ABSTRACT
Background: Low–glycemic index (GI) diets have been proven to have beneficial effects in such chronic conditions as type 2 diabetes, ischemic heart disease, and some types of cancer, but the effect of low-GI diets on weight loss, satiety, and inflammation is still controversial.

Objective: We assessed the efficacy of 2 moderate-carbohydrate diets and a low-fat diet with different GIs on weight loss and the modulation of satiety, inflammation, and other metabolic risk markers.

Design: The GLYNDIET study is a 6-mo randomized, parallel, controlled clinical trial conducted in 122 overweight and obese adults. Participants were randomly assigned to one of the following 3 iso-caloric energy-restricted diets for 6 mo: 1) a moderate-carbohydrate and high-GI diet (HGI), 2) a moderate-carbohydrate and low-GI diet (LGI), and 3) a low-fat and high-GI diet (LF).

Results: At weeks 16 and 20 and the end of the intervention, changes in body mass index (BMI; in kg/m²) differed significantly between intervention groups. Reductions in BMI were greater in the LGI group than in the LF group, whereas in the HGI group, reductions in BMI did not differ significantly from those in the other 2 groups (LGI: −2.45 ± 0.27; HGI: −2.30 ± 0.27; LF: −1.43 ± 0.27; F = 4.616, P = 0.012; pairwise comparisons: LGI compared with HGI, P = 1.000; LGI compared with LF, P = 0.016; HGI compared with LF, P = 0.061). The decrease in fasting insulin, homeostatic model assessment of insulin resistance, and homeostatic model assessment of β cell function was also significantly greater in the LGI group than in the LF group (P < 0.05). Despite this tendency for a greater improvement with a low-GI diet, the 3 intervention groups were not observed to have different effects on hunger, satiety, lipid profiles, or other inflammatory and metabolic risk markers.

Conclusion: A low-GI and energy-restricted diet containing moderate amounts of carbohydrates may be more effective than a high-GI and low-fat diet at reducing body weight and controlling glucose and insulin metabolism. This trial was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN54971867. Am J Clin Nutr 2014;100:27–35.

INTRODUCTION

Despite all the efforts of the scientific community and public health strategies, obesity is still one of the most important public health concerns and has been related to such comorbidities as hypertension, dyslipidemia, type 2 diabetes (T2D)², cardiovascular disease, and cancer (1). Current weight-management strategies have proposed physical activity, changes in diet, and changes in behavior as the keys to preventing and treating excess weight and obesity. Traditionally, these strategies have included energy-restricted diets with >50% of calories from carbohydrates, <30% of calories from fat, and the rest of calories from protein, but there is still no consensus on the role of the quality of the dietary macronutrient composition in long-term weight loss. A recent meta-analysis of randomized controlled trials that compared low-carbohydrate non–energy-restricted diets with energy-restricted low-fat (LF) diets showed that they were all equally effective for weight loss. However, low-carbohydrate diets were related to better improvements in the lipid profile (2). Nonetheless, in a pooled analysis that was based on observational studies, low-carbohydrate diets seemed to be associated with increased risk of all-cause mortality (3).

In 1998, the Food and Agriculture Organization of the United Nations suggested that the glycemic index (GI) of foods, which was a concept introduced by Jenkins et al (4) in 1981 to measure the quality of carbohydrates, could determine health status (5). Since then, several studies have evaluated the importance of

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2 Supported by the Institut d’Investigació Sanitària Pere Virgili (PV11059S) and the Fondo de Investigación Sanitaria (PI120153).
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4 Abbreviations used: CRP, C-reactive protein; GI, glycemic index; GL, glycemic load; GLP-1, glucagon-like peptide-1; HGI, high glycemic index; HOMA-BCF, homeostatic model assessment of β cell function; ITT, intention to treat; LF, low fat; LGI, low glycemic index; PP, per protocol; RCT, randomized, controlled clinical trial; T2D, type 2 diabetes; VAS, visual analog scale.

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dietary GI in different chronic conditions (6–9). However, the European Food Safety Authority has concluded that there is insufficient scientific evidence to recommend low–glycemic index (LGI) diets in the context of obesity treatment (10).

