Interstitial glucose profile associated with symptoms attributed to hypoglycemia by otherwise healthy women¹–³

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ABSTRACT
Background: Reports of postprandial symptoms attributed to hypoglycemia by otherwise healthy individuals appear to be relatively common in UK women. Whether these symptoms are related to blood glucose is a contentious issue, which periodic ambulatory blood glucose measurement has failed to resolve.

Objective: The authors investigated, using continuous glucose monitoring technology, whether postprandial symptoms are associated with interstitial glucose concentrations (IG) in the hypoglycemic range or with a previous fall in IG.

Design: Thirty healthy nonobese women (age 20–48 y) who reported symptoms attributable to hypoglycemia and 20 nonsymptomatic controls wore a subcutaneous probe in abdominal fat for 4–7 d (median: 5 d) and kept a diet and activity diary during this time.

Results: Twenty women reported postprandial symptoms; 41 episodes were recorded. When symptomatic, IG was ≤3.3 mmol/L in 5% of cases. A significant fall in IG over the preceding 60 min was observed before autonomic symptoms (P < 0.005). The proportion of total energy intake derived from dietary fat in the symptomatic group was higher than that in the controls (P < 0.05). The proportion of total sugars was similar between groups; however, the meal preceding symptoms had a higher percentage of energy derived from total sugars when compared with the individuals’ diet over the study period (P < 0.05).

Conclusions: Most symptoms attributable to hypoglycemia were not associated with an IG concentration in the hypoglycemic range. A previous fall in IG may be implicated in the etiology of autonomic symptoms, with the consumption of meals high in sugars potentially playing a role in symptom initiation. Am J Clin Nutr 2008;87:354–61.

KEY WORDS Reactive hypoglycemia, women, continuous glucose monitoring, United Kingdom

INTRODUCTION

Postprandial or reactive hypoglycemia (RH) is a condition that has been popularized in the media and lay literature, particularly those targeting women, over the past 30 y (1). These sources and anecdotal evidence claim that many persons, who are otherwise healthy, experience periodic symptoms such as faintness, irritability, tremor, hunger, and anxiety, which can be attributed to a low blood glucose (BG) concentration (2, 3). Indeed, in several countries, the number of persons being referred to medical agencies for this condition has reached epidemic proportions (4, 5), although less marked in the United Kingdom (6). A recent survey of randomly selected women from Nottinghamshire supports this finding, with only 0.5% of those reporting symptoms that they attribute to hypoglycemia, having sought medical help (7). However, it does not appear that there is an absence of the phenomenon in the United Kingdom. This survey in Nottinghamshire showed that more than one-third reported symptoms that they attributed to a “low blood sugar,” with 18% reporting these symptomatic episodes more than once a week (8).

It has long been contentious whether symptoms are actually related to low BG (9–13), because biochemical hypoglycemia (defined by symptom thresholds from hyperinsulinemic clamp studies; 14, 15) is not commonly observed in symptomatic individuals when symptoms are experienced (6). However, periodic ambulatory blood sampling, which has been used previously to investigate this condition, simply provides a “snapshot” of postprandial BG, and it has been proposed that by the time symptoms are recognized and a blood sample taken, glucose may already be rising under the action of counter-regulatory hormones, such that true nadirs are being missed (1). Moreover, periodic ambulatory blood sampling does not provide information on the BG profile before symptoms and thus cannot elicit whether symptoms are associated with a prior fall in BG.

The MiniMed System Gold (Northridge, CA) continuous glucose monitoring system (CGMS) is composed of an electrochemical sensor attached via a wire to a monitor that is worn by the individual. The electrical current generated at the sensor electrode is proportional to the concentration of glucose in the interstitial fluid (16). The interstitial glucose (IG) concentration is measured every 10 s with these readings and then averaged over 5 min by software in the monitor (17–19). CGMS therefore allows researchers to study both the IG concentration when symptoms are reported and the glucose profile before developing symptoms, which addresses some of the limitations of periodic ambulatory sampling.

