Effect of different macronutrients in excess on gastric sensory and motor functions and appetite in normal-weight, overweight, and obese humans

Moo In Park, Michael Camilleri, Helen O’Connor, LaVonne Oenning, Duane Burton, Debra Stephens, and Alan R Zinsmeister

ABSTRACT

Background: The effects of supplementation with different macronutrients on gastric sensory and motor functions are unclear.

Objective: We aimed to compare the effects of 2 wk of supplementation with different classes of macronutrients on gastric function, satiation, and appetite in healthy and overweight subjects.

Design: In a parallel-group, double-blind study, 52 (14 men, 38 women) healthy normal-weight, overweight, and obese participants [body mass index (BMI; in kg/m²): 19.4–47.0] aged 18–64 y were randomly assigned to consume different isocaloric diets (n = 13 per diet group) adjusted for BMI and activity level. The standard diet provided 20% of energy as protein, 30% as fat, and 50% as carbohydrate. The high-protein, high-fat, and high-carbohydrate diets contained 500 additional kcal in each nutrient class. On 3 separate days, we measured gastric emptying of solids, gastric volumes, postprandial symptoms, appetite, and food choice with validated methods. Age, sex, BMI, and baseline satiation were covariates in the analysis of covariance.

Results: Fat supplementation was associated with increased maximum tolerated volume (MTV) in subjects with a high baseline MTV (P < 0.05), irrespective of BMI. Gastric emptying and volumes, postprandial symptoms, total calories, and food choices at an ad libitum meal were not significantly different after each dietary preload. Fasting gastric volumes tended to be higher with the high-fat than with the high-carbohydrate or high-protein diets (P ≤ 0.1). Gastric emptying and volumes and satiation were not significantly different between the BMI categories (< and >30).


KEY WORDS Gastric emptying, volume, satiation, appetite, satiety, stomach, macronutrients, obesity

INTRODUCTION

Consumption of high-fat diets is implicated in the etiology of obesity, and high-fat diets may lead to physiologic adaptations, including gastrointestinal adaptations, that may predispose to weight gain in the long term. However, it is conceivable that the long-term effects may result from behavioral changes that outlast the early alterations in gastric intestinal physiology, which may facilitate the increased calorie intake in the short term. The presence of nutrients such as glucose (1, 2) and fat (3, 4) in the small intestine slows the rate of gastric emptying. An increase in the intestinal absorptive capacity for fat after consumption of a high-fat diet was shown previously in animal studies (5–7).

Macronutrient intake affects gastrointestinal structure and function in animals and humans (8–22). In rats, exposure to a high-fat diet for 1 (16), 2 (18), or 8 (17) wk increases intestinal villus height (17) and pancreatic lipase secretion (17, 18). A high-fat diet also attenuates the inhibition of gastric emptying and food intake in response to the intraduodenal administration of fat (10–12). In humans, a high-fat diet for 2 wk or a high-glucose diet for 7 d resulted in faster gastric emptying of a high-fat test meal (13) or of a glucose drink, respectively (14). These changes appear to be nutrient-specific (14, 20).

In contrast, food intake from a test meal was unchanged after a high-fat diet in humans (13, 21, 22). Thus, there appear to be different adaptations in gastric function or nutrient intake with macronutrient preloading, which refers to the supplementation of a macronutrient class in excess of required calories. Prior studies have not comprehensively assessed these functions in the same person, and no study has assessed the effects of the major macronutrient classes (carbohydrate, protein, and fat) on gastric sensory and motor functions, appetite, or food choices in healthy normal-weight, overweight, or obese persons.

The aims of this study were to compare the effects of 2 wk of a standard diet supplemented with 500 additional kcal of different classes of macronutrients on gastric function, satiation, appetite, and food choices from a standard meal in normal-weight, overweight, and obese subjects.

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SUBJECTS AND METHODS

Study participants

Healthy normal-weight, overweight, and obese subjects aged 18–65 y of age with a BMI of 19.4–47.0 were recruited during a 13-mo period (June 2004–July 2005) from the local community by public advertisement. The participants were deemed to be unrestrained eaters by scoring <10 on the cognitive restraint scale of the Three-Factor Eating Questionnaire (23), not depressed by scoring <11 on the Hospital Anxiety and Depression Questionnaire (24), and not anorexic nor bulimic. They had sedentary occupations and were willing to avoid exercise for the period of the study. Exclusion criteria were a history of gastrointestinal surgery, any clinically significant abnormality in the prestudy screening, abnormal complete blood count or fasting glucose >150 mg/dL or diagnosed diabetes requiring medical (not just dietetic) therapy, structural or metabolic diseases or conditions that affect the gastrointestinal system, positive symptoms on a validated abridged bowl-disease questionnaire used to screen for functional gastrointestinal disorders (25), any systemic disease or use of medications that could affect gastrointestinal motility, alcoholism not in remission or known substance abuse, or participation in another clinical study within the previous 30 d. The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all participants.

