Article

Subclinical Reactive Hypoglycemia Is Associated with Higher Eating and Snacking Frequencies in Obese or Overweight Men without Diabetes

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Abstract: Impacts of subclinical reactive hypoglycemia on food ingestion are not well studied. In the present study, in obese/overweight males without diabetes (n = 34), continuous glucose monitoring and eating behavior were recorded for 6 days after the 75 g glucose challenge. In 50% of subjects, the minimal sensor glucose levels within 24 h post-challenge (CGMmin) were <70 mg/dL, while symptoms, if any, were subtle. Median eating and snacking frequencies were 3.45 and 0.45 times/day, respectively. In subjects with eating frequency > 3 times/day, CGMmin was significantly lower than CGMmin in those without. The receiver operating characteristic curve of CGMmin for detecting eating frequency > 3 times/day showed the area under the curve of 0.74 with the cutoff point of 65 mg/dL (p = 0.027). Eating frequency of subjects with CGMmin < 65 mg/dL was significantly higher than that of subjects with CGMmin ≥ 65 mg/dL (3.68 vs. 3.3 times/day, p = 0.047). When it was defined as reactive hypoglycemia that either the 2 h post-load blood glucose level, the minimal self-monitored blood glucose level within the 1st day, or CGMmin, was below their respective cutoff for detecting eating frequency > 3 times/day, eating frequency of subjects with the reactive hypoglycemia was significantly higher than that of the subjects without the reactive hypoglycemia (3.75 times/day vs. 3.15 times/day, p = 0.001). In addition, the median snacking frequency was 6 times higher in subjects with reactive hypoglycemia compared to those without it (0.9 times/day vs. 0.15 times/day, p < 0.001). In conclusion, in obese/overweight males without diabetes, subclinical reactive hypoglycemia is significantly associated with higher eating/snacking frequencies.

Keywords: eating frequency; subclinical hypoglycemia; continuous glucose monitoring; non-diabetes; obesity; snacking

1. Introduction

Postprandial low glucose with symptoms typical for hypoglycemia, such as dizziness, tremor, sweating, or palpitation, is termed reactive hypoglycemia, which can occur in people without diabetes [1]. It is thought to be more common in overweight individuals and to be the result of hyperinsulinemia following a large carbohydrate-based meal [2]. On the other hand, hypoglycemia without typical symptoms, i.e., subclinical, is not well studied in the everyday life of people without diabetes.

The previous studies suggest that the glucose threshold for typical symptoms of hypoglycemia is lower than that for activation of appetite. For example, with the use of the hyperinsulinemic glucose clamp, it is reported that activation of the autonomic symptoms such as anxiety, palpitations, sweating, irritability, and tremor began at plasma glucose concentrations of 58 mg/dL [3], while functional MRI combined with a stepped hyperinsulinemic euglycemic–hypoglycemic clamp revealed that mild hypoglycemia of 67 +/− 1 mg/dL preferentially activates limbic-striatal brain regions in response to food intake.

Endocrines 2022, 3, 530–537. https://doi.org/10.3390/endocrines3030043
cues to produce a greater desire for high-calorie foods [4]. It is, therefore, possible that mild hypoglycemia, the glucose levels of which are higher than the threshold of symptomatic autonomic activation but sufficiently lower than that for appetite activation, might lead to an increased frequency of eating, either consciously or subconsciously, to prevent further hypoglycemia.

Recently, we have shown that in middle-aged males with overweight/obesity but without diabetes, eating habits were significantly associated with insulin resistance and compensatory hyperinsulinemia [5]. In the present study, based on the assumptions that, even if without the typical symptoms of hypoglycemia, the observed hyperinsulinemia could still lead to low glucose levels, which are mild but sufficient to elicit the appetite, we examined continuous glucose monitoring (CGM) metrics for low glucose levels and analyzed if the subclinical hypoglycemia is associated with eating or snacking frequency in daily life.

