Comparison of 4 Diets of Varying Glycemic Load on Weight Loss and Cardiovascular Risk Reduction in Overweight and Obese Young Adults

A Randomized Controlled Trial

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Background: Despite the popularity of low–glycemic index (GI) and high-protein diets, to our knowledge no randomized, controlled trials have systematically compared their relative effects on weight loss and cardiovascular risk.

Methods: A total of 129 overweight or obese young adults (body mass index, ≥25 [calculated as weight in kilograms divided by the square of height in meters]) were assigned to 1 of 4 reduced-fat, high-fiber diets for 12 weeks. Diets 1 and 2 were high carbohydrate (55% of total energy intake), with high and low GIs, respectively; diets 3 and 4 were high protein (25% of total energy intake), with high and low GIs, respectively. The glycemic load was highest in diet 1 and lowest in diet 4. Changes in weight, body composition, and blood chemistry profile were studied.

Results: While all groups lost a similar mean±SE percentage of weight (diet 1, –4.2%±0.6%; diet 2, –5.5%±0.5%; diet 3, –6.2%±0.4%; and diet 4, –4.8%±0.7%; *P*=.09), the proportion of subjects in each group who lost 5% or more of body weight varied significantly by diet (diet 1, 31%; diet 2, 56%; diet 3, 66%; and diet 4, 33%; *P*=.01). Women on diets 2 and 3 lost approximately 80% more fat mass (–4.5±0.5 [mean±SE] kg and –4.6±0.5 kg) than those on diet 1 (–2.5±0.5 kg; *P*=.007). Mean±SE low-density-lipoprotein cholesterol levels declined significantly in the diet 2 group (–6.6±3.9 mg/dL [–0.17±0.10 mmol/L]) but increased in the diet 3 group (+10.0±3.9 mg/dL [+0.26±0.10 mmol/L]; *P*=.02). Goals for energy distribution were not achieved exactly: both carbohydrate groups ate less fat, and the diet 2 group ate more fiber.

Conclusion: Both high-protein and low-GI regimens increase body fat loss, but cardiovascular risk reduction is optimized by a high-carbohydrate, low-GI diet.

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THE QUANTITY AND QUALITY of carbohydrates (CHOs) are at the center of debate surrounding the optimal diet for weight loss. High-CHO intake, particularly refined CHOs, can exaggerate postprandial glycemia and has accompanied increases in obesity, type 2 diabetes mellitus, and the metabolic syndrome.[1-3] While a low-fat, high-CHO diet remains the "best practice," several studies suggest that lower-CHO, higher-protein, or low–glycemic load (GL) diets provide benefits for weight loss and cardiovascular risk reduction.[4-11] Compared with the standard diet, restriction or modification of CHO intake can result in beneficial effects on energy expenditure,[6] triglyceride (TG) concentrations, high-density lipoprotein (HDL) cholesterol levels, and glucose homeostasis.[12]

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A unifying hypothesis is that a high-dietary GL (the contribution to postprandial glycemia of all foods in a diet) increases the difficulty of weight control because rapidly digestible CHOs can cause marked fluctuations in blood glucose and insulin levels, in turn stimulating hunger[13] and inhibiting fat oxidation.[14] Both low–glycemic index (GI) and high-protein diets have caught the public's attention, but clinicians and health professionals remain skeptical, calling for greater scientific evidence on which to base advice to patients. One concern is

Table 1. Baseline Characteristics of the Study Participants by Diet Group*

Characteristic	Diet 1 (n = 32)	Diet 2 (n = 32)	Diet 3 (n = 32)	Diet 4 (n = 33)	*P* Value
Age, y	31.8 ± 1.7	30.5 ± 1.4	30.2 ± 1.5	34.6 ± 1.5	.15
Women, No. (%)	25 (78)	23 (72)	24 (75)	26 (79)	.91
Weight, kg	86.0 ± 1.9	87.1 ± 2.7	87.7 ± 2.9	88.4 ± 3.0	.93
Height, m	1.68 ± 0.02	1.67 ± 0.02	1.66 ± 0.02	1.66 ± 0.02	.66
BMI	30.9 ± 0.6	30.6 ± 0.8	31.3 ± 0.8	32.1 ± 0.9	.59
Waist, cm	96.4 ± 2.0	96.8 ± 2.2	96.8 ± 2.2	98.2 ± 2.4	.94
No. of dropouts	5	2	1	5	.24
Cholesterol, mmol/L	4.79 ± 0.19	4.71 ± 0.19	5.15 ± 0.18	4.83 ± 0.14	.30
HDL cholesterol, mmol/L	1.29 ± 0.07	1.17 ± 0.05	1.16 ± 0.05	1.36 ± 0.08	.07
HDL cholesterol ratio	3.94 ± 0.25	4.16 ± 0.24	4.75 ± 0.32	3.83 ± 0.26	.08
LDL cholesterol, mmol/L	2.87 ± 0.16	2.90 ± 0.14	3.33 ± 0.15	2.89 ± 0.14	.07
Triglycerides, mmol/L	1.37 ± 0.15	1.39 ± 0.13	1.41 ± 0.13	1.25 ± 0.12	.84
Free fatty acids, μmol/L	510 ± 33	436 ± 32	545 ± 42	520 ± 53	.26
Glucose, mmol/L	5.04 ± 0.11	4.95 ± 0.07	4.92 ± 0.14	5.04 ± 0.09	.78
Insulin, pmol/L	79 ± 7	83 ± 10	101 ± 12	81 ± 8	.32
HOMA1-IR†	2.6 ± 0.2	2.7 ± 0.4	3.1 ± 0.3	2.7 ± 0.3	.59
HOMA2-IR†	1.5 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	.46
HOMA2-%S	81 ± 8	85 ± 6	70 ± 6	82 ± 6	.41
HOMA2-%B	123 ± 6	122 ± 8	164 ± 24‡	125 ± 10	.10
Leptin, ng/mL	26 ± 2	22 ± 2	23 ± 2	22 ± 2	.46
CRP, mg/L	3.6 ± 0.8	4.3 ± 0.7	3.1 ± 0.6	4.3 ± 0.9	.57

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HOMA1, original HOMA model[16]; HOMA2, updated HOMA nonlinear computer model; IR, insulin resistance; LDL, low-density lipoprotein; %B, β-cell function; %S, insulin sensitivity.