Physiologic mechanisms that relate high glycemic index (HGI) and body weight gain could be based on the postprandial metabolic environment precipitated by hyperglycemia and hyperinsulinemia, which accelerate glucose oxidation and stimulate fat storage. Even so, some authors have suggested that this relation is not of sufficient magnitude or duration to modify fuel oxidation (11). Satiety modulation also appears to be a potential mechanism that relates LGI and weight loss. Short-term satiety has been shown to increase in the vast majority of studies, although results have been inconsistent in long-term studies (12–14). Finally, few randomized clinical trials have been designed to evaluate the effect of GI or glycemic load (GL) on inflammation or related inflammatory markers (15–19). Most of these studies have been conducted in a reduced number of participants, have evaluated few biochemical markers, were of short duration, and usually did not control for other potential dietary confounders. For these reasons, the precise role that dietary GI plays in inflammation is still controversial. We hypothesized that LGI diets exert a greater beneficial effect on weight loss than do HGI or traditional LF diets. The GLYNDIET study was a 6-mo randomized, controlled, dietary-intervention trial designed to assess the efficacy of 2 moderate-carbohydrate diets and an LF diet with different GIs on weight loss and the modulation of satiety, inflammation, and other metabolic risk markers.

SUBJECTS AND METHODS

Study population

The GLYNDIET study was designed as a 6-mo randomized, parallel, controlled, clinical trial with the aim of evaluating the effect of dietary GI on weight loss, satiety, glucose and insulin metabolism, lipid profile, inflammation, and other emergent metabolic risk markers. Full details of the GLYNDIET study protocol have been published elsewhere (20). Eligible participants were community-dwelling men and women aged between 30 and 60 y with BMI (in kg/m²) between 27 and 35 who were noncontrolled T2D defined as glycated hemoglobin >8%; 2) systolic blood pressure >159 mm Hg or diastolic blood pressure >99 mm Hg; 3) plasma LDL cholesterol concentration >160 mg/dL; 4) plasma triglyceride concentration >400 mg/dL; 5) suspicion of secondary obesity; 6) presence of any inflammatory or chronic obstructive pulmonary disease, infection, active neoplastic, endocrine, or hematologic disease at the time of the study; 7) blood leukocyte count ≥11 × 10⁶ cells; 8) use of anti-inflammatory drugs, steroids, hormones or antibiotics that could affect the variables analyzed in the study; 9) changes in medication for lipid profile, diabetes, or hypertension in the previous 3 mo; 10) active alcoholism or drug dependence, excluding tobacco use; 11) a restrictive diet 3 mo before the study or weight loss >5 kg in the previous 3 mo; 12) any medical condition that advised against being included in the study; and 13) problems understanding the study or anticipated difficulty in making dietary changes according to the Prochaska and DiClemente model (21). Participants who fulfilled inclusion criteria were randomly assigned to 3 different dietary intervention groups of the same size. Random assignment was done by using a computer-generated, random-number sequence. Subjects were assigned to blocks of 3 participants balanced for sex, age (≤45 and ≥45 y), and antidiabetic medication use (yes or no). The Institutional Review Board of the Sant Joan University Hospital (Reus, Spain) approved the study protocol on February 2009. All participants gave their written informed consent to participate in the study. This trial was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN54971867.

Diets

The LGI and HGI diets had similar energy contents and macronutrient compositions but included foods with different GIs. GI values of each food were extracted from the International Glycemic Index, and GLs were determined by using glucose as the reference scale (22). The LF diet fulfilled the criteria defined by the American Heart Association (23). The total daily energy expenditure for each participant was estimated by using WHO equations and taking into account the estimated physical activity. Diets were designed at 1500, 1700, 2000, and 2500 kcal/d, and all participants were categorized as having one of the 4 categories of dietary energy content after subtracting 500 kcal/d of the total estimated energy intake to achieve a desired weight loss. Main characteristics of the diets used in the 3 intervention groups are shown in Table 1.

