Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum[1–3]

Alexandra M Johnstone, Graham W Horgan, Sandra D Murison, David M Bremner, and Gerald E Lobley

ABSTRACT

Background: Altering the macronutrient composition of the diet influences hunger and satiety. Studies have compared high- and low-protein diets, but there are few data on carbohydrate content and ketosis on motivation to eat and ad libitum intake.

Objective: We aimed to compare the hunger, appetite, and weight-loss responses to a high-protein, low-carbohydrate [(LC) ketogenic] and those to a high-protein, medium-carbohydrate [(MC) nonketogenic] diet in obese men feeding ad libitum.

Design: Seventeen obese men were studied in a residential trial; food was provided daily. Subjects were offered 2 high-protein (30% of energy) ad libitum diets, each for a 4-wk period—an LC (4% carbohydrate) ketogenic diet and an MC (35% carbohydrate) diet—randomized in a crossover design. Body weight was measured daily, and ketosis was monitored by analysis of plasma and urine samples. Hunger was assessed by using a computerized visual analogue system.

Results: Ad libitum energy intakes were lower with the LC diet than with the MC diet [$P = 0.02$; SE of the difference (SED): 0.27] at 7.25 and 7.95 MJ/d, respectively. Over the 4-wk period, hunger was significantly lower ($P = 0.014$; SED: 1.76) and weight loss was significantly greater ($P = 0.006$; SED: 0.62) with the LC diet (6.34 kg) than with the MC diet (4.35 kg). The LC diet induced ketosis with mean 3-hydroxybutyrate concentrations of 1.52 mmol/L in plasma ($P = 0.036$ from baseline; SED: 0.62) and 2.99 mmol/L in urine ($P < 0.001$ from baseline; SED: 0.36).

Conclusion: In the short term, high-protein, low-carbohydrate ketogenic diets reduce hunger and lower food intake significantly more than do high-protein, medium-carbohydrate nonketogenic diets. *Am J Clin Nutr* 2008;87:44–55.

KEY WORDS Ketogenic low-carbohydrate diets, weight loss, high-protein diets, body composition

INTRODUCTION

With the global rise in obesity has come an intensive search for effective weight-loss strategies. This effort has stimulated the promotion of numerous (alternative) diet plans, mostly based on the message "eat less and exercise more" (1, 2). It is generally accepted that diet composition strongly affects ad libitum energy intake, and laboratory (3, 4) and free-living (5) studies have highlighted protein as being a more satiating macronutrient. Carbohydrate and fat are less satiating (6), even when energy density is controlled. High-protein weight-loss diets have therefore come under scrutiny as a potential tool to aid dieters (7), especially because higher compliance may be anticipated. The greater satiation provided by protein is important because feeling hungry is one of the main reasons that dieters break their weight-loss regimens (8).

Of the research conducted to date, many trials have focused on comparing high-protein, low-carbohydrate (LC) diets and low-fat, high-carbohydrate diets in a free-living environment but with limited subject contact (9–13). Results have indicated greater weight loss with high-protein diets than with the high-carbohydrate, low-fat alternatives for periods up to 6 mo (9–13), but some studies have found no evident difference at 12 mo (12, 14). When carbohydrate intakes are very low (<20 g/d), a ketogenic state occurs because of the reduced glucose availability that results in increased production of ketone bodies from fat reserves (15). Such diets have become popular with dieters (16, 17), but, as yet, there is no consensus as to how they promote intakes below energy requirements. Although a ketogenic state is not absolutely essential for improved satiety (ie, less hunger and less caloric intake) with high-protein diets, voluntary intakes appear to be greater for such diets when their carbohydrate content is moderate (35–45% of energy; 14) rather than low (<10% of energy; 18). The use of ketogenic diets as a weight-loss therapy is not a novel idea (19, 20), and there is renewed interest in high-protein, low-carbohydrate diets as a weight-loss therapy (10, 21–23). To date, however, the data from direct comparisons of high-protein ketogenic diets and high-protein, medium-carbohydrate (MC) nonketogenic diets (21) in studies in which the diets have been completely controlled and the subjects have acted as their own control are too few to allow adequate assessment of the effects on hunger. The current study compares hunger and appetite response in healthy, obese men offered ad libitum access to an LC ketogenic diet or an MC nonketogenic diet in a controlled laboratory setting.

SUBJECTS AND METHODS

Subjects

Twenty men 20–65 y old and with a body mass index (BMI; in kg/m^2) of >30 were recruited by newspaper advertisement to

[1] From the Division of Obesity and Metabolic Health (AMJ, SDM, DMB, and GEL) and Biomathematics and Statistics Scotland (GWH), Rowett Research Institute, Aberdeen, United Kingdom.

[2] Supported by the Scottish Executive Environment and Rural Affairs Department.

[3] Reprints not available. Address correspondence to AM Johnstone, Rowett Research Institute, Aberdeen, UK AB21 9SB. E-mail: a.johnstone@rowett.ac.uk.

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participate in a diet trial. Thus, the subjects were nonrandomly selected persons who were sufficiently motivated to actively respond to the request for volunteers. Inclusion criteria specified that subjects were not consuming any specialized diet and were not on medication. All subjects had normal-range results on clinical biochemistry and hematologic testing. During recruitment, subjects underwent a medical examination, and their general practitioners were contacted to confirm their medical suitability for participation in the study.

Written informed consent was obtained from all participants. The study was approved by the North of Scotland Research Ethics Service.

Study protocol

Participants were resident in the Human Nutrition Unit (HNU) at the Rowett Research Institute (Aberdeen, United Kingdom) but were allowed to leave the unit to go to work. All food and drink consumed during weight-loss and weight maintenance periods was supplied by dietetic staff in the HNU, and the food was weighed before and after consumption to measure intake. The order of treatments was randomized in a within-subject, crossover design, whereby half of the subjects started on the LC ketogenic diet and the other half started on the MC nonketogenic diet (**Figure 1**). The protocol lasted 65 d. On days 1–3 (maintenance period), subjects consumed a mandatory maintenance diet (13%, 30%, and 57% of energy as protein, fat, and carbohydrate, respectively), proportions that were calculated to meet energy requirements (estimated at 1.6 × the measured resting metabolic rate). After this stage, subjects were randomly allocated to 1 of the 2 diets (LC or MC) and were instructed to eat ad libitum for a 4-wk period (days 4–31). Then the subjects were again fed for a 3 d (days 32–34) a fixed mandatory maintenance diet that was calculated to meet their energy requirements (estimated at 1.6 × their new energy requirements). The next stage was the second ad libitum feeding phase, again for 4 wk (days 35–62), but with subjects switched to the other diet (MC or LC). Finally, the study was completed with a 3-d maintenance phase (days 63–65).

