Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes

Karma L Pearce, Manny Noakes, Jennifer Keogh, and Peter M Clifton

ABSTRACT
Background: Large postprandial glucose peaks are associated with increased risk of diabetic complications and cardiovascular disease.
Objective: We investigated the effect of carbohydrate distribution on postprandial glucose peaks with continuous blood glucose monitoring (CGMS), when consuming a moderate carbohydrate diet in energy balance in subjects with type 2 diabetes.
Design: Twenty-three subjects with type 2 diabetes were randomly assigned to each of four 3-d interventions in a crossover design with a 4-d washout period. Identical foods were provided for each treatment with a ratio of total carbohydrate to protein to fat of 40%:34%:26% but differing in carbohydrate content at each meal: even distribution (CARB-E; 70g carbohydrate), breakfast (CARB-B), lunch (CARB-L), and dinner (CARB-D), each providing 125g carbohydrate in the loaded meal in a 9-MJ diet. Glucose concentrations were continuously measured with CGMS. Outcomes were assessed by postprandial peak glucose (G_max), time spent >12 mmol/L (T >12), and total area under the glucose curve (AUC_20).
Results: Daily G_max differed between treatments (P = 0.003) with CARB-L (14.2 ± 1.0 mmol/L), CARB-E (14.5 ± 0.9 mmol/L), and CARB-D (14.6 ± 0.8 mmol/L) being similar but lower than CARB-B (16.5 ± 0.8 mmol/L). Meal G_max was weakly related to carbohydrate amount and glycemic load (r = 0.40–0.44). T >12 differed between treatments (P = 0.014), and a treatment × fasting blood glucose (FBG) interaction (P = 0.003) was observed with CARB-L (184 ± 74 min) < CARB-B (190 ± 49 min) < CARB-D (234 ± 87 min) < CARB-E (262 ± 91 min). Total AUC_20 was not significantly different between treatments. After adjustment for FBG, treatment became significant (P = 0.006); CARB-L (10 049 ± 718 mmol/L × 20 h) < CARB-E (10 493 ± 706 mmol/L × 20 h) < CARB-B (10 603 ± 642 mmol/L × 20 h) < CARB-D (10 717 ± 638 mmol/L × 20 h).
Conclusion: CARB-E did not optimize blood glucose control as assessed by postprandial peaks, whereas CARB-L provided the most favorable postprandial profile. Am J Clin Nutr 2008;87: 638–44.

KEY WORDS Type 2 diabetes, carbohydrate distribution, moderate carbohydrate diet, continuous glucose monitoring, energy balance, postprandial blood glucose

INTRODUCTION
More than 140 million people worldwide have diabetes, predominately type 2, with the prevalence of type 2 diabetes expected to double by the year 2030 (1). In these persons, cardiovascular disease (CVD) is the leading cause of morbidity and mortality, responsible for 50–80% of deaths (2); estimates of the risk of CVD vary from 2-fold (3) to 30-fold (4) compared with persons without diabetes.
Although glycated hemoglobin (Hb A1C) is a standard assessment tool to assess glucose control in type 2 diabetes, postprandial glucose (PPG) peaks were implicated as a risk factor for microvascular and macrovascular complications (4). Endothelial dysfunction and activation of the coagulation cascade (5) are likely to be initial steps involved in producing carotid thickening (5) and atherosclerosis (6).
Although the European Diabetes Policy group has set maximum PPG targets not to exceed either 135 mg/dL (7.5 mmol/L) to reduce the arterial risk and 160 mg/dL (9.0 mmol/L) to reduce microvascular risk (7), the American Diabetes Association (ADA) does not provide such targets, preferring to encourage persons with type 2 diabetes to maintain “blood glucose levels in the normal range or as close to normal as is safely possible” (8). The ADA does state that an understanding of the relation between CVD events and treatments focused at explicitly lowering PPG is critical to reduce mortality as a consequence of CVD (9).
Most studies confirm that the total carbohydrate intake from either a snack or a meal is a consistent predictor of PPG concentrations (10). This has been observed in both single-meal (11) and mixed-meal studies (10). In 2002, the ADA recommended that the carbohydrate and monosaturated fat together should provide large amounts of carbohydrate between meals, we used a moderate-carbohydrate, higher protein, energy-balanced diet (40% carbohydrate, 34% protein, 26% fat) to enable the greatest variation in carbohydrate distribution to be achieved. Studies that used moderate-carbohydrate interventions, comparing isocaloric exchange of carbohydrate with protein, were shown to increase weight loss (12) and fat loss (12); to spare lean mass (13);
to achieve better glycemic control (13) and insulin sensitivity (12); to reduce Hb A1C values (14); and to improve the blood lipid profile (12). Dietary factors other than carbohydrate amount can affect blood glucose concentrations, eg, dietary fiber (15) and glycemic index (GI) (8). The consumption of protein (16) and fat (17), preprandial glucose concentrations (18), the degree of insulin resistance (19), and second meal effects (20) may also modify the effect of dietary carbohydrate on PPG concentrations. In addition, this study targeted persons with poorly controlled glycemia as a higher risk group for diabetic complications and effective clinical intervention. It was also anticipated that they would be more responsive to carbohydrate variability across the day.

