# Improved Plasma Glucose Control, Whole-Body Glucose Utilization, and Lipid Profile on a Low–Glycemic Index Diet in Type 2 Diabetic Men

## A randomized controlled trial

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**OBJECTIVE** — To determine whether a chronic low–glycemic index (LGI) diet, compared with a high–glycemic index (HGI) diet, has beneficial effects on plasma glucose control, lipid metabolism, total fat mass, and insulin resistance in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — Twelve type 2 diabetic men were randomly allocated to two periods of 4 weeks of an LGI or HGI carbohydrate diet separated by a 4-week washout interval, in a crossover design.

**RESULTS** — The LGI diet induced lower postprandial plasma glucose and insulin profiles and areas under the curve than after the HGI diet. At the end of the two dietary periods, the 7-day dietary records demonstrated equal daily total energy and macronutrient intake. Body weight and total fat mass were comparable. Four-week LGI versus HGI diet induced improvement of fasting plasma glucose ($P < 0.01$, $\Delta$ changes during LGI vs. HGI), $HbA_{1c}$ ($P < 0.01$), and whole-body glucose utilization measured by the euglycemic-hyperinsulinemic clamp ($P < 0.05$). LGI diet induced a decrease in fasting plasma total and LDL cholesterol ($\Delta$ changes LGI vs. HGI, $P < 0.01$), free fatty acids ($P < 0.01$), apolipoprotein B, and plasminogen activator inhibitor 1 activity.

**CONCLUSIONS** — Only 4 weeks of an LGI diet was able to improve glycemic control, glucose utilization, some lipid profiles, and the capacity for fibrinolysis in type 2 diabetes. Even if changes in glycemic control were modest during the 4-week period, the use of an LGI diet in a longer-term manner might play an important role in the treatment and prevention of diabetes and related disorders.

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**Abbreviations:** AUC, area under the curve; DEXA, dual-energy X-ray absorptiometry; FFA, free fatty acid; GI, glycemic index; HGI, high GI; HOMA, homeostasis model assessment; LGI, low GI; PAI, plasminogen activator inhibitor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



Diabetes is a chronic evolving disease associated with a variety of micro- and macrovascular complications. Increasing postprandial plasma glucose and insulin excursions are assumed (1,2) to increase severity of diabetes and to be independent predictors of risk for atherosclerotic diseases. As such, interventions to reduce postprandial plasma glucose and insulin peaks are one of the essential therapeutic objectives for diabetic patients and could reduce the risk of developing cardiovascular complications.

Because dietary carbohydrate is one of the main factors in controlling postprandial hyperglycemia, it is reasonable to question whether the type of dietary carbohydrate can modify the evolution and complications of this disease in a clinically significant long-term fashion.

There is growing recognition that the postprandial glycemic (3,4) and insulinemic (5) responses to different foods may vary despite equal amounts of total absorbable carbohydrates. This concept favors the use of low–glycemic index (LGI) carbohydrates. Although focusing on the total amount of carbohydrate intake is important for diabetic patients (6,7), using LGI carbohydrates could lead to additional benefits without increasing the fat content of the diet and consequently increasing plasma free fatty acids (FFAs), with all their deleterious consequences (8).

Whether the glycemic index (GI) of foods has relevance to human health has been a topic of contention. In the literature, there is evidence from some intervention studies that consuming LGI foods is associated with improvement of several measures of carbohydrate metabolism and cardiovascular risk factors in type 2 diabetes (9–12). Even if some studies (13) could not demonstrate a statistically significant improvement in plasma glu-

**Table 1—*Clinical characteristics of subjects***

| | |
|---|---|
| *n* | 12 |
| Age (years) | 54 ± 2 |
| Body weight (kg) | 93 ± 3 |
| BMI (kg/m$^2$) | 31 ± 1 |
| Fasting glycemia (mmol/l) | 8.7 ± 0.7 |
| Plasma cholesterol (mmol/l) | 4.9 ± 0.3 |
| Plasma triacylglycerols (mmol/l) | 1.3 ± 0.2 |

Data are means ± SE.

cose control, the decline in $HbA_{1c}$ levels was twice as great on the LGI diet as on the high–glycemic index (HGI) diet. Until now, however, some professional organizations have taken the position that there is no evidence that chronic consumption of LGI foods will contribute to improved glycemia in people with diabetes (6,7). They have mentioned that in type 2 diabetes, the number of studies comparing LGI with HGI diets for 2 weeks or longer is limited.

