Continuous Glucose Monitoring Results in Idiopathic Postprandial Syndrome

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Abstract

Objective: Although idiopathic postprandial syndrome is popular in the media, it is accepted as a controversial nondisease in the medical community. The aim of this study was to assess interstitial glucose profiles of patients with idiopathic postprandial syndrome, in their routine daily activities.

Material and Methods: Eight women with symptoms of idiopathic postprandial syndrome participated to the study. The subjects were 39±9 years old, with a mean BMI of 23±3 kg/m². Fasting venous glucose was 4.94±0.39 mmol/l. 227 interstitial glucose readings were obtained with GlucoWatch Biographer.

Results: Continuous glucose monitoring showed that preprandial glucose was 4.75±0.87 mmol/l. Peak postprandial glucose level was 9.28 mmol/l, and average time to peak glucose was 74 minutes. Nadir glucose value was 3.5 mmol/l and average time to nadir glucose was 110 minutes. There were ten symptomatic episodes in six patients. There were no glucose readings below 3 and 3.3 mmol/l, commonly accepted threshold values for neuroglycopenic and adrenergic symptoms of hypoglycaemia, respectively.

Conclusion: Subjects reporting symptoms that they attribute to idiopathic postprandial syndrome do not have low interstitial glucose concentrations, as assessed by continuous glucose monitoring with GlucoWatch Biographer.

Key words: Reactive hypoglycaemia, continuous glucose monitoring, postprandial hypoglycaemia, idiopathic postprandial syndrome

Introduction

Reactive hypoglycaemia refers to low blood sugar occurring after meals, not in the postabsorptive state. It can be subdivided into three categories: a) alimentary hypoglycaemia, seen after surgery of the upper gastrointestinal tract, b) early diabetes hypoglycaemia, c) idiopathic or functional postprandial hypoglycaemia (1). Blood glucose values of asymptomatic healthy individuals and patients with idiopathic postprandial syndrome overlap, both after meals and during an oral glucose tolerance test (OGTT). When OGTT is administered to normal healthy subjects, approximately 25 percent have nadir glucose values below 3 mmol/l (2). Patients with low blood glucose levels during an OGTT, may have normal glucose concentrations after a mixed meal test (3). Therefore, reactive hypoglycaemia is currently termed as idiopathic postprandial syndrome (1). Palardy et al. (4) reported home blood glucose monitoring results in 28 patients with symptoms of idiopathic postprandial syndrome. Only 5% (6 out of 132) of the
episodes were associated with a capillary blood glucose level below 2.8 mmol/l. The Palardy study (4), measuring capillary glucose in free living patients, may have missed true nadirs due to limitations in the measurement techniques available (possible lag between nadir and recognising symptoms, difficulty in taking a measurement due to symptoms; tremor, disorientation, confusion, etc.). The use of continuous glucose monitoring could address this problem. The studies that used glucometers in idiopathic postprandial syndrome were performed when continuous glucose monitoring technology was not available. GlucoWatch Biographer (GlucoWatch) is a wrist-watch-like device that measures interstitial glucose levels automatically, every 20 minutes up to 12 hours. Continuous glucose monitoring in reactive hypoglycaemia will answer the following question: Are the so-called hypoglycaemic patients do really have low blood sugar when experiencing symptoms or in their routine daily lives?

**Aim**

The aim of this study is to document preprandial and postprandial interstitial glucose levels in free-living individuals with symptoms of idiopathic postprandial syndrome. The novel aspect of this study is the use of a more frequent glucose measurement technique than previous studies with capillary glucose measurements.

**Material and Method:**

**Subjects**

Eight consecutive women presenting with symptoms suggestive of reactive hypoglycaemia were studied. They had the combination of any of the following complaints for at least twice per week: fatigue, light-headedness, palpitations, tremors, faintness and sweating after meals. Before presenting to endocrine outpatient clinic, all had a presumptive diagnosis of reactive hypoglycaemia. They were either referred by their primary physician who observed a low blood sugar value at OGGT, or the patients self-diagnosed themselves with the information they obtained through Internet or media. All the women were premenopausal. Two of them had iron deficiency anemia. One subject had a history of hypothyroidism due to Hashimoto’s thyroiditis. She was euthyroid during the study period, because she had been on L-thyroxine therapy. The same subject also had depression and was on antidepressants. The rest of the participants were healthy and were not taking any medications. None of them had polycystic ovarian disease.