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The primary purpose of this study was to investigate whether women who report symptoms that suggest RH, but have not been referred for a clinical problem, have a concomitant IG concentration in the hypoglycemic range when symptomatic or demonstrate a fall in IG before symptoms.

SUBJECTS AND METHODS

Protocol

Thirty nonobese, healthy women (age 18-50 y) who reported symptoms that they attributed to hypoglycemia more than once a week and 20 nonsymptomatic controls were recruited into the study. All volunteers were asked to complete a medical screening form before recruitment to ensure that they were healthy and satisfied the inclusion criteria. Volunteers subsequently attended the laboratory in the morning after fasting overnight. A venous sample for the measurement of glycated hemoglobin (HbA1c), whole BG, and serum insulin was taken from each individual and analyzed by reversed-phase cation-exchange chromatography (Menarini Diagnostics, Florence, Italy), the glucose oxidase method (YSI Inc, Yellow Springs, OH), and radioimmunoasay (Euro DPC, Caernarfon, United Kingdom), respectively. Basal insulin sensitivity was then calculated from fasting glucose and insulin measures with the use of the homeostasis model assessment for insulin resistance (HOMA-IR) (20) and quantitative insulin-sensitivity check index (QUICKI) (20).

BMI was calculated from measured height and weight. After the subjects were trained and familiarized with the measurement techniques to be used, a small (23G) subcutaneous probe, for continuous IG monitoring, was inserted into subcutaneous fat in the abdomen at the level of the umbilicus. This probe was attached to the CGMS monitor, which was worn continuously for the active life span of the probe. The subjects were asked to push an event marker button on the monitor each time they ate and, if applicable, to enter a different marker when they were symptomatic. They were also asked not to change their eating or activity patterns during the study and to keep a food and activity diary during this time. The subjects were blinded to their IG concentration during the recording period. The study was carried out in accordance with the Helsinki Declaration of 1975 (revised 1983) and was approved by the Nottingham University Medical School Ethics Committee.

CGMS calibration

Capillary glucose concentrations were measured by the subjects 4 times daily in finger-prick blood samples taken by using a Penlet II and were analyzed by using either a One Touch Profile (Lifescan, High Wycombe, United Kingdom) or a Glucotrend 2 pocket glucose analyzer (Roche, Basel, Switzerland). Readings were then entered into the CGMS monitor to calibrate the subcutaneous probe. Data were downloaded from the monitor at the end of the study period, and the mean absolute difference between the capillary BG and the corresponding IG concentration was calculated by using MiniMed Solutions software (MMT-7310, version 3.0.128). If the mean absolute difference was >15%, the CGMS data were not used for that day. In addition, only days with complete data over the 24-h period (0000 to 0000) were included in the analysis. As a consequence, the first and last days of recording were discarded.

Before being used, all 3 pocket glucose analyzers used were validated against the glucose oxidase method (YSI Inc) in a separate study with the use of a hyperinsulinemic clamp (21) to generate 40 blood samples with glucose concentrations between 2.5 and 7.0 mmol/L. The R² values of the glucose oxidase method versus the pocket monitors were 0.991, 0.995, and 0.997, respectively.

Symptoms of hypoglycemia

To avoid biasing the responses, symptoms of hypoglycemia were not defined for the participants, and any experiences that an individual attributed to a “low blood sugar” were taken as a symptomatic event. All such events were noted in a diary with time of occurrence and symptoms experienced being recorded. In a subsequent analysis of the diaries, symptomatic episodes were subdivided into those associated with neuroglycopenia (neurogenic symptoms) and those associated with the release of epinephrine (autonomic symptoms), according to definitions described by Brun et al and others (1, 14, 22, 23), with those episodes associated with a combination of autonomic and neurogenic symptoms being classified as “mixed.” These authors defined symptoms such as fatigue, headache, dizziness, and “difficulty in thinking” as neurogenic, with palpitations, sweating, anxiety, and tremor described as autonomic. This allowed the more nonspecific symptoms associated with the neurogenic category to be investigated separately from the more specific ones associated with the autonomic category. If the subjects experienced more than one symptomatic episode, each symptom was considered separately and only those episodes that occurred <4 h after eating were classified as postprandial.