Moreover, in a previous study in nondiabetic slightly overweight subjects, such a diet resulted in decreased total fat mass as well as the expression of some genes implicated in lipid metabolism (14).

Thus, the aim of the present study was to evaluate whether the chronic use of an LGI diet compared with an HGI diet might modify plasma lipids, plasma glucose responses and control, insulin sensitivity, and fat distribution in a homogeneous group of type 2 diabetic men. Furthermore, we aimed to determine the effect of these diets on fibrinolysis as a marker of cardiovascular risk.

## RESEARCH DESIGN AND METHODS

— Twelve type 2 diabetic men volunteered to participate in this study. The clinical and biological characteristics of these subjects are given in Table 1. Subjects with abnormal renal, hepatic, and thyroid functions were excluded. One patient was under a dietary regimen alone and 11 patients were receiving antidiabetic agents. None of the patients were or had been treated with insulin. All therapies were continued unchanged throughout the study. The Ethical Committee of Hôtel-Dieu Hospital approved the experimental protocol. The purpose, nature, and potential risks of the study were explained, and a written informed consent was obtained from each subject.

### Study design

The patients were randomly allocated to two periods of 4 weeks of an LGI or HGI diet in a crossover design. The two nutritional periods were separated by a washout interval of 4 weeks. Before the beginning of the study, all the subjects were instructed to maintain their usual lifestyle during the experimental period.

At the beginning and the end of each nutritional period, subjects were hospitalized for 2 days after an overnight fast. During the first day, an indwelling cannula was inserted into an antecubital vein. This cannula served for the hourly withdrawal of blood samples during the 8-h metabolic profile. Each subject consumed an LGI or HGI breakfast at 0830 and lunch at 1230. The meals during the 1-day profile were the same as during the chronic period with HGI or LGI. Blood samples were collected in the fasting state (time 0) and hourly during the 8-h metabolic profile. Blood samples were centrifuged, and plasma was frozen (−20°C) for further measurements of plasma glucose, insulin, and lipids (triacylglycerols, cholesterol, and FFAs). At time 0, plasma apolipoprotein B and plasminogen activator inhibitor (PAI)-1 levels were also measured. During the first day, body lean and fat mass distributions were also measured by dual-energy X-ray absorptiometry (DEXA) with a total-body DEXA scanner (Holojic QDR-2000), as described previously (15).

During the second day, three blood samples were taken at the fasting state, with 5-min intervals, to measure the homeostasis model assessment (HOMA). The estimation of pancreatic β-cell function and insulin sensitivity was calculated using the HOMA/CIGMA software (16).

### Glucose turnover and hepatic glucose production

The studies of glucose dynamics were part of the studies done on the second-day hospitalization and consisted of a first step of 180 min of [6,6-$^2H_2$]glucose (Mass Trace, Wohurn, MA) infusion followed by one step of insulin infusion: a high dose of insulin of 6 mU · kg$^{-1}$ · min$^{-1}$ (180 min).

In the morning of the experiment, at 0800, one catheter was placed in an antecubital vein for infusion of [6,6-$^2H_2$]glucose. Another catheter was placed retrogradely into a contralateral wrist vein for blood sampling. Venous blood was arterialized by placing the hand in a heated box (70°C). A priming dose of [6,6-$^2H_2$]glucose was determined according to basal individual plasma glucose concentrations. After the priming dose, the infusion rate was maintained at 3 mg · kg$^{-1}$ · h$^{-1}$ during 3 h. Blood samples were withdrawn before the isotope infusion and at 10-min intervals during the last 30 min to determine the [6,6-$^2H_2$] glucose enrichment.

The calculation of the hepatic glucose production was made according to the formula $R_a = i/Ep$, where $R_a$ is the rate of glucose appearance, $i$ is the tracer infusion rate, and Ep is the [6,6-$^2H_2$]glucose isotopic enrichment in the plasma, based on the assumption that the plasma glucose steady state was achieved (17). In the basal state, the turnover of glucose equals the hepatic glucose production.