**Noninvasive Glucose Monitoring**

The GlucoWatch Biographer (Cygnus Company, Redwood City, CA) provides frequent, automatic, and noninvasive glucose measurements in every 20 minutes up to 12 hours after a capillary blood glucose measurement for calibration (5). It extracts glucose through the skin by reverse iontophoresis. Iontophoresis is a technique, in which a low-level electric current is applied through the skin between an anode and a cathode (6). Because of applied potential, sodium and chloride ions from beneath the skin migrate toward the cathode and anode, respectively. Uncharged molecules, including glucose are carried along with the ions by convective transport, a process called electroosmosis. The extracted glucose is measured by an amperometric biosensor that detects H2O2. The glucose oxidase reaction produces H2O2 as follows: glucose + O2—→gluconic acid + H2O2. The H2O2 is detected via an electrocatalytic reaction at the platinum-containing electrode in the sensor, where an electric current is produced and oxygen is regenerated as follows: H2O2—→O2+ 2H+ + 2 electrons. The magnitude of the electric current is correlated with the amount of glucose collected through skin at the sensor. The amount of glucose extracted at the cathode is proportional to blood glucose. Extraction and detection are performed through two hydrogel pads that are located under the sensor, in contact with the patients’ skin. Each hydrogel pad contains glucose oxidase. The upper part of the sensor contains two sets of iontophoretic and sensing elements. After three minutes of electric current between the anode and cathode, glucose is accumulated at the cathode and is measured by the sensing electrode. Then, the polarity is alternated and the anode becomes a cathode and vice versa. After three minutes of another glucose extraction, the glucose is measured again at the new cathode. The average measurement of two extractions is given as a blood glucose reading at the screen. After a three hour equilibration period, a finger-prick capillary glucose measurement is obtained for calibration. The calibration translates the electric current to a glucose value, taking into account individual skin permeability and biosensor sensitivity. The calibration value is also used to convert subsequent biosensor measurements into glucose readings (5). The biographer contains skin temperature and skin conductance sensors. Large temperature changes or sweating confound the glucose measurements. Glucose measurements are skipped during sweating and when there is a certain change at skin temperature. Clinical studies in diabetes mellitus show that approximately 20% of glucose readings are skipped (6). GlucoWatch extracts glucose through the skin by reverse iontophoresis. Three minutes is required to extract and seven minutes to measure glucose. Two cycles are averaged into one glucose measurement. Therefore, there is a lag time between GlucoWatch readings and capillary glucose measurements. GlucoWatch readings reflect blood glucose value from 17±7 minutes earlier (7). When correlating glucose results with meal times and symptoms, GlucoWatch readings were corrected taking into account 17±7 minute delay. Preprandial was defined 0 to 40 minutes before, and postprandial as 20 to 240 minutes after meals. Gauging excursions were calculated by using the current and previous reading. The difference between two consecutive glucose measurements was taken, starting with premeal and ending with the next premeal or up to 240-minute value, whichever comes first. Peak and nadir glucose values and time to peak and nadir postprandial glucose values were identified. The standard deviation score (SD score) of GlucoWatch Biographer readings was determined by calculating the variance of glucose values for each application. The square root of the calculated variance was taken to be each subjects’ SD score (8). The mean SD score was presented as an average of all SD scores.

**Laboratory Methods**

Plasma glucose was measured with hexokinase method (cobas c systems, Roche Diagnostics, Mannheim, Germany) after 12 hours of refraining from food. GlucoWatch Biographer was applied in the morning after a light breakfast. After a three-hour
equilibration period, capillary blood glucose measurement was obtained and entered as the calibration value. GlucoWatch was calibrated with Medisense Optium (Medisense UK Limited; Abingdon, Oxon, UK). Glucose measurements with GlucoWatch was commenced before lunch and continued through midnight up to 1 or 2 am. The patients were asked to write down their food intake. Subjects were asked not to exercise and change their usual physical activity pattern during the study period.