Interstitial glucose concentration recording

The symptom event marker was defined as t = 0, and IG at this time was considered to be the symptomatic value. The concentration of IG when the subjects were symptomatic was classified as hypoglycemic if ≤3.3 mmol/L. On the basis of definitions from symptom threshold studies (14) and those previously used in the literature relating to reactive hypoglycemia (6, 24), IG data from 60 min preceding t = 0 and 30 min after this point were extracted for analysis. Symptomatic events were defined as being associated with a previous fall in IG if the glucose concentration decreased by ≥0.5 mmol/L over the preceding 30 min (rate of fall equivalent to 1 mmol/L per hr). This arbitrary value for the decrease in IG was applied to the data because it has been used previously in studies investigating the relation between “rate of BG fall” and symptom thresholds in studies using insulin-induced hypoglycemia (25, 26).

To investigate evidence of counterregulation occurring after t = 0, it was necessary to select only those symptomatic events for which the subjects did not eat, as food consumption would make it difficult to determine whether any increase in glucose concentration observed after the event marker reflected a postprandial rise or a response to hypoglycemia. Most of the subjects (78%) ate within 30 min of experiencing symptoms; 56% and 36% ate within 20 and 15 min of experiencing symptoms, respectively. To maximize the number of suitable data points and enable statistical analysis to be carried out, the IG profile from t = 0 to t = 15 min was studied in 64% of the subjects who had not eaten during this time.

To provide a comparator for t = 0 in the control group, the IG at 2 h and 25 min (2.42 h) after breakfast, lunch, and dinner on the...
first complete day of recording was selected. If another eating episode occurred within 2.42 h of the consumption of the selected meal, the equivalent meal on the next recording day was used. Corresponding IG data for nonsymptomatic occasions were also extracted from the recordings made in the symptomatic group. If symptoms occurred within the time period, the equivalent meal on the next recording day was used, provided it was a nonsymptomatic occasion. IG data from the 3 meals were then averaged to provide a postprandial IG profile for each individual, with individual data then combined to provide mean group profiles. The 2.42-h time point was chosen because this was the IG value closest to the mean time that postprandial symptoms were reported by the symptomatic subjects in the current study.

For further comparison of symptomatic individuals with controls, characteristics of IG over every complete 24-h period were averaged to obtain mean values in each subject; the data for these individual values were then used to calculate group mean data. Similarly, 24-h IG data from the symptomatic group were subsequently subdivided to obtain mean values in each subject for days when symptoms were experienced (symptomatic days). These individual values were then used to calculate group mean data for symptomatic days. Fasting IG was determined from the average concentration in the 30 min before waking, with time of waking documented by the subjects in their diaries. IG values 2 h after all meals and 3 h after breakfast were extracted from the data to use as comparators between the symptomatic and control groups. IG values after breakfast were chosen because this meal showed the least variability between subjects in terms of energy intake.

Diet and activity diaries

The participants were asked to keep a diet diary for the duration of the study, i.e., to document all food intake, including snacks and drinks, using household measures to estimate portion size. The participants were also asked to record all activities of daily living and sleep periods in the diary, including all aspects of activity, not just formal exercise periods. The diaries were subsequently analyzed by using a food-composition and activity database (WISP V2; Tinuviel Software, Anglesey, United Kingdom).

To calculate diet composition, individual macronutrient intakes over all days of the recording period were expressed as a percentage of total energy intake. Individual data were then combined to provide mean diet composition for each group. In the symptomatic group, the composition of the meal preceding symptoms was calculated and expressed as a percentage of the total energy of that meal.

Activity over the duration of the study was calculated as multiples of resting energy expenditure (REE) in metabolic equivalents (METs) (27). REE for each subject was estimated by using the Schofield equation (28), and mean daily energy expenditure was calculated by multiplying this estimate of REE by the individual’s mean MET value. Individual data were then used to derive mean activity levels for each group.