### Euglycemic-hyperinsulinemic clamp studies

A one-step clamp study was then performed at an insulin infusion of 6 mU · kg$^{-1}$ · min$^{-1}$ (180 min) as described previously (18). During the infusion of this high insulin dose of 6 mU · kg$^{-1}$ · min$^{-1}$, hepatic glucose production was supposed to be zero (19), so that the exogenous glucose infusion provides a measurement of the total-body glucose disposal.

### Dietary follow-up

The GIs ascribed to the foods used have been taken from either some published data (20) or an unpublished French work (J. Maffré, J.L. Voltair, G.S., V. Lang, M. Champ, Measurements of the Glycemic Index of Foods in the French Population). The diet in the two experimental periods consisted of ordinary food items. In the LGI period, carbohydrate items with a GI lower than 45 was recommended, whereas foods with a GI higher than 60 were recommended in the HGI period (glucose = 100). This was accomplished by providing a list to each individual of the recommended daily intake of commonly used foods and a substitution list allowing exchanges within food groups. During the LGI period, patients were advised to consume pumpernickel, pasta, lentils, haricot beans, chickpeas, and mung beans, whereas during the HGI diet, they were asked to consume wholemeal bread, French baguettes, potatoes, and rice (white, cooked). Before the beginning of the study, the GI of the subjects' usual diets was 53, as estimated by

**Table 2—*Body weight and dietary intake after 4 weeks of HGI or LGI diets: results of 7-day dietary records***

| | HGI diet | LGI diet |
|---|---|---|
| Body weight (kg) | 92.4 ± 2.5 | 92.7 ± 2.5 |
| BMI (kg/m$^2$) | 30.8 ± 1.2 | 31.0 ± 1.2 |
| Energy (kcal) | 2,291 ± 212 | 2,222 ± 124 |
| Carbohydrates (g) | 217 ± 21 | 200 ± 14 |
| Protein (g) | 114 ± 7 | 115 ± 6 |
| Fat (g) | 95 ± 10 | 92 ± 5 |
| Fibers (g) | 21 ± 3[a] | 34 ± 3[b] |
| Alcohol (g) | 21 ± 3 | 18 ± 5 |
| Estimated GI (%)* | 71.3 ± 1.3[a] | 39.0 ± 1.0[b] |

Data are means ± SE ($n$ = 11). *GI scale (glucose = 100). Values followed by different superscripts for a row are significantly different at $P < 0.0001$, LGI versus HGI diet (Student's $t$ test for paired values).

dietary questionnaires (3-day recall technique). There was an attempt to make the GI distinctly lower than usual in the LGI period and higher than usual during the HGI period.

Each subject entered a run-in period of 15 days. Subjects received individual counseling by a dietitian concerning food intake. Dietary intake was prescribed individually according to data obtained from dietary questionnaires (3-day recall technique). Total energy, carbohydrate, lipid, and protein intakes of the experimental diets were similar to the regular diet of each subject. The only change was the type of carbohydrate in the two diets. To assess compliance with the dietary recommendations, patients were asked to keep a food diary to be completed on the last 7 days of each dietary period. These records were analyzed using the computer program Profile Dossier V3 software (Audit Conseil en Informatique Médicale, Bourges, France), for which the dietary database is made up of 400 foods or groups of foods representative of the French diet. French food contents were obtained from Ciqual Repertory (21).

### Biological assays

Glucose was measured by the glucose oxidase method with a glucose analyzer (Beckman Fullerton, Palo Alto, CA). Insulin was determined by a radioimmunoassay (RIA Diagnostic; Pasteur, Marnes La Coquette, France). The antibody used in the test showed a cross-reactivity of 100% with human insulin and 40% with proinsulin. Plasma triacylglycerols and FFAs were measured with Biomérieux kits (Marcy-l'Etoile, France), total cholesterol with Labintest kits (Aix-en-Provence, France), and apolipoprotein B by an immunochemical assay with Behring kits (Mauburg, Germany). Plasma PAI-1 was measured with Chromolize/PAI-1 kits from Biopool International (Umea, Sweden). Isotopic enrichment for [6,6-$^2H_2$] glucose was determined by capillary gas chromatography coupled with electron-ionization mass spectrometry.