Formulation and preparation of the diets

The composition of each meal, in terms of energy, fat, carbohydrate and protein, was calculated by using *McCance and Widdowson's the composition of foods* (24). The meals and snacks of the LC diet contained 30%, 4%, and 66% of energy as protein, carbohydrate, and fat, respectively; the meals and snacks of the MC diet contained 30%, 35%, and 35% of energy as protein, carbohydrate, and fat, respectively. All meals within both diets had a fixed energy density of 5.5 MJ/kg; this consistent energy density was achieved by ensuring that the weight of each meal was similar by using, if necessary, low-energy density foods (eg, mushrooms). All 3 main meals (ie, breakfast, lunch, and dinner) were offered as fixed 400-g portions, and snacks were available in 150-g portions. More specific information on the diets can be obtained from one of us (AMJ).

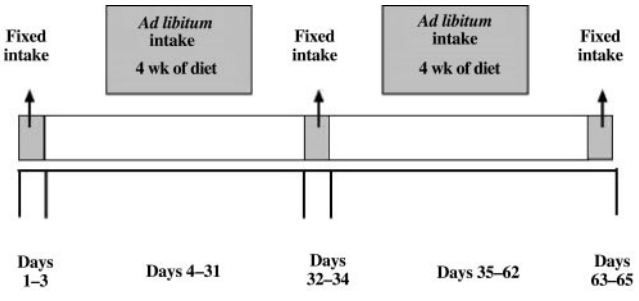

FIGURE 1. Diagram of the study protocol. The order of treatment was randomized in a within-subject, crossover design, whereby one-half of the subjects began with the high-protein, low-carbohydrate (ketogenic) diet and the other half began with the high-protein, medium-carbohydrate (nonketogenic) diet.

The LC meals contained 38.8 g (660 kJ) protein, 39.2 g (1450 kJ) fat, 5.5 g (88 kJ) carbohydrate, and 2198 kJ energy. The MC meals contained 38.8 g (660 kJ) protein, 20.8 g (770 kJ) fat, 48.0 g (767 kJ) carbohydrate, and 2197 kJ energy. The menu plan is given in **Appendix A**, which details the rotating menu with up to 9 meal options for each main meal and 3 sweet and 3 savory snack options. Additional meals were made up on request throughout the day. More information on the formulation of the meals is available by request from one of us (AMJ).

Presentation of the diets and measurement of food intake

While resident at the HNU, each subject was allocated a refrigerator and freezer that were stocked daily with his food. The kitchen research staff prepared and weighed all meals daily; any leftovers were weighed to the nearest gram. Breakfasts were eaten in the HNU. Subjects completed food diaries, which allowed determination of feeding behavior in terms of meal size, frequency, and composition. Subjects had free access to water and decaffeinated beverages. Energy and nutrient intakes were calculated by using WINDIETS software (version 1.0; Univation Ltd; The Robert Gordon University, Aberdeen, United Kingdom).

Measurement of anthropometric variables, resting metabolic rate, and blood pressure

Measurements of body composition and metabolic rate were conducted under standardized conditions. Subjects were instructed to fast overnight (10 h) and not to consume caffeine or to smoke before the tests. At the beginning of the study, height was measured to the nearest 0.5 cm with the use of a stadiometer (Holtain Ltd, Crymych, Dyfed, United Kingdom). Subjects were weighed daily, after voiding, while wearing only a previously weighed dressing gown, to the nearest 50 g on a digital scale (DIGI DS-410; CMS Weighing Equipment, London, United Kingdom). Abdominal and gluteal (hip) circumference was measured at the beginning and end of each dietary intervention period, as described previously (25), according to the guidelines of the International Standards for Anthropometric Assessment (ISAK). Resting metabolic rate was measured at the beginning and the end of each dietary intervention period by using indirect calorimetry over 30–40 min with the use of a ventilated hood system (Deltatrac II, MBM-200; Datex Instrumentarium Corporation, Helsinki, Finland). Subjects refrained from any physical activity before measurement, and they lay still (but awake) on a bed in a thermoneutral room. Resting metabolic rate was calculated (26) from minute-by-minute data, on the basis of the mean of 15 min of stable measurements. Details of calibration burns and repeatability testing were described previously (25). Blood

pressure was monitored at the beginning and the end of each dietary intervention period with the use of an automated system (Omron M5-1; Omron Healthcare Inc, Bannockburn, IL). Subjects were supine for 10 min before the measurement, and the average of 3 measures taken 5 min apart was recorded.

Assessment of appetite

Hunger and appetite were assessed hourly during waking hours with the used of visual analogue scales (VASs), as described previously (27). Instead of the original paper-and-pen method, this study used a handheld electronic computer (Visor Handspring; Palm Inc, Sunnyvale, CA). The questionnaire included 6 questions related to motivation to eat, all in the line-scale format; the questions assessed hunger, thirst, preoccupation with thoughts of food, fullness, desire to eat, and prospective consumption. Scales were recorded from, for example, "not at all hungry" to "extremely hungry," so that higher scores indicated more intense subjective sensations.

Assessment of pleasantness of the meals

Pleasantness was assessed for each meal with the use of the VAS, as described previously (27), and was also logged on the Visor Handspring handheld computer. Subjects were prompted to record on a line scale, 15 min after eating, how pleasant the meals were. Scales were recorded from "extremely unpleasant" to "extremely pleasant," and the higher scores indicated more pleasant meals. The use of this questionnaire rates the whole meal, rather than aspects associated with specific food items. The use of the questionnaire after eating will capture subjects' feelings of palatability in the early postingestion phase.

Self-reported influences on eating behavior and mood

Subjects self-completed 2 questionnaires at the beginning and end of each dietary intervention period. Mood was assessed by using the Hospital Anxiety and Depression Scale (28), in which possible scores range from 0 to 21, and a score up to 7 is considered normal. Influences on eating behavior were assessed by using the Three-Factor Eating Inventory questionnaire (29) that related to "hunger," "cognitive restraint of eating," and "disinhibition"; the questionnaire was scored as described by Stunkard and Messick.

Measurement of body composition

Body composition was calculated with the use of a 4-compartment model (30) that involved dual-energy X-ray absorptiometry (DXA) on a Norland XR-36, Mark II densitometer (Norland Corp, Fort Atkinson, WI), which is equipped with dynamic filtration, and the use of the BodPod system's software (version 2.5.2; Norland Corp). Body density was calculated with the use of air displacement whole-body plethysmography (BodPod Body Composition System; Life Measurement Instruments, Concord, CT), and total body water was measured with the use of deuterium dilution (31).