Although persons with type 2 diabetes are often advised to evenly distribute daily carbohydrate intake over meals and snacks to blunt PPG peaks (21), no studies support whether this approach provides optimal glucose control. The relation between snacks to blunt PPG peaks (21), no studies support whether this approach provides optimal glucose control. It was also anticipated that they would be more responsive to carbohydrate variability across the day.

Our aim was to comprehensively assess diurnal glucose profiles in free-living persons with type 2 diabetes, when carbohydrate distribution at meals is variably distributed, but total carbohydrate remains the same. Our use of a continuous blood glucose monitoring system (CGMS) enables a noninvasive approach to measuring PPG responses. We used an isocaroleric moderate-carbohydrate, higher protein, energy-balanced diet (40% carbohydrate, 34% protein, 26% fat) consumed as 3 meals for each of 4 intervention periods. We hypothesized that an even distribution of carbohydrates may be an optimum pattern compared with 3 other carbohydrate distribution interventions for attenuating PPG excursions.

Subjects and Methods

Subjects

Twenty-four white men (n = 8) and women (n = 16) with type 2 diabetes, aged 30–75 y, with Hb A1C values ≥ 6.5% were recruited by public advertisement. Subjects were excluded if they had a malignancy; a history of liver, kidney, or gastrointestinal disease; or were unable to comply with study requirements. All experimental procedures were approved by the human ethics committees of the Commonwealth Scientific Industrial Research Organisation and the University of Adelaide, and all subjects provided written informed consent.

Of the 24 subjects, 11 managed their diabetes by diet, 11 required oral hypoglycemic medication [4 with metformin (500 mg/d to 3 g/d) and glimepiride (1 normal 160 mg/d and 3 slow release 30–60 mg/d), 1 with metformin (2 g/d) alone, 1 glimepiride 60 mg/d alone, 3 with thiazolidinediones (rosiglitazone 8 mg, pioglitazone 30–45 mg) and metformin (1.5–2 g/d), 2 with glimepiride (1–3 mg) and metformin (500 mg/d to 3 g/d)], and 2 required insulin (1 with Humalog 30 U and Protaphane 30 U, the other with Protaphane 28 U, glimepiride 90 mg, and metformin 850 mg). Other medications included antidepressants, antihypertensives, and lipid-lowering medication. Subjects were asked to maintain their usual daily activities and a constant dose and timing of their medication for the duration of the study. Baseline characteristics are shown in Table 1.

Measurements

CGMS is a well-recognized tool currently used by health professionals in type 1 diabetes to identify timing and causes of hypoglycemia and hyperglycemic spikes with accuracy similar to that of self-monitoring of blood glucose (SMBG) (25). A Medtronic MiniMed CGMS (Northridge, CA) was used to obtain continuous glucose readings (26). Briefly, it consists of 4 components: a sterile, single use glucose oxidase–based electrode sensor system inserted into interstitial fluid, a pager-sized electronic monitor that records and stores data from the sensor, a cable that connects both the monitor and the sensor, and a communication station (Com-Station) that aids in the downloading of data to a personal computer (MEDTRONIC MINIMED software 3.0C program). A senserter, a spring-loaded device, was used to implant the sensor. The sensor obtained a glucose measurement of the extracellular glucose in the range of 2.2–22 mmol/L (40–400 mg/dL) every 10 s, and the monitor stored a smoothed and filtered average of these values in its memory every 5 min, yielding 288 readings/d. This information was not revealed to the wearer. CGMS values < 2.2 mmol/L or > 22 mmol/L were recorded as 2.2 or 22 mmol/L. Fasting blood glucose (FBG) was recorded at 0530 every morning during the 4 d while wearing the CGMS monitor and averaged.