Conventional unit conversion factors: To convert cholesterol, glucose, and triglycerides to milligrams per deciliter, divide by 0.0259, 0.0555, and 0.0113, respectively; to convert insulin values to microunits per milliliter, divide by 6.945.

*Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Values are expressed as mean ± SE unless otherwise indicated.

†Homeostasis model assessment of IR using fasting glucose (millimoles per liter) and insulin (microunits per milliliter) concentrations.

‡One subject was an outlier. Without this subject, the baseline HOMA2-%B value in the diet 3 group was 142% ± 10%.

that many sources of protein, such as meat and dairy products, can also be high in saturated fat. The accelerating obesity epidemic, the widespread popularity of alternate diets, and animal studies showing β-cell disruption on high-GI diets[15] make the need for resolution of the debate more pressing.

We conducted a 12-week parallel, randomized, controlled trial of 4 weight loss diets of defined GL, varying in CHO and protein content and in GI. All diets aimed for the same fat content (30% of total energy intake [E]), type of fat (saturated or unsaturated), and total dietary fiber. The hypothesis was that diets of reduced GL would increase the rate of fat loss, with minimal loss of lean mass, and improve cardiovascular disease risk factors.

METHODS

PARTICIPANTS

Volunteers were recruited locally using notice boards and newspaper advertisements. Young adults, 18 to 40 years of age, with a body mass index (BMI) of 25 or more (calculated as weight in kilograms divided by the square of height in meters), a body weight of less than 150 kg, and weight fluctuations of less than 5 kg in the previous 2 months, who were willing to eat red meat and maintain current physical activity were included. Exclusion criteria were chronic illness, regular medication other than birth control pills, eating disorders, special diets, pregnancy, food allergy, and insufficient command of the English language. In total, 148 individuals were screened between July 2002 and July 2004, and 129 of them (98 women and 31 men) met the inclusion criteria. Of those excluded, 2 were taking medications, 5 were older than 40 years, 3 were non–red meat eaters, 5 weighed more than 150 kg, and 4 were accepted but withdrew before randomization.

Subjects were stratified according to weight (<80 kg, 80-100 kg, and >100 kg) and sex and then randomly assigned to 1 of the 4 diets, which resulted in 4 well-matched groups with no significant differences in baseline characteristics (**Table 1**). Of the 129 enrolled subjects, 13 dropped out (all female): 1 became pregnant, 1 failed to complete the final analysis, 2 moved interstate, and 9 cited disappointment with the rate of weight loss. **Figure 1** shows the flow of participants through the study.

DIETARY INSTRUCTION

All 4 diets were designed as reduced-energy, reduced-fat (30% E), moderate-fiber (30 g/d) eating plans with differences in the quantity and quality of available CHOs. Diet 1 was a high-CHO (55% E) and average-protein (15% E) diet based on high-GI whole grains, including fiber-rich breakfast cereals and breads. Diet 2 had the same macronutrient proportions but was based on previously verified low-GI foods.[17] Diet 3 was a higher-protein (25% E), CHO-reduced (45% E) diet based on lean red meat and high-GI CHO whole grains. Diet 4 had the same macronutrient proportions as diet 3 but specified low-GI CHO choices. The target GL (GI × CHO content), calculated as the sum of foods in sample menus, was highest in diet 1 and lowest in diet 4 (**Table 2**).

Subjects were given eating plans that were devised to help them lose weight (providing approximately 1400 kcal [6000 kJ] for women and 1900 kcal [8000 kJ] for men) and achieve the desired macronutrient distribution. These plans specified the number of servings from each food group and suitable choices within each group. Additional lists of appropriate meals and snacks were also provided. Dairy intake was held constant to minimize confounding from this source. To allow satiety and appetite factors to function, subjects were told to "eat to appetite" but were not required to consume all specified servings and, if hungry, were permitted to increase the number of servings proportionately from each food group.

To maximize compliance, all key CHO and protein foods and some preprepared meals were provided. A color-coded "shop" system (different color for each diet) with bar code reader was used, and subjects collected foods of low or high GI (eg, bread, breakfast cereal, crackers, snack bars, oats, legumes, pasta, and basmati or jasmine rice), red meat portions, and specially prepared frozen meals each week. On the same day, they met with a dietitian who encouraged compliance and answered queries.

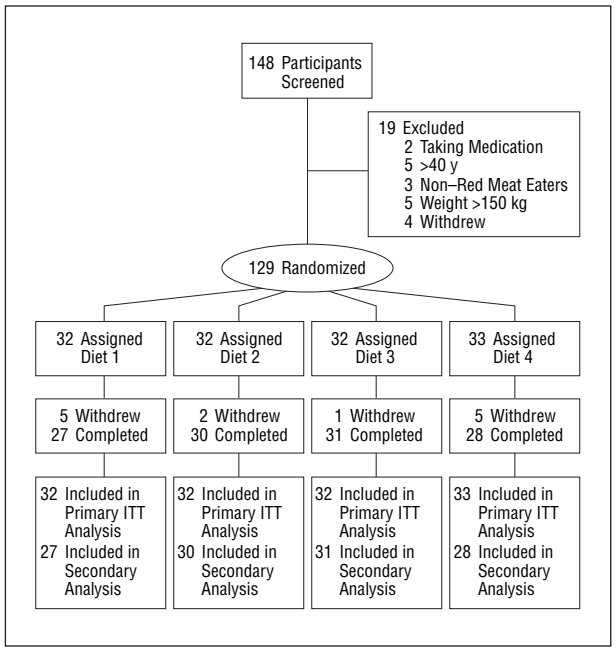

Figure 1. Organization chart of participant flow through the study. Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. ITT indicates intention-to-treat.

PROFILE DAYS

To confirm that the diets produced differences in day-long glycemia and insulinemia, mixed meals representative of each diet (**Table 3**) were fed over a 10-hour period to 11 weight-stable volunteers (mean ± SE age, 26.5±4.4 years; mean ± SE BMI, 30.0±4.3) who had completed the weight-loss intervention. The 4 menus were given in random order on separate days, 3 to 7 days apart. Finger-prick capillary blood samples were collected at 30- to 60-minute intervals, and responses were quantified as the incremental areas under the curve (AUC [mean ± SE]).