Anthropometric and biochemical measurements

Individual examinations were scheduled at baseline, 15 d into the intervention, and monthly until the end of the study. Laboratory technicians and statisticians were blinded to group assignments. Body weight and height were measured by using calibrated scales and a wall-mounted stadiometer with subjects wearing light clothes and no shoes. BMI was calculated. Waist circumference was measured twice midway between the lowest rib and the iliac crest. Body composition was measured by using a bioelectrical impedance analysis (TANITA TBF-300; Tanita), and we encouraged participants to void their bladders before all visits. Blood pressure was measured in the nondominant arm of each participant by using a validated semiautomatic oscillometer (Omron HEM-705CP; OMRON Corp) in duplicate with a 5-min interval between each measurement. Means of these values were recorded. Satiety was evaluated at baseline after a test meal by using visual analog scales (VASs). Physical activity was evaluated by using the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (24). Blood samples

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of diets</th>
<th>LGI diet</th>
<th>HGI diet</th>
<th>LF diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy from protein (% of kcal)</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Energy from carbohydrates (% of kcal)</td>
<td>42</td>
<td>42</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Energy from total fat (% of kcal)</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Glycemic index</td>
<td>34</td>
<td>62</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

1 HGI, high glycemic index; LF, low fat; LGI, low glycemic index.
were collected at baseline and end of the study. Plasma fasting glucose, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, and nonesterified fatty acid concentrations were determined by using standard enzymatic automated methods (COBAS; Roche Diagnostics Ltd). In subjects whose triglyceride concentrations were <400 mg/dL, LDL-cholesterol concentrations were estimated by using Friedewald’s formula. Fasting insulin (Merck Millipore), oxidized LDL (Merdodia), total osteocalcin (DRGinstruments GmbH), and uncarboxylated osteocalcin (Takara Bio) were determined in plasma by using enzyme-linked immunosorbent assay commercial kits. All other metabolic biomarkers [ie, glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide), glucagon-like peptide-1 (GLP-1), peptide YY, leptin, monocyte chemotactic protein-1, adiponectin, plasminogen activator inhibitor-1, soluble intercellular adhesion molecule 1, and soluble vascular cell adhesion molecule 1] were determined by using a MILLIPLEX MAP Plex Kit (Merck Millipore). Insulin resistance and secretion were estimated by using HOMA-IR and homeostatic model assessment of β cell function (HOMA-BCF) methods (25).

Dietary assessment

Dietary intake was estimated at baseline and first, third, and sixth months of the intervention by using 3-d dietary records that included 2 workdays and a weekend day. Energy and nutrient intake were calculated by using Spanish food-composition tables (26).

VASs

At baseline, a fixed breakfast test, according to the nutritional characteristics of the intervention-assigned diets, was served to all subjects (see Supplemental Table 1 under “Supplemental data” in the online issue). VASs were evaluated in a fasted state (immediately before the breakfast) and every 30 min after for a period of 2 h in a controlled environment. Appetite ratings consisted of questions regarding hunger, satiety, fullness, and desire to eat. Participants were instructed to consider the extremes of each rating as the most-intense sensation they could imagine. Questions included “How hungry do you feel now?” “How satiated do you feel now?” “How full do you feel now?” and “How strong is your desire to eat now?” and were accompanied by horizontal lines anchored at each end by the words “Not at all” and “Extremely.”

Statistical analysis

Descriptive data of participants at baseline and differences between final and baseline visits for continuous measures are shown as means (±SEM) or medians and IQRs. Descriptive data for categorical variables are shown as numbers and percentages. The normal distribution of variables was tested by using the Kolmogorov-Smirnov test. An ANOVA and ANCOVA were used to assess differences intervention groups both in anthropometric and biochemical variables, respectively, in those variables with a normal distribution. Changes in biochemical variables were adjusted for their baseline values. The Bonferroni post-hoc test was used for multiple comparisons. Variables without a normal distribution were analyzed by using the Kruskal-Wallis test for comparisons between intervention groups and the Mann-Whitney test for pairwise comparisons by applying Bonferroni correction. These variables were adjusted by baseline values of each variable by using the residual method (27). All statistical analyses were conducted by both intention-to-treat (ITT) and per protocol (PP) approaches. The ITT analysis included all randomly assigned participants. The last observation carried forward was used for handling missing data. The PP analysis excluded participants who did not attend the last visit (see Supplemental Tables 2 and 3 under “Supplemental data” in the online issue for results). A power analysis for ANOVA showed that a sample size of 33 participants was required for each group to detect a mean weight-loss difference similar to that published by other authors (28, 29), with an α error of 0.05, and a power of 0.90. All analyses were done with SPSS 19.0 software (SPSS Inc), and significance was defined as P < 0.05.