The incremental areas under the curve (AUCs) were calculated for plasma glucose and insulin, according to the trapezoidal method previously described (22).

### Statistical analysis

The validity of the crossover design was tested by ANCOVA of the baseline results of the second period, with the baseline results of the first period as the covariable and the treatment of the first period as the main factor. The effects of the two diets were compared by a multiple ANOVA followed by a post hoc test (least significant difference). The main factors considered in the analysis were the type of diet (with two levels: HGI and LGI), the time of the assay (with two levels: day 0 and 4 weeks), and the order of diets (with two levels). The dietetic evaluations at the beginning and the end of each period were compared two by two with a Student's paired $t$ test.

All statistical analysis was performed using the CSS statistical package (StatSoft, Tulsa, OK). Results were considered significant when $P < 0.05$. Data are expressed as mean ± SE.

**RESULTS** — The 12 subjects followed the two dietary periods of 4 weeks each without any difficulty. According to self-report, subjects' lifestyle was unchanged throughout the entire study. There was no effect of the crossover design (LGI or HGI diets) or interaction between diet and period for any of the studied parameters.

### Diets and body weight

Results of the 7-day dietary records were unchanged at the end of the two dietary periods with regard to total energy, macronutrients, and alcohol intake (Table 2). A decrease in the fiber content of the diet, however, was found after the HGI

**Table 3—*Plasma glucose, insulin and $HbA_{1c}$ values during the metabolic day profile before (baseline) and after 4 weeks of HGI or LGI diets***

| | HGI diet | | LGI diet | |
|---|---|---|---|---|
| | Baseline* | 4 weeks* | Baseline* | 4 weeks* |
| Glycemia (mmol/l) | | | | |
| Fasting (0 min) | 9.4 ± 0.5 | 9.8 ± 0.6 | 10.1 ± 0.8† | 9.19 ± 0.7‡§‖** |
| Morning peak (60–0 min) | 4.2 ± 0.3† | 3.7 ± 0.3† | 2.8 ± 0.3‡ | 3.3 ± 0.5‡‖ |
| AUC (mmol · l$^{-1}$ · 8 h$^{-1}$) | 527 ± 57† | 520 ± 61† | 358 ± 90‡ | 274 ± 32‡‖ |
| Insulinemia (pmol/l) | | | | |
| Fasting (0 min) | 113 ± 11 | 125 ± 16 | 111 ± 19 | 123 ± 22 |
| Morning peak (60–0 min) | 142 ± 15 | 171 ± 19 | 126 ± 25 | 149 ± 27 |
| AUC/10$^2$ (pmol · l$^{-1}$ · 8 h$^{-1}$) | 845 ± 10† | 754 ± 27 | 646 ± 36‡ | 618 ± 65‖ |
| $HbA_{1c}$ (%) | 7.45 ± 0.35 | 7.57 ± 0.35† | 7.56 ± 0.36† | 7.17 ± 0.39‡§‖** |

Data are means ± SE. $n$ = 11. *Results during the 8-h metabolic profile before (baseline data) or after (4-week data) the chronic nutritional periods. During the 8-h metabolic profile, values were taken just before (data in the fasting state, 0 min) or after the HGI or LGI meals, respectively. Data followed by different superscripts († and ‡) for a row are significantly different at $P < 0.05$. §Changes during the dietary periods ($\Delta$ = baseline data − 4-week data, HGI vs. LGI). ‖$P < 0.05$ by multiple ANOVA; **$P < 0.01$, for $\Delta$.

