Incompatibility between fasting and postprandial plasma glucose in patients with Cushing’s syndrome

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Abstract. It is shown that glucocorticoids have discordant effects on plasma glucose concentration through their effects on hepatic glycogen deposition, gluconeogenesis and peripheral insulin resistance. Cushing’s syndrome caused by cortisol overproduction is frequently accompanied with diabetes mellitus, but fasting plasma glucose (FPG) and post-glucose load plasma glucose levels are not examined in patients with Cushing’s syndrome. The aim of this study was to investigate FPG, HbA1c and oral glucose tolerance test (OGTT) 2-h PG and their relationship in patients with Cushing’s syndrome, in comparison with control subjects. Sixteen patients with Cushing’s syndrome (ACTH-dependent 31%, ACTH-independent 69% and diabetes mellitus 50%) and 64 controls (32 patients with type 2 diabetes mellitus and 32 non-diabetic subjects matched for age, sex and BMI) were enrolled in this study. HbA1c and FPG in the patients with Cushing’s syndrome were not different from the controls, whereas the FPG/HbA1c ratio was significantly lower in the patients with Cushing’s syndrome than the controls. OGTT 2-h PG was significantly higher in the non-diabetic patients with Cushing’s syndrome than the non-diabetic controls, while HbA1c was not different between both groups and FPG was significantly lower in the patients with Cushing’s syndrome than the controls. HOMA-β but not HOMA-R was significantly higher in the patients with Cushing’s syndrome than the controls. In conclusion, FPG was rather lower in the patients with Cushing’s syndrome than the controls. Postprandial PG or post-glucose loaded PG, but not FPG, is useful to evaluate the abnormality of glucose metabolism in patients with Cushing’s syndrome.

Key words: Cushing’s syndrome, Fasting plasma glucose, Oral glucose tolerance test 2-h plasma glucose, Postprandial plasma glucose, HbA1c

GLUCOCORTICOIDS play role in elevating plasma glucose concentration through their effects on hepatic glycogen deposition, gluconeogenesis and peripheral insulin resistance [1]. Burt et al. reported the discordance between a reduced fasting plasma glucose (FPG) and increased post-glucose load PG levels in rheumatological patients receiving chronic glucocorticoid therapy [2]. They suggested that fasting FPG concentration has poor sensitivity to check diabetes mellitus in glucocorticoid-treated patients.

Cushing’s syndrome caused by cortisol overproduction is frequently accompanied with diabetes mellitus and 20 to 50 % of patients with this syndrome are shown to have diabetes mellitus [3-5]. Diabetes mellitus in Cushing’s syndrome is characterized by the inability of β-cells to compensate for insulin resistance [6]. Since diabetes mellitus causes various health problems such as cardiovascular disease, renal disease and neuropathies, the screening for diabetes in patients with Cushing’s syndrome is important to improve their prognosis. Akaza et al. reported that the number of cardiovascular risk factors such as hypertension, dyslipidemia and impaired glucose tolerance/diabetes mellitus decreased significantly in the surgery group compared with conservative treatment group in subclinical Cushing’s syndrome [7]. These results suggested that mild hypercortisolism involved the development of cardiovasc-
lar risk factors. However, fasting plasma glucose (FPG) and post-glucose load plasma glucose (PG) levels are not examined in non-diabetic patients with Cushing’s syndrome.

The aim of this study was to investigate FPG, HbA1c and oral glucose tolerance test (OGTT) 2-h PG and their relationship in patients with Cushing’s syndrome, in comparison with control subjects.

