Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

A Randomized Trial of Energy-Restricted High-Protein Versus High-Carbohydrate, Low-Fat Diet in Morbid Obesity

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Objective: Conflicting evidence exists as to weight loss produced by diets with different carbohydrate/protein ratio. The aim was to compare the long-term effects of high-protein vs. high-carbohydrate diet (HPD, HCD), combined with cognitive behavior therapy (CBT).

Design and Methods: In a randomized trial, 88 obese participants (mean age, 46.7; mean BMI, 45.6 kg m^{-2}) were enrolled in a 3-week inpatient and 48-week outpatient treatment, with continuous CBT during the study period. All subjects consumed a restricted diet (1,200 kcal day^{-1} for women, 1,500 for men; 20% energy from fat, <10% saturated fat). HPD derived 34% energy from proteins, 46% from carbohydrates; HCD 17% from proteins, 64% from carbohydrates. The primary outcome was 1-year percent weight loss. Secondary outcomes were attrition rates and changes in cardiovascular risk factors and psychological profile.

Results: Attrition rates were similar between groups (25.6%). In the intention-to-treat analysis, weight loss averaged 15.0% in HPD and 13.3% in HCD at 1 year, without any difference throughout the study period. Both diets produced a similar improvement in secondary outcomes.

Conclusions: The relative carbohydrate and protein content of the diet, when combined with intensive CBT, does not significantly affect attrition rate, weight loss and psychosocial outcome in patients with severe obesity.

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Introduction

A low-fat, high-carbohydrate and energy-restricted diet is the recommended dietary approach for obesity treatment because it facilitates energy restriction and improves cardiovascular risk factors (1). This recommendation has been recently challenged by randomized trials showing that diets with a lower carbohydrate content and a higher protein-to-carbohydrate dietary ratio might produce greater weight loss at 6 months [2-6]. However, long-term (1-2 years) weight loss is modest with both approaches (7), and the advantages of low-carbohydrate diets on weight loss are not universally demonstrated (3,4,8-11).

The scarce use of behavioral procedures to improve adherence to low-calorie diets was blamed as the main reason for the unsatisfactory results of both dietary approaches (12). This hypothesis was supported by a randomized trial showing a mean weight loss of 7% after 2 years with either a low-carbohydrate or a low-fat diet combined with a behavioral intervention (12) and partly by a large trial on 811 overweight adults treated with four diets of different nutrient composition (13). A low-fat, average-protein vs. low-fat, high-protein vs. high-fat, average-protein vs. high-fat, high-protein diet, all associated with individual and group behavioral counseling, produced similar weight losses of ~4 kg at 2 years (13), and similar effects on body composition, abdominal fat and hepatic fat (14).

It is also unclear whether the differences in weight loss outcomes between low- and high-carbohydrate diets are due to the different protein-to-carbohydrate ratio or amount and source of fats or to a not controlled energy intake of the diets. To our knowledge, only few studies compared the effects of an energy-restricted high-protein diet (HPD) with an isocaloric high-carbohydrate diet (HCD), carefully matched for energy from fats and saturated fats (13,15), and no differences in weight loss and metabolic profile were reported.

Finally, very few data are available on the effect of low-carbohydrate diets and low-fat, high-carbohydrate and energy-restricted diets in individuals with classes II-III obesity, particularly on psychosocial outcomes, considering the impact of strict adherence to highly selected diets. The only study on these obesity classes found similar,

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modest weight losses in those assigned to either a low-carbohydrate diet or a conventional diet at 1-year (9), but data were limited by high dropout rates and suboptimal dietary adherence.

The purpose of our randomized trial was to evaluate the effects of long-term (1 year) reduced caloric intake associated with different macronutrient composition (HPD and HCD with similar amount of energy from fats and saturated fats) in individuals of class II and III obesity on key clinical end points, namely body weight, cardiovascular risk factors and psychosocial variables. The primary outcome was weight loss at 1 year. To increase compliance to diets, all participants received a 3-week inpatient cognitive behavior treatment (CBT), where they had no access to food other than that served in hospital, and 48 weeks of outpatient CBT (16). We tested the hypothesis if a rigid macronutrient selection resulting in a HPD or a HCD, combined with energy restriction, was able to produce clinically significant differences in weight loss at 1 year under strictly controlled conditions.