OUTCOME MEASURES

At baseline and on completion of the 12-week intervention, dual-energy x-ray absorptiometry (Lunar Prodigy; GE Healthcare, Giles, England) was performed to assess changes in body composition (such as fat mass and lean mass). Weight was recorded weekly on electronic scales (Tanita Corp, Tokyo, Japan). At baseline and at weeks 6 and 12, fasting venous blood samples were obtained for measurement of levels of glucose (glucose hexokinase enzyme assay); insulin and leptin (microparticle enzyme immunometric assay on AxSym; Abbott Diagnostics, Abbott Park, Ill); total cholesterol, HDL cholesterol, and TG by standard automated methods[18]; free fatty acids by a commercially available enzymatic colorimetric test kit (NEFAC; Wako Pure Chemical Industries Ltd, Osaka, Japan); and C-reactive protein by near-infrared immunonephelometry (Beckman Coulter, Sydney, Australia). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald calculation. We defined hyperinsulinemia as fasting insulin levels higher than 16 μIU/mL (110 pmol/L)[19] and hypertriglyceridemia as fasting TG levels greater than or equal to 133 mg/dL (1.5 mmol/L).[11] The homeostasis model assessment (HOMA) was used to assess β-cell function and insulin sensitivity from fasting glucose and insulin concentrations.We used both the original model, HOMA1 [(fasting glucose × fasting insulin)/22.5], and the updated nonlinear computer model, HOMA2, as described by Wallace et al.[16] At baseline and during weeks 4 and 8, subjects were asked to keep a 3-day food diary, including 2 weekdays and 1 weekend day, to assess dietary compliance and to estimate food intake. A dietitian entered the data into a customized database that incorporated the Australian food composition tables and published GI values[17] using the glucose equals 100 scale (FoodWorks Professional 2005; Xyris Software, Brisbane, Australia). Additional GI data were obtained from an online database (www.glycemicindex.com). The study was approved by the human ethics committee of the University of Sydney, Sydney, Australia, and subjects gave written, informed consent.

Table 2. Target and Actual Macronutrient Energy Distribution, Glycemic Index (GI), and Glycemic Load (GL)*

	Diet 1		Diet 2		Diet 3		Diet 4		
Variable	Target	Actual	Target	Actual	Target	Actual	Target	Actual	*P* Value†
CHO, % E	55	60 ± 1	55	56 ± 1	45	42 ± 1	45	40 ± 2	<.001
Protein, % E	15	18 ± 1	15	19 ± 0	25	28 ± 1	25	26 ± 1	<.001
Fat, % E	30	19 ± 1	30	22 ± 1	30	27 ± 1	30	29 ± 1	<.001
Alcohol, % E	0	2 ± 1	0	3 ± 1	0	2 ± 1	0	3 ± 1	.81
GI	67	70 ± 1	40	45 ± 1	57	59 ± 1	34	44 ± 1	<.001
GL, g	127	129 ± 8	75	89 ± 5	87	75 ± 3	54	59 ± 4	<.001

Abbreviations: CHO, carbohydrate; % E, percentage of total energy intake.

*Diet 1, high-CHO/high-GI; diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Target values were the calculated values from sample menus. Actual values, which are expressed as mean ± SE, were calculated from food diaries completed during weeks 4 and 8 of the intervention.

†*P* value for comparison of actual values among the 4 diets.

Table 3. Representative Menu for the 4 Diets Consumed on the 10-Hour Profile Day[a]

Variable	Diet 1	Diet 2	Diet 3	Diet 4
Breakfast	45 g Sultana Bran[b]	45 g Guardian cereal[h]	80 g egg omelet	80 g egg omelet
	120 mL low-fat milk[c]	120 mL low-fat milk	40 g whole-wheat bread	38 g oat-bran bread
	80 g rockmelon	50 g strawberry	80 g spinach	80 g spinach
	80 g pineapple	100 g grapefruit	20 g red capsicum	20 g red capsicum
			80 g tomato, grilled	80 g tomato, grilled
Snack	40 g white bagel[d]	40 g fruit bread[i]	120 g low-fat yogurt[m]	120 g low-fat yogurt
	5 g butter	4 g butter	5 g wheat bran	5 g wheat bran
	10 g strawberry jam	15 g fruit spread	100 g banana	180 g green apple
Lunch	446 g potato soup	50 g oat-bran bread[j]	90 g whole-wheat bread	84 g oat-bran bread
	10 g wheat bran[e]	290 g minestrone soup[k]	60 g lean meat	60 g lean meat
	28 g whole-wheat bread[f]	10 g butter	25 g lettuce	25 g lettuce
	5 g butter	140 g green apple	45 g tomato	45 g tomato
	50 g banana		20 g cheddar cheese	20 g cheddar cheese
Dinner	120 g potato gnocchi[g]	160 g spaghetti[l]	120 g brown rice[n]	160 g brown pasta[o]
	120 g bolognese sauce	120 g bolognese sauce	200 g bolognese sauce	200 g bolognese sauce
	10 g wheat bran	58 g lettuce	15 g wheat bran	5 g wheat bran
	58 g lettuce	68 g tomato	58 g lettuce	58 g lettuce
	68 g tomato	25 g cucumber	68 g tomato	68 g tomato
	25 g cucumber	18 g olive oil	25 g cucumber	25 g cucumber
	18 g olive oil	10 g vinegar	10 g olive oil	10 g olive oil
	10 g vinegar		6 g vinegar	6 g vinegar
Energy, kJ	5330	5300	5350	5340
CHO, g	175	175	140	141
Protein, g	49	47	81	81
Fat, g	42	42	43	43
Energy distribution[p]	56/15/29	53/15/29	42/26/30	42/26/29
Fiber, g	34	37	33	35
GI	65	40	68	34
GL, g	116	65	84	43

Abbreviations: CHO, carbohydrate; GI, glycemic index; GL, glycemic load.
Conventional unit conversion factor: To convert energy (percentage of energy intake) to kilocalories, divide by 4.184.
[a]Diet 1, high-CHO/high-GI; diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI.
[b]Sultana Bran; Kellogg's, Melbourne, Australia.
[c]Lite White (1.4% fat); Dairy Farmers, Sydney, Australia.
[d]White Bagel; Bagel House Bakery, Sydney.
[e]Unprocessed Wheat Bran; Russel's Natural Food Market, Sydney.
[f]Sunblest Wholemeal Bread; Tip Top Bakeries, Sydney.
[g]Golden Pasta Gnocchi (potato); Guzzi's, Sydney.
[h]Guardian; Kellogg's.
[i]Bürgen Fruit and Mixed Grain Bread; Tip Top Bakeries.
[j]Bürgen Oat Bran and Honey Bread; Tip Top Bakeries.
[k]Campbell's Country Ladle Traditional Minestrone Soup; Campbell Australia Pty Ltd, Sydney.
[l]White Spaghetti; San Remo, Adelaide, Australia.
[m]Ski D'Lite Low-Fat Fruit Yogurt; Dairy Farmers.
[n]SunRice Brown Calrose Medium-Grain Rice; SunRice, Sydney.
[o]Wholemeal Spaghetti; San Remo.
[p]Energy distribution is given as percentage energy from CHO/protein/fat.