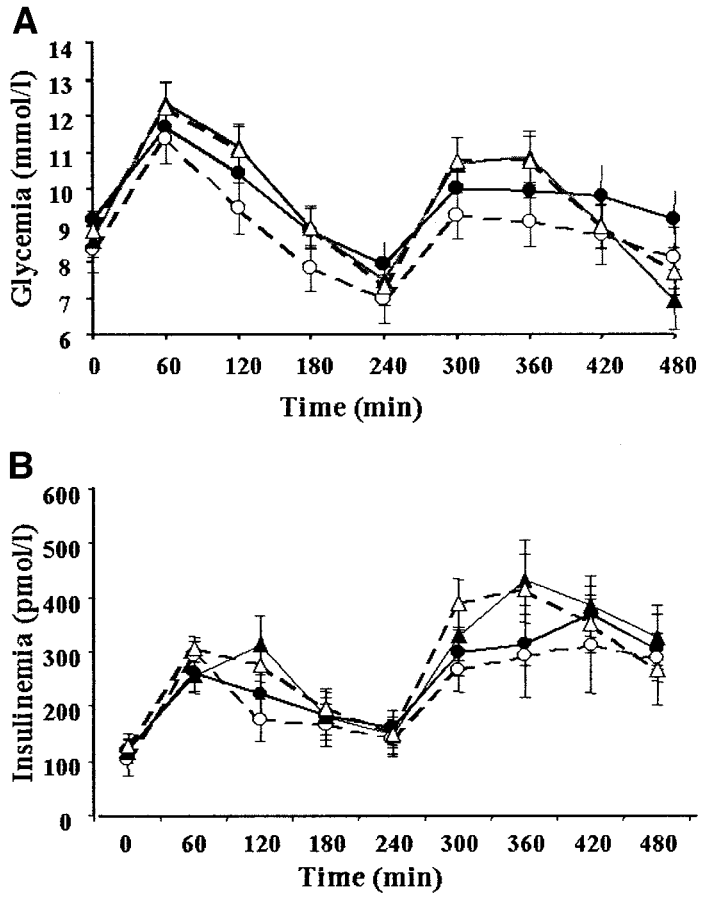


**Figure 1**—*Plasma glucose* (A) *and insulin* (B) *responses to HGI* (△, ▲) *and LGI diets* (○, ●) *during an 8-h metabolic profile before (baseline: LGI = ●, HGI = ▲) and after 4 weeks (LGI = ○, HGI = △) of the respective diets. Data are means ± SE.*

dietary period. The main difference between the two diets was the calculated GI of the diets ($P < 0.0001$). Body weight was comparable between the end of the HGI and LGI periods.

### Glucose and insulin metabolism during the metabolic profiles

As shown in Table 3 and Fig. 1, fasting plasma glucose level fell significantly ($P < 0.05$, multiple ANOVA) after the LGI diet compared with basal values. Moreover, changes ($\Delta$ = baseline − 4 weeks) during the LGI diet were significantly more important than during the HGI dietary period ($P < 0.01$). Morning incremental plasma glucose peaks (at 60 min) were lower with the LGI breakfast than with the HGI breakfast ($P < 0.05$) in the beginning as well as at the end of the two dietary periods (results during the 8-h metabolic profile). The incremental AUCs for plasma glucose were lower after the LGI meals compared with the HGI meals during the 8-h metabolic profiles at baseline (32% decrease, $P < 0.05$, acute effect) and at 4 weeks (47% decrease, $P < 0.05$).

There was no significant change in fasting plasma insulin. The incremental AUCs for plasma insulin during the 8-h metabolic profile was 23% lower after the LGI than after the HGI diet in the beginning of the two dietary periods ($P < 0.05$).

Chronic glucose control as estimated by the $HbA_{1c}$ was lower at the end of the LGI diet than at the end of the HGI diet ($P < 0.05$). Moreover, the changes in $HbA_{1c}$ during the LGI diet were significantly more than during the HGI dietary period ($P < 0.01$).

### Basal and insulin-mediated glucose metabolism

Whole-body peripheral insulin sensitivity measured by the clamp technique was significantly higher after the 4-week LGI diet than after the 4-week HGI diet (glucose disposal: 7 ± 1.3 vs. 4.8 ± 0.9 mg glucose · $kg^{-1}$ · $min^{-1}$, respectively, $P < 0.001$). There was no detected change in hepatic glucose production in the fasting state between the two dietary periods (LGI: 2.02 ± 0.22 vs. 2.32 ± 0.38 mg glucose · $kg^{-1}$ · $min^{-1}$, HGI: 2.30 ± 0.17 vs. 2.3 ± 0.21 mg glucose · $kg^{-1}$ · $min^{-1}$, baseline vs. 4-week values, respectively).

Insulin secretion and sensitivity determined by HOMA remained unchanged during the two dietary periods. There was no significant difference in the insulin secretion index (LGI: 45 ± 6 vs. 49 ± 5%, HGI: 44 ± 4 vs. 45 ± 4%, baseline vs. 4 weeks, respectively) and insulin sensitivity index (LGI: 60 ± 9 vs. 60 ± 8%, HGI: 56 ± 5 vs. 57 ± 10%, baseline vs. 4 weeks, respectively).

