Effect of a Low-Carbohydrate Diet on Appetite, Blood Glucose Levels, and Insulin Resistance in Obese Patients with Type 2 Diabetes

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Background: **It is not known how a low-carbohydrate, high-protein, high-fat diet causes weight loss or how it affects blood glucose levels in patients with type 2 diabetes.**

Objective: **To determine effects of a strict low-carbohydrate diet on body weight, body water, energy intake and expenditure, glycemic control, insulin sensitivity, and lipid levels in obese patients with type 2 diabetes.**

Design: **Inpatient comparison of 2 diets.**

Setting: **General clinical research center of a university hospital.**

Patients: **10 obese patients with type 2 diabetes.**

Intervention: **Usual diets for 7 days followed by a low-carbohydrate diet for 14 days.**

Measurements: **Body weight, water, and composition; energy intake and expenditure; diet satisfaction; hemoglobin A_{1c}; insulin sensitivity; 24-hour urinary ketone excretion; and plasma profiles of glucose, insulin, leptin, and ghrelin.**

Results: **On the low-carbohydrate diet, mean energy intake decreased from 3111 kcal/d to 2164 kcal/d. The mean energy deficit of 1027 kcal/d (median, 737 kcal/d) completely accounted for the weight loss of 1.65 kg in 14 days (median, 1.34 kg in 14 days). Mean 24-hour plasma profiles of glucose levels normalized, mean hemoglobin A_{1c} decreased from 7.3% to 6.8%, and insulin sensitivity improved by approximately 75%. Mean plasma triglyceride and cholesterol levels decreased (change, −35% and −10%, respectively).**

Limitations: **The study was limited by the short duration, small number of participants, and lack of a strict control group.**

Conclusion: **In a small group of obese patients with type 2 diabetes, a low-carbohydrate diet followed for 2 weeks resulted in spontaneous reduction in energy intake to a level appropriate to their height; weight loss that was completely accounted for by reduced caloric intake; much improved 24-hour blood glucose profiles, insulin sensitivity, and hemoglobin A_{1c}; and decreased plasma triglyceride and cholesterol levels. The long-term effects of this diet, however, remain uncertain.**

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According to recent surveys, approximately two thirds of the U.S. population is overweight (1). Several dietary approaches to this public health problem have been recommended. The most popular of these approaches is probably the Atkins Diet, a low-carbohydrate, high-protein, high-fat diet that was first publicized by Dr. Atkins in 1972 (2). Several older uncontrolled studies (reviewed in reference 3) and 4 recent outpatient studies (4–7) have shown that people on low-carbohydrate diets lose weight for periods of up to 1 year. The reasons for this weight loss, however, remain controversial. They include reduced calorie intake, loss of body water, changes in energy expenditure, and different utilization of calories. With respect to the latter, studies have suggested that people on low-carbohydrate diets can eat more calories than people on high-carbohydrate diets and still lose more weight (8, 9).

A low-carbohydrate diet is of particular interest to patients with type 2 diabetes in whom obesity is a major problem. So far, however, patients with type 2 diabetes have been included in only 1 such study (25 of the 64 participants in that study had type 2 diabetes) (5). Fasting plasma glucose levels in these patients decreased from 9.32 mmol/L (168 mg/dL) to 7.88 mmol/L (142 mg/dL) after 6 months.

We designed our study to determine the effects of a strict low-carbohydrate diet (approximately 20 g of carbohydrates per day), which included the diet supplements recommended by Dr. Atkins, on energy intake and expenditure, body weight and body water, glucose metabolism, and insulin sensitivity in obese patients with type 2 diabetes in the controlled environment of a clinical research center.

METHODS

Participants

Ten obese patients with type 2 diabetes participated in the study. **Table 1** shows their baseline characteristics. We recruited patients through advertisements in local newspapers and in the hospital. We offered no financial compensation. All participants received a thorough medical examination and had routine blood and urine tests. We excluded volunteers who had endocrine disorders other than diabetes; who had other clinically significant health problems, including cardiovascular, pulmonary, and renal diseases; and who smoked. Seven patients took glucose-lowering medications (sulfonylureas, metformin, thiazo-

See also:

Print

Editors' Notes 404
Editorial comment. 469
Summary for Patients I-44

Web-Only

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Context

Despite the popularity of low-carbohydrate diets for weight loss, we know little about how low-carbohydrate diets cause weight loss or how they affect glycemic control.

Contribution

In a study that observed 10 obese patients with type 2 diabetes during 7 days of usual diet and 14 days of a low-carbohydrate diet (21 g of carbohydrates per day), participants lost weight and had improvement in glycemic control while eating the low-carbohydrate diet. Reduced calorie intake, not reductions in body water, accounted for the observed weight loss.

Cautions

This study compared low-carbohydrate diet with usual diet rather than a conventional weight loss diet.

–The Editors

lidinediones, or insulin), 8 patients were receiving antihypertensive medications (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, thiazide diuretics, and calcium-channel blockers), and 3 patients were receiving lipid-lowering drugs (statins and fibrates). The doses of these medications had not been changed during the 3 months preceding the study and were continued without changes throughout the control period. The institutional review board of Temple University Hospital, Philadelphia, Pennsylvania, approved the protocol, and all participants gave written informed consent.