Methods

Design

The study was a randomized trial comparing two types of energy restricted diets associated with weight loss CBT conducted over 1 year with outcome assessments after 3 weeks of inpatient treatment, and after 27 weeks and 1 year. The ethical committee of the Local Health Unit 22-Bussolengo approved the study (Study Protocol no. USL22#01/07-CEP31, approved 19/06/07), and all participants gave written informed consent to participation and to the anonymous use of personal data.

Participants

Participants were recruited from consecutive referrals by family doctors and other clinicians to the Weight Disorder inpatient unit of Villa Garda Hospital (Northern Italy). Figure 1 summarizes participant enrollment and flow through the study.

Patients were eligible if they were in the age range 18-65 years and had a body mass index (BMI) $\geq$ 40.0 kg m^{-2} or between 35 and 39.9 with at least one weight loss-responsive comorbidity (e.g., type 2 diabetes, cardiovascular diseases, sleep apnea, severe joint disease, two or more risk factors defined by the Adult Treatment Panel III (17)).

Patients were excluded if they were pregnant or lactating, took medications affecting body weight, had medical comorbidities associated with weight loss or had severe psychiatric disorders (e.g., acute psychotic states, bipolar disorder, bulimia nervosa).

Randomization and intervention

A computer-based minimization algorithm was used by one of the authors (SC), not involved in recruitment, to allocate patients to two treatment arms (i.e., high protein diet—HPD, or high-carbohydrate diet—HCD) balancing age, gender, and BMI. Preprepared blocked randomization lists of varying sizes were used to allocate patients to the two arms in a balanced way.

The treatment was divided into two stages: Stage One (inpatient treatment; 3 weeks); Stage Two (outpatient treatment; 48 weeks).

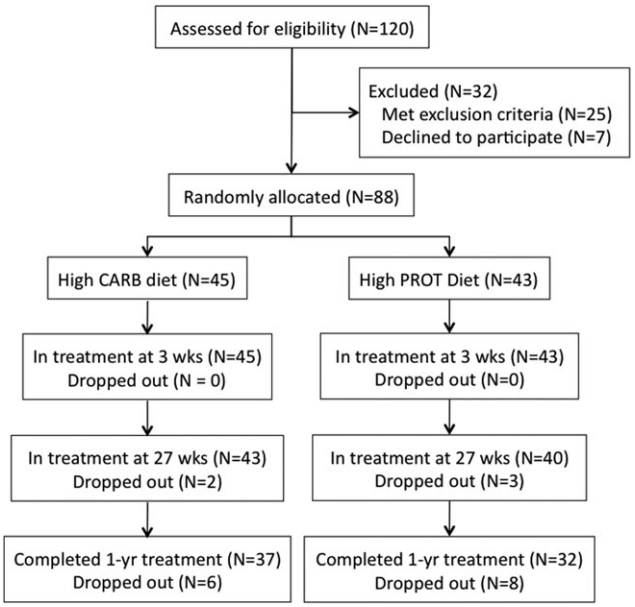

FIGURE 1 CONSORT flow diagram.

Participants started the assigned diet on the second inpatient day, and continued it during the whole Stage Two. They were admitted in consecutive blocks of 8, all following the same diet, to avoid exchanges between participants allocated to different diets. Both diets were energy-restricted (1,200 kcal day^{-1} for women and 1,500 kcal day^{-1} for men), with 20% energy from fats (<10% from saturated fats) and daily multivitamin supplements. HPD derived 34% energy from proteins and 46% from carbohydrates, whereas HCD had 17% energy from proteins and 63% from carbohydrates.

CBT intervention. All participants received a comprehensive manual-based CBT to enhance the adherence to lifestyle modification integrating education with cognitive behavioral procedures and strategies (16).

Stage one included 15 CBT groups (five a week), chaired by physicians, dieticians and psychologists, 18 sessions of aerobic exercises (e.g., 30 min of tapis roulant or cyclette) and six sessions callisthenic, chaired by physical trainers. Education addressed the following main topics: (i) energy balance; (ii) the food pyramid, size of portions and regular eating; (iii) calorie counting; (iv) shopping and food labels; (v) physical activity, when and how much. The cognitive behavioral procedures and strategies included: (i) self-monitoring of food intake, energy and body weight; (ii) stimulus control strategies (in particular how to reduce food stimuli at home); (iii) problem solving; (iv) cognitive restructuring of dysfunctional thoughts that hinder weight loss and weight loss maintenance; (v) relapse prevention. The behavioral component of the program was based on the principles of the LEARN program for weight control (18), the cognitive component on CBT for obesity developed by Cooper et al (19).