The mean of the daily differences (MODD) is a term used to evaluate overall interday glycemic variation when CGMS values were used to evaluate blood glucose concentrations (27). This is the mean of the absolute value of the difference for 2 individual blood glucose values initialized from the time of eating, on 2 different days, during the 20-h time period.

Resting blood pressure was measured by automated oscillometry (model 845XT/XT-IEC; Dinamap, Tampa, FL), with subjects in a seated position. Body height was measured to the nearest 0.1 cm with the use of a stadiometer (SECA, Hamburg, Germany) with subjects barefoot in the free-standing position. Body weight was measured with subjects wearing light clothing.

Table 1: Subject characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 7)</th>
<th>Female (n = 16)</th>
<th>Total (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.6 ± 9.3</td>
<td>60.3 ± 10.5</td>
<td>61.0 ± 10.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.6 ± 23.0</td>
<td>94.9 ± 25.9</td>
<td>94.5 ± 24.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.5 ± 7.7</td>
<td>36.1 ± 9.3</td>
<td>34.7 ± 9.0</td>
</tr>
<tr>
<td>Hb A1C (%)</td>
<td>8.3 ± 1.4</td>
<td>8.5 ± 1.7</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>7.1 ± 1.3</td>
<td>8.4 ± 3.5</td>
<td>7.5 ± 2.2</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>131.8 ± 14.4</td>
<td>139.0 ± 11.0</td>
<td>136.6 ± 12.3</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>76.6 ± 11.6</td>
<td>73.7 ± 9.7</td>
<td>74.7 ± 10.2</td>
</tr>
</tbody>
</table>

* All values are ± 0.5 ± SD. Age, systolic blood pressure (SBP), diastolic blood pressure (DBP), activity level, and glycated hemoglobin (Hb A1C) were assessed at screening (2 wk before commencing the study). Weight, BMI, and fasting blood glucose (FBG) concentrations were obtained at the week 0 visit. For conversion from mmol/L to mg/dL for blood glucose concentrations, multiply by 17.86. Statistics were performed using a one-factor ANOVA. There were no significant difference between sexes.
with no shoes to the nearest 0.05 kg, with the use of calibrated electronic digital scales (AMZ 14; Mercury, Tokyo, Japan). Daily activity levels were recorded, during each intervention, to 5% accuracy, with the use of a pedometer (model HJ-109, Omron Health Care, Tokyo, Japan).

A venous blood sample was collected in a EDTA-coated tube for the measurement of Hb A1c with the use of HPLC ion exchange chromatography on a Bio-Rad VARIANT II [Hercules, CA; method certified by the National Glycohemoglobin Standardization Program and secured to the Diabetes Control and Complication Trial (28) at the Institute of Medical and Veterinary Science (Adelaide, Australia)].

Diet

The study consisted of 4 randomized diet treatments in which the ratio of carbohydrate to protein to fat was 40%:34%:26% (7% saturated fat, 9% monounsaturated fat, 9% polyunsaturated fat). Three-day physical activity diaries (29) were used in conjunction with the Schofield equation (30) to determine individualized energy requirements to maintain energy balance. All treatments contained identical foods and differed only in the way the foods were allocated at each meal (Table 2). For CARB-E, the carbohydrates were evenly distributed across the day (breakfast: 70.7 ± 2.3 g; lunch: 68.5 ± 2.3 g; dinner: 68.2 ± 2.2 g); for CARB-B, the carbohydrates were loaded at breakfast (breakfast: 128.4 ± 4.2 g; lunch: 37.9 ± 1.2 g; dinner: 38.3 ± 1.3 g); for CARB-L, the carbohydrates were loaded at lunch (breakfast: 40.6 ± 1.3 g; lunch: 125.4 ± 4.1 g; dinner: 39.0 ± 1.3 g); and, for CARB-D, the carbohydrates were loaded at dinner (breakfast: 44.1 ± 1.4 g; lunch: 40.5 ± 1.3 g; dinner: 122.7 ± 0.4 g). All foods were provided. Each 24-h treatment was repeated for 3 consecutive days. The GI of the diet was calculated from international tables (31). GI data from persons with type 2 diabetes were used when possible. The glycemic load (GL) of a typical serving of food was calculated as the product of the amount of available carbohydrate and the total GI of the food consumed at a given meal (32) (Table 2).