STATISTICAL ANALYSES

Power calculations indicated that 120 subjects (30 in each arm) provided 90% power to detect a 2-kg difference in body weight change among groups using significance equals 5%. The primary end points were mean absolute change from baseline in body weight and fat mass at week 12. Pearson χ^2 analysis was used to compare the proportion of subjects in each group who achieved 5% or more weight loss. Univariate and repeated-measures analyses of variance were used to assess the changes in weight, body composition, and blood parameters. Changes were assessed with and without adjustment for baseline differences. Missing data were replaced with the last known value for the primary intention-to-treat analysis and excluded in the secondary analysis. A commercially available software package (SPSS Version 12.0; SPSS Inc, Chicago, Ill) was used for all statistical analyses.

RESULTS

WEIGHT LOSS AND BODY COMPOSITION CHANGES

In the primary intention-to-treat analysis, all 4 diets resulted in weight reduction over 12 weeks (mean change, 4.2% to 6.2% of body weight). Reductions in weight, fat mass, and waist circumference were significant within each group (in each case $P<.001$) but not among the 4 diets (**Table 4** and **Figure 2**). There were significant differences in the proportion of individuals who lost 5% or more of initial body weight: 31% of subjects on diet 1, 56% on diet 2, 66% on diet 3, and

Table 4. Primary Intention-to-Treat Analysis of Changes in Weight and Body Composition*

Variable	Diet 1	Diet 2	Diet 3	Diet 4	*P* Value
All subjects (N = 129)	(n = 32)	(n = 32)	(n = 32)	(n = 33)	
Change in weight, kg	–3.7 ± 0.5	–4.8 ± 0.5	–5.3 ± 0.5	–4.4 ± 0.5	.17
Weight change, %	–4.2 ± 0.6	–5.5 ± 0.5	–6.2 ± 0.4	–4.8 ± 0.7	.09
Subjects with ≥5% loss, %	31	56	66	33	.01
Change in waist, cm	–4.3 ± 0.7	–5.6 ± 0.7	–6.3 ± 0.6	–5.0 ± 0.7	.22
Change in fat mass, kg	–2.8 ± 0.5	–4.5 ± 0.5	–4.3 ± 0.5	–3.7 ± 0.5	.08
Change in lean mass, kg	–0.5 ± 0.2	–0.3 ± 0.2	–0.6 ± 0.2	–0.4 ± 0.2	.75
Women (n = 98)	(n = 25)	(n = 23)	(n = 24)	(n = 26)	
Change in weight, kg	–3.1 ± 0.5†	–4.8 ± 0.5‡	–5.4 ± 0.5§	–3.5 ± 0.5	.006
Weight change, %	–3.7 ± 0.6	–5.7 ± 0.6	–6.5 ± 0.5	–4.1 ± 0.7	.004
Subjects with ≥5% loss, %	25	61	75	23	<.001
Change in waist, cm	–3.2 ± 0.7	–5.8 ± 0.8	–6.2 ± 0.8	–3.9 ± 0.7	.02
Change in fat mass, kg	–2.5 ± 0.5‖	–4.5 ± 0.5¶	–4.6 ± 0.5#	–2.9 ± 0.5‖	.007
Change in lean mass, kg	–0.2 ± 0.2	–0.3 ± 0.4	–0.2 ± 0.3	–0.1 ± 0.2	.95

*Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Values are expressed as mean ± SE unless otherwise indicated; all data other than percentage of weight change were adjusted for baseline values.
†Diet 1 vs diet 2, *P* = .009; diet 1 vs diet 3, *P* = .005.
‡Diet 2 vs diet 4, *P* = .03.
§Diet 3 vs diet 4, *P* = .02.
‖Diet 1 vs diet 2, *P* = .01; diet 1 vs diet 3, *P* = .005.
¶Diet 2 vs diet 4, *P* = .04.
#Diet 3 vs diet 4, *P* = .02.

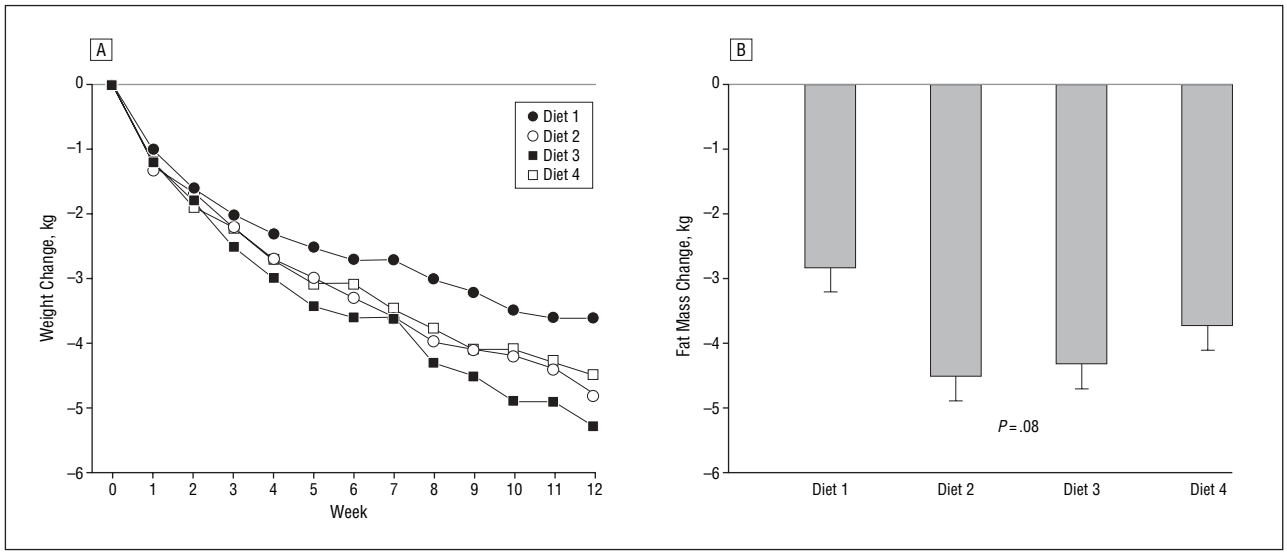

Figure 2. Changes in weight (A) and fat mass (B) over 12 weeks in 129 overweight young adults randomized to 4 diets of varying glycemic load. Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. All values are given as means with error bars indicating standard errors.