RESULTS

Study participants

The study flowchart is shown in Figure 1. A total of 543 participants were screened by telephone to identify 215 eligible participants. Of these individuals, 122 subjects met all inclusion criteria and were randomly assigned to one of the 3 intervention groups. During the intervention, 17 of 122 randomly assigned participants (14%) dropped out of the study. The dropout rate was lower in both LGI- and HGI-diet groups than in the LF-diet group (9.8% compared with 22.5%). One participant was finally excluded from the analysis because she decided to withdraw her informed consent, and she was not included in any of the analyses. Baseline characteristics of participants are shown in Table 2. At baseline, no significant differences were observed between intervention groups in sex, age, anthropometric measurements, blood pressure, or prevalence of comorbidities.

Diets

See Supplemental Table 4 under “Supplemental data” in the online issue for baseline and 6-mo changes in dietary variables. At baseline, study intervention diets were similar between groups, with the exception of percentage of energy coming from protein intake (mean ± SEM: 17.0% ± 0.4%, 18.8% ± 0.5%, and 18.4% ± 0.5% for LGI-, HGI-, and LF-diet groups, respectively; P = 0.023). After 6 mo, subjects in the LF-diet group showed significantly higher intake of carbohydrates and lower intake of fat than did subjects in the HGI- and LGI-diet groups (P < 0.001). Also, participants allocated to the LGI-diet group had significantly lower dietary GI than did those allocated to HGI- and LF-diet groups (P < 0.001).

Total-body weight loss

In the ITT analysis, BMI decreased significantly throughout the 6-mo intervention in the 3 experimental groups (Figure 2). During the first 12 wk of intervention, no significant differences in body weight loss were observed between groups. At weeks 16, 20, and 24, decreases in BMI were higher in the LGI-diet group than in the LF-diet group (Figure 2). No significant changes in waist circumference (Figure 2) or body composition were observed between groups (changes in the percentage of fat-free mass with respect to changes in body weight were 41.5 ±
8.4%, 37.9 ± 8.2%, and 43.7 ± 8.3% in the LGI-, HGI-, and LF-diet groups, respectively; \( P = 0.879 \).

The PP analysis included 104 participants who finished the study. After 6 mo of intervention, changes in BMI were higher in the LGI-diet group than in the LF-diet group (\( P = 0.01 \)). Other anthropometric measurements were similar to those taken in the ITT analysis (see Supplemental Figure 1 under “Supplemental data” in the online issue).

**Glucose metabolism and lipid profile**

Mean (±SEM) values for glucose metabolism and lipid profile at baseline and 6-mo changes are shown in Table 3. Improvements in fasting insulin, HOMA-IR, and HOMA-BCF were greater in the LGI-diet group than in the LF-diet group. No significant differences were observed compared with the HGI-diet group. After adjustment for changes in BMI, the improvement in HOMA-BCF remained significant (\( P = 0.03 \)), and changes in HOMA-IR were slightly attenuated (\( P = 0.05 \)). Changes in lipid profile were not different between groups. PP results (see Supplemental Table 2 under “Supplemental data” in the online issue) were very similar to those shown by using the ITT approach.

**Satiety, inflammation status, and other related markers**

Baseline and 6-mo changes in satiety, inflammation status, and biomarkers of endothelial function are shown in Table 4. No

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**TABLE 2**
Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>LGI diet (( n = 41 ))</th>
<th>HGI diet (( n = 40 ))</th>
<th>LF diet (( n = 40 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F) [n (%)]</td>
<td>33 (81)</td>
<td>33 (83)</td>
<td>31 (78)</td>
<td>0.853</td>
</tr>
<tr>
<td>Age (y)</td>
<td>42.5 ± 1.1(^2)</td>
<td>44.0 ± 1.3</td>
<td>44.1 ± 1.3</td>
<td>0.603</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.7 ± 1.5</td>
<td>82.7 ± 1.6</td>
<td>83.5 ± 1.7</td>
<td>0.912</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>31.3 ± 0.3</td>
<td>30.8 ± 0.3</td>
<td>30.8 ± 0.3</td>
<td>0.544</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>101.8 ± 1.2</td>
<td>100.0 ± 1.3</td>
<td>103.1 ± 1.1</td>
<td>0.204</td>
</tr>
<tr>
<td>Free fat mass (kg)</td>
<td>49.6 ± 1.2</td>
<td>50.3 ± 1.5</td>
<td>51.3 ± 1.6</td>
<td>0.721</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128.0 ± 2.7</td>
<td>128.0 ± 2.4</td>
<td>131.3 ± 2.2</td>
<td>0.555</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.2 ± 1.7</td>
<td>81.2 ± 1.5</td>
<td>82.8 ± 1.4</td>
<td>0.493</td>
</tr>
<tr>
<td>Hypercholesterolemia [n (%)]</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>5 (13)</td>
<td>0.459</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>7 (17)</td>
<td>5 (13)</td>
<td>5 (13)</td>
<td>0.791</td>
</tr>
<tr>
<td>Current smokers [n (%)]</td>
<td>8 (20)</td>
<td>5 (13)</td>
<td>5 (13)</td>
<td>0.591</td>
</tr>
<tr>
<td>Leisure-time physical activity (kcal/d)</td>
<td>205.5 ± 47.1</td>
<td>280.9 ± 47.2</td>
<td>200.0 ± 37.3</td>
<td>0.355</td>
</tr>
</tbody>
</table>