Statistical analysis

All data were coded and analyzed by using SPSS software (version 14.0, 2005; SPSS Inc, Chicago, IL). Normally distributed mean data are expressed as means ± SDs, whereas nonparametric data are expressed as medians and ranges. For normally distributed mean data, comparisons between 2 groups were analyzed by using either unpaired- or paired-samples t test where appropriate; a Mann-Whitney U test was used for data not normally distributed. Comparisons of mean data between >2 groups and changes in group IG profiles over time were made by using one-factor ANOVA, and comparisons of symptomatic IG profiles over time between groups were made by using 2-factor ANOVA (with repeated measures). Relations were considered significant when \( P < 0.05 \).

RESULTS

Subjects

The test and control groups were matched for age and BMI \( (P = 0.221 \) and \( P = 0.189 \), respectively), and Hb \( A_1c \) and fasting BG were not significantly different between groups \( (P = 0.746 \) and \( P = 0.569 \), respectively) (Table 1). However, there was a trend for a greater fasting serum insulin concentration \( (P = 0.064 \) and lower insulin sensitivity and higher insulin resistance measures

| TABLE 1 | Characteristics of all subjects (test group who reported hypoglycemic symptoms and a nonsymptomatic control group) and a subset of the test group who experienced postprandial symptoms during the recording period (symptomatic group)\(^1\) |
|-----------------|-----------------|-----------------|
| **Control group** | **Test group** | **Symptomatic group** |
| **(n = 20)** | **(n = 30)** | **(n = 20)** |
| Median age (y) | 25 (20–38) | 26 (20–48) | 26 (20–48) |
| Mean BMI (kg/m\(^2\)) | 22.8 ± 2.17 | 21.9 ± 2.40 | 22.2 ± 2.64 |
| Mean Hb \( A_1c \) (%) | 5.18 ± 0.23 | 5.16 ± 0.21 | 5.16 ± 0.20 |
| Mean fasting blood glucose (mmol/L) | 4.04 ± 0.37 | 3.98 ± 0.35 | 3.89 ± 0.32 |
| Mean fasting insulin (mIU/L) | 3.35 (2.02–6.70) | 3.12 (1.71–8.24) | 3.13 (1.77–8.24) |
| Mean QUICKI | 0.42 ± 0.02 | 0.43 ± 0.03 | 0.43 ± 0.03 |
| Mean HOMA-IR | 0.62 (0.40–1.30) | 0.54 (0.28–1.45) | 0.55 (0.28–1.45) |
| Mean activity (METs) | 1.64 ± 0.14 | 1.60 ± 0.12 | 1.61 ± 0.87 |
| Mean energy expenditure (kJ) | 9725 ± 863 | 9175 ± 1060 | 9313 ± 1000 |
| Mean energy intake (kJ) | 9751 ± 1986 | 9357 ± 1797 | 9743 ± 2003 |
| Mean energy balance (kJ) | 26 ± 1930 | 182 ± 1862 | 430 ± 1907 |

\(^1\) Hb \( A_1c \), glycated hemoglobin; QUICKI, quantitative insulin-sensitivity check index; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalents. Normally distributed data were compared by using an unpaired t test. Nonparametric data were compared by using a Mann-Whitney U test. No significant differences were observed between groups.
(QUICKI: $P = 0.072$; HOMA-IR: $P = 0.091$) in the control group, although all values were in the normal range. Of the 30 participants in the test group, 22 experienced a symptomatic episode during the recording period, and 20 experienced symptoms <4 h after eating. This symptomatic subset of 20 participants was representative of the original cohort with respect to age and BMI ($P = 0.160$ and $P = 0.289$, respectively), and no significant differences in HbA1c ($P = 0.764$) or fasting BG ($P = 0.192$) were observed relative to the controls. Serum insulin, QUICKI, and HOMA-IR measures in this subset were not significantly different from those of the overall test group, but there was no longer a statistical trend for them to differ from the control group.