Stage Two included 12 sessions of 45 min each over 48 weeks with a CBT-trained dietitian. The first 4 sessions were carried out every

2 weeks, followed by 4 sessions every 4 weeks and then by 4 sessions every 6 weeks in the last 24 weeks. Every session had the following content: (i) weighing the patient and recording on a graph; (ii) checking home weight control; (iii) reviewing the self-monitoring record of food and drink intake and of number of daily steps assessed by a pedometer; (iv) setting the agenda collaboratively; (v) working through agenda topics; (vi) agreeing on new homework assignments; (vii) summarizing the session. The first 24 weeks of stage two (27 weeks from treatment start) were dedicated to address barriers to weight loss, the remaining sessions to weight maintenance. In this last phase the calorie content was gradually increased to maintain the weight in ±3 kg range, without changes in macronutrient composition.

Outcomes and measurements

Outcomes. The primary outcome was percent weight loss at study end (1-year). Secondary outcomes were attrition rates and changes in cardiovascular risk factors and psychological profile.

Case report form. The case report form was filled out by physicians at the time of enrollment by directly interviewing patients. It included demographic and weight data, and a detailed weight and diet history.

Weight and height. Weight was measured on the first and the last day of Stage One and at each treatment session of Stage Two on calibrated scales with participants wearing light clothing and no shoes. Height was measured by a stadiometer at baseline.

Clinical variables and laboratory tests. Clinical variables were collected at baseline and at 3 and weeks 27, and at 1 year. Blood pressure was measured in a recumbent position following a 20-min rest period using an automated digital cuff (705IT; Omron, Vernon Hills, IL), with cuff sizes based on measured arm circumference. Fasting blood samples were obtained at baseline and at 27 weeks and 1 year. Plasma glucose, total cholesterol, HDL-cholesterol, and triglycerides were measured by common standard laboratory techniques [CHOL, HDL-C plus (2nd generation) and TG assays (Roche Diagnostics, Indianapolis, IN)]. Creatinine, aminotransferases and GGT were also measured by standard assays (Roche Diagnostics, Indianapolis, IN). Insulin levels were measured by ADVIA Insulin Ready Pack 100 (Bayer Diagnostics s.r.l., Milan, Italy).

Psychosocial measures. At baseline, at 3 and 27 weeks, and at 1 year all participants completed a battery of questionnaires measuring body image dissatisfaction, binge eating, depression, and quality of life.

The body uneasiness test-A (20) was used to evaluate body uneasiness. The term body uneasiness was used to describe not only body dissatisfaction but also body-associated emotions, such as anxiety, alarm, trepidation, worry, mistrust, misgiving, doubt, suspicion, and embarrassment. The test was initially described and validated on Italian patients with obesity and has good internal consistency (21).

The binge eating scale (BES) (22) was used to measure the severity of binge eating. The scale has adequate internal consistency and validity (22), good test–retest reliability, and moderate associations with binge-eating severity as measured by food records (23).

The beck depression inventory (BDI) was used to assess the presence and severity of depression. The inventory has excellent internal reliability, good test–retest reliability, good criterion validity (24).

The beck anxiety inventory (BAI) was used to assess the presence and severity of anxiety. The inventory has been has excellent internal reliability, good test–retest reliability, good criterion validity.

BES, BDI, and BAI are validated in their Italian versions [25-27].

Adherence to cognitive strategies and to diet

During the in-hospital period, patients were allowed no extra food. In the outpatient stage two, patients were asked to record physical activity and food intake every day on a diary, to be checked by dietitians at each visit. The attendance to individual counseling sessions and the number of diaries were used as behavioral measures of adherence to the program, whereas the adherence to the predetermined diet was given a semiquantitative score from 0 (low adherence) to 4 (complete adherence to calorie restriction and to either HPD or HCD, based on a predefined checklist, based on analysis of diaries by an experienced dietitian).

Sample size determination

Percent weight loss was considered as the primary end-point. In our previous experience with the above program, the mean weight loss at 1-year was 12% ± 4%, with a dropout rate of 15%. Considering the difficulties in maintaining the rigid macronutrient selection of HPD or HCD, we concluded that a rigid dietary scheme should only be proposed if the advantage on weight loss exceeded 3%. Accordingly, the sample size was estimated as 38 subjects per group with a α error of 0.05 and a β error of 0.10. This number was increased by 15% to account for dropouts.