Table 1. **Characteristics of Study Participants***

Characteristic	Value
Men/women, *n/n*	3/7
Race, *n*	
Black	7
White	3
Age, *y*	51 ± 9.5 (36–64)
Height, *cm*	169.7 ± 10.4 (154–185)
Weight, *kg*	114.75 ± 12.9 (96.4–141.8)
Fat, *kg*	51.5 ± 11.5 (28.4–67.7)
Body mass index, kg/m^2	40.3 ± 5.7 (33–52)
Known duration of diabetes, *y*	4.9 ± 4.1 (0.1–12.0)
Diabetes treatment, *n*	
Diet alone	3
Metformin	1
Metformin + insulin	2
Metformin + sulfonylurea	2
Metformin + thiazolidinedione	1
Metformin + sulfonylurea + thiazolidinedione	1
Cormorbid conditions, *n*	
Obesity	10
Hypertension	7
Dyslipidemia	5
Coronary artery disease	2
Gout	1
Asthma	1
Nephropathy	1
Proliferative retinopathy	0
Painful neuropathy	0

* Values expressed with plus/minus sign are means ± SD (range). All data were obtained on day 1 of study.

Study Design

Before hospitalization, an investigator interviewed all study participants about their recent diet and exercise habits and asked them to continue their usual diets and physical activities and to keep daily diet and activity records.

Usual Diet (Days 1 to 7)

We instructed patients to continue their usual diet (**Table 2**). The clinical research center kitchen provided all food and beverages, and we weighed and recorded everything that was consumed. The food was prepared in the hospital kitchen, as well as in the clinical research center kitchen, and also included foods from local fast food establishments. Participants selected from standard hospital menus each day during their usual diet; participants were also encouraged to request food from the "outside." To supplement the hospital menus, we used brand-name foods or fat foods for which nutrient data were available (for example, McDonald's sandwiches, donuts from Dunkin' Donuts, and Oreo cookies). To maintain their usual physical activity, the patients walked in the hospital with a nurse or used a stationery exercise bike, lifted weights, or did calisthenics. Each morning, we determined body weights, vital signs, and fasting blood glucose levels and collected 24-hour urine samples (for measurement of ketone bodies and nitrogen).

Low-Carbohydrate Diet (Days 8 to 21)

We reduced carbohydrate intake to approximately 21 g/d, but patients could eat protein and fat as much and as often as they wanted (**Table 2**). Participants chose food items from a modified hospital diet that included only allowable foods without sauces, gravies, or other ingredients that contain carbohydrates. These items included beef patties, ground turkey patties, chicken breasts, turkey slices, fresh ham slices, raw or steamed vegetables, butter, and diet gelatin. We allowed limited amounts of cheese and cream cheese. As with their usual diets, participants could request allowable items that were not available from the hospital kitchen, such as fresh fish, eggs, various cuts of beef, cream, and additional vegetables. In addition, specific brands of salad dressings and snack foods suggested by Dr. Atkins were made available on request, including Atkins-brand foods. We weighed and recorded all food consumed, and we determined body weights, vital signs, fasting plasma glucose levels, and 24-hour urine outputs daily.

Measurements

We weighed all consumed (served items minus returned items) food and beverages with a Mettler balance to the nearest gram. We determined the caloric and nutrient

Table 2. **Diet Composition***

Variable	Control Group (n = 10)†	Low-Carbohydrate Group (n = 10)‡	Difference	*P* Value§
Carbohydrates, *g*	309, 296 (182 to 552)	21, 22 (14 to 32)	288, 272 (165 to 538)	0.002
Simple carbohydrates, *g*	120, 97 (74 to 219)	10, 11 (7 to 14)	110, 84 (62 to 211)	0.002
Complex carbohydrates, *g*	169, 157 (89 to 301)	7, 7 (3 to 12)	162, 150 (84 to 297)	0.002
Fiber, *g*	20, 17 (10 to 37)	4, 4 (2 to 7)	16, 14 (6 to 30)	0.002
Protein, *g*	137, 128 (88 to 218)	151, 145 (120 to 190)	–14, –12 (–62 to 42)	0.13
Fat, *g*	154, 163 (86 to 209)	164, 159 (138 to 200)	–10, –12 (–72 to 64)	>0.2
Saturated fatty acids, *g*	52, 53 (24 to 77)	56, 58 (46 to 65)	–4, –10 (–35 to 18)	>0.2
Monounsaturated fatty acids, *g*	43, 47 (25 to 57)	46, 46 (34 to 64)	–3, –4 (–26 to 21)	>0.2
Polyunsaturated fatty acids, *g*	21, 21 (12 to 31)	12, 12 (8 to 17)	9, 10 (2 to 17)	0.002
Transaturated fatty acids, *g*	2.95, 2.85 (0.7 to 5.0)	0.78, 0.70 (0 to 2)	2.17, 2.10 (0.4 to 5.0)	0.002
Other fats, *g*	34, 36 (9.7 to 66)	47, 46 (31 to 75)	–13, –10 (–44 to 15)	0.0037

* Data are expressed as mean, median (range).
† The displayed means and medians are from days 1–7 (usual diet period).
‡ The displayed means and medians are from days 8–21 (low-carbohydrate period).
§ Per Wilcoxon signed-rank test on paired differences.

value of the ingested food with The Food Processor program, version 8.1 (ESHA Research, Salem, Oregon), on all days except the clamp days (days 1, 8, and 22).