2. Materials and Methods

Study subjects: Obese/overweight (body mass index, BMI ≥ 25) male subjects without documented diabetes were recruited as described previously [5,6]. In brief, a total of 50 (age 50–65 years) male participants, who have no documented dysglycemia (previous diagnosis of diabetes or HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL in the preceding 1 year), were recruited into the study. Persons with either normal or impaired glucose tolerance by the 75 g oral glucose tolerant tests (OGTT) were included and individuals with more than 1900 CGM consecutive readings were chosen for the analysis (n = 34).

Study protocol: Participants were asked to wear iPro™ 2 Professional CGM (Medtronic, Minneapolis, MN, USA) for 6 days during which a seven-point (preprandial, 1~2 h postprandial, and pre-bedtime) self-monitored blood glucose profile was created with a glucometer (Glutest Neo Alpha; Sanwa Kagaku Kenkyusho Co, Osaka, Japan). The sensor was calibrated four times throughout the day according to the manufacturer’s instructions and the data begin at 178.5 (IQR 138.8–218.8) min after the glucose challenge. In the present study, we focused on the CGM data within the initial 24 h. During the study period, participants were asked to keep daily logs of food intake, exercise, subjective symptoms (dyspepsia and bowel movement, etc.), and emotional or physical stress (hectic schedule and interpersonal relations, etc.), and to take photographs of every meal, snack or drink content with the date and time stamp.

Definition of eating behaviors: The food or drink groups and times of ingestion were evaluated using the diet logs and the photographs. Participants were asked to take pictures of all foods they ate during the study and to specify each food as breakfast, lunch, dinner, or night meal, and this information was used to identify meals for the analysis. In the present study, we defined snacking as the ingestion of any caloric foods other than those having with (or as) meals or with alcohol. For frequencies during the study, where more than two occasions occurred within the 15 min period, all events were taken as a single occasion. The average number of occasions on which the participant consumed food or drink items per day was estimated from the food pictures with time and date stamps. Eating frequency was calculated as a sum of meal frequency and snacking frequency. Two researchers independently determined eating frequency, the results of which were almost similar (Pearson’s correlation coefficient > 0.9).

Insulin secretion/resistance indices: Based on simultaneous measurements of blood glucose and insulin concentrations under fasting conditions or during the OGTT, indirect indices of insulin secretion or insulin resistance were determined. The homeostatic model assessment (HOMA)-β and the quantitative insulin sensitivity check index (QUICKI) were determined by the following formulae: fasting insulin × 360/(fasting glucose level − 63) and 1/(log[fasting insulin level] + log[fasting glucose level]), respectively [7]. HOMA-IR, the insulinogenic index, Matsuda index [8], and disposition index (the product of insulino-genic index and Matsuda index) were calculated online [9].
Assessing hypoglycemia: For the indices of hypoglycemia within 24 h after OGTT, the minimal CGM glucose level (CGMmin), and the percent of time below range (TBR; the percentage of time when the CGM-recorded value was less than the selected glucose thresholds) were determined. In the present study, sensor glucose < 70 mg/dL was analyzed as hypoglycemia because a blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes [10]. In addition, sensor glucose < 65 mg/dL, the cutoff point of the receiver operating characteristic (ROC) analysis for detecting the eating frequency > 3 times/day, was also examined. To assess reactive hypoglycemia, we determined levels of 2 h post-load blood glucose, and minimal self-monitored blood glucose within the 1st day, in addition to CGMmin within 24 h after glucose challenge. In the present study, since the optimal cutoff points in the ROC analyses of these parameters for detecting subjects with eating frequencies > 3 times/day were 73, 69, and 65 mg/dL, respectively, subjects with either 2 h post-load blood glucose < 73 mg/dL, minimal self-monitored blood glucose within the 1st day < 69 mg/dL, or CGMmin within 24 h after glucose challenge < 65 mg/dL were defined as those with reactive hypoglycemia.

