Prospective Short-Term Effects of Glucocorticoid Treatment on Glucose and Lipid Metabolism in Japanese

Yasuo Kuroki, Hiroshi Kaji, Seiji Kawano, Fumio Kanda, Yutaka Takai, Michiko Kajikawa and Toshitsugu Sugimoto

Abstract

Objective Glucocorticoid (GC) causes various metabolic abnormalities; however, few prospective studies have examined the changes in glucose and lipid metabolism in newly GC-treated patients.

Methods and Patients The present study was therefore performed to analyze markers of glucose and lipid metabolism on days 0, 3, 7, 14, 28 and at month 3 of treatment in patients starting GC therapy. Then, we analyzed the relationships between the changes in these parameters and the initial dose of prednisolone (PSL), separating groups into different regimens by the GC dose.

Results The fasting plasma glucose (FPG) level transiently increased on day 3 of PSL administration but was restored by day 7. The immunoreactive insulin (IRI) level and HOMA-R transiently increased on day 3 and then fell, although remaining significantly higher than each basal level by day 7. A transient elevation in FPG level on day 3 was observed only in groups with a PSL dose \( \geq 40 \) mg. On the other hand, total cholesterol and low-density lipoprotein cholesterol levels increased on day 3 of PSL administration and similar levels were maintained after day 7. High density-lipoprotein cholesterol levels were significantly increased on day 3; subsequently then gradually increased from days 3 to day 28. Triglyceride levels did not change during treatment. No relationship was apparent between the GC dose and the changes in each lipid parameter.

Conclusion GC treatment induced changes in FPG, IRI, LDL-CHOL and HDL-CHOL levels from day 3 after start of GC. The dose of GC seemed to influence glucose metabolism, but not lipid metabolism.

Key words: glucocorticoid, glucose, cholesterol, insulin

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Introduction

Glucocorticoids (GC) are used to treat autoimmune, neurological, dermatological and respiratory diseases, and their anti-inflammatory effects are effective for treating various diseases; however, GC treatment is greatly limited by its various serious side effects, which are dependent on the dose and duration of GC (1). Although the side effects of GC include immunosuppression and osteoporotic fractures, various metabolic abnormalities can occur, such as the development of central adiposity, hepatic steatosis, dyslipidemia, increased breakdown of skeletal muscle mass and glucose intolerance (2). As for GC and glucose metabolism, GC excess increases insulin resistance by affecting the muscles as well as the liver and partly through the suppression of insulin secretion, resulting in glucose intolerance or secondary diabetes mellitus in susceptible patients (2). The frequency of glucose intolerance or diabetes is high in GC-treated patients or patients with Cushing’s syndrome (3); however, few prospective studies have examined the change in glucose metabolism in newly GC-treated patients.

On the other hand, GC excess is related to an increase in serum lipid levels, especially total cholesterol (Total CHOL)
Table 1. Patient Profiles in GC-treated Patients

<table>
<thead>
<tr>
<th>Initial dose of PSL</th>
<th>P</th>
<th>H</th>
<th>M</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>10</td>
<td>13</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.1 ± 21.3</td>
<td>62.8 ± 16.1</td>
<td>57.5 ± 16.8</td>
<td>41.2 ± 16.8</td>
</tr>
<tr>
<td>M : F</td>
<td>2:3</td>
<td>9:4</td>
<td>3:3</td>
<td>0:5</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>2</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuro-immuno disease</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>85.4 ± 13.1</td>
<td>94.8 ± 13.8</td>
<td>84.4 ± 7.2</td>
<td>93.0 ± 13.1</td>
</tr>
<tr>
<td>IRI (μU/mL)</td>
<td>6.2 ± 5.4</td>
<td>10.9 ± 8.3</td>
<td>3.7 ± 1.7</td>
<td>4.9 ± 3.5</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>1.3 ± 1.0</td>
<td>2.8 ± 2.6</td>
<td>0.9 ± 0.4</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>5.0 ± 0.8</td>
<td>4.9 ± 0.7</td>
<td>5.4 ± 0.3</td>
<td>5.1 ± 0.7</td>
</tr>
<tr>
<td>Total-CHOL (mg/dL)</td>
<td>174.3 ± 51.0</td>
<td>174.0 ± 50.0</td>
<td>185.7 ± 37.5</td>
<td>166.0 ± 47.4</td>
</tr>
<tr>
<td>HDL-CHOL (mg/dL)</td>
<td>35.4 ± 7.5</td>
<td>40.4 ± 11.9</td>
<td>42.0 ± 13.2</td>
<td>49.2 ± 15.4</td>
</tr>
<tr>
<td>LDL-CHOL (mg/dL)</td>
<td>107.7 ± 43.4</td>
<td>104.9 ± 37.1</td>
<td>109.5 ± 25.2</td>
<td>95.4 ± 30.3</td>
</tr>
</tbody>
</table>