Statistical analyses

Statistical analyses were performed using SPSS version 20.0 (SPSS, USA). Initially, a descriptive analysis was carried out on clinical data, the response to questionnaires and patients' outcomes. Mean differences between groups at each time point were also calculated. *t* tests or Mann–Whitney tests (as appropriate for the distribution of the data) were used to compare continuous measures between groups. Repeated analysis of variance was performed to determine the effects of time and of different diets and their interaction on psychosocial variables. Kaplan–Meier survival analysis was used to test time differences to drop-out and to achievement of weight loss targets between groups. Since three sets of variables were tested (anthropometric, clinical-laboratory and psychological) and three time points were tested, the α value was set at 0.005.

Outcome analyses were carried out both on intention-to-treat (adjusted by last-observation-carried-forward analysis) and per protocol.

Results

Sample

A total of 88 eligible patients were recruited (Figure 1). Their mean age was 46.7 ± 11.1 years (range 19-65 years), and the mean BMI 45.6 ± 6.7 kg m^{-2} (range 35.1-64.5 kg m^{-2}). The majority (58%) were female and married (65.9%). The two groups allocated to HPD

TABLE 1 Clinical and demographic characteristics at baseline in patients allocated either to high-protein or to high-carbohydrate diet. Data are presented as mean (SD) or frequency (%)

	High PROT diet ($N = 43$)	High CARB diet ($N = 45$)	*t* test	*P*
Demographic/anthropometric variables				
Female sex, *n* (%)	26 (60.5%)	25 (55.6%)	0.22	0.641
Age (years)	46.7 (10.3)	46.6 (12.0)	0.05	0.959
Body mass index (kg m^{-2})				
Mean	45.8 (6.5)	45.4 (7.0)	0.29	0.768
35.0–39.9, *n* (%)	8 (18.6)	10 (22.2)	0.18	0.674
$\geq$ 40, *n* (%)	35 (81.4)	35 (77.8)		
Waist circumference (cm)	131.4 (16.9)	132.0 (16.5)	−0.16	0.870
Historical variables				
Body mass index at age 20 (kg m^{-2})	27.6 (6.9)	28.6 (7.0)	−0.68	0.498
Maximum body mass index (kg m^{-2})	46.4 (6.9)	47.2 (9.2)	−0.44	0.660
Age at first dieting (years)	26.7 (11.5)	29.6 (13.9)	−1.02	0.312
Blood pressure and laboratory tests				
Systolic blood pressure (mmHg)	139.9 (21.3)	140.9 (18.8)	−0.46	0.644
Diastolic blood pressure (mm Hg)	85.5 (10.9)	82.7 (8.9)	−0.70	0.483
Glucose (mg dl^{-1})	105.9 (29.6)	108.4 (34.4)	−0.35	0.725
Insulin (μU ml^{-1})	14.3 (7.3)	16.9 (18.2)	−0.87	0.385
Triglycerides (mg dl^{-1})	156.9 (76.5)	157.2 (76.7)	−0.02	0.982
Total cholesterol (mg dl^{-1})	207.9 (41.9)	192.9 (35.9)	1.80	0.075
HDL cholesterol (mg dl^{-1})	44.1 (10.0)	39.7 (9.3)	2.11	0.038
LDL cholesterol (mg dl^{-1})	140.5 (38.8)	127.7 (32.5)	1.66	0.101
Uric acid (mg dl^{-1})	7.7 (9.8)	13.3 (20.5)	−1.61	0.110
Creatinine (mg dl^{-1})	0.8 (0.2)	0.9 (0.2)	−0.91	0.363
ALT (U l^{-1})	31.6 (16.5)	34.4 (24.7)	−0.05	0.963
GGT (U l^{-1})	29.8 (13.2)	34.0 (21.5)	−0.16	0.874
Psychosocial measure (scores)				
Beck anxiety inventory	11.8 (11.7)	15.2 (11.3)	−1.40	0.165
Beck depression inventory	16.2 (11.9)	14.9 (11.3)	0.52	0.601
Binge eating scale	13.5 (9.8)	13.9 (9.6)	−0.17	0.865
Body uneasiness test—GSI	59.9 (33.2)	65.0 (33.5)	−0.71	0.478

and HCD had very similar demographic and clinical characteristics, except HDL cholesterol level (Table 1).