At the end of each day, all patients rated their level of appetite, satisfaction with the diet, energy level, and general well-being by using visual analogue scales (10).

We assessed body composition and body water by using bioelectrical impedance analysis (11) with the Weight Manager 2.05 software (RJL Systems, Clinton Township, Missouri) on days 1, 8, and 22. We determined total energy expenditure with the doubly labeled water method in 6 of 10 patients. (We added these measurements to the protocol only after the first 4 patients had been studied.) We collected 2 mL of saliva 30 minutes after awakening on day 3 and again on day 15, and again 30 minutes later. The patients then drank the doubly labeled water containing 240 g of $^2H_2{}^{18}O$ and 10 g of ^2H_2O. We collected 2-mL saliva samples 5 hours and 6 hours later. We repeated saliva collections (2 mL of saliva 30 minutes and again 1 hour after awakening) on each of the 5 days after the administration of the doubly labeled water and stored the samples at −4 °C until analyzed. We measured saliva isotope enrichment with an isotope ratio mass spectrometer (PDZ Europa Limited, London, United Kingdom). We calculated isotope loss rates by regression analysis, and we calculated total energy expenditure according to the method of Schoeller and colleagues (12).

We performed euglycemic hyperinsulinemic clamps with serial measurements of insulin and glucose on days 1, 8, and 22 after an overnight fast as described previously (13).

We collected blood for 24 hours (every hour between 8 a.m. and 1 a.m. and at 4 a.m. and 6 a.m.) for measurement of glucose, insulin, leptin, and ghrelin levels at the end of the control period (day 7) and at the end of the low-carbohydrate diet period (day 21) in 9 patients (1 patient declined to participate).

We determined glucose turnover with 6,6 $^2H_2$ glucose as described (14, 15). We calculated rates of glucose appearance and disappearance by using Steele's equation (16). We determined endogenous glucose production by subtracting the rate of glucose infusion needed to maintain euglycemia from the rate of glucose appearance.

We determined basal metabolic rates by indirect calorimetry with a metabolic measurement cart (DeltaTrac II, Sensor Medics, Yorba Linda, California) as described elsewhere (17, 18).

Analytical Procedures

We measured plasma glucose levels with a glucose analyzer (YSI, Yellow Springs, Ohio). We determined serum insulin level after protein precipitation with polyethylene glycol by radioimmunoassay (Linco, St. Charles, Missouri) with a specific antibody that cross-reacts only minimally (<0.2%) with proinsulin. We measured β-hydroxybutyrate, acetoacetate, serum creatinine, and blood urea nitrogen levels enzymatically. We measured urinary nitrogen level with the Kjeldahl method (19). We determined glucagon, ghrelin (coefficient of variation, 10.0%), leptin (coefficient of variation, 6.2%), and cortisol (coefficient of variation, 4.0%) levels in duplicate by radioimmunoassay with kits (Linco).

Statistical Analysis

Data are expressed as means ± SD (range) in **Table 1** and as means, medians (range) in **Tables 2** to **5**. For diet composition end points, we compared results during the control period (days 1 to 7) with those during the low-carbohydrate period (days 8 to 21). We compared caloric intake and total energy expenditure results on days 3 to 7 (control) and days 15 to 21 (low-carbohydrate) because total energy intake could be measured only during these periods. For all other end points, we compared day 7 (control) results with day 21 (low-carbohydrate) results. We calculated within-patient diet changes (control vs. low-carbohydrate) by end point and analyzed them by using Wilcoxon signed-rank tests for paired data. We performed all statistical analysis with the SigmaStat statistical software (SPSS, Inc., Chicago, Illinois).