Statistical analysis: Baseline data are expressed as the median and interquartile range (IQR) stratified by the presence/absence of reactive hypoglycemia or the CGMmin category (<65 vs. ≥65 mg/dL). The Mann–Whitney U test was used for the comparison of continuous variables based on the categorical data. The two-sided Fisher’s exact test was used to test whether there was a correlation between categorical variables. The association between CGMmin and average snacking frequency during the study was investigated with a scatter plot and linear regression analysis using Spearman’s rank correlation coefficient (ρ). The association between CGMmin and average eating frequency during the study was investigated with a scatter plot and linear regression analysis using Pearson’s correlation coefficient (r). The normality for the two variables was confirmed by the Shapiro–Wilk test (p = 0.662 and p = 0.324, respectively). To measure the diagnostic accuracy of CGMmin for predicting the frequency of snacking ≥ once/day, the ROC curve analysis was applied, and the AUC was computed. The cutoff point was determined via the closest to top left of the ROC curve method to maximize the overall accuracy of the classification rate and assign equal weight to the sensitivity and the specificity. As to the statistical power, sample sizes were calculated as 34 for linear bivariate correlation (one tail, α error = 0.05, power = 0.95) and 32 for Mann–Whitney U test (one tail, effect size = 0.9, α error = 0.05, power = 0.7, allocation ratio = 0.4). Analyses were performed with JMP version 10.0.0 (SAS Institute Inc., Cary, NC, USA) or R software version 4.1.2 (1 November 2021, https://www.r-project.org/). Statistical significance was defined as a p-value of <0.05.

Ethics statement: The study was approved by the institutional review board of Toyooka Public Hospital (#146; 3 October 2017) and the Japan Conference of Clinical Research review board (JCCR#3-132; 21 October 2016). It was performed in accordance with the principles established by the Helsinki Declaration. Before study enrollment, written informed consent was obtained from all participants.

3. Results

Among all participants (n = 34), median (IQR) age was 54 (52–58) years, BMI was 27.8 (26.5–29.1), HbA1c level was 5.3 (5.2–5.5)%, fasting plasma glucose level was 92 (87–96) mg/dL, and 2 h post-challenge glucose level was 112 (95–143) mg/dL. As shown in Table 1, the median (IQR) CGMmin within 24 h after OGTT was 70 (58.8–85.3) mg/dL. Half of the participants exhibited their CGMmin < 70 mg/dL. Median (IQR) TBR 70 was 0.2% (0–3.9%). Among a quarter of the participants, the average time spent with glucose levels below 70 mg/dL was ≥55.4 min/day.
Table 1. CGM metrics within 24 h after OGTT.

| Parameters                  | Data                         | n  |
|-----------------------------|------------------------------|----|
| CGMmin < 70 mg/dL           | % of subjects                | 17 |
| Sensor data, hours          | Median (IQR)                 | 34 |
| CGMmean, mg/dL              | 107.5 (94.8–117)             | 34 |
| CGMmax, mg/dL               | 154 (132.8–169.3)            | 34 |
| CGMmin, mg/dL               | 70 (58.8–85.3)               | 34 |
| CGMsd, mg/dL                | 17.1 (12.8–22.4)             | 34 |
| TAR 140, %                  | 4.5 (0–15)                   | 34 |
| TAR 140, min/day            | 64.8 (0–216)                 | 34 |
| TBR 70, %                   | 0.2 (0–3.9)                  | 34 |
| TBR 70, min/day             | 2.9 (0–55.4)                 | 34 |

OGTT, oral glucose tolerance test; CGM, continuous glucose monitoring; CGMmean, CGMmax, and CGMmin, mean, maximal, and minimal sensor glucose level during 24 h after glucose challenge, respectively; CGMsd, standard deviation of sensor glucose level during 24 h after 75-g glucose challenge; TAR 140 and TBR 70, percentages of time when sensor glucose levels are above 140 and below 70 mg/dL, respectively; IQR, interquartile range.

During the 6-day study period, median meal, snacking, and eating frequencies were 3.0, 0.45, and 3.45 times/day, respectively (Table 2). Approximately one-quarter of the subjects snack daily.