### 24-h IG data

Participants wore the subcutaneous probe for 4–7 d (median: 5 d). A comparison of the 24-h IG profiles, in terms of the variables shown in Table 2, showed no significant differences between the symptomatic group and the controls or any indication of differences in terms of trends. There was no statistical distinction seen between the 2-h postprandial ($P = 0.684$) or 3-h postbreakfast ($P = 0.792$) IG comparator of each group. Moreover, all 24-h IG variables, recorded on days when symptoms were reported, were statistically similar to control data.

The mean time course of IG (for 3 meals) over a 90-min period around the 2.42-h postprandial time point in the symptomatic group when no symptoms were reported and in controls is shown in Figure 1. There were no significant changes in IG over this time period for either group and no statistical differences observed between the groups ($P = 0.807$).

### Hypoglycemic episodes

A total of 50 symptomatic episodes were recorded. At the time that symptoms were reported in the CGMS ($t = 0$), mean IG was 4.45 ± 0.83 mmol/L (range: 3.0–6.2 mmol/L), with 2 (4%) of the episodes being ≤3.3 mmol/L (3.0 mmol/L for both). The mean time that symptoms were experienced after eating was 2.88 ± 1.32 h (2 h and 53 min ± 1 h and 19 min). Fifteen episodes were classified as autonomic, 25 as neurogenic, and 10 as mixed. However, 1 autonomic (4.92 h), 3 mixed (4.25–6.0 h), and 5 neurogenic (4.17–5.42 h) episodes were experienced >4 h after eating. None of these nonreactive symptomatic episodes were associated with a prior fall in IG or a glucose concentration of ≤3.3 mmol/L and were omitted from further analysis, which left 41 symptomatic episodes (Table 3). Two (5%) of these 41 postprandial episodes recorded an IG of ≤3.3 mmol/L at $t = 0$. At the corresponding postprandial time point (2.42 h) in the control group, there were no IG values ≤3.3 mmol/L (Figure 2).

When episodes were subdivided by symptom type, mean IG and the mean time after eating when symptoms were reported were not statistically different between the 3 groups ($P = 0.363$ and $P = 0.785$, respectively). When individuals contributed more than one symptomatic episode to a group, the $n$ value used for SEM calculations was the number of subjects, not the number of symptomatic episodes. Comparison of the mean IG profiles shown in Figure 2 (−60 to 0 min) with 2-factor repeated-measures ANOVA indicated that the 3 symptomatic curves differed over time ($P < 0.01$). There was a trend for mean IG to fall in the 60 min preceding neurogenic symptoms ($P = 0.086$). Further analysis of this curve showed that IG did not change between −60 and −10 min ($P = 0.229$), but a significant fall in glucose concentration (at a rate equivalent to 1.1 mmol/L per hour) occurred between −10 min and $t = 0$ ($P < 0.05$). In contrast, a significant change in IG over the preceding 60 min before autonomic symptoms was observed ($P < 0.005$) at a rate of fall over the linear section of the curve (−55 to −10 min) equivalent to 1.0 mmol/L per hour. The IG profile over the preceding 60 min before $t = 0$ min did not change in the group experiencing mixed symptoms or in the controls ($P = 0.457$ and $P = 0.221$, respectively).

When individual data were studied, 6 of 20 (30%) events associated with neurogenic symptoms followed a fall in IG of ≥0.5 mmol/L, from a peak over the previous 30 min, compared with 8 of 14 (57%) for autonomic episodes and 0 of 7 for episodes with mixed symptoms (chi-square testing was not valid). In control subjects, this fall in IG of >0.5 mmol/L was seen in 2 of the 20 (10%) postprandial profiles.

After symptoms were reported, both the neurogenic and autonomic groups showed a significant increase in IG over the subsequent 30 min ($P < 0.05$ for neurogenic and $P < 0.001$ for autonomic events); no significant change was observed after $t = 0$ in the mixed group or controls ($P = 0.779$ and $P = 0.490$, respectively). However, when only those neurogenic episodes not followed by food intake were analyzed, ($n = 15$), there was no significant change in IG over the subsequent 15 min ($P = 0.253$), whereas autonomic episodes ($n = 8$) were followed by a significant increase at a mean rate equivalent to 1.2 mmol/L per hour ($P < 0.05$).