### Plasma lipids

Plasma lipids and lipoprotein levels before and after the two dietary periods are shown in Table 4. There was no significant change in triacylglycerol levels. Both total and LDL cholesterol decreased during the LGI period ($P < 0.05$, baseline vs. 4 weeks). Moreover, changes during the LGI period were significantly different from changes during the HGI period ($P < 0.05$). The same profile was found for plasma FFAs: a decrease after the 4-week LGI period rather than after the HGI diet. Changes during the LGI dietary period were different from changes during the HGI period ($\Delta$ changes, LGI vs. HGI, $P < 0.01$). Plasma apolipoprotein B decreased significantly during the LGI period ($P < 0.01$, baseline vs. 4 weeks). This decrease was more important than changes during the HGI period ($P < 0.01$).

### Fat and lean mass distribution measured by DEXA

Four weeks of the LGI diet, compared with the same period of the HGI diet, was not able to induce any significant modification in fat or lean body mass.

### PAI-1 activity

Plasma PAI-1 activity decreased on the LGI diet ($P < 0.05$) and remained unchanged during the HGI dietary period. The changes in PAI-1 activity were significantly different during the LGI diet compared with the HGI diet ($P < 0.01$, Table 4).

**Table 4—*Fasting plasma lipid and lipoprotein concentrations, total fat and lean body mass measured by DEXA, and plasma PAI-1 at baseline and after 4 weeks of HGI or LGI diets***

| | HGI diet | | LGI diet | |
|---|---|---|---|---|
| | Baseline* | 4 weeks* | Baseline* | 4 weeks* |
| Total cholesterol (mmol/l) | 4.79 ± 0.24 | 4.90 ± 0.20 | 5.33 ± 0.43† | 4.46 ± 0.29‡§‖** |
| LDL cholesterol (mmol/l) | 2.89 ± 0.26 | 3.03 ± 0.21 | 3.46 ± 0.44† | 2.63 ± 0.26‡§‖** |
| HDL cholesterol (mmol/l) | 1.22 ± 0.13 | 1.28 ± 0.13 | 1.32 ± 0.11† | 1.29 ± 0.11 |
| Triacylglycerols (mmol/l) | 1.51 ± 0.0.26 | 1.32 ± 0.19 | 1.24 ± 0.20 | 1.21 ± 0.19 |
| FFA (mmol/l) | 1.30 ± 0.25 | 1.47 ± 0.26† | 1.21 ± 0.19 | 1.02 ± 0.18‡§‖** |
| Apolipoprotein B (g/l) | 1.04 ± 0.06 | 1.05 ± 0.06 | 1.07 ± 0.07† | 1.01 ± 0.06†‡§** |
| Total fat mass (kg) | 24.9 ± 2.4 | 25.5 ± 2.6 | 26.3 ± 3.1 | 25.5 ± 2.7 |
| Lean mass (kg) | 65.3 ± 0.9 | 63.8 ± 0.9 | 63.7 ± 1.1 | 63.9 ± 0.9 |
| PAI-1 activity | 23.4 ± 5.2 | 24.6 ± 5.3 | 25.6 ± 3.8† | 15.8 ± 1.8‡§‖** |

Data are means ± SE ($n = 12$). LDL was calculated by use of the Friedewald formula. *Results during the 8-h metabolic profile before (baseline data) or after (4-week data) the chronic nutritional periods. During the 8-h metabolic profile, values were taken just before (data in the fasting state, 0 min). Data followed by different superscripts (including * and †) for a row are significantly different at $P < 0.05$. §Changes during the dietary periods ($\Delta$ = baseline data − 4-week data, HGI vs. LGI). **$P < 0.05$ by paired Student's test; ‖$P < 0.01$, and ††$P < 0.001$ by ANOVA.

**CONCLUSIONS** — To our knowledge, this is the first study demonstrating the capacity of a 4-week LGI diet compared with an HGI diet over the same period to improve both fasting glycemia and $HbA_{1c}$ as well as whole-body glucose utilization in individuals with type 2 diabetes.