Compliance and metabolic profile

Compliance with the dietary regimen was monitored by daily body weight measurements and urine testing plus weekly blood sample analysis. All subjects steadily lost weight, and this was an indicator that they were in negative energy balance. Subjects were asked for daily spot samples of urine for compliance testing. This was relevant for the LC diet, because the samples of urine were tested for acetoacetate concentration (a ketone body) with single-use dipsticks (Combur Test; Roche Diagnostics Ltd, Lewes, United Kingdom), and the colorimetric result was recorded as negative, 1+, 2+, or 3+ in comparison with a reference. In addition to this qualitative approach, urinary elimination of 3-hydroxybutyrate (3-OHB) was quantified on two 24-h collections of urine/wk by using the same procedure as for plasma (*see* below).

Fasted plasma concentrations were measured at 4 timepoints, at the start (before treatment) and the end (after treatment) of each of the 2 dietary phases. For hormone and metabolite analysis, whole blood was sampled from a large antecubital vein in the morning after an overnight fast, before breakfast, by using an 18G butterfly needle (Sarstedt, Nuernbrecht, Germany) and an adapter and collected into separate EDTA and lithium heparin tubes. The samples were immediately centrifuged ($1000 \times g$ at 4 °C for 10 min), and the plasma was stored at −80 °C for subsequent analysis. Insulin was measured on duplicate samples by using an enzyme-linked immunosorbent assay kit (Mercodia, Uppsala, Sweden), with within-assay and between-assay CVs of 5% and 3%, respectively. A discrete automated clinical analyzer (Kone Oyj, Espoo, Finland) was used for the analysis of plasma 3-OHB, glucose, triacylglycerol, and total, LDL, and HDL cholesterol by using commercial kits (Labmedics; Salford, Manchester, United Kingdom). Homeostasis model assessment of insulin resistance (HOMA-IR) was measured by using the fasting glucose and insulin values (32).

Statistical analysis

Data on energy intake, body weight and composition, blood metabolites, and meal ratings were analyzed by hierarchical (split-plot) ANOVA, with subject, period (order) within subject, and day within period as blocking factors (random effects) and diet, order, and day as treatment terms (fixed effects). Diet and order were tested against the period-within-subject error term, their interaction was tested against the subject error term, and day and all relevant interactions were tested against the day-within-period error term. The VASs were affected by a high rate of noncompliance (47%), which led to unbalanced data, and so were additionally analyzed by residual maximum likelihood (REML) with random effects for subject, period within subject, and day within period and with fixed effects for diet, day, time of day, and their interactions. This was done to confirm the results of the ANOVA, which used missing value imputation. All analyses were performed by using GENSTAT software (version 8.1; Lawes Agricultural Trust, VSN International Ltd, Hemel Hempstead, United Kingdom).

To determine appropriate subject numbers, energy intake was considered as the main outcome variable. We wished to detect a difference of ≥1 MJ/d between the treatments. A within-subject variation (SD) of 2.87 MJ was calculated from previous data from a group of subjects ($n = 150$) who were feeding ad libitum (25). The within-subject variability (SD) for the experiment (over 28 d) was estimated as $2.87/\sqrt{28} = 0.542$. Thus, their ratio is 1/0.542—ie, 1.8—that gives a minimum of 10 subjects (at

95% power) to detect at 5% significance. More subjects were used, because intake differences would be compared over shorter intervals (eg, 10 d) and, thus, over smaller weight differences within the experimental design.

RESULTS

Ad libitum energy and macronutrient intakes

Three subjects withdrew for personal reasons, and therefore, the data presented include only the 17 volunteers who completed the study.

The subjects' baseline characteristics are described in **Table 1**. Volunteers consumed significantly ($P = 0.020$) more energy (0.7 MJ/d) when following the MC nonketogenic diet than when following the LC ketogenic diet (**Table 2**). Average daily ad libitum energy intake for each diet is shown in **Figure 2**. The diets were isoenergetic, which meant that the subjects consumed significantly more food, including more protein (12 g/d; $P = 0.022$) and carbohydrate (148 g/d; $P = 0.001$), but significantly less fat (51 g/d; $P < 0.001$) with the MC nonketogenic diet than with the LC ketogenic diet (Table 2). There were no significant time effects within the ad libitum periods, as assessed by diet × days of diet or diet × week interactions, or any significant period (order) or period × diet effects.

The fact that all meals and snacks within the diet also had the same energy density ensured that the amount (weight) of food eaten, and thus the "gut fill," did not compromise energy intake. The energy density of the meals was chosen to approximate that of a healthy diet (6). The subjects' average (SD) consumption of beverages was not different did not differ between the LC and MC diets (1.655 ± 1.05 and 1.662 ± 1.12 kg, respectively). These beverages were free of both calories and caffeine, and thus the difference in energy intake was due to weight of food eaten, rather than fluid intake. The total weight of food intake was 1.25 ± 0.56 and 1.46 ± 0.43 kg with the LC and the MC diet, respectively. The amount and type of refusal of food (eg, salad return or meat return) were accounted for in these calculations.

Appetite

Subjects felt significantly ($P = 0.014$) less hungry (−4.6 on the VAS) while following the LC ketogenic diet than while following the MC nonketogenic diet (**Table 3**). The average daily hunger score for each diet, with the data averaged across the day (from 0800 to 2200), is shown in **Figure 3**. There was a

TABLE 1
Baseline characteristics of participants

Characteristic	Value
Men (*n*)	17
Age (y)	38 ± 10 (23–57)[1]
Height (m)	1.78 ± 0.05 (1.67–1.84)
Body weight (kg)[2]	111.1 ± 13.0 (87.5–131.4)
BMI (kg/m^2)	35.1 ± 3.8 (30.0–41.5)
Percentage body fat (%)[3]	36.6 ± 6.0 (26.3–48.0)

[1] $\bar{x}$ ± SD; range in parentheses (all such values).
[2] Body weight was measured at the end of maintenance with all subject data pooled, before random assignment to diet treatment.
[3] Measured by using a 4-compartment model (26).