Table 3. **Metabolic Balances in 10 Patients***

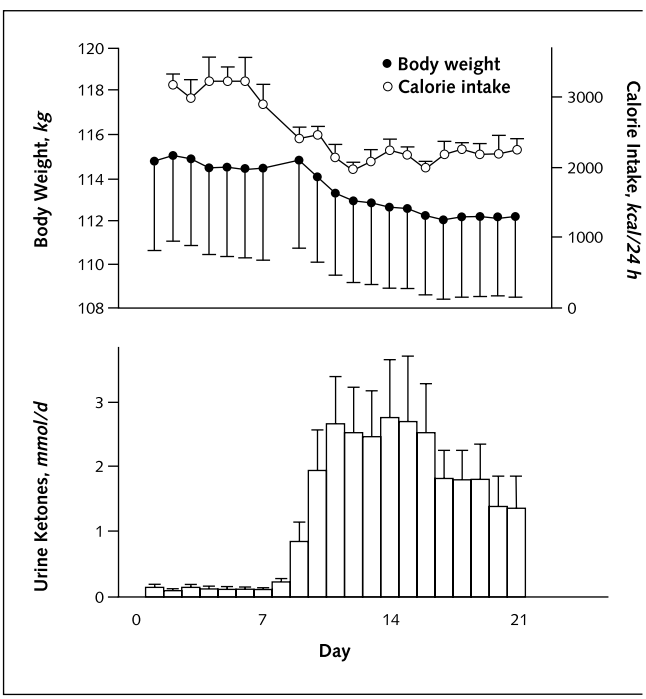
Variable	Control Group (n = 10)	Low-Carbohydrate Group (n = 10)	Difference	P Value†
Body weight, *kg*‡	114.43, 113.28 (96.2 to 141.6)	112.41, 111.31 (94.7 to 132.9)	2.02, 1.97 (–1.4 to 8.6)	0.042
Body water, *kg*‡	46.30, 43.99 (37.6 to 65.3)	45.94, 44.22 (36.3 to 64.4)	0.37, 0.45 (–2.3 to 4.1)	>0.2
Body weight – water, *kg*‡	68.13, 68.98 (47.7 to 84.4)	66.48, 67.76 (44.5 to 81.2)	1.65, 1.34 (–1.9 to 7.7)	0.049
Fat-free mass, *kg*‡	62.32, 59.52 (49.3 to 88.6)	62.73, 60.51 (49.3 to 88.0)	–0.43, –0.61 (–3.9 to 5.7)	>0.2
Fat mass, *kg*‡	52.13, 53.65 (29.8 to 70)	49.69, 50.20 (25.4 to 66.4)	2.45, 2.72 (–2.5 to 7.9)	0.026
Calorie intake, *kcal/d*§	3111, 3022 (1917 to 4810)	2164, 2116 (1748 to 2671)	947, 905 (–14 to 2379)	0.001
Total energy expenditure, *kcal/d*§‖	3284, 2924 (2652 to 5202)	3190, 2497 (2476 to 4753)	94, 40 (–72 to 449)	0.12
Resting energy expenditure, *kcal/d*‡	1945, 1822 (1670 to 2737)	1842, 1800 (1558 to 2339)	103, 67 (–117 to 399)	0.048
Caloric deficit, *kcal/d*		1027, 737 (399 to 1030)		
Predicted weight loss, *kg*¶		1.60, 1.15 (0.64 to 3.61)		

* Data are expressed as mean, median (range).
† Per Wilcoxon signed-rank test on paired differences.
‡ The displayed means and medians are from day 7 (last day of usual diet) for the control group and from day 21 (last day of low-carbohydrate diet) for the low-carbohydrate group.
§ The displayed means and medians are from days 3–7 in the control group and days 15–21 in the low-carbohydrate group. Total energy expenditure was measured only during these days.
‖ Measured in 6 patients and calculated in 4 patients (see text).
¶ See text for calculation (1 g fat = 9 kcal; 1 g protein = 4 kcal; 1 g carbohydrate = 4 kcal).

Role of the Funding Sources

This study was funded by grants from the National Institutes of Health and the American Diabetes Association. These sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the report for publication.

Figure 1. **Daily body weights and energy intakes (*top*) and urinary ketone body excretion (*bottom*).**



Data are from 10 patients with type 2 diabetes while on their usual high-carbohydrate, high-protein, high-fat diet (days 1 to 7) and while on a low-carbohydrate, high-protein, high-fat diet (days 8 to 21). Values are means ± SE.

RESULTS

Body Weight and Body Water

Body weight was stable during the usual diet period, with a mean weight of 114.75 kg and 114.43 kg on days 1 and 7, respectively. During the low-carbohydrate diet, mean body weight decreased by 2.02 kg from 114.43 kg (last day of the usual diet) to 112.41 kg (last day of the low-carbohydrate diet) ($P = 0.042$) (**Figure 1**, **Table 3**).

During the low-carbohydrate diet, mean body water decreased from 46.30 kg to 45.94 kg ($P > 0.2$). Body water decreased in 6 patients, increased in 3 patients, and did not change in 1 patient. After subtraction of body water, mean body weight decreased from 68.13 kg to 66.48 kg (mean change, −1.65 kg; $P = 0.049$) (**Table 3**).

Energy Intake and Expenditure

Mean energy intakes and expenditures were in balance (3111 kcal/d vs. 3284 kcal/d; $P = 0.12$) during the usual diet period, resulting in stable body weights.

During the low-carbohydrate diet, mean total energy expenditure (in 4 of these patients, we calculated total energy expenditure by using their resting energy expenditure and the resting–total energy expenditure ratio obtained in the 6 patients in whom total energy expenditure was measured) exceeded mean calorie intake (3190 kcal/d vs. 2164 kcal/d; $P = 0.001$), resulting in a mean energy deficit of 1027 kcal/d (median, 737 kcal/d). The decrease in mean body fat (from 52.13 kg to 49.7 kg) indicated that all weight loss during the low-carbohydrate diet was due to loss of adipose tissue. Thus, we can estimate that the mean caloric deficit (1027 kcal/d × 14 d = 14 378 kcal) should have resulted in a mean weight loss of 1.60 kg (median, 1.15 kg), which did not differ from the actual measured mean weight loss (corrected for loss of body water) of 1.65 kg (median, 1.34 kg) (**Table 3**).

The results were similar for the group of 6 patients in whom total energy expenditure was measured (**Table 4**).