\(^2\) Mean ± SEM (all such values).

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\(^1\) \( P \) values of differences between intervention groups (ANOVA was used for continuous variables, and the chi-square test was used for categorical variables). HGI, high glycemic index; LF, low fat; LGI, low glycemic index.
significant differences were observed in baseline peripheral blood metabolic marker concentrations between groups. The exception was concentrations of adiponectin, which were lower in the LF-diet group. At 6 mo, a decrease in GLP-1 observed in the HGI-diet group differed from changes observed in the LF-diet group (median 6 IQR: 2.1.65 6 2.88 compared with 0.30 6 3.28 pg/mL, respectively; P = 0.028). These differences were attenuated after adjustment for changes in BMI (P = 0.144; data not shown). Diets were not observed to have any significant effects on other biomarkers analyzed although they tended to improve throughout the intervention in the LGI diet. PP changes in metabolic risk markers were similar to those shown by using the ITT approach (see Supplemental Table 3 under “Supplemental data” in the online issue).

**DISCUSSION**

To our knowledge, this is the first study to simultaneously evaluate the effectiveness of moderate-carbohydrate LGI, moderate-carbohydrate HGI, and LF diets with weight loss as the main outcome. Results of the current randomized, controlled, clinical trial (RCT) showed that the LGI diet reduced weight more effectively than did a traditional LF diet. Moreover, the LGI diet led to a significantly greater improvement in insulin resistance and sensitivity than did the LF diet. LGI and HGI diets were not observed to have different effects on body weight and insulin metabolism. Postprandial satiety and hunger rates, lipid
such as protein or total fiber. Recently, long-term effects of LGI on weight loss (30) than did HGI or other control diets. Un-
between 5 wk and 6 mo showed that LGI diets had a greater effect
meta-analysis conducted on 6 RCTs with a total of 202 subjects
of GI and GL on weight management remains controversial. A
markers were similarly affected by the 3 dietary interventions.
profile, inflammation, and related peripheral metabolic risk
Even though GI and GL modulation has emerged as a dietary
Total osteocalcin (ng/mL)$$^3$$
Baseline 7.74 ± 0.54
6-mo change 1.90 ± 0.38
Uncarboxylated osteocalcin (ng/mL)$$^3$$
Baseline 7.09 ± 0.64
6-mo change 0.91 ± 0.41
Total cholesterol (mmol/L)$$^4$$
Baseline 4.99 ± 0.13
6-mo change −0.05 ± 0.11
HDL cholesterol (mmol/L)$$^4$$
Baseline 1.45 ± 0.05
6-mo change 0.03 ± 0.03
LDL cholesterol (mmol/L)$$^4$$
Baseline 3.05 ± 0.11
6-mo change 0.03 ± 0.08
Oxidized LDL (mU/L)$$^4$$
Baseline 48.69 ± 2.21
6-mo change −0.46 ± 1.64
Total-cholesterol:HDL-cholesterol ratio$$^4$$
Baseline 3.51 ± 0.11
6-mo change −0.13 ± 0.05
LDL-cholesterol:HDL-cholesterol ratio$$^4$$
Baseline 2.16 ± 0.09
6-mo change −0.04 ± 0.05
Triglycerides (mmol/L)$$^4$$
Baseline 1.00 ± 0.47
6-mo change −0.27 ± 0.42
Nonesterified fatty acids (µmol/L)$$^4$$
Baseline 534.18 ± 30.92
6-mo change −26.02 ± 25.15
1 ANCOVA models were used to assess differences between intervention groups in variables with normal distributions, and the Kruskal-Wallis test was used in variables without normal distributions. Changes in biochemical variables were adjusted for baseline values of each biochemical variable. HGI, high glycemic index; HOMA-BCF, homeostatic model assessment of β cell function; LF, low fat; LGI, low glycemic index.
2 Values are means ± SEMs.
3 Values are medians ± IQRs (variable without a normal distribution).
4 Significant difference compared with LF-diet group ($P < 0.005$).