### Table 2

Comparison of 24-h interstitial glucose (IG) concentration characteristics between the symptomatic group and the controls

<table>
<thead>
<tr>
<th></th>
<th>Control group ($n = 20$)</th>
<th>Symptomatic group ($n = 20$)</th>
<th>Symptomatic days ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h IG, from midnight (mmol/L)</td>
<td>4.84 ± 0.49</td>
<td>4.86 ± 0.34</td>
<td>4.88 ± 0.46</td>
</tr>
<tr>
<td>Fasting IG (mmol/L)</td>
<td>4.36 ± 0.66</td>
<td>4.42 ± 0.49</td>
<td>4.43 ± 0.64</td>
</tr>
<tr>
<td>Time IG was below fasting values (%)</td>
<td>26.4 ± 12.3</td>
<td>29.7 ± 11.7</td>
<td>31.3 ± 15.5</td>
</tr>
<tr>
<td>Time IG was above fasting values (%)</td>
<td>69.3 ± 13.0</td>
<td>65.6 ± 12.5</td>
<td>64.2 ± 16.2</td>
</tr>
<tr>
<td>Maximum IG during recording period (mmol/L)</td>
<td>6.80 ± 0.67</td>
<td>6.68 ± 0.90</td>
<td>6.69 ± 1.00</td>
</tr>
<tr>
<td>Minimum IG during recording period (mmol/L)</td>
<td>3.53 ± 0.55</td>
<td>3.59 ± 0.49</td>
<td>3.61 ± 0.62</td>
</tr>
<tr>
<td>2-h Postprandial IG, all meals (mmol/L)</td>
<td>4.88 ± 0.48</td>
<td>4.96 ± 0.70</td>
<td>4.95 ± 0.79</td>
</tr>
<tr>
<td>3-h Postbreakfast IG (mmol/L)</td>
<td>4.79 ± 0.62</td>
<td>4.73 ± 0.61</td>
<td>4.58 ± 0.62</td>
</tr>
</tbody>
</table>

*All values are $\bar{x}$ ± SD. Control group data were compared with symptomatic group data by using an unpaired $t$ test; within the symptomatic group, symptomatic days were compared with all days by using a paired $t$ test. No significant differences were observed.*
Dietary and activity diaries

Energy intake, daily activity levels, and energy balance were not significantly different between the original test group and controls (P/L1155 0.497, P/L1155 0.341, and P/H11005 0.789, respectively; Table 1), although there was a trend for a greater energy expenditure (P/H11005 0.078) in the control group. When the symptomatic group (n/L1155 20) was compared with controls, energy intake (P/H11005 0.990), daily activity levels (P/H11005 0.465), and energy balance (P/H11005 0.538) remained matched, and the trend for higher energy expenditure in the control group was no longer observed (P/H11005 0.202).

The only macronutrient in the diet that differed significantly during the study period was the percentage of total energy intake derived from fat; controls consumed a smaller proportion than did the symptomatic group (P/L50141 0.05). The macronutrient composition of the meal preceding symptoms had a higher proportion of energy derived from total sugars than did the individuals’ diets over the study period (P < 0.05). Moreover, there was a trend for this meal to have a lower proportion of protein (P = 0.083) and a higher proportion of carbohydrate (P = 0.051) (Table 4).