Study design

This was a randomized, parallel-group, double-blind, controlled dietetic study. A Mayo Clinic General Clinical Research Center (GCRC) research dietitian interviewed subjects at the screening visit to ensure that their usual dietary intake was within a normal range (15–20% protein, 50–60% carbohydrate, and 25–35% fat) and that their body weight had been stable for 1 mo. The weight-maintenance calorie requirement was determined on a validated abridged bowl-disease questionnaire used to screen for functional gastrointestinal disorders (25), any systemic disease or use of medications that could affect gastrointestinal motility, alcoholism not in remission or known substance abuse, or participation in another clinical study within the previous 30 d. The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all participants.

After the initial screening, the subjects underwent a baseline satiation assessment by means of a liquid-nutrient (ENSURE; Ross Laboratories, Abbott Park, IL) test drink and were randomly assigned to 1 of 4 study diets for 14 d. Randomization was balanced by sex and body mass index (BMI) in fixed block sizes according to a schedule provided by the study statistician (ARZ) to the research dietitians (HO and LO). A standard diet consisted of weight-maintenance calories with a macronutrient distribution of 20% protein, 30% fat, and 50% carbohydrate. Three diets contained an additional 500 kcal of protein, fat, or carbohydrate. The fourth diet (standard diet) also included 500 kcal over weight-maintenance calories. In all 4 diets, most of the extra calories were provided as an ice cream shake flavored to disguise the additional protein, carbohydrate, or fat. The shakes were supplemented with BeneProtein (Novartis, Minneapolis, MN) and skim milk powder for the high-protein diet, with whipping cream for the high-fat diet, and with Polycose (Ross Laboratories) for the high-carbohydrate diet. The standard diet included a similarly flavored ice cream shake. These precautions were taken to ensure that subjects could not discriminate between diets.

Several menus with a variety of choices having the assigned composition of macronutrients and calories were calculated by the GCRC dietitians and prepared by the metabolic kitchen staff for each group. The composition of the 4 macronutrient preload diets, based on REE and activity level, is shown in Table 1. All food was weighed before being served and subjects were required to consume 2 meals daily under the supervision of the GCRC dietary assistants to ensure compliance. A third packed meal was provided for ingestion away from the GCRC. Food intake was calculated by using the commercially available nutrient analysis software ProNutra (version 3.0; Viocare Technologies, Princeton, NJ). It was anticipated that participants would increase body weight an average of 0.4 kg/wk.

After completion of the 14-d study diet period, physiologic measurements were performed on 3 separate days: scintigraphic gastric emptying of solids on day 1, liquid-nutrient test drink to measure maximum tolerated volume (MTV) and postprandial symptoms on day 2, and 99mTc single-photon emission computed tomography (SPECT) imaging to measure fasting and postprandial gastric volumes followed by an ad libitum meal to measure appetite and food choices 4 h later on day 3 (Figure 1). On all study days, the participants attended the study center after fasting overnight for ≥8 h.

Physiologic tests

All studies were conducted at the Physiologic Imaging Laboratory within the GCRC. The laboratory has separate sections for imaging, satiation testing, and consumption of the ad libitum meals.

Gastric-emptying time of solids

Gastric emptying of solids (egg meal) was measured by using the scintigraphic method that was validated and reported previously (27, 28). One mCi [99mTc]sulfur colloid was added to 2 raw eggs during the scrambling cooking process. The meal also included a slice of bran bread and 240 mL skim milk. The meal provided 296 kcal, 32% of energy as protein, 35% of energy as fat, and 33% of energy as carbohydrate. Anterior and posterior gamma camera images were obtained at standardized times over 4 h while the participants were standing; in between images, the participants were in a seated position. Data were analyzed as in previous studies (27–29) and summarized as the gastric-emptying half-time (GE\textsubscript{1/2}).