Attrition

All patients completed the inpatient stage one. Nineteen patients (21.6%; 25.6% in HPD and 17.8% in HCD) dropped out between week 15 and study end, without statistically significant differences in attrition rates between groups (Chi-square = 0.79, $P = 0.341$). In particular, HPD patients had higher attrition rates at 27 weeks, but lower rates between 27 and study end compared to HCD group (27-week: HPD 18.6% vs. HCD 4.4%; 27-week to study end: HPD 7.0% vs. HCD 13.3%; chi-square = 4.23, $P = 0.040$). The average time to dropout was also not different between groups (HPD: 270.3 $\pm$ 10.1 days and HCD: 292.7 $\pm$ 6.4 days; log-rank = 1.11, $P = 0.293$).

Body weight

In the intention-to-treat analysis, subjects of both groups lost about 4% of their initial weight during Stage One and about 15% at both week 27 and 1 year (HPD: 16.2% and 15.0%; HCD: 14.7% and 13.3%, respectively; 27 week $t = -0.23$, $P = 0.820$; study end $t = -0.28$, $P = 0.777$). The results were not systematically different when analyzed per protocol. Weight loss at week 27 or at 1-year (HPD: 15.5 and 15.0%, HCD: 14.1 and 13.3%, respectively) was again not different between groups. No differences in weight loss from baseline to any time point were found between groups (Table 2 and Figure 2).

An analysis was also carried out on time to weight loss targets (>5%; >10%; >15% of initial body weight). Kaplan–Meier analysis in completers showed that all patients, except four, reached the weight loss target of 5% at 1 year. Neither was time to weight loss >10 and >15% different between the two groups (log-rank = 0.60, $P = 0.328$; log-rank = 0.31, $P = 0.579$; log-rank = 0.13, $P = 0.721$, respectively) (Figure 3).

Blood pressure, laboratory tests and psychosocial measures

All laboratory tests significantly changed from baseline with no differences between groups (Table 2). We only observed a trend for a

TABLE 2 Absolute changes from baseline in body weight, cardiovascular risk factors and body composition, as determined by a last-observation-carried-forward analysis

	3 weeks		27 weeks		1 year	
	High PROT diet	High CARB diet	High PROT diet	High CARB diet	High PROT diet	High CARB diet
Body mass index (kg m^{-2})	−2.0 (0.8)	−1.9 (0.8)	−6.5 (3.5)	−6.1 (2.7)	−6.2 (4.5)	−5.7 (3.3)
Weight (kg)	−5.9 (2.7)	−5.5 (2.3)	−19.0 (11.3)	−17.2 (8.2)	−18.1 (14.3)	−15.9 (10.1)
Systolic blood pressure (mmHg)	−16.6 (16.7)	−19.1 (16.3)	−7.5 (17.1)	−10.1 (18.9)	−10.3 (21.5)	−10.1 (19.1)
Diastolic blood pressure (mmHg)	−9.1 (9.1)	−5.7 (8.9)	−4.2 (10.3)	−3.1 (9.2)	−6.4 (11.0)	−1.4 (9.9)
Triglycerides (mg dl^{-1})	–	–	−37.9 (66.1)	−30.5 (78.0)	−45.6 (57.2)	−31.5 (75.3)
Total cholesterol (mg dl^{-1})	–	–	−18.7 (35.3)	−5.4 (35.6)	−11.6 (40.9)	−7.2 (33.2)
HDL cholesterol (mg dl^{-1})	–	–	1.9 (7.3)	4.8 (16.4)	4.4 (7.3)	5.9 (16.0)
LDL-cholesterol (mg dl^{-1})	–	–	−17.2 (31.1)	−3.7 (29.8)	−11.6 (37.5)	−4.6 (30.7)
Glucose (mg dl^{-1})	–	–	−0.9 (23.4)	−10.9 (24.7)	−4.5 (22.7)	−9.3 (25.5)
Insulin (μU ml^{-1})	–	–	−2.0 (9.3)	−4.2 (17.4)	−2.2 (9.7)	−6.3 (22.6)
Uric acid (mg dl^{-1})	–	–	−2.2 (9.6)	−7.5 (20.2)	−2.2 (9.7)	−6.3 (22.6)
Creatinine (mg dl^{-1})	–	–	0.02 (0.1)	0.00 (0.1)	−0.03 (0.2)	0.02 (0.1)
ALT (U l^{-1})	–	–	6.0 (11.0)	9.1 (18.6)	1.9 (32.5)	10.4 (17.0)
GGT (U l^{-1})	–	–	4.6 (19.2)	9.7 (14.0)	1.1 (37.8)	10.5 (13.9)