Experimental design

Subjects followed four, 3-d treatment protocols in a randomized crossover study design. Subjects attended the outpatients’ clinic on a Monday afternoon. Subjects were weighed before the CGMS sensor was inserted subcutaneously into their abdominal wall or upper buttocks (a palm width below the waist) with the use of the senserter. The CGMS monitor was initialized and calibrated with the use of capillary SMBG measurements (Medisense, Optimum; Abbott Laboratories, Abbott Park, IL) before leaving the clinic in accordance with the Medtronic Minimed operating instructions. The subjects consumed food of their choice for the remainder of the day (excluding alcohol) before fasting from 0000. The subjects calibrated the sensor 3 additional times with the use of SMBG before retiring to bed.

During the following 3 consecutive days, subjects were asked to consume only the provided foods and to calibrate the sensor 4 times daily (before breakfast, lunch, and dinner and at retiring) with the use of SMBG. Kitchen scales were provided (DZC 5000A; Procon Technology, Brisbane, Australia). Subjects were free to consume breakfast at any time they wanted, provided that meals were consumed 6 h apart. Each day they recorded the number of steps taken, the time of eating episodes, SGBM results, and other matters that could potentially influence glucose values. Subjects also completed weighed food diaries that were analyzed with the use of FOODWORKS software (version 4; Xyris Software, Highgate Hill, Australia). The software is based on Australian Food Composition tables and food manufacturers’ data.

On Friday morning subjects returned to the clinic to be weighed, to have the CGMS sensor removed, and to have the data downloaded to the computer. Subjects were also interviewed about dietary compliance, activity levels, and adverse events. The process was repeated for 4 consecutive weeks.

Even though subjects were instructed to consume their meals 6 h apart, the minimum length of time between meals was 5 h. Accordingly, the 24-h CGMS trace was divided into 5-h intervals from the time of meal initiation for breakfast, lunch, and evening meals with a 5-h overnight slice beginning 5 h after consuming the evening meal (fasting block), representing a total of 20 h of blood glucose data during a 24-h period of monitoring. The 3 d of monitoring produced 3 × 20 h of blood glucose data used in the analysis. Outcome was assessed by postprandial peak glucose (Gmax), time spent > 12 mmol/L (T > 12), and total area under the glucose curve (AUC20).

Statistical analysis

All data are presented as means ± SEMs unless otherwise indicated. Statistical analysis was performed with the use of SPSS for WINDOWS 14.0 software (SPSS Inc, Chicago, IL) with statistical significance set at an α level of P < 0.05. Dietary compliance data were analyzed with the use of repeated-measures analysis of variance with sex as a between-subject factor. The total 20-h glucose AUC responses were calculated with the use of zero as a baseline, with the trapezoidal rule (33). In the initial analysis of AUC20, Gmax, and T > 12, treatment was assessed with the use of a repeated-measures analysis of variance with the use of sex as a between-subject factor. In secondary analysis, FBG was included as a covariate and oral hypoglycemic medication as a factor.

RESULTS

Subjects

All treatments (data not shown).

FBG concentrations did not differ significantly between days, by treatment, or by time (Figure 1). The MODD value was used to assess interday glycemic variation. The MODD value for treatment CARB-E varied between 1.3 and 1.6 mmol/L, representing comparisons between days 1 and 3, 1 and 2, and 2 and 3. Similarly, the MODD value for treatments CARB-B, CARB-L, CARB-D were completed for 3 full days by 21, 22, 19, and 24 subjects, respectively. No adverse events were reported.

Overall the minimum mean compliance to the dietary protocol across all 4 treatments as assessed by energy intake was 96.9% ± 0.9%, and carbohydrate intake was 98.9% ± 0.9% with no significant difference between treatments or sex (n = 23). The mean daily number of steps was 6117 ± 469 with no differences between treatments. No weight change was observed between treatments (data not shown).

Glycemic control

FBG concentrations did not differ significantly between days, by treatment, or by time (Figure 1). The MODD value was used to assess interday glycemic variation. The MODD value for treatment CARB-E varied between 1.3 and 1.6 mmol/L, representing comparisons between days 1 and 3, 1 and 2, and 2 and 3. Similarly, the MODD value for treatments CARB-B, CARB-L,
and CARB-D were 1.3–1.4 mmol/L, 0.0–1.2 mmol/L, and 1.4–1.5 mmol/L, respectively. Consequently, because no significant differences within treatment were observed \((P > 0.05)\), all available data were used to produce a daily average.