Results

The average age of the participants was 39±9 (range: 24 to 48). Body mass index (BMI) was 23±3 (range: 19.9 to 28). Bioelectrical impedance analysis showed that average fat ratio of the subjects was 25.4±3.1% (range: 21.9 - 29.5%). There were no obese participants; only one subject was overweight with a BMI of 28. The average fasting plasma glucose level was 4.94±0.39 mmol/l (range: 4.33 – 5.39). Analysis of the food records showed that the patients ate a vegetable dish with two slices of white bread at lunch. They ate meat or chicken with either two slices of white bread or four tablespoonsfuls of rice or macaroni for dinner. For evening snack they ate a high carbohydrate evening snack, a cake or desert with fruit juice or hot tea with sugar. The evening snacks are estimated to contain around 55 to 70 grams of carbohydate and 350 to 400 kilocalories. For night-time snack, two of the patients drank an alcoholic beverage, one 250 ml of red wine, the other 330-ml beer, the rest ate a fruit (a banana or an apple). There were 288 possible data points with GlucoWatch. Sixty-one readings were skipped by the device due to either diaphoresis, skin temperature changes or failed internal quality check. If the measurements do not meet the internal quality control criteria preinstalled by the manufacturer, the screen shows a “SKIP” message. The median number of recorded data points was 27.5 (range: 26 – 33). There were 35 to 36 possible data points with each application, so between three to 10 readings were skipped per application. The missing data were evenly distributed between subjects. 227 valid readings (79% of possible data points) were obtained. The average prelunch glucose value was 4.63 mmol/l, average preevening-snack glucose was 4.61 mmol/l, average predinner glucose was 4.37 mmol/l and average prenighttime-snack glucose was 5.01 mmol/l. Prelunch, predinner and presnack interstitial glucose values were classified as preprandial readings. Postlunch, postdinner, and all glucose values after snacks were classified as postprandial values and labelled according to time the reading was obtained. Preprandial and postprandial glucose values are summarised in the table. Average preprandial glucose level was 4.75 ±0.87 mmol/l. Peak postprandial glucose value was 9.28 mmol/l. Average time to peak glucose value was 74 minutes. Nadir postprandial glucose value was 3.50 mmol/l. Average time to nadir glucose value was 110 minutes. There were no glucose readings below 3.3 mmol/l. Nine readings (4% of the measurements) were below 3.89 mmol/l. 36 readings (16%) were below 4.4 mmol/l. Seven readings (3%) were above 7.78 mmol/l, three readings (1%) were above 8.33 mmol/l, and two readings (1%) were above 8.89 mmol/l. Minimum and maximum glucose values at each time point are given in the table. The largest upward excursion occurred immediately after food intake at 20 minutes. The highest average glucose increase was 0.96 mmol/l, and maximum glucose increase was 4.28 mmol/l. The maximum downward excursion occurred between 40 and 60 minutes postprandially and was 3.39 mmol/l. The largest average downward postprandial glucose excursion was 0.96 mmol/l, and occurred between 200 and 220 minutes. As a measure of the variation in glycaemic excursions, standard deviation score was calculated. Mean SD score of the subjects with idiopathic postprandial syndrome was 0.94 ± 0.22 mmol/l (range: 0.57 to 1.26).

Discussion

The rate and the magnitude of the change in blood glucose levels, and the chronicity are important factors affecting the symptomatology of declining blood glucose levels. At plasma glucose concentration of less than 3.33 mmol/l, adrenergic symptoms of hypoglycaemia start and may cause pallor, irritability, palpitations, tremor, and tachycardia (1). When plasma glucose concentrations decrease to less than 3 mmol/l, patients experience neuroglycopenic symptoms (1). These threshold values are average levels and may differ among individuals. The controversy stems from the definition of reactive hypoglycaemia. Lay literature warns