High-protein diet ($N = 43$) high-carbohydrate diet ($N = 45$). Data are presented as mean (SD). No significant differences between groups were observed at any time-point.

larger reduction of LDL cholesterol in HPD from baseline to 27 weeks ($P = 0.021$). Also psychosocial measures decreased significantly from baseline to 1 year, with no differences between groups both in the *per protocol* (not reported in details) and in the intention-to-treat analysis (Table 3).

Adherence to cognitive strategies and to the experimental diet

In completers, no differences in adherence were observed between groups. Attendance to individual sessions and adherence with diary compilation were very high (95 and 79%, respectively in HPD and HCD) and not different between groups ($t = -0.24$, $P = 0.806$ for attendance to individual sessions; $t = -0.26$, $P = 0.906$ for diary compilation). The total number of diaries was not different (on average, 3.7 ± 1.3 diaries/week in HPD and 3.8 ± 1.2 in HCD; $z = -0.44$, $P = 0.660$); compliance was particularly high during the first 27 weeks (5.5 ± 1.9 diaries/week vs. 5.5 ± 1.5, respectively, $z = -0.064$, $P = 0.522$). Adherence to dietary composition and total calorie intake targets averaged a score of 2.95 ± 1.10 in HPD and 3.04 ± 0.63 in HCD ($z = -0.48$, $P = 0.630$) on a maximum score of 4 during the

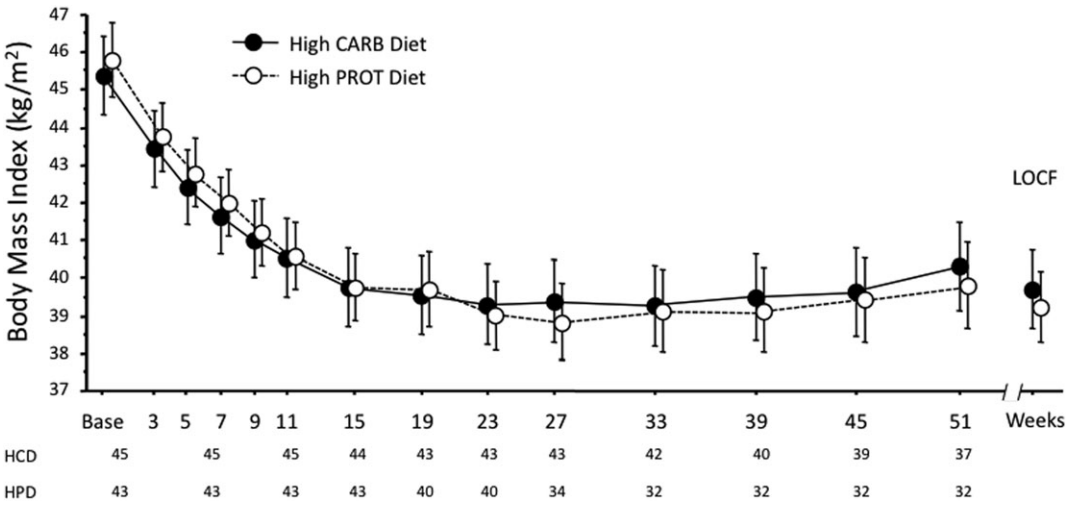

FIGURE 2 Mean body weight for participants in the high-protein and high-carbohydrate diet. Error bars represent 95% confidence intervals.