DISCUSSION

To our knowledge, the current study was the first to record IG continuously in free-living, nondiabetic subjects who report symptoms that they attribute to hypoglycemia. Most research in this area has focused on patient groups. However, despite that more than one-third of women in Nottinghamshire (United Kingdom) reported experiencing periodic symptoms (8), there appears to be a low incidence of medical referrals for the condition in the United Kingdom (7). As media articles in the United Kingdom generally do not present RH as a disease state, but a consequence of a diet high in refined carbohydrate, it seems likely that rather than the UK population being exempt from this phenomenon, symptomatic individuals are similar to those seeking medical help in other countries, but regard their symptoms as benign. Indeed, many studies in the literature investigating RH have used patient groups presenting only with self-reported symptoms that suggest hypoglycemia (6, 24, 29–31). Moreover, a similar nonreferral population had previously shown lower capillary BG 3 h after eating, when compared with nonsymptomatic controls (32), and a similar incidence of symptomatic BG readings <3.3 mmol/L when compared with other reports in the patient literature (6, 24).

It has long been contentious whether symptoms are actually related to low BG (10, 11), because previous studies using periodic finger-prick sampling have not been able to provide information regarding the BG profile preceding the development of symptoms, and biochemical hypoglycemia (defined by symptom thresholds from hyperinsulinemic clamp studies; 14) has not

**TABLE 3**

Characteristics of interstitial glucose (IG) concentration when postprandial symptoms were experienced

<table>
<thead>
<tr>
<th></th>
<th>All symptoms (n = 41)</th>
<th>Autonomic symptoms (n = 14)</th>
<th>Neurogenic symptoms (n = 20)</th>
<th>Mixed symptoms (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IG (mmol/L)</td>
<td>4.39 ± 0.65</td>
<td>4.19 ± 0.65</td>
<td>4.46 ± 0.69</td>
<td>4.60 ± 0.53</td>
</tr>
<tr>
<td>Mean time after eating (h)</td>
<td>2.43 ± 0.97</td>
<td>2.41 ± 0.96</td>
<td>2.39 ± 1.10</td>
<td>2.60 ± 0.67</td>
</tr>
<tr>
<td>No. of episodes associated with IG ≤ 3.3 mmol/L</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*P/L50141 ± SD (all such values). One-factor ANOVA was used to compare the 3 subgroups defined by symptom type. No significant differences were observed.*
commonly been observed in symptomatic individuals when symptoms were experienced. However, the current data reinforce findings from these other studies, ie, that symptomatic events associated with capillary BG of \( \leq 3.3 \text{ mmol/L} \) are uncommon (incidence range: 0–17%) (6, 24, 32).

Hyperinsulinemic clamp studies have been used to investigate BG thresholds at which symptoms of hypoglycemia develop in healthy individuals (14, 25, 33) and these values have been used to define hypoglycemia. However, the prerequisite in the RH literature for BG to be \( \leq 3.3 \text{ mmol/L} \) when symptoms are experienced, for diagnosis of hypoglycemia to be confirmed, may be too limited. Brun et al (1) reported that, after consumption of a high-glucose-index breakfast, individuals prone to RH reported symptoms at a BG concentration (4.0 mmol/L) higher than traditional threshold values. Moreover, subjects are usually semisupine during protocols used to investigate symptom thresholds, whereas it has been shown that symptoms and physiologic responses to insulin-induced hypoglycemia are increased when upright (34, 35). Therefore, symptom thresholds, defined by hyperinsulinemic clamp studies, may underestimate hypoglycemia in free-living, ambulatory individuals.

Hyperinsulinemic clamp studies also have concluded that the rate of fall of BG does not affect whether hypoglycemic symptoms are experienced and that absolute BG determines the initiation of these symptoms (25, 26). However, in the current study, a fall in IG appeared, in some cases, to be associated with initiation of these symptoms (25, 26). However, in the current study, most neurogenic symptomatic episodes (70%) were not associated with an IG in the euglycemic range. However, such a dysfunction would not be expected to be intermittent, and it is likely that explanations other than those relating to BG regulation are pertinent in these cases.