The lowest daily \(G_{\text{max}}\) values were achieved for CARB-L \((14.2 \pm 1.0 \text{ mmol/L})\) followed by CARB-E \((14.5 \pm 0.9 \text{ mmol/L})\) and CARB-D \((14.6 \pm 0.8 \text{ mmol/L})\) with the highest value for CARB-B \((16.5 \pm 0.8 \text{ mmol/L})\). A significant difference was observed between treatments overall \((P = 0.003)\), with the difference between CARB-B and CARB-E \((P = 0.018)\), CARB-B and CARB-L \((P = 0.002)\), and CARB-B and CARB-D \((P = 0.004)\) being significant.

In \(T > 12\), treatment became significant \((P = 0.014)\) only after adjustment for FBG \((P = 0.003)\) with the lowest values for CARB-L \((184 \pm 74 \text{ min})\) and CARB-B \((190 \pm 49 \text{ min})\) and the highest values for CARB-D \((234 \pm 87 \text{ min})\) and CARB-E \((262 \pm 91 \text{ min})\). With the glucose AUC_{20} data, treatment alone had no effect, but it became significant after adjusting for FBG \((P = 0.006)\) (Figure 1E). AUC_{20} for CARB-L \((10\,049 \pm 718 \text{ mmol/L \times 20 h})\) was lowest with CARB-E \((10\,493 \pm 706 \text{ mmol/L \times 20 h})\).

### TABLE 2

<table>
<thead>
<tr>
<th>Sample menu of foods and carbohydrate distribution during the day for an 8000-kJ diet</th>
<th>CARB-E</th>
<th>CARB-B</th>
<th>CARB-L</th>
<th>CARB-D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakfast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed-grain bread (g)</td>
<td>108</td>
<td>46</td>
<td>194</td>
<td>82</td>
</tr>
<tr>
<td>Polysaturated margarine (g)</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Spreads (g)^2</td>
<td>30</td>
<td>2</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Fruit (g)^3</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>Ham (g)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reduced-fat cheese (g)^4</td>
<td>30</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skim milk (g)^5</td>
<td>30</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total carbohydrate (g)</td>
<td>52</td>
<td>—</td>
<td>94</td>
<td>—</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>21</td>
<td>—</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>10</td>
<td>—</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>GL^6</td>
<td>47</td>
<td>—</td>
<td>87</td>
<td>—</td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed-grain bread (g)</td>
<td>86</td>
<td>37</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Polysaturated margarine (g)</td>
<td>6</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Spreads (g)^2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fruit (g)^3</td>
<td>100</td>
<td>13</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>Vegetables (g)^7</td>
<td>80</td>
<td>1</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td>Ham (g)</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Tuna (g)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reduced-fat cheese (g)^4</td>
<td>—</td>
<td>—</td>
<td>30</td>
<td>3</td>
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<tr>
<td>Skim milk (g)</td>
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<td>—</td>
<td>230</td>
<td>12</td>
</tr>
<tr>
<td>Total carbohydrate (g)</td>
<td>51</td>
<td>—</td>
<td>28</td>
<td>—</td>
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<tr>
<td>Protein (g)</td>
<td>25</td>
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<td>35</td>
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<td>Fat (g)</td>
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<td>—</td>
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<tr>
<td>GL^6</td>
<td>34</td>
<td>—</td>
<td>22</td>
<td>—</td>
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<tr>
<td><strong>Dinner</strong></td>
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<td></td>
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</tr>
<tr>
<td>Mixed-grain bread (g)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Polysaturated blended oil (g)</td>
<td>8</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Spreads (g)^2</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fruit (g)^3</td>
<td>200</td>
<td>22</td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>Vegetable (g)^7</td>
<td>218</td>
<td>6</td>
<td>218</td>
<td>6</td>
</tr>
<tr>
<td>Skinless chicken (g)</td>
<td>280</td>
<td>0</td>
<td>280</td>
<td>0</td>
</tr>
<tr>
<td>Diet yogurt (g)</td>
<td>200</td>
<td>11</td>
<td>200</td>
<td>11</td>
</tr>
<tr>
<td>Skim milk (g)</td>
<td>200</td>
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<tr>
<td>Total carbohydrate (g)</td>
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<tr>
<td>Protein (g)</td>
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<td>74</td>
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<tr>
<td>Fat (g)</td>
<td>24</td>
<td>—</td>
<td>26</td>
<td>—</td>
</tr>
<tr>
<td>GL^6</td>
<td>16</td>
<td>—</td>
<td>23</td>
<td>—</td>
</tr>
</tbody>
</table>