Table 2. Eating behaviors during 6 days after OGTT.

| Parameters                  | Data                         | n  |
|-----------------------------|------------------------------|----|
| Meal Frequency, times/day   | Median (IQR)                 | 34 |
| Snacking Frequency, times/day | 3.0 (2.85–3.04)             | 34 |
| Eating Frequency, times/day | 3.45 (3.11–3.98)             | 34 |
| % of subjects               |                             |    |
| Meal Frequency > 3 times/day | 23.5                         | 8  |
| Snacking Frequency = 0 times/day | 23.5                 | 8  |
| Snacking Frequency ≥ once/day | 23.5                         | 8  |
| Eating Frequency > 3 times/day | 76.5                         | 26 |
| Eating Frequency ≥ 4 times/day | 23.5                         | 8  |

OGTT, 75-g oral glucose tolerance test.

As shown in Supplementary Figure S1, a scatter plot showed a significant trend toward higher snacking frequency deviation as CGMmin decreased (Spearman’s rank correlation coefficient ($\rho = -0.36$, $p = 0.039$). In addition, there is a significant trend toward higher eating frequency deviation as CGMmin decreased (Pearson’s correlation coefficient ($r = 0.35$, $p = 0.043$) (Supplementary Figure S2).

The ROC curve of CGMmin for detecting the snacking frequency ≥ once/day revealed the AUC of 0.73 (95% confidence interval: 0.57–0.92) with the optimal cutoff point of 65 mg/dL (sensitivity 76.9%, specificity 62.5%) ($p = 0.033$) (Supplementary Figure S3). The decrease of 1 mg/dL of CGMmin leads to a 5.9% increase in the risk of having the snacking frequency > once/day category.

When the subjects were divided according to the presence or the absence of CGMmin < 65 mg/dL, there were no significant between-group differences concerning anthropometric or laboratory data (Supplementary Table S1). The eating frequency of the subjects with CGMmin < 65 mg/dL was significantly higher than that of the subjects with CGMmin ≥ 65 mg/dL (3.75 times/day vs. 3.3 times/day, $p = 0.035$). Although it did not
reach a statistical significance, there was a tendency toward higher snacking frequency in subjects with CGMmin < 65 mg/dL (Supplementary Table S1).

We next examined the effects of reactive hypoglycemia on eating behaviors. As shown in Table 3, the eating frequency of subjects with reactive hypoglycemia was significantly higher than that of the subjects without reactive hypoglycemia (3.75 times/day vs. 3.15 times/day, \( p = 0.001 \)). In addition, the median snacking frequency was 6 times higher in subjects with reactive hypoglycemia compared to those without it (0.9 times/day vs. 0.15 times/day, \( p < 0.001 \)), while there was no significant between-group difference concerning meal frequency (Table 3).

Table 3. Median (IQR) of anthropometric, glucose/insulin, and eating behavior-related parameters in the presence or the absence of reactive hypoglycemia.

| Parameters                   | Median (IQR) | n  | Median (IQR) | n  | p-Value |
|------------------------------|--------------|----|--------------|----|---------|
| RH (+)                       |               |    | RH (-)       |    |         |
| Age, year                    | 54 (52–59)   | 19 | 57 (52–58)   | 15 | 0.688   |
| BMI                          | 27.8 (26.6–29.4) | 19 | 27.8 (26.1–28.7) | 15 | 0.521   |
| HbA1c, %                     | 5.3 (5.2–5.5) | 19 | 5.4 (5.1–5.6) | 15 | 0.575   |
| 1,5-AG                       | 19.5 (15.7–23.4) | 19 | 20.7 (13.8–24.1) | 15 | 0.986   |
| HOMA-\( \beta \)             | 120.8 (65.1–162.6) | 19 | 90.6 (69.3–127.9) | 15 | 0.231   |
| HOMA-IR                      | 2.25 (1.0–2.9) | 19 | 1.8 (1.3–2.32) | 15 | 0.521   |
| Insulinogenic Index          | 0.6 (0.4–1.3) | 19 | 0.55 (0.31–1.03) | 15 | 0.795   |
| Matsuda Index                | 3.26 (1.47–4.04) | 19 | 2.24 (3.09–6.05) | 15 | 0.64    |
| Disposition Index            | 2.8 (1.35–7.61) | 19 | 2.87 (1.57–5.06) | 15 | 0.931   |
| QUICKI                       | 0.34 (0.33–0.38) | 19 | 0.35 (0.34–0.37) | 15 | 0.742   |
| Meals, times/day             | 3.0 (2.85–3.15) | 19 | 3.0 (2.85–3.0) | 15 | 0.23    |
| Snacking, times/day          | 0.9 (0.3–1.5) | 19 | 0.15 (0–0.6) | 15 | \(<0.001^*\) |
| Eating, times/day            | 3.75 (3.45–4.5) | 19 | 3.15 (2.85–3.45) | 15 | 0.001^* |