### TABLE 4

Macronutrient composition of the diet in the symptomatic and control groups over the duration of the study period, and the composition of the meal preceding symptoms

<table>
<thead>
<tr>
<th>Mean diet composition during study</th>
<th>Meal composition preceding symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>Symptomatic group</td>
</tr>
<tr>
<td>( n = 20 )</td>
<td>( n = 20 )</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>13.5 ± 2.3</td>
</tr>
<tr>
<td>Total fat (% of energy)</td>
<td>31.7 ± 5.1(^1)</td>
</tr>
<tr>
<td>Carbohydrate (% of energy)</td>
<td>47.2 ± 6.1</td>
</tr>
<tr>
<td>Total sugars (% of energy)</td>
<td>21.2 ± 5.4</td>
</tr>
<tr>
<td>Starch (% of energy)</td>
<td>24.6 ± 3.9</td>
</tr>
</tbody>
</table>

\(^1\) ± SD (all such values). Controls were compared with the symptomatic group by using an unpaired \( t \) test; within the symptomatic group, the meal preceding symptoms was compared with the diet on all days by using a paired \( t \) test.

\(^2\) Significantly different from the symptomatic group, \( P < 0.05 \).
Autonomic symptoms are more specific, but could equally be explained by other situations, unrelated to hypoglycemia, by characterized by an epinephrine-mediated response. In these cases, symptoms would not necessarily be related to prior changes in IG, although as a consequence of epinephrine release into the blood, a rise in IG would be expected. Indeed, in those episodes not followed by eating, an increase in IG was observed after symptoms were noted, which suggests that symptoms may have been mediated by epinephrine. Moreover, a prior fall in mean IG was associated with the initiation of autonomic symptoms, and 64% of the individual episodes were either preceded by a fall in IG of ≥0.5 mmol/L over the preceding 30 min or accompanied by a glucose concentration of ≤3.3 mmol/L. However, whether this observation is of clinical significance is unclear, because it was difficult to determine what was unique about these IG profiles (in terms of magnitude or rate of fall) to cause a response, when at other times similar IG curves did not induce symptoms. Indeed, no differences in mean 24-h IG data could be determined between groups, and the IG profiles around the 2.42-h postprandial time point for both the control and the symptomatic groups on a nonsymptomatic occasion did not differ. Therefore, it seems reasonable to conclude that experiencing these symptoms does not reflect a pathologic state with regard to glucose regulation. However, it was interesting to observe that symptomatic IG profiles before t = 0 were numerically lower than corresponding IG values in the control group or in the symptomatic group when asymptomatic. Although it is not ideal to compare symptomatic IG curves with an arbitrary postprandial time period, it suggests that symptomatic events may be associated with small changes in the glucose concentration around which IG is regulated.

The link between rapidly absorbable sugars and RH has long been postulated (13, 36) and is presented as a truism in the media. Previous research and the current study did not observe any differences in the proportion of energy derived from carbohydrates and total sugars in the habitual diet of symptomatic individuals when compared with controls (6, 32). However, a trend for higher total sugar intakes (as a proportion of total energy) was previously reported in symptomatic individuals on days when symptoms were reported (when compared with controls) (32). Furthermore, in the current study, the meal preceding symptoms had a higher proportion of energy derived from total sugars than did the individuals’ diets over the study period and that of controls. We recognize the potential problems of comparing the composition of a single meal with that of a complete diet. However, symptoms were recorded at all times of the waking day, so the previous meal represents a variety of different meals in the different subjects. Clearly, more work is needed to further investigate the potential role of dietary sugars in RH.

In conclusion, most of the symptoms attributed to a low BG concentration in the current study, by otherwise healthy women, were not associated with hypoglycemia (as assessed by CGMS and defined by counterregulatory threshold studies). It appears that the experiencing of autonomic symptoms was related to changes in IG, whereas most neurogenic and all mixed symptomatic episodes were unrelated to IG dynamics. It did not appear that the experiencing of symptoms reflected pathology in glucose regulation in these individuals, and factors other than BG dynamics per se must be involved in the initiation of symptoms. The consumption of meals high in sugars potentially plays a role.

The authors’ responsibilities were as follows—EJS: designed the study, collected and analyzed the data, and wrote the manuscript; and MH and IAM: provided significant advice and consultation regarding the study design and interpretation of data and reviewed the manuscript. None of the authors had any conflict of interests.

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