profile, inflammation and related peripheral metabolic risk markers were similarly affected by the 3 dietary interventions.
Even though GI and GL modulation has emerged as a dietary alternative for the prevention or treatment of obesity, the effect of GI and GL on weight management remains controversial. A meta-analysis conducted on 6 RCTs with a total of 202 subjects who were randomly assigned to dietary interventions that ranged between 5 wk and 6 mo showed that LGI diets had a greater effect on weight loss (30) than did HGI or other control diets. Unfortunately, the studies did not adjust for potential confounders such as protein or total fiber. Recently, long-term effects of LGI compared with HGI diets have been assessed by a meta-analysis of 14 RCTs. Although the decrease in total body fat–free mass was significantly more pronounced after LGI diets, no significant changes were observed in weight and waist circumference compared with HGI diets have been assessed by a meta-analysis of 14 RCTs. Although the decrease in total body fat–free mass was significantly more pronounced after LGI diets, no significant changes were observed in weight and waist circumference compared with HGI diets. In our study, subjects assigned to an LGI- or HGI diet lost more weight than did those in the LF-diet group, even after adjustment for potential dietary confounders. Our results suggested that diets rich in fat mainly derived from plant sources and with moderate amounts of carbohydrate, such as the Mediterranean Diet, are more effective at managing obesity than traditional LF diets are,
Analysis showed that LGI diets had a significantly greater effect on fasting insulin than did HGI diets (31). In the GLYNDIET study, both insulin sensitivity and resistance significantly improved in participants in the LGI-diet group even after adjustment for changes in body weight, which suggested additional mechanisms that link GI and GL and insulin metabolism rather than body-weight reduction. Improvements in glycemia and insulinemia attributable to LGI diets could be mediated by changes in the incretin axis. In this regard, a 28-d weight-maintaining, HGL controlled diet led to significantly lower postprandial concentrations of GLP-1 than did a low-GL diet after a test breakfast (33). Results of our study support a long-term effect of GI on the incretin axis. However, the significant decrease in glucagon-like peptide-1 circulating concentrations observed in the HGI-diet group could explain the higher decrease of glucose concentrations observed in the same dietary intervention group. Additional research is needed to understand the exact long-term effect of GI and GL on the incretin axis and its implication in obesity and T2D. Because of the postulated effect of both osteocalcin and uncarboxylated osteocalcin forms on insulin resistance (34), the slightly higher increase in osteocalcin and uncarboxylated

irrespective of the quality of the carbohydrates determined by the GI. Nonetheless, the LGI diet had a slightly greater effect on body weight loss than did the HGI diet, which indicated that these diets can be used for clinical weight management.

In the current study, no differences were observed between diets in satiety or hunger rates derived from VASs, which suggested that the effect on body weight of LGI or HGI diets is mediated by other mechanisms rather than short-term satiety modulation. Despite this, and in line with results of short-term satiety studies (12), we observed a nonsignificant tendency to higher satiety rates and lower hunger rates in the LGI-diet group than in other groups.

Insulin sensitivity has been thought to have an important association with the effectiveness of GI on weight change (32). However, reports on the effect of dietary GI or GL on glucose and insulin metabolism have provided inconsistent data. Results of a recent systematic review and meta-analysis of RCTs showed no significant effects of diets with a different GI or GL on fasting glucose and glycated hemoglobin. However, the same meta-analysis showed that LGI diets had a significantly greater effect on fasting insulin than did HGI diets (31). In the GLYNDIET study, both insulin sensitivity and resistance significantly improved in participants in the LGI-diet group even after adjustment for changes in body weight, which suggested additional mechanisms that link GI and GL and insulin metabolism rather than body-weight reduction. Improvements in glycemia and insulinemia attributable to LGI diets could be mediated by changes in the incretin axis. In this regard, a 28-d weight-maintaining, HGL controlled diet led to significantly lower postprandial concentrations of GLP-1 than did a low-GL diet after a test breakfast (33). Results of our study support a long-term effect of GI on the incretin axis. However, the significant decrease in glucagon-like peptide-1 circulating concentrations observed in the HGI-diet group could explain the higher decrease of glucose concentrations observed in the same dietary intervention group. Additional research is needed to understand the exact long-term effect of GI and GL on the incretin axis and its implication in obesity and T2D. Because of the postulated effect of both osteocalcin and uncarboxylated osteocalcin forms on insulin resistance (34), the slightly higher increase in osteocalcin and uncarboxylated