In the literature, there are eight studies that compared chronic HGI with LGI diets, keeping the same carbohydrate intake, in an exclusive group of type 2 diabetic patients. Only one study found a significant amelioration of $HbA_{1c}$ after 12 weeks of an LGI diet compared with an isoglucidic HGI diet (9) with a randomized crossover design. A recent study, however, showed that decreased $HbA_{1c}$ was achieved when an LGI diet was associated with a low glycemic load (23). Three other studies mentioned a decrease in fructosamine (11,12,24), with a GI between 83 and 87 for the HGI diet and 57 and 60 for the LGI diet. None of the above-mentioned studies showed a significant decrease in fasting plasma glucose between the HGI and LGI diets.

Other short-term (25–27) and long-term studies (12 weeks in a parallel design) (28) demonstrated improvement in at least one measure of glycemic control in the LGI group (baseline vs. end) but not when compared with the HGI diet. Some other studies, however, did not demonstrate any significant amelioration in glucose control (13,29). This might be because, in the study by Heilbronn et al. (13), the effect of LGI and HGI diets was evaluated during an energy-restricted program (GI was 75 vs. 43, HGI vs. LGI). In the second study (29), the GI of the HGI foods was very low (63 vs. 43) and approached values of GI of the LGI diets in other studies (11,12,24,25). Therefore, there was no difference between the two LGI diets.

The differences between these studies and our study could be due to the homogeneous group of patients in the present study (a group of men) and the presence of a washout period between the two dietary periods. In the other studies, the participating subjects were composed of a combination of men and women. Ovarian hormone pulsatility may affect endocrine pancreas function. It has been shown that plasma glucose kinetics and carbohydrate oxidation are lower during the luteal phase compared with the follicular phase in women (30,31). Therefore, the presence of women might increase the within-subject variations. Another important outcome in the present study is the fact that the GI value was reduced to 39, which is the lowest value achieved in the published studies. The amelioration of $HbA_{1c}$ by LGI diet, in our study, is in accordance with the overall results of the recent meta-analysis of Brand-Miller et al. (32). The authors took 14 studies, comprising a total of 356 subjects (203 with type 1 diabetes and 153 with type 2 diabetes). They demonstrated that LGI diets globally reduced $HbA_{1c}$ by 0.43% points over and above that produced by HGI diets.

The unique change in the present study was the quality of carbohydrates in the two diets while keeping equal energy and macronutrient intake. However, some difference was found in the fiber content of the two dietary periods. The fiber intake was lower during the HGI diet than during the LGI diet (21 ± 3 vs. 34 ± 3 g/day). Nonetheless, the two values are within the recommended range (20–35 g/day), and the 34 g/day could not be considered a high-fiber diet. In a previous study, increasing the fiber content of the diet from 11 to 27 g/1,000 kcal did not lead to improvement in plasma glucose or lipid concentrations (33) in type 2 diabetes. In contrast, when increasing the fiber content from 24 to 50 g/day, both plasma glucose and lipids were improved (34). However, a recent study demonstrated that when a high amount of fiber per day (53 g) was present in an LGI diet, an improvement of dyslipidemia without any decrease in fasting plasma glucose or $HbA_{1c}$ was found in type 2 diabetes (27). However, diets containing much more fiber (40–65 g/day), mainly as soluble fibers, have been shown to improve diabetes control and $HbA_{1c}$ in type 1 diabetic subjects (35). Therefore, in the present study, the 34 g/day of dietary fibers might not be a factor in the improvement of glucose control.

Mechanisms underlying the improvements of fasting glycemia and $HbA_{1c}$ in the present study could be due in part to the increased whole-body glucose disposal measured by the euglycemic-hyperinsulinemic clamp method. This is the first time that lowering the dietary GI, without changing carbohydrate intake or body weight, has been shown to improve peripheral insulin sensitivity. A recent

controlled randomized trial (12) demonstrated an improvement in peripheral insulin sensitivity after both the LGI and HGI diets. The difference between the results of our study and those of Jarvi et al. (12) could be because, first, in our study, the GI of the LGI diet was lower (GI = 39) than that in the study of Jarvi et al. (GI = 57). Second, there was no change in body weight in the two dietary periods in our study, whereas in that of Jarvi et al., a reduction of weight was demonstrated during the two dietary periods, which in and of itself ameliorates insulin sensitivity after the two dietary periods.