Satiation and postnutrient challenge symptoms

The subjects ingested a liquid nutrient (1 kcal/mL) at a rate of 120 mL every 4 min while seated (30, 31). The participants...
Gastric volume assessment by radioscintigraphic method

We used a method developed and validated in our laboratory to measure the gastric volume during fasting and after ingestion of 300 mL liquid nutrient (300 kcal). This method uses SPECT (32, 33) after intravenous administration of $^{99m}$Tc sodium per-technetate (0.12 mCi/kg), which is taken up by the gastric mucosa (34, 35). The camera (SMV-GE, Fairfield, CT) has a weight limit of 300 lb (136 kg); therefore, morbidly obese persons could not participate in this study. The camera rotates around the thorax and abdomen while the participant is supine. The stomach was identified in the transaxial SPECT images and separated from background by using a semiautomated segmentation algorithm. A 3-dimensional rendering of the stomach and its volume was obtained using the AVW 3.0 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) image processing libraries.

Ad libitum meal: food intake and macronutrient choice

Four hours after ingesting 300 mL liquid nutrient as part of the SPECT study, the subjects were invited to eat, over a 30-min period, as much as they wished from a standard ad libitum meal. The ad libitum meal included vegetable lasagna [Stouffers, Nestle USA, Inc, Solon, OH; nutritional analysis of each 326-g box: 420 kcal, 17 g protein (16% of energy), 38 g carbohydrate (37% of energy), and 22 g fat (47% of energy)], vanilla pudding [Hunts, Kraft Foods North America, Tarrytown, NY; nutritional analysis of each 99-g carton: 130 kcal, 1 g protein (3% of energy), 21 g carbohydrate (65% of energy), and 4.5 g fat (32% of energy)], and skim milk [nutritional analysis of each 236-mL carton: 90 kcal, 8 g protein (36% of energy), 13 g carbohydrate (64% of energy), and 0 g fat].

Data analysis

The geometric mean of counts in the anterior and posterior gastric regions of interest was used to estimate the GE$_{1/2}$ of solids. The MTV of the liquid-nutrient drink ingested was recorded. Individual symptoms scores (maximum score; 100) for bloating, fullness, nausea, and pain and the aggregate or sum of the individual symptom scores (maximum score: 400) were documented.

Fasting and postprandial gastric volumes were measured by ANALYZE with the use of reconstructed 3-dimensional images of the stomach. Two time periods, 0–16 and 17–32 min after the meal, were assessed and the average of these 2 postprandial gastric volume estimates were calculated. Food intake during the 14-d diet periods and the total amount (g and kcal) and the macronutrient content of food consumed at the ad libitum meal were analyzed by using validated software (ProNutra version 3.0; Viocare Technologies Inc, Princeton, NJ).

Statistical methods

The primary endpoints of the study were GE$_{1/2}$, fasting gastric volume, change in gastric volume after the standardized meal, maximum volume of liquid nutrient to reach full satiation, aggregate symptom score 30 min after ingestion of liquid nutrient to full satiation, calories ingested, and macronutrients (g) eaten at the ad libitum meal.

The effects of the different diets were assessed by using 2 complimentary approaches with the SAS Statistical Software Package (SAS Institute Inc, Cary, NC). The first approach considered the study design as a one-factor, parallel-group design with subjects randomly assigned to the different diets. An analysis of covariance (covariates: BMI and baseline satiation volume or aggregate symptom score) was used to compare treatment groups. This analysis also considered interaction terms of BMI and baseline satiation (MTV) with treatment group (diet) to examine whether the treatment effects depended on baseline MTV or BMI. However, with this approach, the treatment effect for a diet cannot strictly be attributed to the largest dietary constituent in a particular diet, eg, the high-fat diet had different amounts of protein and carbohydrate and a greater amount of fat than did the standard diet.
Thus, a second approach that was complementary to the first approach was used. In general, for the mixture-component studies, altering the proportion of one dietary component results in changes in at least 1 of the other 2 dietary components and, thus, comparison of any 2 diets involves the effects of ≥2 dietary constituents. Thus, the effect of each dietary component (eg, fat) per se must be assessed by using a mixture-components analysis (36). This approach uses the actual proportions of the individual dietary constituents in each diet as regressor (predictor) variables and accounts for the constraint on the proportions of the components (fat, protein, and carbohydrate) in each diet that must sum up to 1 (or 100%). A mixture-components analysis assesses the individual effects of each component in relation to a “reference mixture” (the standard diet in this case). The covariates BMI and baseline MTV were also included in these analyses for each endpoint as “dummy regression” variables (ie, normal versus overweight/obese and baseline response below versus above the overall median baseline response) along with interaction terms for covariate level by dietary constituent proportion.