**Subjects and Methods**

**Subjects**

We recruited 16 patients with Cushing’s syndrome (4 males and 12 females; ACTH-dependent pituitary adenoma in 5 patients, cortisol-producing adrenal adenoma in 9 patients and ACTH-independent macronodular adrenal hyperplasia in 2 patients). The diagnosis of Cushing’s syndrome has been done based on the Cushingoid features with pituitary or adrenal lesion and laboratory test results, such as lack of serum cortisol suppression in low dose dexamethasone suppression test, loss of circadian rhythm of serum cortisol and serum cortisol suppression in high dose dexamethasone suppression test (<50% of basal levels). Thirty-two patients with type 2 diabetes mellitus and 32 non-diabetic subjects matched for age, sex and BMI were used as controls. The diagnosis of diabetes mellitus was based on American Diabetes Association criteria [8]. Thirty-five subjects (4 non-diabetic Cushing’s syndrome and 31 non-diabetic control) were performed 75g OGTT. Hypertension was defined as follows: a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg at clinic; a systolic blood pressure ≥135 mmHg and/or a diastolic blood pressure ≥85 mmHg at home; a systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg by ambulatory blood pressure monitoring [9]; or when patients took antihypertensive medications. Dyslipidemia was defined as a low-density-lipoprotein cholesterol ≥140 mg/dL, and/or a high-density-lipoprotein cholesterol <40 mg/dL, and/or a triglyceride level ≥150 mg/dL [10], or when patients took antilipidemic medications. We excluded patients and controls with chronic liver diseases, chronic renal diseases, and anemia by which the measurement of HbA1c may be influenced. The institutional committee approved the protocol of this study, and all the participants gave their written informed consent.

**Laboratory methods**

Blood samples were taken in the early morning after overnight fast. PG and immunoreactive insulin (IRI) were determined by the glucose oxidase methods and chemiluminescent enzyme immunoassay (CLEIA), respectively. The homeostasis model assessment (HOMA) was used to evaluate insulin resistance and beta-cell function [11]. The HOMA-R and HOMA-β were calculated as (FPG × IRI) /405 and (IRI × 360)/(FPG - 63) (FPG in mg/dL, IRI in μU/mL), respectively. HbA1c was measured by high performance liquid chromatography. HbA1c values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values in accordance with the official equation [12]. The reference range of HbA1c is between 4.6% and 6.2%.

Regarding serum cortisol measurement, 2 hospitals were used electrochemiluminescent immunoassay (ECLIA, Roche Diagnostics, Tokyo, Japan) (Analytical sensitivity: 0.018 µg/dL), 1 hospital was used chemiluminescent immunoassay (CLIA, Beckman Coulter, Inc. Tokyo, Japan) (Analytical sensitivity: 0.4 µg/dL), respectively. The reference range of serum cortisol is between 4.0 μg/dL and 18.8 μg/dL. Urinary free cortisol was measured by radioimmunoassay (Fujirebio Inc. Tokyo, Japan) (Analytical sensitivity: 0.17 µg/dL).

**Statistical analyses**

Data are expressed as mean ± SD, or numbers with percentages as appropriate. For statistical analyses, unpaired Student’s t test was used to compare 2 groups. Categorical variables were analyzed by using the chi-square test. To analyze univariate regression analysis was performed with the StatView computer program (Ver 5.0 for Windows; Abacus Concepts, Berkeley, CA). A P < 0.05 were considered to be statistically significant.

**Results**

Mean age of the patients with Cushing’s syndrome was 49.9 ± 10.2 years and mean body mass index (BMI) was 24.9 ± 5.3 kg/m² (Table 1). Half of these patients were diagnosed to have diabetes mellitus. Serum cortisol levels in these patients were high at 22.0 ± 8.0 µg/dL. There was no difference in FPG and HbA1c between the patients with Cushing’s syndrome and the controls.
HbA1c and FPG in the patients with Cushing’s syndrome were not different from the controls, whereas the FPG/HbA1c ratio was significantly lower in the patients with Cushing’s syndrome than the controls (15.4 ± 4.4 vs. 18.3 ± 2.3, \( P < 0.001 \)) (Table 1 and Fig. 1). FPG was significantly correlated with HbA1c in the controls (\( R = 0.885, \ P < 0.0001 \)), but not in the patients with Cushing’s syndrome (\( R = 0.394, \ P = 0.131 \)) (Fig. 2). The regression line in the patients with Cushing’s syndrome shifted downwards as compared with the controls.

**Table 1** Clinical characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cushing’s syndrome</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>( n )</td>
<td>64</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (25.0)</td>
<td>4 (25.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32 (50.0)</td>
<td>8 (50.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.6 ± 5.5</td>
<td>49.9 ± 10.2</td>
<td>0.683</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>24.6 ± 3.5</td>
<td>24.9 ± 5.2</td>
<td>0.79</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>118 ± 33</td>
<td>105 ± 41</td>
<td>0.181</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5 ± 1.3</td>
<td>6.9 ± 4.5</td>
<td>0.417</td>
</tr>
<tr>
<td>FPG/HbA1c ratio</td>
<td>18.3 ± 2.3</td>
<td>15.4 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cortisol (μg/dL)</td>
<td>n.d.*</td>
<td>22.9 ± 8.0</td>
<td>-</td>
</tr>
</tbody>
</table>

n.d.*, not determined; FPG, Fasting plasma glucose. All data were expressed as mean ± SD or as numbers and percentage.