The decrease in FFAs by the LGI compared with the HGI diet in the present study could be another important factor resulting in improved plasma glucose control and insulin sensitivity. In type 2 diabetes, elevated fasting FFA levels are suggested to lead to hyperglycemia by increasing glucose production (36). This hypothesis is unlikely in the present study, since the lowering of FFAs by the LGI diet was not accompanied by decreased hepatic glucose production. This is supported by the results of Roden et al. (37), who found that the increase in plasma glucose was not always associated with increased glucose production, suggesting that FFAs could affect glucose levels via another mechanism. Sustained elevation of FFAs has been demonstrated to induce apoptosis of pancreatic β-cells and to accumulate in nonadipose depots, inducing an increase in intrahepatic and intramyocellular lipids that are highly correlated with insulin resistance (38). In fact, the evidence for inhibitory effects of fatty acids on whole-body glucose utilization and oxidation is decisive and well established (39). The question is, however, why were FFAs reduced on an LGI diet and increased on an HGI diet? This could be due to a defect in buffering the flux of fatty acids in the circulation during the HGI diet. Our hypothesis is that during the HGI period, a more insulin-resistant state than the LGI period, the ability of insulin to suppress fatty acid release from adipose tissue might be impaired. Moreover, the pathway of fatty acid trapping (adipocyte uptake of fatty acids liberated from plasma triacylglycerol by LPL) in adipose tissue could also be defective, therefore adding to impaired buffering of fatty acids and their accumulation in the circulation. Further experiments are needed to confirm this hypothesis.

Moreover, excess FFAs are a major risk factor for cardiovascular disease and sudden death in patients with insulin resistance as well as in individuals with normal glucose tolerance (40). Thus, reducing plasma FFA levels by LGI diets may reduce the incidence of cardiovascular diseases in these at-risk patients. Similarly, the decrease in plasma total cholesterol, as well as LDL cholesterol by LGI diet, as found in the present study, could be considered another additional beneficial effect. In the literature, there is an important body of evidence in support of the cholesterol-lowering effect of LGI diets (9,11,12).

Another interesting finding in the present study is the capacity of the LGI diet, compared with the HGI diet, to improve PAI-1 levels. This result is consistent with the finding of a recent study by Jarvi et al. (12). A positive association has been suggested between triglycerides and PAI-1 levels (41). However, this hypothesis is unlikely in the present study, because there were no changes in triglyceride levels between the two diets. On the other hand, previous studies demonstrated that increasing the fiber content of the diet, especially as guar gum and oat husk, results in decreasing PAI-1 activity (42). Moreover, diets high in both complex carbohydrates and dietary fibers have been found to reduce the levels of plasminogen and PAI-1. Therefore, both the difference in the fiber content between the LGI and HGI diets as well as reducing the GI of the diet could be implicated in improving PAI-1 levels.

Despite the beneficial effects of an LGI diet in type 2 diabetes, in the present study, there was no detected effect on total fat mass as measured by DEXA. These findings differ from the results found previously in nondiabetic slightly overweight subjects (14), where LGI diets decreased total fat mass without any change in plasma glucose control. This contradiction simply might be because the diabetic subjects were more insulin resistant than nondiabetic subjects, as shown by the HOMA results. Therefore, adipose tissue might need longer periods to respond to such dietary modification.

This study represents one more study in the growing literature providing evidence of the chronic utility of LGI diets and clearly demonstrating the capacity of this type of diet (if well respected in a homogeneous group even for 4 weeks) to significantly improve plasma glucose control and whole-body glucose utilization, as well as plasma FFAs, total and LDL cholesterol, and PAI-1 levels. Even if we considered that the improvement in glucose control was modest, the clinical significance of this type of diet could be more apparent in the long term. In type 2 diabetes, the beneficial effects of this type of diet on glucose metabolism and cardiovascular risk factors could be mainly attributed to the decrease in plasma FFAs. Nevertheless, we believe that it would be of great benefit for healthy nondiabetic subjects to begin to have the ability to choose LGI foods. This strategy might decrease the risk of developing metabolic disorders and cardiovascular diseases.

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