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<thead>
<tr>
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<th>HGI diet (n = 40)</th>
<th>LF diet (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric inhibitory polypeptide (pg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.71 ± 19.91</td>
<td>19.77 ± 16.58</td>
<td>23.11 ± 12.59</td>
<td>0.804</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−5.66 ± 19.45</td>
<td>−7.67 ± 8.35</td>
<td>−5.41 ± 13.87</td>
<td>0.511</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 (pg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>64.63 ± 16.25</td>
<td>64.23 ± 18.44</td>
<td>66.51 ± 14.23</td>
<td>0.944</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−0.49 ± 4.11</td>
<td>−1.65 ± 2.88³</td>
<td>0.30 ± 3.28</td>
<td>0.028</td>
</tr>
<tr>
<td>Peptide YY (pg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>111.64 ± 20.41</td>
<td>110.40 ± 24.35</td>
<td>111.00 ± 23.96</td>
<td>0.531</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−2.99 ± 7.19</td>
<td>−3.48 ± 9.24</td>
<td>−1.92 ± 5.55</td>
<td>0.231</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 (pg/mL)³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>159.72 ± 10.84</td>
<td>170.66 ± 10.72</td>
<td>190.61 ± 10.76</td>
<td>0.133</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−12.56 ± 7.74</td>
<td>−15.17 ± 7.81</td>
<td>−6.02 ± 7.87</td>
<td>0.700</td>
</tr>
<tr>
<td>C-reactive protein (µg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.99 ± 4.34</td>
<td>3.58 ± 6.25</td>
<td>3.70 ± 5.59</td>
<td>0.520</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−0.19 ± 1.78</td>
<td>−0.07 ± 2.74</td>
<td>−0.04 ± 1.72</td>
<td>0.457</td>
</tr>
<tr>
<td>IL-6 (pg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.67 ± 1.18</td>
<td>1.36 ± 0.90</td>
<td>1.66 ± 1.11</td>
<td>0.324</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−0.27 ± 0.86</td>
<td>0.12 ± 0.91</td>
<td>−0.01 ± 0.72</td>
<td>0.162</td>
</tr>
<tr>
<td>Leptin (ng/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14.47 ± 12.46</td>
<td>13.74 ± 10.36</td>
<td>13.01 ± 14.67</td>
<td>0.663</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−5.64 ± 7.23</td>
<td>−6.03 ± 6.81</td>
<td>−3.75 ± 4.81</td>
<td>0.144</td>
</tr>
<tr>
<td>Monocyte chemotactic protein-1 (pg/mL)⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>96.22 ± 4.33</td>
<td>95.78 ± 4.29</td>
<td>95.76 ± 4.30</td>
<td>0.997</td>
</tr>
<tr>
<td>6-mo change</td>
<td>−5.39 ± 5.01</td>
<td>−2.87 ± 3.05</td>
<td>−9.79 ± 3.05</td>
<td>0.271</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63.18 ± 71.84</td>
<td>69.97 ± 72.10</td>
<td>51.29 ± 44.02</td>
<td>0.020</td>
</tr>
<tr>
<td>6-mo change</td>
<td>1.95 ± 21.76</td>
<td>0.33 ± 26.89</td>
<td>0.24 ± 14.79</td>
<td>0.840</td>
</tr>
<tr>
<td>Intercellular adhesion molecule 1 (pg/mL)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.51 ± 0.25</td>
<td>0.57 ± 0.21</td>
<td>0.53 ± 0.25</td>
<td>0.375</td>
</tr>
<tr>
<td>6-mo change</td>
<td>0.01 ± 0.09</td>
<td>0.01 ± 0.14</td>
<td>0.02 ± 0.12</td>
<td>0.343</td>
</tr>
<tr>
<td>Vascular cell adhesion protein 1 (pg/mL)⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.71 ± 0.26</td>
<td>8.23 ± 0.25</td>
<td>8.05 ± 0.25</td>
<td>0.364</td>
</tr>
<tr>
<td>6-mo change</td>
<td>0.19 ± 0.20</td>
<td>−0.07 ± 0.20</td>
<td>0.18 ± 0.20</td>
<td>0.592</td>
</tr>
</tbody>
</table>