Table 4. **Metabolic Balances in 6 Patients***

Variable	Control Group ($n = 6$)	Low-Carbohydrate Group ($n = 6$)	Difference	*P* Value†
Body weight, *kg*‡	112.60, 114.80 (96.2 to 125.2)	110.43, 113.09 (94.7 to 122.5)	2.17, 2.50 (0.22 to 3.2)	0.006
Body water, *kg*‡	45.80, 44.44 (37.6 to 55.8)	45.12, 44.67 (36.3 to 52.6)	0.68, 0.68 (–2.3 to 4.1)	>0.2
Body weight – water, *kg*‡	66.80, 65.59 (47.7 to 81.2)	65.31, 64.79 (44.5 to 81.2)	1.49, 1.70 (–0.88 to 3.18)	0.048
Fat-free mass, *kg*‡	61.74, 59.96 (49.3 to 76.4)	61.53, 61.05 (49.3 to 71.8)	0.16, –0.62 (–3.3 to 5.7)	>0.2
Fat mass, *kg*‡	50.86, 50.61 (29.8 to 70.0)	48.89, 48.16 (25.4 to 66.4)	2.02, 2.56 (–2.5 to 4.4)	0.011
Calorie intake, *kcal/d*§	3057, 3022 (2724 to 3514)	2101, 2009 (1748 to 2671)	956, 1077 (486 to 1296)	<0.001
Total energy expenditure, *kcal/d*§	3179, 2939 (2652 to 4432)	3123, 2978 (2476 to 4349)	57, 29 (–71 to 229)	>0.2
Resting energy expenditure, *kcal/d*‡	1895, 1875 (1670 to 2218)	1836, 1800 (1701 to 2140)	60, 59 (–117 to 202)	>0.2
Caloric deficit, *kcal/d*		1022, 754 (548 to 2001)		
Predicted weight loss, *kg*†‖		1.59, 1.17 (0.85 to 3.11)		

* Data are expressed as mean, median (range).
† Per Wilcoxon signed-rank test on paired differences.
‡ The displayed means and medians are from day 7 (last day of usual diet) for the control group and from day 21 (last day of low-carbohydrate diet) for the low-carbohydrate group.
§ The displayed means and medians are from days 3–7 in the control group and days 15–21 in the low-carbohydrate group. Total energy expenditure was measured only during these days.
‖ See text for calculations (1 g fat = 9 kcal; 1 g protein = 4 kcal; 1 g carbohydrate = 4 kcal).

Their predicted mean weight loss was 1.59 kg, which did not differ from the observed and water-corrected mean weight loss of 1.49 kg. Thus, our results suggested that the weight loss was completely accounted for by a reduction in caloric intake and a relatively small loss of body water, which occurred in 6 patients but not in the other 4 patients.

Assessment of Diet Satisfaction

The patients' answers to questionnaires (visual analogue scales) indicated that they considered the low-carbohydrate diet and their usual diet to be about equal with respect to feelings of hunger, satisfaction provided by the diets, feelings of comfort or discomfort, and energy levels (**Table 5**).

Ketone Bodies

Mean plasma total ketone body levels were 130 μmol/L (91.5% β-hydroxybutyrate) on day 7 and increased 5-fold to 653 μmol/L (97.4% β-hydroxybutyrate) on day 21 ($P < 0.001$).

Mean urinary ketone body excretion (**Figure 1**) increased sharply in all patients during the first week of the low-carbohydrate diet from 0.10 mmol/d (on day 8) to a peak of 2.75 mmol/d (on day 15; $P < 0.001$) (**Figure 1**, *bottom*).

Profiles of 24-Hour Plasma Glucose, Insulin, Leptin, and Ghrelin

Mean fasting plasma glucose levels decreased from 7.5 mmol/L (135 mg/dL) (on day 8) to 6.3 mmol/L (113 mg/dL) (on day 22; $P = 0.025$) (**Figure 2**). Mean 24-hour plasma glucose level profiles were significantly lower after than before the low-carbohydrate diet.

During the low-carbohydrate diet period, decreasing glucose levels necessitated decreasing insulin doses in 2 patients, decreasing thiazolidinedione and metformin doses in 1 patient each, and discontinuing sulfonylurea therapy in 1 patient.

Mean hemoglobin A_{1c} decreased from 7.3% on day 8 to 6.8% on day 22 ($P = 0.006$). Mean 24-hour serum insulin and leptin levels profiles were statistically significantly lower at the end of the low-carbohydrate diet than before this diet, while ghrelin profiles increased marginally.