A small number of subjects did not complete all of the studies and, to use an intention-to-treat analysis, the missing data were imputed for GE_{1/2}, fasting gastric volumes and changes in gastric volumes, MTV, and aggregate symptom scores for these subjects. The method of imputation used the overall (subjects with no missing data) mean value for each of these endpoints. The corresponding error df in each analysis was decreased by one for each missing value imputed to adjust for the artificial reduction in variation induced by substituting the same value for the missing data. A per protocol analysis of the ad libitum meal values (total calories and amounts of fat, carbohydrate, and protein consumed) used just the subjects with no missing values. In addition, Pearson correlation coefficients were computed to assess the association of BMI with these responses to the ad libitum meal. The data are presented as raw observed means (±SDs), medians (quartile values), or percentages as appropriate by using just the subjects with no missing data.

Sample size assessment

With 13 subjects per group, there was 80% power to detect differences between specific pairs of diet treatment groups of ≈30% in the primary endpoints of the study, based on mean values and variation in these endpoints in prior studies (31, 37, 38). It was anticipated that the analysis of covariance would provide similar power for somewhat smaller differences by incorporating relevant covariates (eg, baseline value) and by pooling the residual variation across all 4 diet groups.

RESULTS

Participant characteristics

Eighty-seven volunteers were screened, and 52 (BMI: 19.4–47.0) were enrolled in the study. Twenty-one volunteers failed the Three-Factor Eating Questionnaire, 2 volunteers had a low hemoglobin concentration (<11.5 g/dL), 2 volunteers had hypertension, 1 volunteer had a recent attack of panic disorder, and 9 volunteers did not consent to participate in the study. Forty-eight volunteers complied with the diets and completed all of the physiologic studies; 2 participants did not complete the gastric volume measurement. Four of the volunteers did not tolerate the preload meals (2 in the high-carbohydrate diet group and 2 in the standard diet group), and we could not obtain gastric volume measurements in an additional 2 volunteers because of technical errors (1 each in the high-fat and high-protein diet groups). Thus, 4 gastric emptying times, 6 gastric volumes, 4 MTVs, and 4 aggregate symptom scores were imputed.

Demographic characteristics and baseline measurements of satiation from a liquid-nutrient test drink are shown in Table 2. No significant differences were detected between the diet groups.

Effects on the gastric emptying of solids

The effects of individual classes of macronutrients (Figure 2) in excess of caloric requirements on the GE_{1/2} of solids were not significant: standard diet (median: 103 min; interquartile range, IQR: 88–125 min), high-protein diet (median: 114 min; IQR: 100–137 min), high-carbohydrate diet (median: 119 min; IQR: 105–125 min), and high-fat diet (median: 118 min; IQR: 97–128 min).

Effects on maximum tolerated volume and postprandial symptoms

Individual classes of macronutrients in excess of caloric requirements did not significantly alter the volume ingested at the point of maximum satiation or the aggregate symptom score 30 min later (Table 2). However, the statistical analysis detected an interaction between treatment group and baseline MTV (P < 0.01). Thus, an effect of fat was detected in subjects with high baseline MTV values (P < 0.05). For example, in those subjects with high baseline MTV values (above the median value for the entire group) who consumed the high-fat diet, MTV values 2 wk after the high-fat diet were higher than MTV values in other diet groups (Figure 3). The individual symptoms did not differ significantly between the diet groups (Table 2).

Effects on gastric volumes

Fasting gastric volumes did not differ significantly between the 4 diet groups (Figure 2, left panel): standard diet (median: 229 mL; IQR: 191–279 mL), high-protein diet (214 mL; IQR: 153–225 mL), high-carbohydrate diet (207 mL; IQR: 166–227 mL), and high-fat diet (230 mL; IQR: 192–279 mL). Relative to the other diet groups, the fasting gastric volume in the high-fat diet group was numerically, although not statistically, greater (P = 0.11; Figure 4, left panel). The high-fat and high-protein diets contained the same amounts of carbohydrate and reciprocal amounts of fat and protein. The comparison between fasting gastric volumes in these 2 groups was not significant in a post hoc 2-group comparison (P = 0.09).