Value are expressed as the mean ± SD

and low-density-lipoprotein cholesterol (LDL-CHOL) (4). Several reports have indicated that levels of high density-lipoprotein cholesterol (HDL-CHOL) and apolipoprotein A-1 are high in GC-treated patients (5, 6). Although most reports examined the effects of chronic GC excess on lipid and glucose metabolism using long-term GC-treated patients, few studies have examined the prospective effects of GC therapy on glucose and lipid metabolism. Moreover, no reports have analyzed groups with different GC doses.

The present study was therefore performed to analyze markers of glucose and lipid metabolism on days 0, 3, 7, 14, 28 and at month 3 of treatment in patients starting GC therapy. We then analyzed the relationship between the changes in these parameters and the initial dose of PSL.

**Subjects and Methods**

**Patients and study protocol**

Thirty-four patients (14 men and 20 women) who were scheduled to start GC therapy were enrolled in this study. Fasting morning blood and urine samples were collected from the patients before they started treatment and on days 3, 7, 14, 28 and at month 3 of PSL therapy. Serum and urinary chemistry determinations were performed by standard automated techniques. Immunoreactive insulin (IRI) was measured as previously described (7). HOMA-R was calculated using the following equation: HOMA-R=FPG ×IRI/405. The levels of fasting plasma glucose (FPG), serum IRI, T-CHOL, HDL-CHOL, LDL-CHOL and triglyceride (TG) were measured each day. Ca and vitamin D supplements were administered to all patients, but no other drugs that could influence glucose and lipid metabolism, including lipid-lowering drugs, non-cardioselective β-blocker or hormone replacement therapy were taken during this study. The subjects were divided into the following four groups: 10 patients receiving pulse therapy (P), 13 patients receiving PSL at doses <40 mg/day (H), 6 patients receiving PSL at doses ≥20 mg/day and <40 mg/day (M), and 5 patients receiving PSL at doses ≤10 mg/day (S). The underlying diseases were classified as collagen diseases (n=15), hematopoietic diseases (n=7), neuroimmune diseases (n=7) and other diseases (n=5). All subjects were free from GC treatment until this study. In Group P, methylprednisolone (1 g) was infused for 3 days, and then GC dose was tapered. The initial dose of PSL was maintained in each patient of Groups H and M at least until day 14, and then GC dose was tapered. The data for days 3 and 14 were not obtained in many patients of group S, because all patients in group S were outpatients, and not in hospital. Therefore, the data for days 3 and 14 in group S were not included in Figs. 1 and 2. All patients included in this study gave written informed consent for participation, and the study protocol was approved by the Institutional Review Board of each hospital.

**Statistical analysis**

Statistical analysis was performed with the Stat View ver.6.0 software package (SAS Institute Inc.). The unpaired Student’s t-test was used to compare differences in patient profiles among groups. Changes in glucose and lipid metabolism markers during GC therapy were assessed using the nonparametric Student’s t-test. Results are presented as the mean ± SEM, and p<0.05 was considered to indicate a significant difference. The figures show data expressed as a percentage of the baseline value.

**Results**

**Patient profiles**

The clinical characteristics and baseline data of GC-treated patients are shown in Table 1. Baseline data of all glucose and lipid metabolism were not significantly different among groups.
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Short-term effects of GC therapy on glucose metabolism parameters FPG, serum IRI and HOMA-R levels were followed on days 3, 7, 14, 28 and at month 3 in patients with GC treatment. *p<0.05, **p<0.01, compared to each baseline level. HOMA-R=FPG × IRI/405.

Figure 1. Short-term effects of GC therapy on glucose metabolism parameters FPG, serum IRI and HOMA-R levels were followed on days 3, 7, 14, 28 and at month 3 in patients with GC treatment. *p<0.05, **p<0.01, compared to each baseline level. HOMA-R=FPG × IRI/405.

Figure 2. Effects of various GC regimens on FPG, IRI and HOMA-R. FPG, serum IRI and HOMA-R levels were followed at days 3, 7, 14, 28 and month 3 in patients with GC treatment. P: pulse therapy, H: PSL at doses ≥40 mg/day, M: PSL at doses ≥20 mg/day and <40 mg/day and S: PSL at doses ≤10 mg/day *p<0.05, **p<0.01, compared to each baseline level.