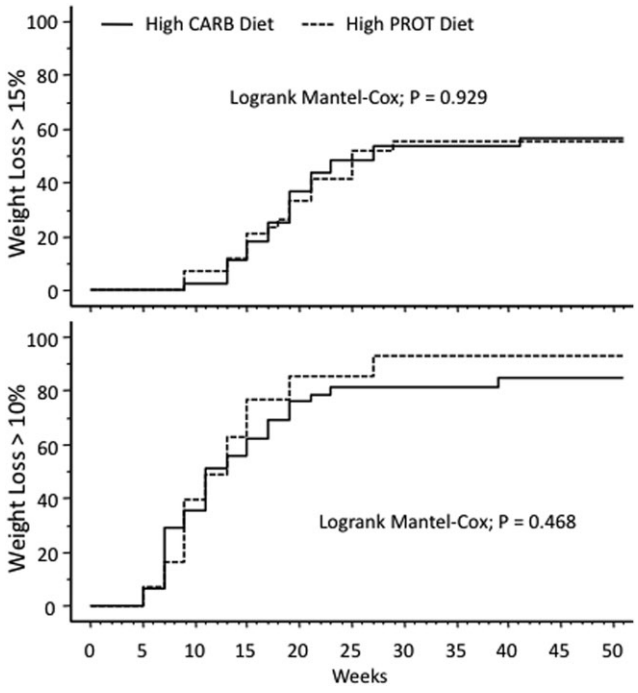

FIGURE 3 Proportion of patients reaching a weight loss >15% (upper panel) and >10% (lower panel) in the high-protein and high-carbohydrate diet.

whole outpatient phase, and 3.23 ± 1.06 and 3.37 ± 0.41 ($z = -0.32$, $P = 0.751$) during the first 27 weeks.

Weight loss at 1 year was not associated with attendance to individual sessions, both total (beta = 0.07, $t = 0.61$, $P = 0.546$) and during the first 24 weeks of outpatient treatment (beta = 0.10, $t = 0.85$, $P = 0.400$). In the HCD group, it was associated both with the number of compiled diaries (beta = 0.34, $t = 2.12$, $P = 0.041$) and with adherence to dietary composition (beta = 0.48, $t = 3.21$, $P = 0.003$).

Discussion

The main finding of our study is that the weight loss outcomes of rigid HPD and HCD programs are not statistically different and both diets produce similar attrition rates and similar effects on cardiovascular risk factors and psychosocial variables in participants with severe obesity.

The attrition rate observed in HPD (25.6%) and in HCD (17.8%) groups, although moderately higher than that expected on the basis of our previous experience, was similar to that reported in controlled behavior treatment studies (28), but much lower than the common 50% attrition rate observed in standard weight loss treatments in the community (29).

After 1-year dietary restriction, the completers had clinically significant weight loss when treated by either HPD (15%) or HCD (13.3%), but the difference between groups was not statistically significant. These data confirm a previous study showing that any difference in diet adherence may be overcome by a comprehensive lifestyle intervention based on behavior therapy and suggest that the two diets can be used in association with CBT to achieve long-term weight loss. The percentage weight loss obtained in our setting was higher than the mean 8-10% obtained by traditional lifestyle modification programs based on CBT (1). Of note, 13 subjects in HPD and 8 in HCD experienced a weight loss exceeding 20%, and 2 subjects in HPD and 1 in HCD lost more than 30% of their initial body weight by the end of the weight-loss program. The high percent weight loss was probably due to a combination of factors. The inpatient stage was expected to facilitate initial adherence to diet, as patients were not exposed to additional food stimuli. Deconditioning of patients from their food and non-food related eating stimuli operated by the 3 weeks of inpatient treatment might also be the reason for long-term adherence after discharge.

Contrary to a previous study that used similar energy deficit and macronutrient composition (15), we did not find any short-term differences in weight loss between HPD and HCD. Again, we suggest that the inpatient stage might have facilitated adherence to dietary prescription and that the higher weight loss previously observed with HPD might be the effect of higher dietary adherence more than the metabolic result of the different macronutrient composition. Our data are also consistent with short-term metabolic ward studies showing that, in the presence of a fixed energy content, macronutrient composition does not influence weight loss (30,31).

The maintenance of weight loss observed in both treatment arms from week 27 to 1 year confirms that a continuous contact after the

TABLE 3 Anthropometric and psychosocial measures (score values) at each time point, as determined by a last-observation-carried-forward analysis, in individuals in the high-protein ($N = 43$) and the high-carbohydrate diet ($N = 45$)

	3 weeks		27 weeks		1 year	
	High PROT diet	High CARB diet	High PROT diet	High CARB diet	High PROT diet	High CARB diet
Body mass index (kg m^{-2})	43.7 (5.9)	43.3 (6.7)	39.2 (5.8)	39.2 (6.9)	39.6 (6.1)	39.7 (7.0)
Beck anxiety inventory (score)	7.5 (10.1)	6.4 (7.1)	9.2 (12.0)	7.6 (7.7)	10.0 (12.4)	5.9 (6.6)
Beck depression inventory (score)	9.1 (7.8)	11.4 (8.9)	8.0 (8.6)	9.2 (9.6)	10.1 (10.3)	9.2 (11.1)
Binge eating scale (score)	7.5 (7.7)	8.1 (6.5)	5.6 (5.6)	5.5 (6.6)	6.9 (6.7)	5.8 (6.9)
Body uneasiness test-GSI (score)	45.8 (34.6)	52.9 (31.9)	35.2 (31.9)	38.1 (25.5)	38.5 (37.2)	35.0 (26.0)