The changes in postprandial volume relative to fasting (Figure 4, right panel) were not significantly different between the groups: standard diet (median: 776 mL; IQR: 684–813 mL), high-protein diet (median: 702 mL; IQR: 655–801 mL), high-carbohydrate diet (median: 717 mL; IQR: 667–793 mL), and high-fat diet (median: 772 mL; IQR: 737–799 mL).

Effects on food intake at an ad libitum meal

Total calories, total weight of the food, and the distribution of macronutrients consumed at a standard ad libitum meal were not significantly different between the diet groups (Table 3). However, a significant association was found between BMI and the amounts of carbohydrate (Spearman r = 0.44, P = 0.002) and protein (Spearman r = 0.30, P = 0.037) consumed at the ad
libitum meal offered in the study, particularly carbohydrate. This reflects a tradeoff between fat and carbohydrate because the correlation was positive (with increasing BMI) for the proportion of carbohydrate (Spearman $r = 0.65$, $P < 0.001$), but negative for the proportion of fat consumed (Spearman $r = -0.52$, $P < 0.001$).

Gastric functions in different BMI groups across all diets and assessment of study power

No significant differences between normal-weight or overweight and obese persons in the $GE_{1/2}$ of solids, MTV, aggregate symptom score, or fasting and postprandial gastric volumes were observed after ingestion of each preload meal (Table 4).

In view of the lack of significant effects, we assessed the study’s power to identify the anticipated effects. The overall observed variation with no imputation in the primary endpoints was very similar to the estimates that were used before the study to assess the chosen sample sizes, eg, for $GE_{1/2}$ the observed CV was 21%, whereas the prestudy estimate was 31%. Similarly, for

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>High-carbohydrate diet ($n = 13$)</th>
<th>High-fat diet ($n = 13$)</th>
<th>High-protein diet ($n = 13$)</th>
<th>Standard diet ($n = 13$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>35 ± 12$^2$</td>
<td>43 ± 14</td>
<td>37 ± 9</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>3:10</td>
<td>4:9</td>
<td>4:9</td>
<td>3:10</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.2 ± 6.8</td>
<td>27.4 ± 8.0</td>
<td>27.5 ± 5.6</td>
<td>28.8 ± 8.6</td>
</tr>
<tr>
<td>MTV (mL) Baseline</td>
<td>1302 (1065–1539)$^4$</td>
<td>1302 (1065–1599)</td>
<td>1065 (948–1185)</td>
<td>948 (808–1332)</td>
</tr>
<tr>
<td>After diet</td>
<td>1185 (1065–1422)</td>
<td>1362 (918–1659)</td>
<td>1070 (601–1422)</td>
<td>1005 (711–1065)</td>
</tr>
<tr>
<td>Aggregate symptom scores$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>186 (136–245)</td>
<td>131 (93–170)</td>
<td>112 (111–137)</td>
<td>163 (114–200)</td>
</tr>
<tr>
<td>After diet</td>
<td>197 (165–218)</td>
<td>152 (95–210)</td>
<td>146 (122–193)</td>
<td>127 (95–206)</td>
</tr>
<tr>
<td>Fullness score$^s$</td>
<td>70 (62–82)</td>
<td>75 (65–80)</td>
<td>61 (44–72)</td>
<td>72 (63–77)</td>
</tr>
<tr>
<td>Baseline</td>
<td>75 (63–85)</td>
<td>80 (74–86)</td>
<td>73 (63–82)</td>
<td>73 (62–85)</td>
</tr>
<tr>
<td>After diet</td>
<td>32 (7–58)</td>
<td>27 (0–47)</td>
<td>6 (0–39)</td>
<td>16 (2–51)</td>
</tr>
<tr>
<td>Nausea score$^s$</td>
<td>15 (9–73)</td>
<td>7 (0–27)</td>
<td>5 (0–35)</td>
<td>22 (5–39)</td>
</tr>
<tr>
<td>Baseline</td>
<td>32 (7–58)</td>
<td>27 (0–47)</td>
<td>6 (0–39)</td>
<td>16 (2–51)</td>
</tr>
<tr>
<td>After diet</td>
<td>55 (44–76)</td>
<td>33 (0–58)</td>
<td>35 (18–60)</td>
<td>53 (0–62)</td>
</tr>
<tr>
<td>Bloating score$^s$</td>
<td>61 (51–72)</td>
<td>39 (4–56)</td>
<td>47 (33–66)</td>
<td>24 (7–69)</td>
</tr>
<tr>
<td>Baseline</td>
<td>20 (8–35)</td>
<td>15 (0–23)</td>
<td>0 (0–11)</td>
<td>12 (0–17)</td>
</tr>
<tr>
<td>After diet</td>
<td>21 (7–38)</td>
<td>11 (7–33)</td>
<td>7 (0–22)</td>
<td>6 (0–21)</td>
</tr>
</tbody>
</table>