<table>
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<th>Time (minute)</th>
<th>Average glucose (mmol/l)</th>
<th>Standard deviation (mmol/l)</th>
<th>Minimum glucose (mmol/l)</th>
<th>Maximum glucose (mmol/l)</th>
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the public against adrenergic symptoms [9]. The scientific community defines hypoglycaemia according to threshold plasma glucose value for neuroglycopenia (1, 3). Panic attack, anxiety, somatisation, and certain depressive syndromes may also cause hyperadrenergic symptoms similar to idiopathic postprandial syndrome. These psychological disturbances may coexist with idiopathic postprandial syndrome (10). In this study, continuous glucose monitoring with GlucoWatch Biographer revealed that nadir glucose value was 3.5 mmol/l, in patients with idiopathic postprandial syndrome. Time to nadir glucose was 110 minutes. There were no glucose values below the commonly accepted threshold values for either adrenergic or neuroglycopenic symptoms of hypoglycaemia. The current study is in agreement with earlier studies utilising finger-prick capillary blood glucose measurements. Paldary et al. (4) reported that only 16% of capillary glucose values were less than 3.3 mmol/l in patients experiencing hypoglycaemic symptoms. In a more recent study, Simpson et al. (11) reported that capillary blood glucose levels were 3 mmol/l or lower in 14% of the subjects with symptoms of reactive hypoglycaemia. Snorgaard & Binder (12) failed to record any blood glucose value below 3.3 mmol/l in their patients who had been referred for reactive hypoglycaemia. The failure to detect hypoglycaemia may be due to following methodological reasons in studies utilising capillary glucose measurements: 1) when the patient experiences symptoms and performs a finger-prick measurement, blood glucose level may already be rising under the action of counter-regulatory hormones, 2) hypoglycaemic patients are usually not experienced in using glucometers, and 3) hypoglycaemia may impair the patients' cognitive function and operative ability. Capillary blood glucose values provide a "snapshot" of postprandial glucose fluctuations. Continuous blood glucose monitoring gives a better picture. In this study, none of the symptoms were associated with an interstitial glucose concentration equal or less than 3 mmol/l. Continuous glucose monitoring results in patients with idiopathic postprandial syndrome were not reported in the literature before. Tamada et al. (5) reported that the correlation coefficient between capillary glucose and GlucoWatch readings was 0.88. The mean absolute error between GlucoWatch and capillary blood glucose measurement was 15.6%. Comparative data shows that GlucoWatch measurements are more accurate and show less variation at low or low-normal capillary blood glucose levels than high levels. For capillary blood glucose levels below 3.9 mmol/l, the mean error was 0.17 mmol/l and mean absolute relative error was 18% in a home-environment correlation study. For blood glucose levels between 10 and 13.3 mmol/l, the mean error was -0.72 mmol/l and mean absolute relative error was 23 percent [6]. Lay literature claims that eating refined carbohydrates triggers hypoglycaemic attacks [9]. In opposite to this statement, consumption of alcoholic drinks like wine or beer, and high glycaemic index foods did not cause low glucose values in subjects with idiopathic postprandial syndrome, in this study. In spite of the fact that, there is no evidence, including the current study that shows patients with idiopathic postprandial syndrome have low glucose levels after meals, patients claiming that they have reactive hypoglycaemia seek medical and nutritional advice. In order to help these individuals, at first an insulinaemia should be excluded with appropriate extent of tests according to the clinical presentation, then no further glucose profiles should be obtained and a trial of dietary treatment should be considered with psychological counselling. Dietary intervention is effective in alleviating symptoms in patients with idiopathic postprandial syndrome even if they do not have low blood sugar values. Food intake relieved 86% of episodes associated with capillary glucose value equal or less than 3.3 mmol/l and 53% of episodes associated with a capillary glucose value over 3.3 mmol/l, in a study performed by Paldary et al. (4). One limitation of this study is the absence of the control group. There are other studies in the literature that compared capillary glucose levels of normal subjects with patients with postprandial syndrome. For example, Snorgaard and Binder (12) reported similar blood glucose levels both in normal controls and in patients with idiopathic postprandial syndrome. Therefore, I doubt if a control group had been included, were the conclusions would have been different. Continuous Glucose Monitoring System (CGMS ® System Gold ™, Medtronic Minimed, Northridge, California, USA) provides interstitial glucose reading via a subcutaneous sensor every five minutes for up to three days. Further studies with CGMS may be considered in patients with idiopathic postprandial syndrome, as there will be more number of data points with this system.

**Conclusion**

Continuous glucose monitoring with GlucoWatch Biographer in free-living patients with symptoms of idiopathic postprandial syndrome revealed no evidence of low interstitial glucose levels either pre- or postprandially in this study, confirming results of previous studies utilizing capillary blood glucose measurements.

**References**