Data are presented as mean (SD). No significant differences between groups were observed at any time-point.

weight loss phase facilitates weight loss maintenance (30). The positive effect on weight-loss maintenance may be achieved also with monthly sessions, provided by registered dietitians trained in CBT for obesity. We were unable to confirm the advantages provided by HPD in the maintenance phase reported in the large DiOGenes project, where only the association of high-protein, low glycemic index diet prevented weight regain (32). Contrary to the POUNDS LOST study (13), weight loss at the end of the study was not associated with attendance to individual sessions, both total and in the first 24 weeks of outpatient treatment. We speculate that the initial inpatient weight loss treatment phase and the high participation to the outpatient sessions (95%), promoted by the prolonged team-patients contact during the inpatient phase, might have obscured the adherence effect on weight loss observed in the POUNDS LOST study (33). In our experience, the 1-year weight loss was associated with the number of compiled diaries and with adherence to dietary composition only in the HCD group. This result is difficult to explain. In keeping with other studies (34), it shows that adherence is a multidimensional and complex construct, which needs to be tested by multiple measures.

Data appear to be very solid. No statistically significant differences at any time point were observed between the two experimental arms in all parameters when analyzed either on intention-to-treat or per protocol. The similar weight loss achieved by HPD and HCD gave us the opportunity to assess the relative effects of the different macronutrient content on cardiovascular disease risk factors. The similar and favorable changes observed of both diets on blood pressure, triglycerides, total, LDL and HDL cholesterol, glucose, and insulin levels support the hypothesis that a different carbohydrate and protein content, in the presence of an identical low-fat content, has no major effects on cardiovascular risk factors, independent of weight loss. A previous study on glucose and lipid metabolism, which used two diets with energy deficit and macronutrient content similar to our HPD and HCD (15), is in agreement with our results. The same consideration applies to hepatic and renal function. A low-fat, energy-restricted diet makes the difference on cardiovascular disease risk factors in obese patients, whereas the different carbohydrate and protein content has a very marginal role on the total effect, with low glycemic index and low protein diets associated with low grade inflammation (35).

Weight loss was associated with a significant reduction, all within the normal/healthy range, of anxiety, depression, binge eating, and body uneasiness from baseline to end of treatment, again with no differences between HPD and HCD. The effects of selective diets have rarely been investigated. A study comparing an energy-restricted low-fat, high-carbohydrate diet with a very low-carbohydrate, high-fat diet concluded for a more favorable effect of fat restriction on mood states (36), but no data are available as to the comparison of high-carbohydrate vs. high-protein diets. Our study confirms several observations showing that weight loss treatment based on behavior therapy is associated with a significant improvement in the psychological variables [37-39], but the different macronutrient content has no specific effect on psychological functioning.

The strengths of the study are a long treatment period, a sample comprising both women and men with morbid obesity, the high adherence to diet. The main limitation is the very particular setting, including an initial inpatient period, rarely used in obesity treatment in the community, which makes it difficult to extend the results to a general setting. An additional limits is the lack of urinary markers of compliance to diets (urinary nitrogen) to support the adherence registered by food diaries (40). Finally, our study was underpowered to detect small differences in weight loss outcome. The 3% difference in weight loss assumed in the calculation of the sample size might be considered too challenging. But it was also extremely difficult—and it will be difficult in the community—to maintain a rigid nutrient selection (in addition to energy restriction) for long periods, with the risk of increasing the dropout rate.

In conclusion, the content of carbohydrates and proteins in the diet, combined with an intensive weight loss CBT, does not influence weight loss in patients with severe obesity when the amount of fat and energy are kept constant. The weight loss produced by both diets was also associated with a similar improvement of cardiovascular risk factors and psychological functioning. From a general point of view, the relative protein and carbohydrate content of the diet, when energy-restricted and low-fat to tackle cardiovascular risk factors, may be left to patients' choice and taste. O

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