Euglycemic Hyperinsulinemic Clamps

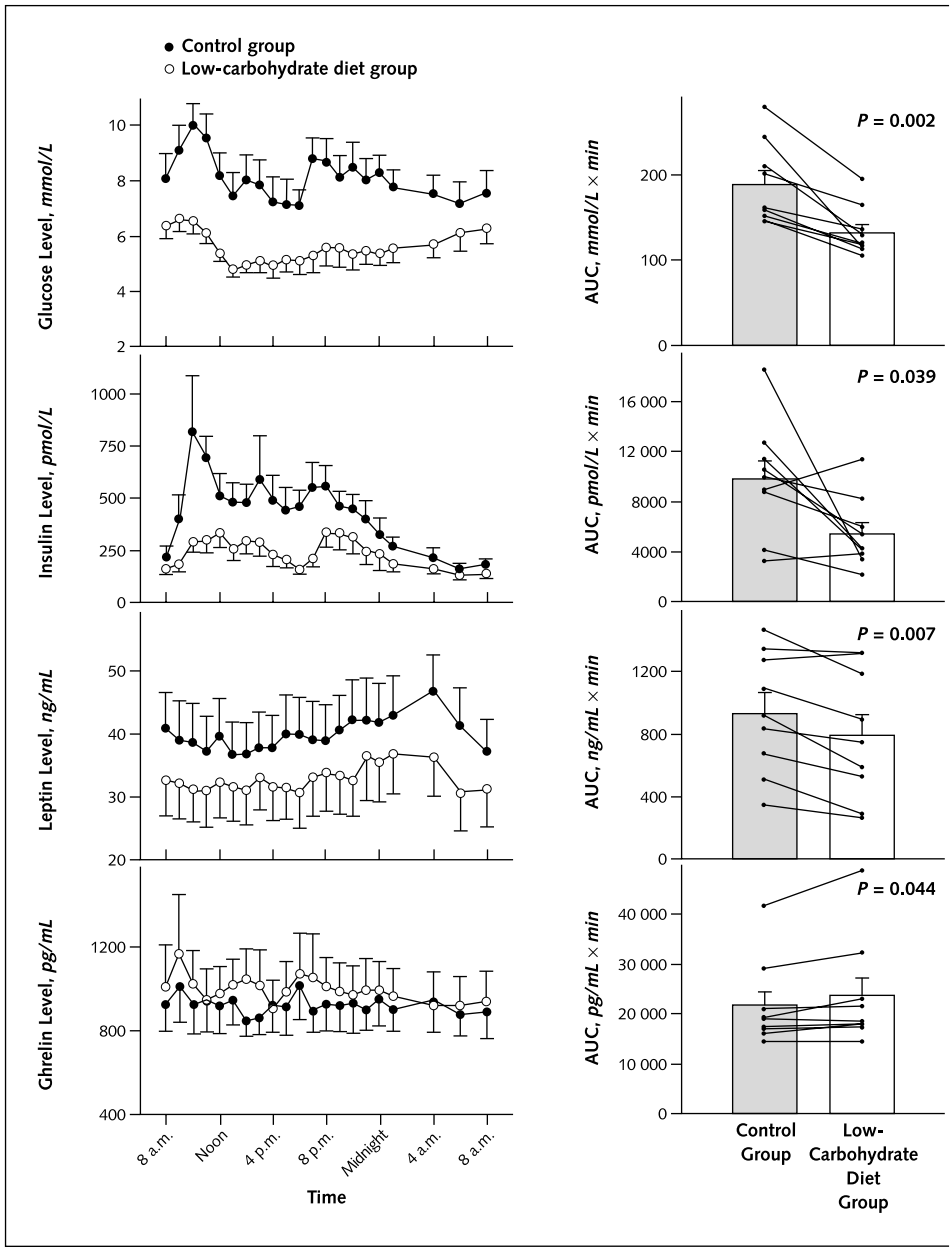
Mean glucose infusion rates needed to maintain euglycemia increased from 12.9 μmol/kg of body weight per minute (on day 8) to 16.8 μmol/kg per minute on day 22 (increase, 30%; $P = 0.03$) (**Figure 3**). After adjustment for the lower clamp insulin levels seen during the last clamp

Table 5. **Visual Analogue Scale Results***

Variable	Control Group ($n = 10$)	Low-Carbohydrate Group ($n = 10$)	Difference†
Hunger‡	6.6, 7.2 (4.3 to 8.0)	6.7, 6.9 (5.0 to 8.9)	−0.12, 0.33 (−1.2 to 2.1)
Satisfaction§	4.1, 3.7 (2.3 to 7.2)	3.6, 3.0 (1.8 to 7.4)	0.46, 0.08 (−3.8 to 5.2)
Queasiness‖	6.6, 8.0 (2.0 to 9.0)	7.5, 7.5 (4.9 to 8.8)	−0.89, −0.25 (−4.7 to 1.2)
Energy¶	5.0, 5.7 (1.0 to 6.5)	4.6, 4.5 (3.3 to 6.9)	0.38, 0.55 (−4.0 to 2.7)

* Data are expressed as mean, median (range).
† No difference was statistically significant.
‡ 0 = hungry and 10 = full.
§ 0 = satisfied and 10 = unsatisfied.
‖ 0 = queasy or nauseous and 10 = not queasy or nauseous.
¶ 0 = energetic and 10 = tired.

Figure 2. **Profiles of 24-hour plasma glucose, insulin, leptin, and ghrelin.**



Data are from 9 patients (1 patient declined to participate) with type 2 diabetes obtained on day 7 on their usual high-carbohydrate, high-protein, high-fat diet and after 2 weeks (day 21) on a low-carbohydrate diet. Individual values and means of the areas under the curves (*AUCs*) of these profiles are shown on the right. During the low-carbohydrate diet, insulin doses were decreased in 2 patients, metformin and thiazolidinediones doses were decreased in 1 patient each, and sulfonylureas were discontinued in 1 patient. Values are means ± SE.

(648 pmol/L vs. 498 pmol/L), glucose infusion rates increased by approximately 75% (from 0.033 μmol · kg^{-1} · min^{-1}/pmol · L^{-1} to 0.058 μmol · kg^{-1} · min^{-1}/pmol · L^{-1}; $P = 0.008$).

Mean insulin-stimulated rates of glucose disappearance, after adjustment for the difference in clamp insulin concentrations, increased from 0.01 μmol · kg^{-1} · min^{-1}/pmol · L^{-1} to 0.03 μmol · kg^{-1} · min^{-1}/pmol · L^{-1}; $P = 0.046$)—that is, the increase in glucose disappearance accounted for essentially all of the increase in the glucose infusion rates. Endogenous glucose production did not statistically significantly change.