BMI, body mass index; 1,5-AG, 1,5-anhydroglucitol; HOMA, homeostatic model assessment; QUICKI, quantitative insulin sensitivity check index; IQR, interquartile range; RH, reactive hypoglycemia. Frequencies of meals, snacking, and eating were defined as described in the materials and methods. \( p \)-values were obtained from a Mann–Whitney \( U \) test used to compare the two categories (subjects with vs. without RH). *, \( p < 0.05 \).

Furthermore, the proportion of subjects without any snacking during the study was significantly lower with reactive hypoglycemia (5.3% vs. 46.7%, Fisher’s exact \( p = 0.011 \)), while that of subjects with daily (i.e., \( \geq \) once/day) snacking was significantly higher (42.1% vs. 0%, Fisher’s exact \( p = 0.005 \)) (Table 4). Likewise, the proportions of subjects with eating frequencies > 3 and \( \geq \) 4 times/day were significantly higher with reactive hypoglycemia.

Table 4. Proportions of the eating behavior categories in subjects with and without reactive hypoglycemia.

| Parameters                      | %  | n  | %  | n  | p-Value |
|---------------------------------|----|----|----|----|---------|
| Meal Frequency \( > 3 \times \text{day} \) | 31.6 | 6  | 13.3 | 2  | 0.257   |
| Snacking Frequency = 0 times/day | 5.3  | 1  | 46.7 | 7  | 0.011^* |
| Snacking Frequency \( \geq \) once/day | 42.1 | 8  | 0   | 15 | 0.005^* |
| Eating Frequency \( > 3 \times \text{day} \) | 94.7 | 18 | 53.3 | 8  | 0.011^* |
| Eating Frequency \( \geq 4 \times \text{day} \) | 42.1 | 8  | 0.0 | 15 | 0.005^* |

RH, reactive hypoglycemia; frequencies of meals, snacking, and eating were defined as described in the materials and methods. The \( p \)-values were obtained from a two-tailed Fisher’s exact test used to compare the two categories (subjects with vs. without RH). *, \( p < 0.05 \).

4. Discussion

In the present study, glucose profiles of obese/overweight males without diabetes within 24 h after OGTT revealed that a substantial proportion of the subjects exhibited glucose levels below the threshold for hypoglycemia without any notable symptoms. In addition, the lower CGMmin was significantly associated with higher eating frequency during 6 days after OGTT. The subjects with the CGMmin < 65 mg/dL category ate significantly
Endocrines 2022, 3

more frequently than those with the CGMmin ≥ 65 mg/dL category. Furthermore, when either the 2 h post-load blood glucose level was < 73 mg/dL, the minimal self-monitored blood glucose level within the 1st day < 69 mg/dL, or the CGMmin < 65 mg/dL was defined as reactive hypoglycemia, both snacking and eating frequencies were significantly higher in subjects with reactive hypoglycemia than those in subjects without it. Approximately 40% of subjects with reactive hypoglycemia snacked daily, while none of the subjects without reactive hypoglycemia did.