33% on diet 4 (*P* = .01). Sex influenced fat mass changes, with a significant interaction with diet (*P* = .008). In a subanalysis of women (n = 98), there were highly significant mean ± SE differences in fat mass change (–2.5 ± 0.5 kg, –4.5 ± 0.5 kg, –4.6 ± 0.5 kg, and –2.9 ± 0.5 kg for diets 1, 2, 3, and 4, respectively; *P* = .007) (Table 4). The GI had a significantly different effect (*P* = .02) in the high-CHO diets (lowering the GI doubled the fat loss from 2.8 kg to 4.5 kg) than in the high-protein diets (lowering the GI did not increase fat loss). This effect was more pronounced in women (*P* = .001). Declines in lean body mass reached significance in the 2 high-GI groups (*P* = .03 for diet 1 and *P* = .02 for diet 3), but overall there were no significant differences among the 4 diets (*P* = .75).

The pattern of findings (changes in weight, waist circumference, fat mass, and lean mass) was unchanged in the secondary sensitivity analysis, from which subjects who had not completed the study were excluded (data not shown). The proportion of subjects with a weight loss of 5% or more (n = 116) remained significant (37%, 60%, 68%, and 32% for diets 1, 2, 3, and 4, respectively; *P* = .02). The findings were also similar when the analysis was confined to those with high fasting insulin levels (≥16 μIU/mL [≥110 pmol/L], n = 37) or high fasting TG levels (≥133 mg/dL [≥1.5 mmol/L], n = 38). Among the lat-

Table 5. Primary Intention-to-Treat Analysis of Changes in Cardiovascular Risk Factors From Baseline to End of Week 12*

Absolute Change	Diet 1 (n = 32)	Diet 2 (n = 32)	Diet 3 (n = 32)	Diet 4 (n = 33)	*P* Value†
Cholesterol, mmol/L	0.05 ± 0.10	−0.18 ± 0.10§	+0.24 ± 0.10§	−0.05 ± 0.10	.04
HDL cholesterol, mmol/L	+0.08 ± 0.04	+0.03 ± 0.04	+0.05 ± 0.04	+0.07 ± 0.04	.82
HDL cholesterol ratio	−0.23 ± 0.11	−0.21 ± 0.11	+0.02 ± 0.11	−0.37 ± 11	.11
LDL cholesterol, mmol/L	0.04 ± 0.10	−0.17 ± 0.10‖	+0.26 ± 0.10‖	−0.04 ± 0.09	.02
Triglycerides, mmol/L	−0.14 ± 0.07	−0.05 ± 0.07	−0.18 ± 0.07	−0.19 ± 0.07	.39
Free fatty acids, µmol/L	−63 ± 35	+3 ± 36	−44 ± 35	−57 ± 34	.56
Glucose, mmol/L	−0.04 ± 0.10	−0.06 ± 0.10	−0.05 ± 0.10	+0.02 ± 0.10	.94
Insulin, pmol/L	−8.1 ± 6.9	−13.3 ± 6.9	−17.1 ± 7.0	−10.4 ± 6.8	.82
HOMA1-IR‡	−0.3 ± 0.2	−0.5 ± 0.2	−0.6 ± 0.2	−0.3 ± 0.2	.72
HOMA2-IR‡	−0.1 ± 0.1	−0.2 ± 0.1	0.3 ± 0.1	−0.2 ± 0.1	.77
HOMA2-%S	+1.7 ± 7.3	+9.3 ± 7.4	+25.7 ± 7.4	+16.4 ± 7.2	.13
HOMA2-%B	−11.3 ± 17.8	−15.0 ± 17.8	−16.5 ± 18.1	+11.8 ± 17.5	.64
Leptin, ng/mL	−1.9 ± 1.5	−7.5 ± 1.5¶	−5.4 ± 1.5	−1.0 ± 1.4¶	.006
CRP, mg/L	−0.8 ± 0.4	−1.1 ± 0.4	−0.8 ± 0.4	−0.01 ± 0.4	.18

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HOMA1, original HOMA model[16]; HOMA2, updated HOMA nonlinear computer model; IR, insulin resistance; LDL, low-density lipoprotein; %B, β-cell function; %S, insulin sensitivity.

Conventional unit conversion factors: To convert cholesterol, glucose, and triglyceride values to milligrams per deciliter, divide by 0.0259, 0.0555, and 0.0113, respectively; to convert insulin values to microunits per milliliter, divide by 6.945.

*Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Values are expressed as mean ± SE unless otherwise indicated; all data other than percentage of weight change were adjusted for baseline values.

†Univariate analysis of variance of the absolute change between 0 time and week 12. Similar results were obtained using repeated-measures analysis of variance of data from 0, 6, and 12 weeks (data not shown).

‡Homeostasis model assessment of IR using fasting glucose (millimoles per liter) and insulin (microunits per milliliter) concentrations.

§Diet 2 vs diet 3, *P* = .03.

‖Diet 2 vs diet 3, *P* = .01.

¶Diet 2 vs diet 4, *P* = .01.