**Fig. 1** HbA1c, fasting plasma glucose (FPG) and the FPG/HbA1c ratio in 16 patients with Cushing’s syndrome (CS; hatched columns) and 32 control subjects (open columns)

**Fig. 2** Relationship between HbA1c and fasting plasma glucose (FPG) in 16 patients with Cushing’s syndrome (CS; closed circles) and 32 control subjects (open circles)
In order to elucidate the effect of cortisol in glucose metabolism, we compared these parameters described above between 8 non-diabetic patients with Cushing’s syndrome and 32 non-diabetic controls. Mean age (45.8 ± 10.7 yr. vs. 48.5 ± 11.9 yr., P = 0.530), the percentage of male (25% vs. 25%, P = 1.000) and BMI (23.1 ± 2.1 kg/m² vs. 23.8 ± 3.9 kg/m², P = 0.502), were not different between the non-diabetic patients with Cushing’s syndrome and the non-diabetic controls. HbA1c in the non-diabetic patients with Cushing’s syndrome were not different from the non-diabetic controls (5.6 ± 0.4 % vs. 5.5 ± 0.4 %, P = 0.543). However, both of FPG and the FPG/HbA1c ratio which was as a marker to evaluate the incompatibility between FPG and mean plasma glucose levels, were significantly lower in the non-diabetic patients with Cushing’s syndrome than the non-diabetic controls (FPG; 81 ± 6 mg/dL vs. 95 ± 8 mg/dL, P < 0.001, the FPG/HbA1c ratio; 14.7 ± 1.5 vs. 17.5 ± 1.1, P < 0.001) (Fig. 3). In thirty-five subjects (4 non-diabetic patients with Cushing’s syndrome and 31 non-diabetic controls) who performed OGTT, OGTT 2-h PG was significantly higher in the non-diabetic patients with Cushing’s syndrome than the non-diabetic controls (144 ± 19 mg/dL vs. 113 ± 20 mg/dL, P = 0.007) while HbA1c was no difference between the non-diabetic patients with Cushing’s syndrome and the non-diabetic controls (5.6 ± 0.4 % vs. 5.5 ± 0.4%, P = 0.556) and FPG was significantly lower in the non-diabetic patients with Cushing’s syndrome than the non-diabetic controls (86 ± 11 mg/dL vs. 95 ± 8 mg/dL, P = 0.042) (Fig. 4). Regarding insulin resistance and β-cell function, HOMA-R and HOMA-β in 38 subjects (7 non-diabetic patients with Cushing’s syndrome and 31 non-diabetic controls) were evaluated. HOMA-R in the non-diabetic patients with Cushing’s syndrome was not different from the non-diabetic controls (1.27 ± 0.6 % vs. 1.43 ± 0.60 %, P = 0.533). On the other hand, HOMA-β was significantly higher in the non-diabetic patients with Cushing’s syndrome than the non-diabetic controls (139.8 ± 96.8 mg/dL vs. 68.9 ± 26.8 mg/dL, P = 0.0008).

Next, we also compared the clinical characteristics of non-diabetic and diabetic patients with Cushing’s syndrome. The clinical characteristics such as age, sex, BMI, serum cortisol levels, urinary free cortisol, the frequency of hypertension and dyslipidemia in the non-diabetic patients with Cushing’s syndrome were not different from the diabetic patients with Cushing’s syndrome. FPG and HbA1c was significantly higher in the diabetic patients with Cushing’s syndrome than the non-diabetic patients with Cushing’s syndrome (128 ± 49 mg/dL vs. 81 ± 6 mg/dL, P = 0.019, 8.2 ± 1.6 % vs. 5.6 ± 0.4 %, P < 0.001, respectively) while FPG/HbA1c ratio was no difference between the diabetic patients with Cushing’s syndrome and the non-diabetic patients with Cushing’s syndrome (16.1 ± 6.2 vs. 14.7 ± 1.5, P = 0.523) (Table 2). To determine whether hypercortisolism is related to glucose intolerance, univariate analysis of relationship between cortisol secretion such as serum cortisol and urinary free cortisol levels and the markers of glycemic control such as FPG and HbA1c. There was no significant relationship between them (data not shown).

