the study period. Several studies allowed modification of doses of diabetes medication based on blood glucose results. Only a few studies included in this meta-analysis enrolled elderly participants. The dropout rate in many of the studies was high, and lack of long-term adherence to the diets being studied was also noted. Most of the studies did not examine the impact of these diets on other important potential mediators of cardiovascular risk, such as inflammation and endothelial dysfunction. Studies have also taken different approaches to restriction of the carbohydrate intake, including raising the protein component of the diet or increasing fat content with and without maintaining eucaloric substitutions of macronutrients.

With regard to studies excluded from our analysis, it should be pointed out that one trial conducted in Japan showed similar reductions in fasting blood glucose and weight in both the low- and high-carbohydrate arms in

patients with diabetes (13). Other excluded studies from Australia indicate that a high-protein diet with moderate carbohydrate intake (40% to 42% of calories) in comparison to a low-protein diet with similar carbohydrate content resulted in comparable reductions in HbA1c and fasting glucose among patients with diabetes (15,16).

Restricted-carbohydrate diets may be high in protein, which has the potential to result in glomerular hyperfiltration and acceleration of the compromised renal function observed in patients with diabetes (12,39). Hypercalciuria and nephrolithiasis may be problematic for some individuals consuming higher-protein diets to achieve low-carbohydrate intake (8). However, definitive proof of adverse effects on kidney function remains to be established (8,39,40). Potential decreased nutrient content of a low-carbohydrate diet is of concern. Carbohydrate-restricted diets may be deficient in a number of nutrients, including water-soluble vitamins folate, thiamin, and pyridoxine fat-soluble vitamins A and E, minerals including calcium, potassium, and magnesium, as well as fiber. Nutritional inadequacy may be an impediment to the widespread acceptance of this management tool among food and nutrition professionals (12).

Various safety concerns have been raised about low-carbohydrate diets in raising uric acid levels for gout patients and being related to various side effects, including constipation, diarrhea, dizziness, halitosis, headaches, and insomnia (36). Vulnerable populations, such as the young, reproductive-aged women, hypertensive individuals, and those with already compromised nutrient intake, may not be suitable for this dietary intervention. On the other hand, there is no objective data documenting a deleterious clinical outcome from these diets (12).

SUMMARY

Diabetes mellitus is, in part, a disorder of carbohydrate metabolism that results in hyperglycemia. Carbohydrates are the component of the diet that exerts the greatest influence on postprandial blood glucose (41). Thus, it is logical that diets lower in carbohydrates would result in less hyperglycemia. Use of a balanced diet, exercise, and blood glucose-lowering medication should be combined to achieve glycemic control and a healthy weight. Results of our meta-analysis suggest short-term use of restricted-carbohydrate diets in patients with diabetes may result in improvements in glycemic control and triglycerides. The analysis also indicates that moderate carbohydrate restriction may provide some benefit. However, concerns have been raised about the sustainability of outcomes once patients resume more moderate carbohydrate intake (42).

Until further research has demonstrated long-term safety and sustained adherence, use of carbohydrate restriction as a tool for diabetes management will remain highly controversial (1). The latest position statement of the American Diabetes Association advocates a diet pattern incorporating carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat milk (43). The American Diabetes Association also states that, "low carbohydrate diets, restricting total carbohydrate to less than 130 grams per day are not recommended" (44). Type 2 diabetes remains a life-long debilitating disease, which, to modify its natural history, requires a commitment to

permanent lifestyle modification of both diet and physical activity, and oftentimes substantial medication use. There is currently ongoing a large, randomized National Institute of Health–sponsored prospective trial of dietary intervention in conjunction with activity enhancement that is designed to examine the impact of modest sustained weight loss on the time to incidence of cardiovascular events in people with type 2 diabetes (45). The mainstay of the dietary component of this trial is a modestly fat-restricted diet replete in vegetables and fruit. The Look AHEAD (Action for Health in Diabetes) trial has recently shown that weight loss was 8.6% of initial body weight in the intensive lifestyle intervention group vs 0.7% in the control group. HbA1c, glucose, HDL, and triglycerides were more favorable for the intensive group (46).

We included studies with a wide range of dietary carbohydrate content in this meta-analysis, from 4% to 45% of calories, to try to determine if there is a moderately restricted carbohydrate amount that would impact diabetes-related outcomes. Long-term, randomized, controlled studies of restricted-carbohydrate diets in patients with diabetes should be conducted in order to evaluate the overall sustainability of outcomes and safety of these diets. Details of diet interventions, furthermore, may be more important than carbohydrate restriction, per se. For example, elimination of simple sugars and high fructose–containing beverages from the diet, because they are devoid of nutrients, differs in impact on nutrient intakes from elimination of nutrient-rich items, such as baked potatoes and unrefined rice. Studies thus also need to be directed to examining the effects of either increased fat or increased protein intake on outcomes, as well as the effect of specific fats and carbohydrate foods excluded. While restricted-carbohydrate diets may have beneficial effects on glucose, HbA1c, and triglycerides, the impact of these diets on cardiovascular outcomes remains to be determined. Currently, there is insufficient evidence to recommend restricted-carbohydrate diets <130 g in patients with diabetes. The sustainability effect on cardiovascular outcomes and overall safety in patients with diabetes warrants further study in long-term, randomized, controlled studies of restricted-carbohydrate diets.

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