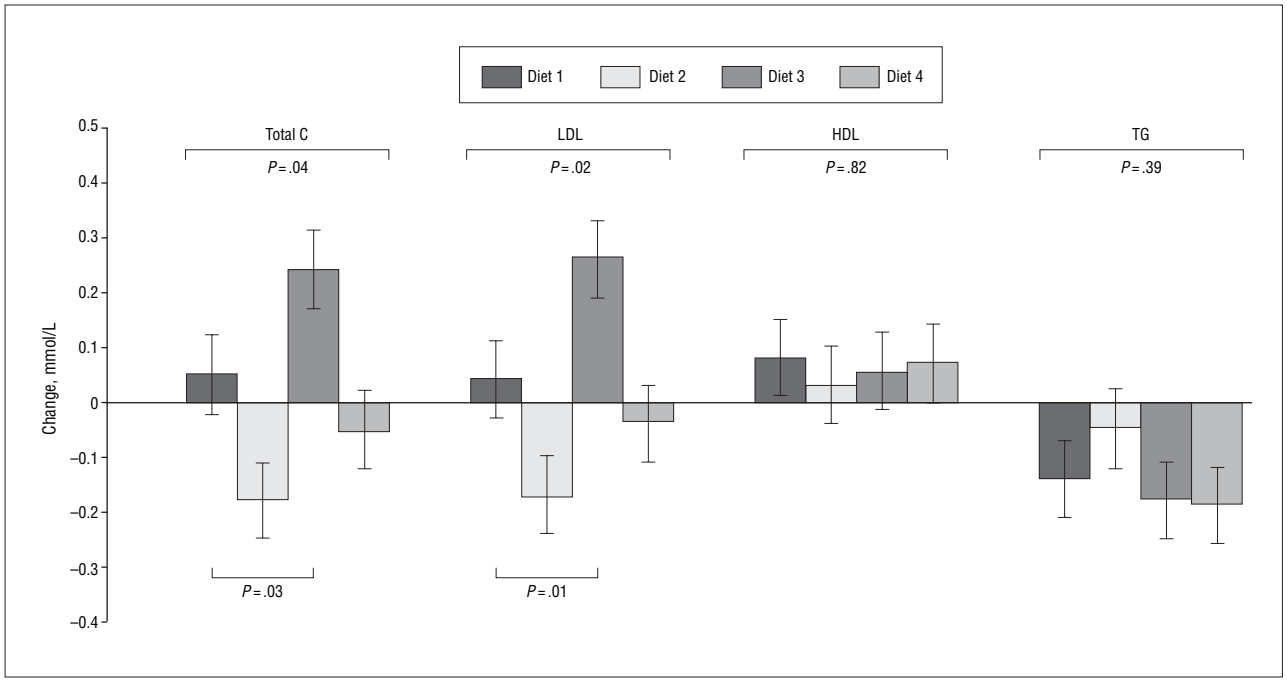

Figure 3. Changes in blood lipid fractions from 0 to 12 weeks in 129 overweight young adults randomized to 4 diets of varying glycemic load. Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Total C indicates total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and TG, triglycerides. All values are given as means with error bars indicating ±SE. To convert cholesterol values to milligrams per deciliter, divide by 0.0259.

ter, the subjects on the diet with the lowest GL (diet 4) achieved greater fat loss (−2.0±0.8 [mean±SE] kg, −4.9±0.8 kg, −4.4±0.9 kg, and −5.6±1.0 kg for diets 1, 2, 3, and 4, respectively; *P*=.03).

CARDIOVASCULAR RISK FACTORS

In both the primary intention-to-treat analysis (**Table 5** and **Figure 3**) and the secondary sensitivity analysis (data

Table 6. Nutrient Intake Determined From Food Diaries Completed at Baseline and During the Intervention*

Variable	Diet 1	Diet 2	Diet 3	Diet 4	*P* Value†
Energy, kJ					
Baseline	9630 ± 470	9030 ± 460	9220 ± 450	8890 ± 470	.41
Intervention	6010 ± 240	6150 ± 190	5950 ± 170	5970 ± 190	.90
CHO, g					
Baseline	262 ± 14	239 ± 13	248 ± 14	251 ± 19	.78
Intervention	209 ± 9	200 ± 7	146 ± 6	143 ± 7	<.001
Protein, g					
Baseline	99 ± 5	93 ± 5	89 ± 5	93 ± 4	.54
Intervention	63 ± 3	69 ± 2	95 ± 2	93 ± 3	<.001
Total fat, g					
Baseline	93 ± 6	82 ± 6	88 ± 5	73 ± 5	.06
Intervention	32 ± 2	36 ± 2	44 ± 2	48 ± 2	<.001
Saturated fat, g					
Baseline	36 ± 3	33 ± 3	32 ± 3	27 ± 3	.16
Intervention	9 ± 1	10 ± 1	13 ± 1	13 ± 1	<.001
Monounsaturated fat, g					
Baseline	33 ± 2	29 ± 2	31 ± 2	26 ± 2	.10
Intervention	9 ± 1	11 ± 1	16 ± 2	17 ± 1	<.001
Polyunsaturated fat, g					
Baseline	14 ± 1	13 ± 1	14 ± 2	10 ± 1	.03
Intervention	4 ± 0	8 ± 0	6 ± 1	7 ± 0	<.001
Fiber, g					
Baseline	23 ± 1	20 ± 1	19 ± 1	21 ± 1	.14
Intervention	23 ± 1	30 ± 1	21 ± 1	24 ± 1	<.001
Calcium, mg					
Baseline	984 ± 69	844 ± 79	824 ± 61	932 ± 62	.30
Intervention	648 ± 47	637 ± 42	697 ± 44	719 ± 42	.50
Iron, mg					
Baseline	13 ± 1	12 ± 1	12 ± 1	14 ± 1	.21
Intervention	10 ± 1	11 ± 1	13 ± 1	13 ± 1	.01
Zinc, mg					
Baseline	13 ± 2	11 ± 1	11 ± 1	12 ± 1	.19
Intervention	8 ± 0	7 ± 0	11 ± 0	12 ± 1	<.001

Conventional unit conversion factor: To convert energy (percentage of energy intake) to kilocalories, divide by 4.184.

*Intakes were based on the analysis of 3-day food diaries completed at baseline and during weeks 4 and 8 (average is shown as intervention). Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Values are expressed as mean ± SE intake per day unless otherwise indicated.

†*P* value for differences among the 4 diets.

not shown), there was no differential effect of diet composition on the levels of HDL cholesterol, TG, free fatty acids, and C-reactive protein; total HDL cholesterol ratio; or glucose homeostasis. However, there were divergent effects on total and LDL cholesterol levels ($P=.04$ and $P=.02$, respectively). Both parameters increased in the diet 3 group (+5% and +8%, respectively) in contrast to a reduction in the diet 2 group (–4% and –6%, respectively; $P=.03$ and $P=.01$ for pair-wise comparisons). The increase in LDL cholesterol levels in the diet 3 group was greater in women (+10%) and significantly different from the decrease seen in the diet 2 group (–9%; $P=.001$). Overall, the GI, but not the protein content, had a significant effect on change in total cholesterol levels ($P=.02$) and LDL cholesterol levels ($P=.009$).