TABLE 2
Average maintenance intakes at study beginning and average daily nutrient intakes on the high-protein, low-carbohydrate (LC; ketogenic) and high-protein, medium-carbohydrate (MC; nonketogenic) diets[1]

		Total fluid and food intake			
Dietary intake	Maintenance intake	LC diet	MC diet	SED	P^2
Energy intake (MJ)	12.6	7.25	7.95	0.27	0.020
Energy density (kJ/100 g)	6.59	2.49	2.54	0.05	NS
Weight (kg)	1.913	2.910	3.123	0.113	0.079
Protein					
(g)	94	123	135	4.75	0.022
(%)	13	30	30		
Total fat					
(g)	126	129	78	4.85	<0.001
(%)	37	66	34		
Monounsaturated fat (g)	38.4	51.8	26.8	2.38	<0.001
Saturated fat (g)	43.8	46.3	28.9	1.85	<0.001
Polyunsaturated fat (g)	19.1	19.2	10.7	1.06	<0.001
Total carbohydrate					
(g)	396	22	170	9.00	<0.001
(%)	50	5	36		
Sugar (g)	145.8	16.2	67.1	6.30	<0.001
Starch (g)	196.9	2.0	95.3	4.5	<0.001
NSP (g)	25.1	6.7	11.7	0.7	<0.001

[1] SED, SE of the difference between means; NSP, nonstarch polysaccharide. The data are for 17 subjects analyzed by ANOVA.
[2] The *P* value indicates a significant difference between LC diet and MC diet fluid and food intakes across the 4-wk intervention period. The maintenance intakes are included only as a guide to the groups' weight maintenance requirements. Ad libitum fluid intakes (SD) of calorie-free, caffeine-free beverages did not differ significantly between diets (1.655 ± 1.05 and 1.662 ± 1.12 kg for the LC diet and MC diet, respectively).

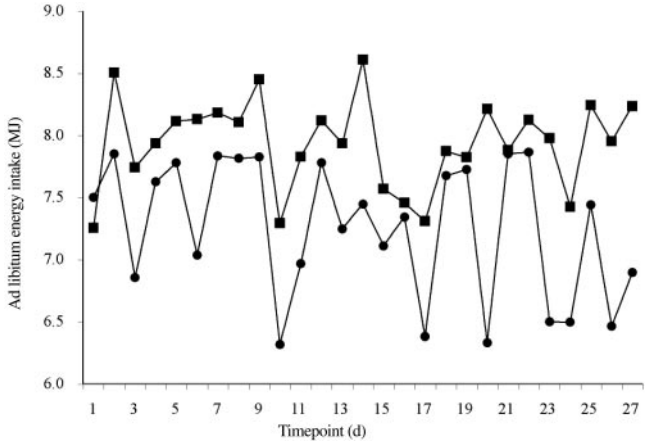

FIGURE 2. Plot of average daily ad libitum energy intake (MJ) for the high-protein, low-carbohydrate (ketogenic) diet (●) and the high-protein, medium-carbohydrate (nonketogenic) diet (■). Average ad libitum energy intakes of the 17 subjects over the 4-wk period were significantly ($P = 0.02$) lower with the LC diet than with the MC diet: 7.25 and 7.95 MJ/d (SED: 0.27), respectively (ANOVA).

TABLE 3
Hunger and pleasantness ratings for the 2 dietary regimens on the Visual Analogue Scale[1]

	Visual Analogue Scale rating			
	LC diet (ketogenic)	MC diet (nonketogenic)	SED	P^2
	mm			
Motivation to eat				
Hunger	16.8	21.4	1.76	0.014
Fullness	54.3	54.2	2.02	0.975
Desire to eat	18.7	23.0	2.59	0.093
Prospective consumption	23.1	26.4	1.92	0.070
Thirst	33.7	33.7	1.2	0.970
Preoccupation with thoughts of food	13.6	15.6	1.410	0.177
Postmeal ratings				
Pleasantness	86.6	88.8	1.67	0.213
Satisfying	86.0	88.5	1.67	0.164

[1] LC, high-protein, low-carbohydrate (ketogenic); MC, high-protein, medium-carbohydrate (nonketogenic); SED, SE of the difference between means. The data are for 17 subjects analyzed by ANOVA.

[2] The P value refers to analysis between diet, averaged across the 4-wk intervention period.

significant effect of day and a significant day × diet interaction ($P < 0.001$ for both). The latter suggests that subjects responded differently over time (days) to the 2 diets or, more specifically, that hunger was reduced over week 1 to a greater extent with the LC ketogenic diet than with the MC nonketogenic diet. There was no significant diet × time interaction for any of the appetite scores. Order effect was considered by the period and period × diet interactions. There were no period × diet interactions for any of the appetite variables, but there were period effects for prospective consumption ($P = 0.037$) and thirst ($P = 0.035$), whereby values were higher in the first period than in the second. This suggests adaptation throughout the study duration. Despite encouragement, subjects in general became less compliant at completing their hourly questionnaires, and this needed to be accommodated within the statistical analysis (as described in Subjects and Methods). There were no significant differences ($P > 0.10$) between diets for thirst, desire to eat, prospective consumption, preoccupation with thoughts of food, or fullness.

Pleasantness of the diets

Subjects had no significant overall preferences for either diet, as assessed by the postmeal questionnaires (Table 3) for pleasantness ($P = 0.213$) or satisfaction ($P = 0.164$). The mean daily score for diets on each day is shown in **Figure 4**. Breakfast was the most enjoyable meal of the day ($P < 0.001$) and dinner the least enjoyable ($P < 0.001$), with average meal scores of 89.7, 87.5 and 85.8 mm (SED: 1.10) for breakfast, lunch, and dinner, respectively. A diet × day interaction ($P = 0.021$) indicated that the subjects perceived pleasantness improved with the MC diet and declined with the LC diet over the first few days. There was no correlation of the difference in pleasantness between the LC and MC diets and the difference in energy intake. There were no period or diet × period effects.

Self-reported influences on eating behavior and mood

On average, there was no significant difference in perceived anxiety or depression according to diet composition. Mean ± SD scores for anxiety with the LC diet were 4.1 ± 3.3 and 3.4 ± 2.5 and those for depression were 2.5 ± 2.1 and 2.8 ± 2.2 before and after treatment, respectively. Similarly, mean scores for anxiety with the MC diet were 4.1 ± 3.4 and 3.4 ± 2.3 and those for depression were 3.6 ± 2.2 and 2.9 ± 2.6 before and after treatment, respectively. There was a period effect with anxiety: scores decreased between weight-loss periods 1 and 2 ($P = 0.043$).

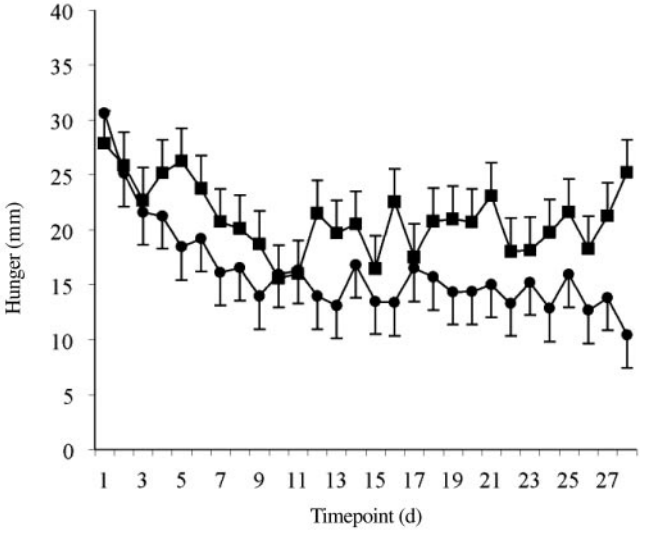

FIGURE 3. Plot of mean (±SEM) daily hunger (mm), as assessed with the Visual Analogue Scale, with consumption of the high-protein, low-carbohydrate (ketogenic) diet (●) and the high-protein, medium-carbohydrate (nonketogenic) diet (■). Over the 4-wk period, hunger was significantly ($P = 0.014$) lower with the LC diet than with the MC diet in the 17 subjects (ANOVA).