Discussion

In this study, we demonstrated that FPG is lower and OGTT 2-h PG is higher in patients with Cushing’s syndrome than controls, although HbA1c is not different between the groups.

Glucocorticoids are known to induce insulin resistance in the liver by increasing hepatic gluconeogenesis [1]. Rizza et al. showed that cortisol increased fasting glucose production and more insulin was required to reduce glucose production after cortisol infusion than saline by euglycemic hyperinsulinemic clamp studies on healthy volunteers [13]. On the other hand, synthetic glucocorticoids particularly increase postprandial PG, but not FPG, in patients with chronic obstructive pulmonary disease [14]. It has been reported that endogenous glucocorticoid excess in patients with Cushing’s syndrome predominantly increases postprandial PG with FPG often in the normal range [3]. The latter two reports showed FPG was not increased by glucocorticoids. The different points of Rizza’s study from the latter two reports are 1) Study subjects were healthy volunteers, and 2) Glucocorticoid treatment period was much shorter (24-h infusion) in healthy volunteers than in patients with chronic obstructive pulmonary disease or Cushing’s syndrome [3, 13, 14].

Interestingly, FPG in patients with Cushing’s syndrome was rather lower than in controls even though HbA1c was the same level between both groups in this study. These data suggest that FPG is an unsuitable marker to evaluate the abnormality of glucose metabolism in patients with Cushing’s syndrome. OGTT is
Fig. 3  HbA1c, fasting plasma glucose (FPG) and the FPG/HbA1c ratio in 8 non-diabetic patients with Cushing’s syndrome (CS; hatched columns) and 32 non-diabetic controls (nonDM; open columns)

Fig. 4  HbA1c, fasting plasma glucose (FPG) and oral glucose tolerance test 2-h plasma glucose (OGTT 2-h PG) in 4 non-diabetic patients with Cushing’s syndrome (CS; hatched columns) and 31 non-diabetic controls (nonDM; open columns)

Table 2  Clinical characteristics of non-diabetic and diabetic patients with Cushing’s syndrome

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic patients with Cushing’s syndrome</th>
<th>Diabetic patients with Cushing’s syndrome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Male (%)</td>
<td>2 (25.0)</td>
<td>2 (25.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.5 ± 11.9</td>
<td>51.2 ± 8.9</td>
<td>0.608</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 3.9</td>
<td>26.0 ± 6.4</td>
<td>0.421</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>81 ± 6</td>
<td>128 ± 49</td>
<td>0.019</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ± 0.4</td>
<td>8.2 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPG/HbA1c ratio</td>
<td>14.7 ± 1.5</td>
<td>16.1 ± 6.2</td>
<td>0.523</td>
</tr>
<tr>
<td>Serum cortisol (μg/dL)</td>
<td>20.7 ± 11.7</td>
<td>23.3 ± 6.4</td>
<td>0.590</td>
</tr>
<tr>
<td>Urinary free cortisol (μg/day)</td>
<td>471.7 ± 527.6</td>
<td>413.4 ± 331.3</td>
<td>0.795</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>8 (100)</td>
<td>7 (87.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td>0.619</td>
</tr>
</tbody>
</table>

FPG, Fasting plasma glucose. All data were expressed as mean ± SD, or as numbers and percentage.
Corticosteroids excess may induce the compensatory reaction in body. As a result, FPG may be not increased. We showed that HOMA-β but not HOMA-R was significantly higher in the non-diabetic patients with Cushing’s syndrome than in controls. Further prospective studies in a large number of patients are needed to confirm our results.

In conclusion, we found that FPG was rather lower in patients with Cushing’s syndrome than in controls. Postprandial PG or post-glucose loaded PG, but not FPG, is useful to evaluate the abnormality of glucose metabolism.

Disclosure

The authors declare no personal financial or institutional interest in this article.

References

FPG is low in Cushing’s syndrome