Diet had significant effects on changes in leptin levels ($P<.006$), which decreased more in the diet 2 group, with a significant interaction between GI and CHO content ($P=.003$; Table 5). Hence, lowering the GI resulted in a larger decrease in leptin levels when the CHO intake was high, whereas the reverse was true when the CHO intake was lower. However, on an individual basis, the absolute decrease in leptin levels correlated significantly with change in fat mass ($r=0.27$; $P=.003$), with no additional effect of GI or CHO content. Changes in fat mass were also correlated with changes in fasting insulin concentration ($r=0.19$; $P=.03$) and changes in insulin sensitivity as measured by HOMA2 ($r=0.20$; $P=.02$).

DIETARY ADHERENCE

The analysis of the food diaries showed that all 4 groups achieved their intended CHO and protein distributions (Table 2). There was no difference in apparent energy intake ($P=.41$; **Table 6**). In pair-wise comparisons, there was a 2-fold difference in GL between the 2 extreme diets (129±8 [mean±SE] g/d vs 59±4 g/d, diet 1 vs diet 4, respectively; $P<.001$), but the intermediate diets were not different from each other (89±5 g/d vs 75±3 g/d, diet 2 vs diet 3, respectively; $P=.25$) (**Figure 4**). Mean dietary fiber intake was 25 g/d across all groups, but diet 2 was the only group to achieve the target intake (30 g/d; $P<.001$). All groups reduced fat intake, but the high-CHO groups ate less fat than the high-protein groups (–10 g/d; $P<.001$). Accordingly, the high-CHO groups ate less of each type of fat, although the ratio of saturated to un-

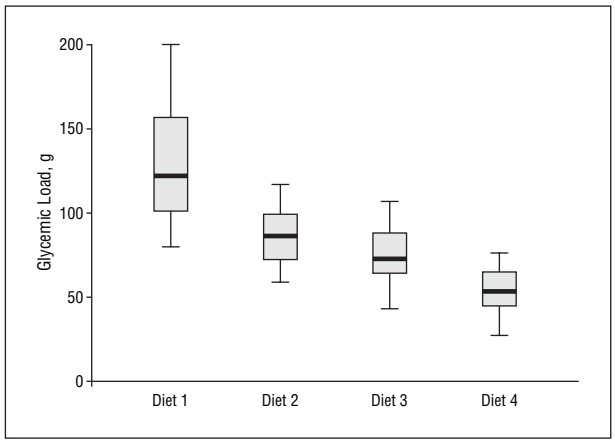

Figure 4. Box plot of glycemic load (glycemic index [GI] × carbohydrate [CHO] content) of the 4 diets based on food diaries completed during weeks 4 and 8 of the intervention. Diet 1, high-CHO/high-GI; diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI.

saturated fatty acids (approximately 0.6) remained constant (Table 6). The cholesterol intake was relatively low in all groups, but the high-protein groups consumed more cholesterol than the high-CHO groups (293 ± 18 [mean ± SE] mg/d, 239 ± 18 mg/d, 125 ± 10 mg/d, and 119 ± 14 mg/d on diets 1, 2, 3, and 4, respectively; $P < .001$).

PROFILE DAYS

Postprandial glucose and insulin concentrations fluctuated throughout the day as predicted by the calculated GI and GL of the meals (**Figure 5**). The incremental glucose AUC over 10 hours was highest in the diet 1 group (315 ± 36 mmol/L · min) and lowest in the diet 4 group (196 ± 30 mmol/L · min; $P = .02$ for all groups). Similarly, the insulin AUC was highest in the diet 1 group (7940 ± 1160 pmol/L · min) and lowest in the diet 4 group (4340 ± 800 pmol/L · min; $P = .005$ for all groups). The GL