Short-term changes in glucose metabolism parameters

First, we examined the short-term changes in FPG, IRI and HOMA-R in all GC-treated patients. As shown in Fig. 1, the FPG level transiently increased on day 3 of PSL administration but was restored by day 7. The IRI level and HOMA-R transiently increased on day 3 and then fell, although remaining significantly higher than each basal level by day 7. Significantly higher levels of IRI and HOMA-R continued at least until 3 months after starting GC. Differences among groups P, H, M and S were analyzed as shown in Fig. 2. A transient elevation in FPG level on day 3 was observed only in groups P and H (Fig. 2). Interestingly, a transient peak on day 3 in IRI and HOMA-R levels was also observed only in groups P and H (Fig. 2); however, the continuous increases after day 7 of IRI and HOMA-R levels seemed to be maintained in all groups.

Short-term changes in lipid metabolism parameters

Next, we examined the short-term changes in serum T-CHOL, TG, HDL-CHOL and LDL-CHOL levels in all GC-treated patients. As shown in Fig. 3, T-CHOL and LDL-CHOL levels increased on day 3 of PSL administration and similar levels were maintained after day 7. HDL-CHOL levels significantly increased on day 3, and then progressively increased from days 3 to day 28. TG levels did not change during treatment. Differences among groups P, H, M and S were analyzed as shown in Figs. 4 & 5. No relationship between the GC dose and changes in each lipid parameter seemed to exist.
Several reports have indicated that FPG and IRI levels were increased in patients with Cushing’s syndrome or treated with GC (3). In clinical studies, glucose metabolism abnormality by GC excess is mainly considered to be due to increased insulin resistance in tissues after GC exposure (8-10). Insulin intolerance is derived from the inhibition of glucose uptake in muscle tissues, gluconeogenesis in the liver, and inhibition of insulin signaling in cells (2). On the other hand, GC impairs insulin secretion in vitro (2). Acute administration of GC impairs insulin secretion in healthy volunteers (11-13). In these studies, insulin release during glucose infusion or a meal test is decreased, although the IRI level remains unchanged following GC treatment. Since healthy subjects can compensate for GC-induced insulin resistance, 2-5-days of exposure to high doses of dexamethasone or PSL in healthy subjects resulted in hyperinsulinemia or increased insulin secretion during hyperglycemic clamp studies or intravenous glucose tolerance tests (8, 9, 14-17). These findings suggest that chronic GC excess might impair insulin secretion secondary to enhanced insulin resistance in patients with subclinical insulin secretion impairment.

Several studies have reported that elevation of FPG and serum IRI are observed in the early phase of GC administration (8, 9, 14-17). In the present data, FPG was transiently increased at day 3 after GC treatment initiation, and then it returned to the normal range after day 7. Serum IRI level was increased at day 3, and then somewhat returned to the lower level, but was still significantly higher at day 7 and thereafter compared to the baseline level before treatment. Since the changes in HOMA-R were similar to the IRI level during GC treatment, these data suggest that increased insulin resistance by GC treatment worsens in the very early phase at the start of GC treatment, and then continues at a lower level than the initial phase after day 7. The recovery of FPG to the basal line after day 7 is considered to be due to the compensation of insulin secretion from β cells against increased insulin resistance by GC treatment. Zarkovic et al. recently reported that GC-induced insulin resistance develops quickly, in about 4 hr, and does not change during further GC treatment (18). Although the present study did not examine the time point within 2 days, the effects of GC on glucose metabolism seem to be very rapid.

Analysis of subgroups with different GC doses suggested that the early changes in FPG and IRI by GC treatment at day 3 seemed to be dependent on the GC dose, although
Figure 5. Effects of various GC regimens on HDL-CHOL and LDL-CHOL. Serum levels of HDL-CHOL and LDL-CHOL were followed on days 3, 7, 14, 28 and at month 3 in patients with GC treatment. P: pulse therapy, H: PSL at doses ≥40 mg/day, M: PSL at doses ≥20 mg/day and <40 mg/day and S: PSL at doses ≤10 mg/day *p<0.05, **p<0.01, compared to each baseline level.

In conclusion, GC treatment induced changes in FPG, IRI, LDL-CHOL and HDL-CHOL levels from day 3 after GC initiation. The dose of GC seemed to influence glucose metabolism, but not lipid metabolism.

References