1 CARB-E, carbohydrate was evenly distributed across the day; CARB-B, carbohydrate was loaded at the breakfast meal; CARB-L, carbohydrate was loaded at the lunch meal; CARB-D, carbohydrate was loaded at the evening meal; GL, glycemic load.

2 Low-joule spreads (diet jam, vegemite).

3 Apple, pear, or fruit salad.

4 Fat < 65%.

5 Calculated as amount of carbohydrate (g) × glycemic index (32). Glycemic index calculated from tables (31).

6 Lettuce and tomato.

7 Carrots, beans, or broccoli.
20 h), CARB-B (10,603 ± 642 mmol/L × 20 h), and CARB-D (10,717 ± 638 mmol/L × 20 h) differing from CARB-L by 4%, 5%, and 6%, respectively. No statistical difference was observed between the CARB-E, CARB-B, CARB-L, and CARB-D treatments when mode of diabetes control (diet, insulin, or other diabetes medication) was included as a between-subject factor for AUC (P = 0.497), Gmax (P = 0.693), or T12 (P = 0.068).

**Glycemic load**

Because the daily AUC20 did not differ significantly across the treatments, it did not matter how the total daily GL was divided across meals. However, this was not the case with T12 and Gmax because both T > 12 and Gmax differed significantly across treatments. In the loaded meals, daily Gmax was equivalent to meal Gmax. Mean Gmax was greatest with CARB-B because this had the greatest meal GL, but this was not true when comparing meal GL to CARB-D and CARB-L. Daily T > 12 did not correlate with daily GL. For all 276 meals the correlation between carbohydrate amount and Gmax was 0.40; ie, carbohydrate amount accounted for only 16% of the variance in Gmax, whereas the use of GL did not significantly improve the correlation (r = 0.44).

**DISCUSSION**

The main findings of this study are that a more even distribution of carbohydrates did not provide the most favorable total PPG profile. Lunchtime appeared to be the most favorable time to consume carbohydrates based on Gmax, AUC20, and T12, but carbohydrate amount and GL at each meal was only weakly related to the Gmax of that meal, and they accounted for only 16–17% of the variance in Gmax.

Data from several large epidemiologic (5, 34, 35) and intervention (36) studies in persons with type 2 diabetes have emphasized the importance of mealtime hyperglycemia as the predominant factor associated with increased risk of cardiovascular morbidity and mortality. Although Gmax was higher with CARB-B consistent with the higher GL, the Gmax was lower for CARB-L compared with CARB-D despite a higher GL in the former.

When the T > 12 was examined, the lowest mean occurred with CARB-L followed closely by CARB-B, despite its higher peak values. When carbohydrates were loaded in the evening meal, CARB-D, a greater absolute amount of fat, protein, and meal volume at that meal might have led to a more delayed and sustained postprandial peak, the fat slowing the rate of gastric emptying (15), and the protein-induced insulin release may lower the peak (37). The lowest GL value for the loaded meal in CARB-D could not explain the highest T > 12 values for that arrangement.

The highest value for the T > 12 occurred with CARB-E; in this arrangement the carbohydrate was evenly distributed across the 3 meals, providing 3 opportunities for sustained PPG output. Because persons with diabetes have excessive basal glucose production in the presence of fasting hyperinsulinemia (38) and defective suppression of endogenous glucose production (39), repeated exposure to a carbohydrate load is likely to maintain undesirable but consistently higher concentrations of glucose.