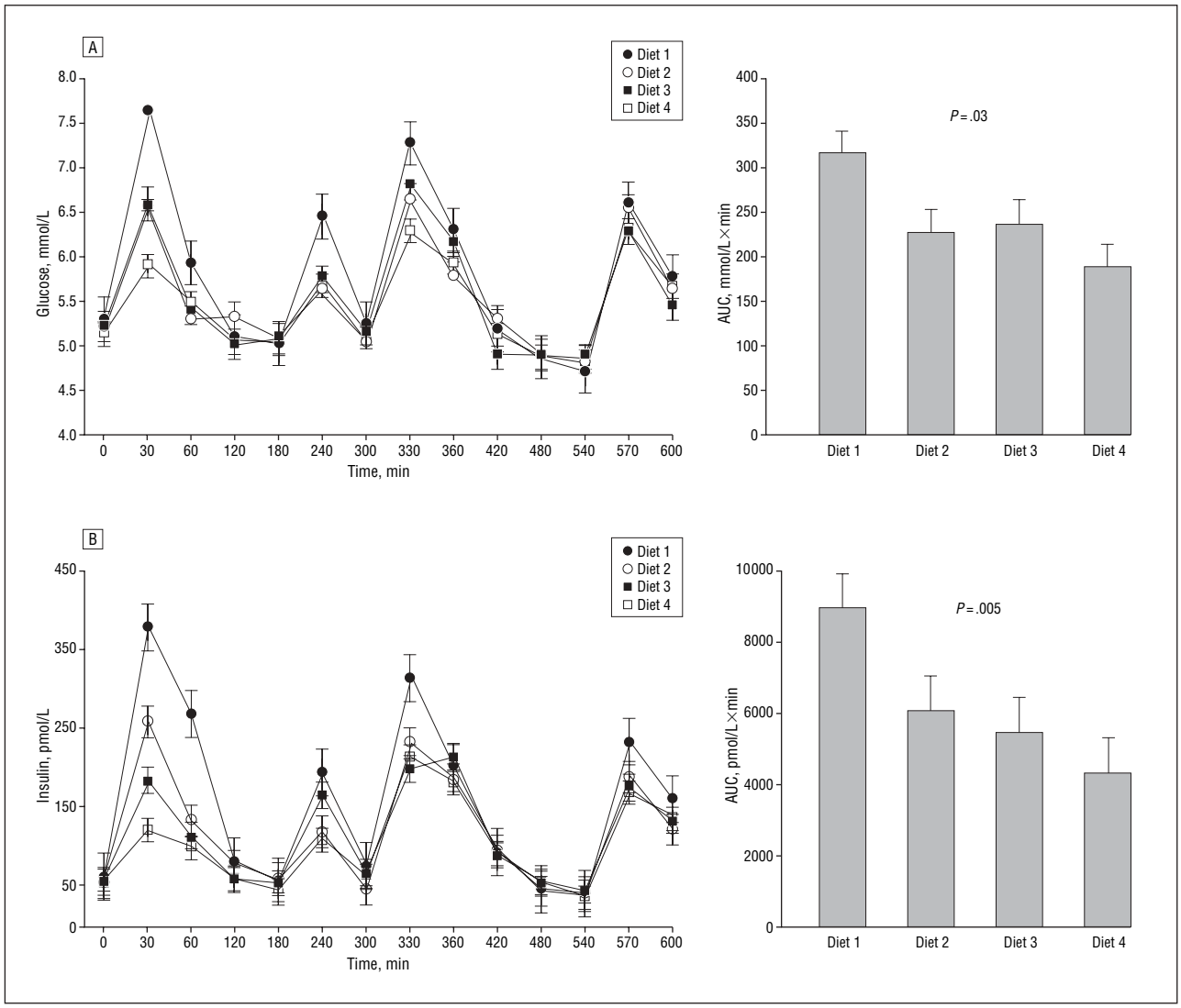

Figure 5. Mean plasma glucose (A) and insulin (B) profiles over 10 hours (h) in overweight female subjects after consumption of representative mixed meals for each of the 4 diets. Breakfast was eaten at time 0 (0800 h), the morning snack at 180 minutes (1100 h), lunch at 300 minutes (1300 h), and dinner at 540 minutes (1700 h). Diet 1, high-carbohydrate (CHO)/high–glycemic index (GI); diet 2, high-CHO/low-GI; diet 3, high-protein/high-GI; and diet 4, high-protein/low-GI. Eleven subjects took part in the profile day, with each one consuming each of the 4 diets on 4 separate days. AUC indicates area under the curve. All values are given as means with error bars indicating standard errors. To convert glucose values to milligrams per deciliter, divide by 0.0555; to convert insulin values to microunits per milliliter, divide by 6.945.

was significantly correlated with the blood glucose AUC ($r=0.35$; $P=.022$) and the insulin AUC ($r=0.35$; $P=.02$). Varying the GI had a stronger effect ($P=.03$) on glycemia than varying the protein content ($P=.05$), but protein content had a greater effect on insulinemia ($P=.002$).

COMMENT

The findings of this study suggest that postprandial glycemia and dietary GL may be unrecognized determinants of the effectiveness of energy-restricted diets. The conventional diet (diet 1) was associated with the highest level of postprandial glycemia as well as with the slowest rate of weight loss. Subjects instructed to follow a high-CHO, low-GI (diet 2) or a high-protein, high-GI diet (diet 3) were twice as likely to achieve the clinical goal of a weight loss of 5% or more. In women in particular (n=98), these 2 reduced-GL diets were associated with 80% greater fat loss compared with the conventional low-fat diet (diet 1; $P<.007$), without compromising lean mass. The low-GI, high-CHO diet (diet 2), however, produced the best clinical outcomes, reducing both fat mass and LDL cholesterol levels. The high-protein, high-GI diet (diet 3) produced an increase in total and LDL cholesterol concentrations (+8% overall, +10% in women), which contrasted with the decrease in LDL cholesterol concentrations that was seen with both low-GI diets ($P=.01$). The favorable result for diet 2 could not simply be the result of its low-fat content (actual 22% E), because the other high-CHO group also achieved a very low-fat intake (actual 19% E) yet the slowest rate of fat loss. Similarly, the increase in total and LDL cholesterol levels with diet 3 could not be the result of higher fat (actual 27% E) or meat intake, because the subjects on diet 4 ate similar amounts (actual fat 29% E) but showed no unfavorable effects. The changes in cholesterol levels were associated statistically with differences in the GI and not with the protein content ($P<.009$). The diet 2 group achieved a higher fiber intake than the other groups (approximately 7 g more), which may partly account for the favorable result. Soluble fibers intrinsic to legumes and low-GI whole grains (but not to high-GI whole grains) bind dietary cholesterol[20] and may be critical in the context of a high-protein diet.

Our study suggests that dietary GL may be more relevant to women than to men. Women generally lose weight more slowly and display differences in postprandial glucose and fat oxidation, which might influence the rate of fat loss.[21] The GL might also be more important in individuals with hypertriglyceridemia.[11] In this subgroup, the diet with the lowest GL (diet 4) produced the greatest fat loss and improvement in the total HDL cholesterol ratio. In the total group, however, there was no support for the hypothesis that the lowest GL (diet 4) would be associated with the best outcomes. One explanation might be that more "extreme" diets require greater discipline, which often declines over time. Alternately, genetic or metabolic predisposition may need to be taken into account to determine the effectiveness of one diet over another.[19]

The strengths of the study include the study design, number of diets compared simultaneously, large sample size, high continuation rate, high compliance rate, provision of key foods, and detailed and repeated ascertainment of dietary measurements. A particular strength was extensive knowledge of the GI of individual Australian foods.[17] Importantly, the day-long profiles confirmed that the 4 diets produced differential postprandial responses, as predicted by their calculated GL, CHO content, and GI. A further strength was that the subjects were free-living young adults who represent an important target for early intervention.

The study has limitations. Diet goals for energy distribution were not met exactly. We cannot discount the effect of these differences on study outcomes. One interpretation could be that the most successful diet was not only low GI but also very low fat (22% E) and higher in fiber (30 g/d). A 12-week period provides no information about the sustainability or long-term effects of the diets on cardiovascular function, exercise tolerance, renal function, or bone health. However, this is a common time frame for a "diet-only" intervention[22]; insufficient weight loss might dictate pharmacological approaches with both expense and adverse effects.

In conclusion, at least in the short term, our findings suggest that dietary GL, and not just overall energy intake, influences weight loss and postprandial glycemia. Moderate reductions in GL appear to increase the rate of body fat loss, particularly in women. Diets based on low-GI whole grain products (in lieu of whole grains with a high GI) maximize cardiovascular risk reduction, particularly if protein intake is high. Reassuringly, this advice can optimize clinical outcomes within current nutrition guidelines, without the concerns that apply to low-CHO diets. Multicenter studies to evaluate weight reduction, weight maintenance, and long-term outcomes, particularly in individuals with established risk factors, are clearly warranted.

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