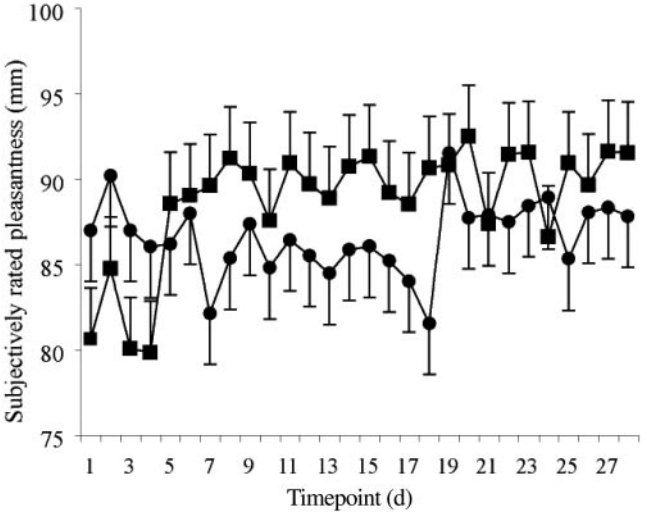

FIGURE 4. Plot of mean (±SEM) daily pleasantness (mm), as assessed with the Visual Analogue Scale, of the high-protein, low-carbohydrate (ketogenic) diet (●) and the high-protein, medium-carbohydrate (nonketogenic) diet (■). The pleasantness of the 2 diets for the 17 subjects did not differ significantly (ANOVA).

There was no diet effect or diet × period effect, even with covariate adjustment for baseline (before treatment) scores.

Influences on eating behavior, as assessed by the Three-Factor Eating Inventory questionnaire, showed no diet effects in any variable (ie, restraint, disinhibition, and hunger) but, when adjusted for covariate analysis [based on baseline (before treatment) levels], there were significant order effects and order × diet effects, which reflected higher scores during period 1 than in period 2. Specifically, restraint increased on both diets with mean scores for LC of 5.8 ± 4.6 to 6.7 ± 4.8 and those for MC were 5.8 ± 4.0 to 6.5 ± 4.8 before and after treatment, respectively. The influence of disinhibition remained unchanged on both diets with mean values for LC of 6.7 ± 2.4 to 6.8 ± 3.0 and those for MC of 3.3 ± 3.4 to 6.2 ± 3.0 before and after treatment, respectively. Finally, hunger declined with both diets: from 6.3 ± 1.8 to 5.8 ± 2.3 with the LC diet and from 7.0 ± 2.5 to 6.7 ± 2.5 before and after weight loss, respectively.

Subjects were encouraged to record in their electronic notepad how they felt about the regimen. It is noted that some of the subjects felt the regimen caused bad breath or a change in their bowel movements (or both). The effect of the dietary regimen on gut health and, specifically, on the microbial population has been reported elsewhere (33).

TABLE 4
Average measured change (Δ) in body weight (kg) and composition (kg) with the study diets for the 4-wk intervention period[1]

	Body composition[2]				
	Before treatment	After treatment	Δ	SED	*P*
	kg				
Body weight				0.62	0.006
LC diet	108.02	101.69	−6.34		
MC diet	108.18	103.83	−4.35		
Fat mass				0.57	0.083
LC diet	38.53	33.39	−5.13		
MC diet	38.85	34.76	−4.09		
Fat-free mass				0.45	0.054
LC diet	69.49	68.29	−1.20		
MC diet	69.33	69.07	−0.26		
Total body water				0.48	0.158
LC diet	50.78	49.83	−0.95		
MC diet	50.51	50.27	−0.24		

[1] n = 17 subjects analyzed by ANOVA. LC, high-protein, low-carbohydrate (ketogenic); MC, high-protein, medium-carbohydrate (nonketogenic); SED, SE of the difference between means.
[2] Measured with the use of a 4-compartment model (26).

Weight loss and body composition

The mean changes in body weight over the duration of the LC (ketogenic) and MC (nonketogenic) diets are illustrated in **Figure 5**. Weight loss during the 4-wk period was significantly (P = 0.006) greater with the LC than with the MC diet (6.34 ± 2.24 and 4.35 ± 2.61 kg, respectively; it was equivalent to a 5.8% and 4.0% reduction in body weight ($P < 0.001$), respectively, expressed as a proportion of body weight at the start each diet phase. There was a significantly (P = 0.002; SED: 0.282) greater weight loss during week 1 of the LC ketogenic diet than during week 1 of the MC nonketogenic diet (2.68 and 1.62 kg, respectively). There was a significant period effect (P = 0.005), in that subjects lost more weight during weight-loss period 1 than during period 2. There were no diet × order effects.

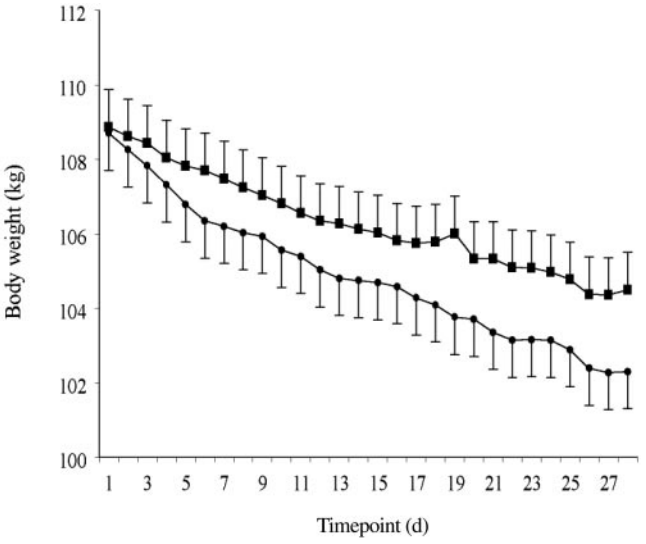

FIGURE 5. Plot of mean (±SEM) daily body weight (kg) with consumption of the high-protein, low-carbohydrate (ketogenic) diet (●) and the high-protein, medium-carbohydrate (nonketogenic) diet (■) in the 17 subjects. Average weight loss was significantly (P = 0.006) greater with the LC diet than with the MC diet: 6.34 and 4.35 kg, respectively (ANOVA). Subjects regained some of their lost weight during the maintenance period.