$^1$ ANOVA was used for the statistical analysis of baseline scores and age; ANCOVA was used for the statistical analysis of postdiet changes with BMI and baseline MTV or aggregate symptom scores as covariates. A separate statistical analysis used a mixture-components analysis (36) and included the same covariates. No statistically significant differences in any of the variables analyzed were observed.

$^2$ ± SD (all such values).

$^3$ Medians; interquartile ranges in parentheses (all such values).

$^4$ Maximum score = 400.

$^5$ Maximum individual score = 100.
fasting gastric volume, the observed CV was 25%, and the pre-
study estimate was 31%. The postprandial gastric volume CV
was 10%, and the prestudy estimate was 15%. Only the MTV had
an observed CV of 34% greater than the prestudy estimate of
25%. Thus, the study was not underpowered on the basis of the
variation that we expected. The proposed sample sizes provided
80% power to detect differences between any 2 diet groups (\(n/L_1155\) per group) of 17–36% on the basis of the prestudy estimates.
In fact, smaller effect sizes in gastric emptying and gastric vol-
umes would have been detectable with the smaller CV that we
actually observed.

DISCUSSION

This study was conducted in otherwise healthy persons across
a wide range of body mass, from normal weight to obese (BMI:
19.4–47.0). Ingestion for 2 wk of different classes of macronu-
trient diets, 500 kcal in excess of required calories, did not sig-
nificantly change gastric functions or symptoms after a challenge
meal. However, the MTV of liquid nutrient was higher in those
with high baseline MTV values randomized to fat supplementa-
tion of the diet. There was also a significant association between
BMI and the amounts of carbohydrate and protein consumed at
the ad libitum meal offered in the study, particularly carbohy-
drate. This reflects a tradeoff between fat and carbohydrate con-
sumed, with increasing BMI associated with more carbohydrate
and less fat consumed.

The results of this comprehensive study suggest that gastric
ejecting solids and change in gastric volume with ingestion of
a standard meal do not appear to determine the change in
satiation at a challenge test, during which participants ingested a
liquid nutrient to the maximum volume possible. Satiety at an ad
libitum meal was not significantly different between the 4 diet
groups. Although satiation is a significant factor in determining
the effects of fat supplementation, irrespective of BMI, these data
need to be discussed relative to the findings of previous studies.

Gastric emptying may be influenced by patterns of previous
nutrient intake in animals (1–4), but the data from previous
human studies were conflicting and included small numbers of
participants (13, 14, 20). We used standard validated question-
naires to exclude persons with eating disorders or restrained
feeding patterns. Our data show that the gastric emptying of
solids was not significantly different between the 4 diet groups
after 2 wk of supplementation with different classes of macro-
nutrients in normal-weight, overweight, and obese people.

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td>Energy and macronutrient intakes from the ad libitum meal(^1)</td>
</tr>
<tr>
<td>High-carbohydrate diet ((n = 13))</td>
</tr>
<tr>
<td>Meal energy (kcal)</td>
</tr>
<tr>
<td>Meal weight (g)</td>
</tr>
<tr>
<td>Fat (g)</td>
</tr>
<tr>
<td>Protein (g)</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
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</table>

\(^1\) All values are medians; interquartile ranges in parentheses. No significant differences were observed between groups (ANOVA).
Fat supplementation resulted in increased MTV of the nutrient drink, but this effect was independent of BMI and was influenced by high baseline satiation volume. Previous studies have shown that BMI and gastric volume are independent determinants of MTV (37) and that postprandial symptoms of satiation in dyspepsia and obesity are significantly influenced by fasting gastric volume (37, 38). No significant differences in fasting gastric volume were associated with the supplementation of the 4 different classes of macronutrients. These data suggest that, if healthy persons ingest a consistently high-fat diet, time to satiation may be delayed and lead to ingestion of more food to achieve a satisfactory level of fullness and, ultimately, to obesity.