Increasing evidence suggests that the postprandial state and indeed the hyperglycemic spikes are a contributing factor to atherosclerosis and the onset of cardiovascular complications. In persons with type 2 diabetes, the Diabetes Intervention Study showed that PPG concentrations after breakfast was found to predict myocardial infarction and mortality in patients with
newly diagnosed disease (40), whereas the San Luigi Gonzaga Diabetes Study showed the postprandial state after lunch predicted the occurrence of cardiovascular events in a 5-yr follow-up study (41). Because glycemia reached after a 2-h postglucose load as measured by the oral glucose tolerance test was shown to correlate with the postprandial state after a mixed meal (42), a body of evidence from the DECODE study, the Chicago Heart Study, the Hoorn Study, and the Honolulu Heart study [reviewed in Ceriello (43)] support a relation between increased postprandial glycemia and cardiovascular risk. Hence, strategies to minimize PPG concentrations are vital to reduce diabetic complications.

Carbohydrate distribution had little influence on 20-h average glucose ($AUC_{20}$). However, when the data were examined further with the use of the average FBG as a covariate, CARB-L produced a more favorable profile, but the differences from the other treatments were small (4–6%).

Overall, CARB-L resulted in lower $AUC_{20}, G_{\text{max}}$, and $T > 12$ values; this represented the most favorable time to eat carbohydrate. On the basis of weight stability, dietary compliance, low but stable activity levels, the provision of all food, and the similarity between each day of the same treatment, the glucose changes that resulted from consuming the prescribed treatments were considered to be mainly attributed to the distribution of carbohydrates and not other confounding factors (15). Other observations included a trend toward a higher FBG value compared with premeal blood glucose values, with lower premeal glucose values throughout the day, as observed by others (10), with values returning to approximately the same values the following morning, which is in part explained by circadian rhythm (44) (Figure 1).

Although we expected to see some variability in interday glycemia because of subtle differences in timing of exercise, meals, and medication and poor health, the interday glycemic variation expressed as the MODD showed a maximum value of 1.6 mmol/L across all 4 treatments, essentially little difference in glycemic response across the 3 treatment days. This variability is much smaller than the MODD value of 4.3 mmol/L observed by others in subjects with type 2 diabetes (27) and was due to the tight control and reproducibility of food consumption during the 3 d in our study.

Limitations to the study include variability in the data highlighted by individual differences in maximum glucose response times to a carbohydrate load; the differences in lag times observed were up to 105 min. This led to discrepancies observed between the maximum glucose concentrations calculated for $G_{\text{max}}$ compared with the maximum glucose values resulting from $AUC_{20}$. A possible explanation for this may be the highly variable rate of gastric emptying observed in subjects with type 2 diabetes (45), the different action of medication in 11 subjects (sulfonylureas that stimulate the pancreas to produce more insulin and biguanides that reduce the amount of glucose produced by the liver) (46), and the amount of glucose absorbed from food along with an insulin-sensitizing effect on muscle tissue through nonoxidative pathways (47).

The strengths of this study include the use of CGMS as a noninvasive diurnal glucose monitoring tool in free-living persons. Without the use of the CGMS sensors, it would have been impossible to detect the dynamic changes in blood glucose concentrations that cannot be detected with intermittent SMBG. The study diet composition of the main meals was similar to that of a higher carbohydrate diet, which, in addition to 3 main meals, incorporated higher carbohydrate snacks (48). The lower carbohydrate diet also enabled the greatest variation in carbohydrate distribution to be achieved. It was anticipated that persons with poorly controlled diabetes would be more responsive to carbohydrate variability across the day. Meal frequency and energy distribution were selected to reflect what many working persons with diabetes had reported in previous studies conducted by our group (data not published) and other groups (49). Exceptional compliance across all 4 treatments we believe was in part due to the provision of all foods and the selection of commonly consumed items in the Australian diet. In addition, continuous glucose monitoring enabled a detailed glucose profile to be obtained.

In conclusion, our results show for this acute study in persons with poorly controlled diabetes that on a 40% carbohydrate dietary pattern even carbohydrate distribution is not optimal for minimizing PPG peaks. Minimizing carbohydrate at breakfast and shifting it to the lunch meal may provide lower diurnal glucose excursions ($AUC_{20}, T > 12$, and $G_{\text{max}}$). Importantly, we consider these studies in support of concept studies. Larger chronic studies involving subjects of different nationalities would be required to determine the applicability of this approach to the management of type 2 diabetes.

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The author’s responsibilities were as follows—KLP, MN, and PMC; conceived of and designed the study and contributed to data analysis and manuscript writing; KLP, MN, PMC, and JK: contributed to designing the study dietary protocol; KLP: implemented the study including the dietary protocol, collected the data, and wrote the manuscript. None of the authors had a personal or financial conflict of interest.

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