Hormones

We measured plasma levels of several hormones known to influence carbohydrate metabolism. Comparisons of plasma hormone levels before and after the low-carbohydrate diet showed the following mean values: glucagon, 78 ± 31 pg/mL vs. 89 ± 47 pg/mL; cortisol, 229 ± 82 nmol/L vs. 249 ± 79 nmol/L; human growth

hormone, 0.5 ± 0.3 ng/mL vs. 0.5 ± 0.3 ng/mL; and adiponectin, 3.7 ± 1.5 μg/mL vs. 3.7 ± 1.5 μg/mL. None of these differences were statistically significant.

Serum Lipid Levels

Comparisons of mean serum levels before and after the low-carbohydrate diet showed that triglyceride levels decreased by 35% from 1.84 ± 0.63 mmol/L (162.83 ± 5.58 mg/dL) to 1.19 ± 0.03 mmol/L (105.31 ± 2.65 mg/dL) ($P < 0.001$) and that total cholesterol levels decreased by 10% from 4.68 mmol/L (180 mg/dL) to 4.24 mmol/L (163 mg/dL) ($P < 0.02$). Low-density lipoprotein cholesterol levels (2.61 ± 0.88 mmol/L [101 ± 35 mg/dL] vs. 2.56 ± 0.88 mmol/L [99 ± 35 mg/dL]) and high-density lipoprotein cholesterol levels (1.16 ± 0.3 mmol/L [45 ± 12 mg/dL] vs. 1.14 ± 0.4 mmol/L [44 ± 15 mg/dL]) did not change.

Renal Function

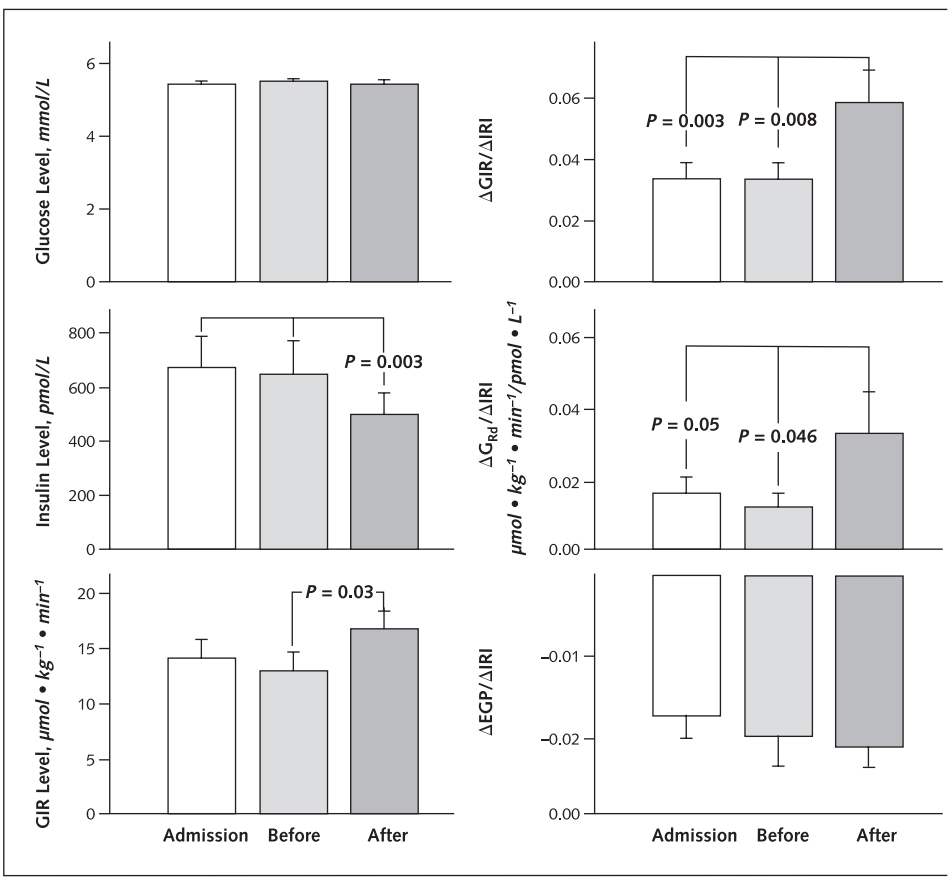
Mean blood urea nitrogen modestly increased from 5.85 ± 1.23 mmol/L (16.4 ± 3.5 mg/dL) to 7.14 ± 1.92 mmol/L (20.0 ± 5.4 mg/dL) ($P < 0.01$). Mean serum creatinine levels (88.4 ± 27.8 μmol/L [1.0 ± 0.3 mg/dL] vs. 97.2 ± 27.8 μmol/L [1.1 ± 0.3 mg/dL]), serum uric acid levels (0.40 ± 0.15 mmol/L vs. 0.41 ± 0.09 mmol/L), urinary creatinine levels (10.5 ± 4.1 mmol/L [119 ± 47 mg/dL] vs. 9.6 ± 4.1 mmol/L [109 ± 79 mg/dL]), and urinary albumin excretion levels (0.55 ± 1.13 μmol/L vs. 0.31 ± 0.44 μmol/L) did not statistically significantly change.