¹ ANCOVA models were used to assess differences between intervention groups in variables with normal distributions, and the Kruskal-Wallis test was used in variables without normal distributions. Changes in biochemical variables were adjusted for baseline values of each biochemical variable. HGI, high glycemic index; LF, low fat; LGI, low glycemic index.

² Values are medians ± IQRs (variable without a normal distribution).

³ Significant difference compared with LF-diet group (P < 0.005).

⁴ Values are means ± SEMs.
osteoocalcin in the LGI-diet group than HGI- or LF-diet groups observed in our study reinforced the beneficial role that this type of diet plays in insulin metabolism. Overall, our results are in line with those of a previous meta-analysis (32) and support findings from prospective cohort studies that consistently indicated that the consumption of lower GI are associated with lower T2D risk (7). As expected, we observed that HDL cholesterol tended to increase, and triglycerides slightly decreased, although differences observed between groups were NS.

Inflammatory modulation has also been postulated as a potential mechanism that links dietary GI and GL with the management of obesity and its related comorbidities, although both observational and intervention studies have reported inconsistent data. Moreover, few clinical trials have evaluated the effect of GI and GL on inflammatory markers, and most studies have focused on C-reactive protein (CRP) (15–19). In 773 obese adults from the Diet, Obesity, and Genes trial, changes in CRP were significantly greater in LGI- than HGI-diet groups (19). Decreased IL-6, TNF-α, plasminogen activator inhibitor-1, and leptin concentrations have also been observed after weight loss induced by LF or LGI hypocaloric diets with no between-group differences (35). In our study, subjects allocated to the LGI-diet group show a significant reduction in peripheral CRP and leptin concentrations and a tendency to a higher decrease in IL-6 after the intervention. However, changes were shown to be different between intervention groups. In our study, the GI and GL of the diet were not observed to have any effect on the other inflammatory markers analyzed although, as expected, most of markers tended to improve because of the weight loss in all intervention groups.

Among the strengths of this study were its medium-term duration; randomized design balanced in each intervention group for sex, age, and use of T2D drugs; and differences between diets in relation to GI and GL. Moreover, to our knowledge, our trial is the first study to simultaneously analyze the effect of LGI, HGI, and LF diets on weight loss, satiety, glucose and insulin metabolism, and several associated metabolic risk markers.

There were also some study limitations. First, because the study has been conducted in a Mediterranean country, dietary fat sources were derived mainly from vegetable foods. Therefore, both LGI and HGI diets were rich in vegetable fatty acids, which limited the generalizability of our results to non-Mediterranean populations.

Second, our findings should not be generalized to obese people with obesity-related diseases (eg, T2D) who were not represented in our study subjects. Finally, we used dietary food records during the follow-up as an indirect marker of dietary compliance. A lack of specific biochemical markers of dietary compliance related to GI and GL was also a limitation of the study.

In conclusion, we showed that following a moderate-carbohydrate, LGI diet may be more effective for weight loss than a moderate-carbohydrate, HGI diet or a conventional LF diet. Metabolic benefits observed for insulin resistance and sensitivity in subjects who were consuming an LGI diet and the tendency to improve other inflammatory and associated metabolic risk markers also indicated that LGI diets are better tools for managing obesity and its associated comorbidities. Additional insights into this topic require additional studies to focus on mechanisms linking GI with body weight control.

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The authors’ responsibilities were as follows—MB and JS-S: contributed to the conception, design, and implementation of the project; MJ-F, NI-J, AD-L, MG-F, AR-S, PH-A, RB, and MB: contributed to data collection and analytical procedures; MJ-F, JS-S, and MB: conducted the statistical analysis, interpreted data, and wrote the manuscript; and all authors: read and approved the final version of the manuscript. None of the authors had a personal or financial conflict of interest.

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