The significantly (P = 0.006) greater weight loss with the LC diet (1.99 kg) than with the MC diet was due, in part, to the difference in water loss with the ketogenic diet, although this difference did not reach significance (0.71 kg; P = 0.158) (**Table 4**). There also tended to be greater losses of fat mass (1.05 kg; P = 0.083) and fat-free mass (0.94 kg; P = 0.054) with the LC diet than with the MC diet. In the 4-compartment model used, glycogen is considered part of the fat-free mass, and it cannot easily be directly measured. Examination of the change in protein mass (rather than in fat-free mass), calculated from the 4-compartment model, indicated that there was a weight loss of 0.25 and 0.02 kg with the LC ketogenic and MC nonketogenic diets, respectively (P = 0.281; SED: 0.202).

When considered over the span of 4 wk, however, only 35% of the difference in total weight loss between the 2 diets was accounted for by water depletion. The remainder of the difference was accounted for mainly by fat mass and some lean mass. These additional losses probably are associated with the 0.7 MJ/d lower energy intake with the LC diet than with the MC diet. This difference would be supported by other data from this study (34), which indicate that the energy cost is comparable to measured negative energy balance.

Compliance and metabolic profile

Values for blood variables at the beginning and end of each diet phase are shown in **Table 5**, after analysis for changes between (and within) diets, where appropriate. Both fasting glucose ($P < 0.001$) and HOMA ($P < 0.001$) were significantly lower than baseline with the LC diet. In contrast, these values were unchanged with the MC diet, which led to significant

TABLE 5
Average plasma concentration of metabolites before and after each dietary regimen[1]

	Plasma					
	Before treatment	After treatment	Δ	*P* for change[2]	SED	*P* for diet[3]
	mmol/L					
Urea					0.21	NS
LC diet	4.84	5.21	0.37	—		
MC diet	4.51	5.10	0.59	—		
3-OHB					0.40	0.036
LC diet	0.20	1.52	1.32	0.007		
MC diet	0.28	0.28	0.00	NS		
Glucose					0.12	0.035
LC diet	5.90	5.28	−0.62	<0.001		
MC diet	5.98	5.65	−0.35	NS		
Insulin (IU/mL)					0.85	0.035
LC diet	10.07	6.09	−3.98	<0.001		
MC diet	10.54	9.48	−1.41	NS		
HOMA-IR					0.24	0.038
LC diet	2.66	1.44	−1.22	<0.001		
MC diet	2.81	2.39	−0.52	NS		
Total cholesterol					0.10	0.002
LC diet	5.14	4.75	−0.39	NS		
MC diet	5.32	4.40	−0.92	<0.001		
HDL cholesterol					0.02	NS
LC diet	1.10	1.13	0.03	—		
MC diet	1.12	1.04	−0.08	—		
LDL cholesterol					0.09	0.004
LC diet	3.13	2.95	−0.18	NS		
MC diet	3.37	2.70	−0.67	0.002		
Triacylglycerol					0.05	NS
LC diet	1.76	1.07	−0.69	—		
MC diet	1.60	0.99	−0.61	—		

[1] 3-OHB, 3-hydroxybutyrate; HOMA-IR, homeostasis model assessment of insulin resistance; Δ, change; SED, SE of difference between means; LC diet, high-protein, low-carbohydrate (ketogenic) diet; MC diet, high-protein, medium-carbohydrate (nonketogenic) diet. These data are for 17 subjects analyzed by ANOVA.
[2] Within diet (ANOVA).
[3] Between diets (ANOVA; SED).

between-diet effects ($P < 0.035$, and $P = 0.038$, for glucose and HOMA, respectively). Total and LDL cholesterol were reduced to a significantly greater extent with the MC diet than with the LC diet ($P = 0.002$ and $P = 0.004$, respectively), but there was no significant diet effect on HDL or triacylglycerol. There were significant diet effects for glucose ($P = 0.035$), insulin ($P = 0.035$), and HOMA-IR ($P = 0.038$), which reflected the differing carbohydrate intakes. There was a similar small increase in plasma concentration of urea with both diets, which probably reflects the elevated protein intake and which was considered an indicator of compliance. There was no difference in response between diets. Furthermore, as anticipated, fasted plasma 3-OHB increased 6-fold ($P = 0.007$) with the LC ketogenic diet.

Daily urine testing with indicator sticks (acetoacetate) showed that all subjects became ketotic after 1–3 d of the LC diet and remained so for the duration of the dietary period. This effect was also reflected in the concentration of 3-OHB in the 24-h urine collections, which did not change significantly ($P > 0.05$) between the end of week 1 and the end of week 4 [2.98 and 2.99 mmol/L (SED: 0.36) and 0.47 and 0.18 mmol/d (SED: 0.21), respectively] of the LC and MC diets, respectively. Total urine output of 3-OHB differed significantly ($P < 0.001$) between diets, but did not change significantly between the end of week 1 and the end of week 4 of each diet: 4.37 and 5.02 mmol/d (SED: 0.62), respectively, with the LC diet and 0.30 and 0.51 mmol/d (SED: 0.29), respectively, with the MC diet.

The decrease in blood pressure did not differ significantly between diets, so these improvements were probably a response to the weight loss. Similarly, changes in waist and gluteal circumferences did not differ significantly ($P > 0.01$) between the 2 diets.

Efficacy of the 3-d maintenance diet

The 3-d maintenance diet was designed to *1*) neutralize the ketogenic state and replete liver carbohydrate stores and *2*) to return hunger to baseline levels—equivalent to the maintenance period 1, before ad libitum feeding—recognizing that a carry-over effect from the weight-loss phase existed. This design is particularly relevant for the subjects who were given the LC ketogenic diet first and then the MC nonketogenic diet. The plasma data would support that the 2 goals above were achieved, in that fasted plasma 3-OHB concentrations did not differ significantly ($P > 0.05$) between the 2 phases for the maintenance periods 1 and 2. In addition, glucose concentration did not differ

significantly between diets ($P > 0.05$) for maintenance period 1 or period 2. Moreover, comparison of fasted plasma 3-OHB concentrations at maintenance period 2 and at the end of the MC nonketogenic diet showed no significant difference between the 2 phases. The data from all 3 maintenance periods indicated that hunger had returned to baseline or below within 3 d.