The present study shows that subjects with reactive hypoglycemia within 24 h after OGTT had higher eating frequency than those without. One possible reason for the association is that, upon low glucose, these subjects might unconsciously (or consciously with hunger) prevent symptomatic hypoglycemia by increasing eating frequency. Since the perception of hunger is regulated by the plasma glucose concentration [11] and is synchronized with transient and dynamic blood glucose declines [12], the observed latent reactive hypoglycemia in obese people could lead to an increased feeling of hunger and possibly inadvertent overeating.

The traditional diet is organized around three meals/day (i.e., breakfast, lunch, and dinner). Although this three-meal frequency of eating is embedded deeply in popular culture, more frequent meals or snacks per day are documented in modern lifestyles [13] and are positively associated with overweight and obesity [14]. While a consensus on clear definitions or distinctions between a meal and a snack remains vague, this greater frequency of eating is largely attributed to an increase in snacking [15], most of which includes sugary ingredients. In the present study, there was a significant trend toward higher snacking frequency in subjects with reactive hypoglycemia compared to those without. Given snacks such as cakes, chocolate, ice cream, muffins, sugary drinks, potato chips, candies, etc., are rich in carbohydrates with a high glycemic index, ingestion of snacks could lead to postprandial surges in glucose, which often trigger delayed insulin secretion and promote subsequent reactive hypoglycemia. In fact, as we previously documented [5], snacking habits are associated with higher levels of indices for insulin secretion. It is shown that, upon food cues, mild hypoglycemia (lowering glucose to approximately 65 mg/dL) activated limbic-striatal brain regions and produced a greater desire for high-calorie foods [4]. A role of glucose fluctuation with high glycemic index foods on triggering addiction-like neurochemical and behavioral responses is also suggested [16]. Taken together, these results suggest that subclinical reactive hypoglycemia after ingestion of high glycemic index snacks, augments the desire for food and addiction-like responses, leading to higher snacking frequency. Therefore, snacking begets snacking through subclinical reactive hypoglycemia.

Limitations of the current study include: (1) since the present study focused on middle-aged males with overweight/obesity, the association of hypoglycemia and eating behaviors in other populations should be determined elsewhere; (2) since lifestyle behaviors are self-reported, participants might over-or under-report their eating or snacking habits. During the study, we evaluated food items by photographs taken by the individual participants, where a reporting bias may also exist; (3) since, for dietary behaviors, only the occasions were considered, the present study does not tell the effect of hypoglycemia on the amount or the contents of the foods.

5. Conclusions

In obese/overweight males without diabetes, subclinical reactive hypoglycemia is not rare and associated with higher snacking frequency. Since even subclinical, reactive hypoglycemia increases eating behaviors, snacking habits could be strengthened, thus creating the vicious cycle of reactive hypoglycemia and snacking that is hard to break. Particularly in modern environments flooded with high-calorie and high glycemic index foods, approaches that alleviate subclinical reactive hypoglycemia would be mandatory for the prevention or treatment of obesity and related morbidities.
**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines3030043/s1, Figure S1: Scatter plot showing the significant association between snacking frequency and the minimal CGM sensor glucose level, Figure S2: Scatter plot showing the significant association between eating frequency and the minimal CGM sensor glucose level, Figure S3: The ROC curves of the minimal CGM sensor glucose level for detecting snacking frequency $\geq$ once/day; Table S1: Median (IQR) of anthropometric, glucose/insulin, and eating behavior-related parameters in subjects with the minimal CGM sensor glucose levels within 24 h after OGTT < 65 mg/dL and $\geq$65 mg/dL.

**Author Contributions:** I.K. contributed to the conception and design of the study, analyzed data, and wrote the manuscript. A.O. contributed to the acquisition of data, data analysis, and interpretation of the results. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Japan Agency for Medical Research and Development (AMED; Grant Number JP16ek0210034) and the clinical research fund from Toyooka Public Hospital.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Toyooka Public Hospital (protocol code 146, date of approval; 3 October 2017).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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