Discussion

Body Weight, Body Water, and Energy Intake and Output

During the usual diet period (days 1 to 7), when all patients maintained their usual eating and activity patterns, mean caloric intakes and total energy expenditures were in balance (approximately 3100 kcal/d) and body weights remained stable. During the low-carbohydrate diet period (days 8 to 22), mean carbohydrate intakes were reduced from approximately 300 g to approximately 20 g. Although patients had free access to all noncarbohydrate food items, they increased their protein and fat intakes very little. Their mean caloric intakes decreased by approximately

Figure 3. **Plasma glucose and insulin levels and glucose infusion rates (*GIR*) needed to maintain euglycemia, rates of glucose disappearance (G_{Rd}) and endogenous glucose production (*EGP*).**



Data were obtained during euglycemic hyperinsulinemic clamping performed in 10 obese patients with type 2 diabetes before (admission); after 1 week of their usual high-carbohydrate, high-protein, high-fat diet (before); and after 2 weeks of a strict low-carbohydrate diet (after). Glucose infusion rates are shown uncorrected and corrected for differences in clamp insulin levels (ΔGIR/ΔIRI). Rates of glucose disappearance and EGP are shown corrected for differences in basal rates and clamp insulin levels (ΔG_{Rd}/ΔIRI and ΔEGP/ΔIRI, respectively). IRI = immunoreactive insulin.

1000 kcal/d, while their mean total energy expenditures remained essentially unchanged (approximately 3284 kcal/d vs. 3190 kcal/d; $P = 0.12$). Changes in body water varied (decreases in 6 patients, increases in 3 patients, and no change in 1 patient). These changes may have reflected changes in natriuresis due to increased ketone body excretion and "obligatory water changes" due to changes in glycogen stores (20, 21). Mean body weight decreased by 2.02 kg. Corrected for changes in body water, the mean weight loss was 1.65 kg. Because all weight loss was due to loss of fat, we estimated that the caloric deficit plus changes in body water accounted for all weight loss (**Table 3**). Thus, our data did not support the concept that the weight loss induced by the low-carbohydrate diet was due to different metabolic utilization of macronutrients (8, 9).

Appetite

Patients spontaneously reduced their mean energy intake to approximately 2200 kcal/d, which is approximately the caloric intake of normal-weight individuals with the same height as our patients (22, 23). How the selective reduction in carbohydrate intake (there was very little compensatory increase in protein or fat intake) reduced appetite is not known. Lack of diet variety and palatability has been incriminated but was not supported by the patients' recordings in the visual analogue scale questionnaire (**Table 5**). However, several humoral satiety factors changed. We consider it unlikely that the relatively small increase in mean blood ketone body levels (from 0.13 mmol/L to 0.65 mmol/L) may have had anorectic effects (24). On the other hand, the decreased serum insulin levels may have reduced appetite because, in contrast to rodents, studies in humans have found that insulin increased food intake (25–27). Mean plasma leptin levels were lower, perhaps because of caloric restriction (28, 29) and decreased insulin levels (30) or perhaps because leptin sensitivity had increased. In view of the appetite-suppressing effect of leptin (31), lower leptin levels may have stimulated appetite and limited diet-induced weight loss.

Glycemic Control

During the low-carbohydrate diet, 24-hour glucose profiles improved dramatically and mean hemoglobin A_{1c} decreased from 7.3% to 6.8 % ($P < 0.01$) in only 2 weeks. Hemoglobin A_{1c} equilibrates in approximately 8 weeks. Thus, assuming no further change in glycemic control, hemoglobin A_{1c} should have been approximately 5.6% after 8 weeks on the low-carbohydrate diet. This level would have been compatible with the observed normalization of the 24-hour glucose profiles in our patients (**Figure 2**). These findings emphasized that postprandial glucose levels are primarily determined by the amount of ingested carbohydrates (32). Insulin sensitivity also improved, primarily because of an increase in mean peripheral glucose uptake, although the high mean clamp insulin levels may have obscured a possible effect on the liver. The reason for this is that the liver is more insulin-sensitive than muscle and, therefore, the relatively high clamp insulin levels might have fully compensated an existing hepatic insulin resistance. Others have reported that low-carbohydrate diets improved insulin–glucose ratios, suggesting improved insulin sensitivity (5). Whether similar improvements in glycemic control can been achieved with more conventional diets, resulting in similar reductions in energy intake, remains to be investigated.

Lipids

Mean plasma low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels did not change. Mean total plasma cholesterol and triglyceride levels, however, decreased by 10% and 35%, respectively. Decreased plasma triglyceride levels have been a consistent finding in studies using low-carbohydrate diets (4, 5, 21, 33). Decreased cholesterol levels were also seen in another 2-week study (21) but not in a 12-month study (4), which suggests that this decrease may be a transient phenomenon.

Summary

In this strictly supervised inpatient study, short-term use of a low-carbohydrate diet in obese patients with type 2 diabetes resulted in spontaneous reduction in energy intake to a level appropriate for their height, in weight loss that was mainly due to reduced calorie intake and variable changes in body water, in markedly improved glycemic control and insulin sensitivity, and in decreased plasma triglyceride and cholesterol levels. Thus, the low-carbohydrate diet was beneficial for weight and blood glucose level control in this small short-term study. Its long-term effects, however, remain uncertain, particularly since long-term adherence to this diet has been poor (7). Moreover, the reduced fiber intake may have adverse long-term health effects.

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