DISCUSSION

Effect of diet composition on ad libitum energy intake

The primary aim of this study was to determine whether the ketotic state was a major factor in the reduced voluntary intake (and, thus, weight loss) associated with a very-low-carbohydrate diet. To achieve this objective, the macronutrient content of the 2 diets was strictly controlled, unlike the protocol in other studies, in which fat or protein content was allowed to vary over the experimental periods (11–13). The current data suggest that reducing the carbohydrate content between the 2 high-protein diets resulted in an energy intake decrease of 0.7 MJ/d (294 kcal/d) and a corresponding effect on the negative energy balance. The reduction in intake, as a proportion of initial maintenance requirements, varied from 18% to 83% with the LC ketogenic diet and from 29% to 94% with the MC nonketogenic diet. The reasons for this large interindividual variation of response to the diet manipulation are unknown. Numerous physiologic and psychological factors influence appetite and food intake, including the effects of altered fuel status across the brain on both mood and satiety centers (35). It is also likely that the degree of dietary restraint was an important psychological factor determining daily energy intake (8).

A large decrease in energy intake (average: 40%) was observed between the maintenance diet and the 2 high-protein diets, a finding that is similar to responses observed previously (14). Although the effect of protein on satiety was not tested directly, the observed decrease in intake supports the notion that protein is the most satiating of the macronutrients (36). Indeed, Weigle et al (37) showed that increasing the dietary protein content from 15% to 30% produced a sustained decrease in ad libitum intakes.

Effect of diet composition on hunger

Hunger predicts a failure to comply with a calorie-restricted regimen (8) and an inability to maintain weight loss (38, 39). Proponents of high-protein diets say that one advantage of those diets over other weight-loss regimens is the improved satiety that leaves the dieter feeling less hungry (7). Therefore, even if weight loss was similar between dietary strategies, high-protein diets should allow better compliance. This is the ultimate "holy grail" for dieters—to eat less to lose weight, and yet not to feel hungry. Limited data are available on daily hunger scores during ketogenic and nonketogenic diets, and daily hunger scores were a key component of the current study. The Eating Inventory Questionnaire has been used as an indicator of less hunger with LC diets than with low-fat diets, with values recorded at baseline, week 1, and week 6 (9). Other studies (21, 40) reported two 6-wk protocols that utilized a weekly measurement of prelunch hunger on a Likert scale. In the first trial (21), subjects following a high-protein, low-fat diet reported feeling more satiated in the first 4 wk than did subjects following a high-carbohydrate, low-fat diet, but, in the second study (40), there was no difference between the diets. Unfortunately, that study was probably underpowered for a between-group comparison. Furthermore, only one rating taken prelunch would not reflect the diurnal pattern known to affect appetite (41).

In the present study, the observed decrease in hunger between the LC ketogenic and MC nonketogenic diets is due to the difference in carbohydrate or fat intake (or both), because the energy density and protein content were held constant. Others have examined the satiating effect of fat and found no effect (42). The suggestion that ketone bodies have an anorexic effect in humans is not novel (43), and high plasma 3-OHB concentrations act as a satiety signal in rodents (44). During insulinopenia (eg, type 1 diabetes) or hyperketonemia (eg, acute or prolonged fasting), the normal reliance of the brain on glucose as the major energy substrate (>97%) is reduced; instead, ketone bodies provide as much as 30–50% of the metabolic fuel (45). Given that the brain is a major regulator of appetite (46), the provision of an alternative fuel supply may affect the motivation to eat.

The discrepancy between hunger and these other measures of appetite is not a novel feature of the current study. One may anticipate that the questions overlap; however, in the current study, subjects consumed a similar weight and energy density of food, and thus the sensitivity of the questions relating to gut fill (ie, unfullness, desire to eat, prospective consumption, and preoccupation with thoughts of food) is reduced. In the present study, the question relating to motivation to eat (hunger) is the most sensitive in terms of dietary manipulation. The issue of what the questions relate to is addressed in a review (47) by means of principal components analysis. It is argued that these questions do not relate to one single phenomenon—ie, motivation to eat—but, rather, that they address more than one underlying motivation.

Palatability of the diet

Hunger, or at least motivation to eat, is influenced by the palatability of the diet, which is an important determinant of intake (48), both in short-term (49) and longer-term (50) trials. Indeed, it has been suggested that lower energy intakes with LC diets are due to a lower palatability, or greater monotony, of the diet (9). This possibility is not supported by the current study, in which there was no significant difference between the 2 diets. Others also failed to show a lower palatability of their LC diets (14). In the current study, the subjects were provided a wide variety of both savory and sweet palatable foods. In real life, dieters may, by default, adopt more limited diet choice because their nutritional knowledge is less than that of dietetic professionals. Were the study conducted over a longer time, palatability ratings may gradually decrease, because desire for even a favorite food will wane if the food is offered repeatedly (51).

Influence on body weight and composition

There is growing evidence that weight loss, at least in the short term, is significantly greater in obese persons following low-carbohydrate diets than in those following low-fat diets (8, 12, 13). The present data also support this possibility. Astrup et al (52) suggested that the apparent paradox that ad libitum intake of high-fat foods leads to weight loss is due to the depletion of hepatic glycogen stores through carbohydrate restrictions and to the associated loss of water.

Volek et al (53) concluded that low-carbohydrate diets favor loss of fat and preservation of lean body mass, a response partly mediated by reduced plasma insulin. They also found that LC diets promote trunk or abdominal fat loss (54), which would be particularly advantageous for patients with the metabolic syndrome. Further work utilizing magnetic resonance imaging (MRI) would allow precise quantification of subcutaneous and visceral fat loss.

Effect on metabolic health risk factors

One aim for weight-loss strategies is the reduction of comorbidity risk. Low-carbohydrate diets inevitably contain high fat, which has caused concerns among nutritionists (55). Nonetheless, evidence of adverse effects in controlled situations is lacking: many studies report an improvement in fasting blood lipids or glucose or both (12, 13, 56). Several reviews concluded that, in subjects who lose weight with low-carbohydrate diets, there is a marginal reduction in total and LDL cholesterol and a consistent decrease in triacylglycerol concentrations (54, 57, 58). Such conclusions are supported by the present study. Nonetheless, greater (and statistically significant) improvements in total and LDL cholesterol were observed with the MC diet; they probably reflect the 40% decrease in fat intake with this diet.

It is well recognized that LC diets promote reductions in fasting glucose and insulin concentrations (54) and improve insulin sensitivity (59). Indeed, decreases in fasting insulin concentrations have been reported after 3 or 4 d of consumption of a low-carbohydrate diet (60, 61), and improvements in HOMA have been noted within 2 wk (62). In view of current theories that insulin resistance is a precursor for many other obesity-associated morbidities (63), the use of a low-carbohydrate diet may be a preferred option, at least in the early phase of weight loss. It is not known, however, whether these effects persist or whether insulin insensitivity returns rapidly when carbohydrate intake is increased.