The effects of a longer duration and larger supplementation of high-fat diets on fasting gastric volume deserve further study to more clearly establish whether there is a behavioral or physiologic adaptation or other reason for modification of diet choices. Such studies are also needed to more clearly elucidate the relation between retardation of fullness after meals and gastric volumes. Bulimia is associated with increased gastric capacity (39), but obesity per se does not induce a greater gastric capacity (39, 40). Our current data showed that MTV and fasting gastric volume were not significantly different between normal-weight or overweight and obese subjects after 2 wk of supplementation with different amounts of macronutrients in the diet.

Cunningham et al (13) observed that feelings of hunger before a test meal and of fullness after a meal were not significantly different between healthy male volunteers who ingested a high-fat or a low-fat diet for 14 d in a crossover study. The overall observations concerning satiation with a test meal were generally similar to those in our study, although the calorie intake in the study by Cunningham et al was markedly higher (4600-kcal preload/d and 2150 kcal/d from a test meal) than that in our study (average 3200-kcal preload/d and 1100 kcal from a test meal). We elected to assess the effect of macronutrient preloading on a standard test meal to avoid the potential effect of the test meal itself on gastric functions.

In a second study from Adelaide, ingestion of a high-fat diet (4800 kcal) for 2 wk by normal-weight or overweight healthy males was associated with higher hunger ratings during duodenal lipid infusion than was the same infusion after a lower-fat diet (2670 kcal) (22). The differences observed may have been due to changes in gastric accommodation induced by intraduodenal lipid after the different fat contents in the diet (22). However, in response to the more physiologic, balanced-nutrient, orally administered liquid-nutrient meal, the postprandial gastric volumes after the 4 diets were very similar in our study.

Three studies have shown that calorie intake from a test meal was unchanged after the ingestion for 2 wk of a high-fat diet (13, 21, 22). In one study, increased food consumption measured through the use of a daily diary was noted (21). In our study, food intake at a single meal after supplementation with different classes of macronutrients did not differ significantly between the diet groups, although BMI influenced the choice of carbohydrate and fat offered.

The distribution of the macronutrient consumed at the ad libitum meal was not significantly different between the diet groups. This information is consistent and expands on the data from Adelaide (22) in men, because our study evaluated subjects of both sexes and with a broad spectrum of BMI, from normal weight to obesity. It remains to be shown whether the 2-wk period of preload meal supplementation with different macronutrients might have been too short to induce a change in food choice in healthy persons. Our study presents the fourth independent confirmation in humans that 2 wk of supplementation with fat or other macronutrients does not result in the gastrointestinal adaptation observed in animal studies.

A limitation in the study design in humans is that there are limitations in the degree to which a specific class of macronutrient can be enriched by using normal food. This contrasts with animal studies, for which the diet can be enriched to almost 100% with one class of macronutrient. However, the approach used in our human study was previously used to show differences in pancreatic enzyme secretion in response to dietary changes (41).

A second possible limitation is the magnitude of effect demonstrable with the sample size studied. The effect sizes that could be detected with the sample size used ranged from 16% to 31%; this magnitude of change reflects the typical effects reported in disorders of gastric function seen in functional dyspepsia. Therefore, the effect sizes demonstrable were clinically relevant. Post hoc evaluation showed that the observed CVs were actually smaller than anticipated and, therefore, our planned sample sizes were appropriate.

In summary, a high-fat diet may facilitate adaptive changes that contribute to the development of obesity through reduced postprandial satiation in persons with a high baseline MTV. Given the lack of significant changes in gastric motor functions studied, the data are consistent with the hypothesis that a high fat intake influences the central control of appetite and behavioral choices in food intake. An additional effect that may contribute to obesity is adaptation in absorptive function, as suggested by fat-induced changes in villus height and nutrient absorption (5–7, 16–18). Additional well-controlled large studies with a longer preload duration in healthy normal-weight and obese persons are needed to elucidate the presence and extent of gastrointestinal sensory, motor, absorptive, and behavioral adaptations to diets enriched with specific macronutrients.

MC was the principal investigator. MIP, DS, and DB recruited the subjects and conducted the studies. HO and LO planned the meal contents. ARZ analyzed the data. All authors were involved in writing the manuscript. None of the authors had any conflicts of interest to declare.

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