Some concern has been expressed in the literature with respect to the safety and efficacy of high-protein ketogenic diets (52, 55), because not all patients will be medically suitable for consideration for such weight-loss diets (64). The current data, however, would suggest that these diets are safe within this relatively short period of time (2 mo), as assessed by the reported clinical biochemistry, and that, under medically supervised conditions, they could be used to achieve considerable weight loss to improve mortality and morbidity in obese patients.

Efficacy of the 3-d washout period

The 3-d maintenance period was sufficient to restore plasma 3-OHB and glucose concentrations to baseline, before starting the second ad libitum feeding phase. Other variables, eg, total cholesterol, remained reduced throughout this period and this was accounted for within the statistical analysis (order effect).

In conclusion, the low-carbohydrate component of the high-protein regimen affects subjective motivation to eat, and volunteers feel less hungry and consume less energy, at least in the short term. Whether LC (ketogenic) diets are a suitable tool for weight loss will remain an important issue for some time, as more complex interactions between phenotype and diet composition are identified (23). This regimen appears to reduce calorie intake without increased hunger, and, therefore, it promotes compliance. The current evidence would support the use of such diets, in the short term at least, as a measure to reduce mortality and morbidity in obese subjects who would benefit from a modest weight loss.

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APPENDIX A
Menu plan

Meal options
High-protein, low-carbohydrate (ketogenic) diet
Breakfast (made-to-order as 400-g portion)
Scrambled eggs and turkey slice
Mixed grill 1 and grapefruit
(grilled bacon, tomato, mushrooms, and fried egg)
Mushroom and cheese scrambled eggs and bacon
Mixed grill 2
(turkey slice, mushrooms, baked beans, fried egg, tomato, and cheese)
Spanish-style omelette and yogurt
(eggs with ham, cheese, grilled tomato, baked beans, and mushrooms; Greek-style yogurt)
Smoked haddock and raspberry yogurt
(haddock and boiled egg; cheese and cucumber salad; and raspberry yogurt drink
Turkey slice and poached egg
(turkey slice; poached egg; feta cheese salad—tomato, cucumber, raisins, and mushrooms)
Raspberry yogurt and bacon and poached egg
(raspberry yogurt drink; poached egg; grilled bacon; and cucumber and mushrooms)
Salmon scrambled eggs
(scrambled egg; salmon; celery, raisin, and mushroom salad)
Lunch (400 g)
Day 1
Chicken breast salad
Prawn and salmon salad
Day 2
Cottage cheese and ham salad
Tuna salad with mayonnaise
Day 3
Ham and cheese salad
Avocado and bacon salad
Day 4
Pork salad
Tuna and egg salad
Day 5
Cheese and chicken Caesar salad
Cottage cheese and ham salad
Day 6
Avocado and bacon salad
Tuna salad with mayonnaise
Day 7
Ham and cheese salad
Pork salad
Dinner (400 g)
Day 1
Chili beef
Ham and cauliflower bake
Day 2
Chicken Creole
Salami and ham stew
Day 3
Pork loin and ratatouille
Ham and cauliflower bake
Day 4
Chicken curry
Salmon and prawns
Day 5
Steak and mushrooms
Chicken Creole

(*Continued*)

APPENDIX A (*Continued*)

Meal options
Day 6
Chicken stir fry
Chili beef
Day 7
Salami and ham stew
Chicken curry
Snacks (150 g)
Day 1
Chocolate mousse
Chicken soup
Tuna salad
Day 2
Orange mousse
Chicken soup
Scrambled egg with ham and tomato
Day 3
Chilled cappuccino
Chicken soup
Smoked ham wrap
Day 4
Chocolate mousse
Chicken soup
Pork kebabs
Day 5
Strawberry mousse
Chicken soup
Smoked ham wrap
Day 6
Chilled cappuccino
Chicken soup
Egg salad with mayonnaise
Day 7
Raspberry mousse
Chicken soup
Pork kebabs
High-protein, medium-carbohydrate (nonketogenic) diet
Breakfast options (made to order as 400-g portion)
Porridge, turkey slice, and raspberry yogurt
Mixed grill 1, toast, and yogurt
(grilled bacon, mushrooms, white bread, baked beans, mushrooms, heated tomato, and yogurt drink)
Crumpet and ham and yogurt
(toasted crumpet with ham and poached egg; Greek-style yogurt)
Mixed grill 2 and toast
(turkey slice, white bread, mushrooms, poached egg, and grilled tomato)
Mixed grill 3 and toast
(grilled sausage, turkey slice, white bread, grilled tomato, ketchup, and scrambled egg)
Kedgeree
(rice, smoked haddock, and boiled egg)
Red fruit smoothie
(raspberries, strawberries, and yogurt)
All-bran cereal, poached egg, and yogurt
(raspberry yogurt drink, poached egg, All-bran, and milk)
Continental
(croissant, turkey slice, strawberry jam, butter, and yogurt smoothie)
Lunch (400 g)
Day 1
Chicken and macaroni salad
Prawn and salmon salad

(*Continued*)

APPENDIX A (*Continued*)

Meal options
Day 2
Cottage cheese and ham salad
Tuna salad with mayonnaise
Day 3
Prawn and ham salad
Avocado and bacon salad
Day 4
Pork salad
Tuna salad with mayonnaise
Day 5
Cheese and chicken Caesar salad
Cottage cheese and ham salad
Day 6
Avocado and bacon salad
Tuna salad with mayonnaise
Day 7
Chicken and sweetcorn salad
Pork salad
Dinner (400 g)
Day 1
Chili beef risotto
Spaghetti carbonara
Day 2
Chicken Creole
Salami and ham stew
Day 3
Pork grill
Spaghetti carbonara
Day 4
Chicken curry
Salmon and egg-fried rice
Day 5
Steak and mash
Chicken Creole
Day 6
Chicken stir fry
Chili beef
Day 7
Salami and ham stew
Chicken curry
Snacks (150 g)
Day 1
Chocolate mousse
Chicken soup
Tuna salad roll
Day 2
Strawberry cooler
Chicken soup
Turkey cheese and tomato sandwich
Day 3
Chilled cappuccino
Chicken soup
Tuna salad roll
Day 4
Rhubarb and ginger fool
Chicken soup
Hummus and pita bread
Day 5
Chocolate mousse
Chicken soup
Cheese and tomato sandwich

(*Continued*)

APPENDIX A (*Continued*)

Meal options
Day 6
Strawberry cooler
Chicken soup
Salmon and toast
Day 7
Raspberry cooler
Chicken soup
Cheese and tomato sandwich