

OBSERVATIONS

# Improvement in Insulin Sensitivity During Mifepristone Treatment of Cushing Syndrome: Early and Late Effects

Increased adiposity and direct effects of glucocorticoid excess on muscle, liver, and  $\beta$ -cells are responsible for the high prevalence of impaired glucose tolerance (IGT) and type 2 diabetes in patients with Cushing syndrome (CS) (1,2). In the SEISMIC study, the glucocorticoid receptor antagonist mifepristone improved glucose tolerance and produced weight loss over 24 weeks in CS patients (3). Using oral glucose tolerance test data from SEISMIC, our goal was to assess whole-body insulin sensitivity (Matsuda index),  $\beta$ -cell function (insulinogenic index,

homeostasis model assessment- $\beta$  [HOMA- $\beta$ ]), disposition index (4,5), weight (WT), and waist circumference (WC) over time. Complete data in patients not receiving insulin were available in 19 patients, 8 with diabetes and/or IGT (C-DM) and 11 with hypertension only (C-HT).

Within-group comparisons for change over time were analyzed with a mixed-effects repeated measures two-way ANOVA with cohort (C-DM and C-HT), time, and cohort by time interaction as fixed effects; unpaired Student *t* tests were used to assess differences between groups (Table 1). Matsuda index improved in the total population, with the greatest improvement occurring between baseline and week 6 and lesser changes occurring from week 6 to 24. Further analysis (piecewise linear mixed-model regression) showed that a two-phase model (0–6 weeks and 6–24 weeks) for Matsuda index change over time was better than the linear model ( $P = 0.007$ ; Akaike information criteria). In contrast, WT and WC declined linearly over the 24 weeks, with the largest declines occurring during the final 18 weeks of treatment (baseline to week 6: WT,  $-1.19 \pm 3.17\%$ ,  $P = 0.1$ ;

WC,  $-1.31 \pm 3.38\%$ ,  $P = 0.07$ ; week 6 to 24: WT,  $-6.66 \pm 6.52\%$ ,  $P = 0.0003$ ; WC,  $-6.36 \pm 5.83\%$ ,  $P = 0.0002$ , ANOVA). At baseline, C-DM patients had compromised insulin secretory responses, as evidenced by lower insulinogenic index<sub>0–30</sub>, insulinogenic index<sub>0–120</sub>, and HOMA- $\beta$ . C-HT patients experienced declines in insulinogenic index<sub>0–30</sub>, insulinogenic index<sub>0–120</sub>, and HOMA- $\beta$  by week 24, whereas these parameters trended nonsignificantly up in C-DM patients. The disposition index was lower at baseline in C-DM patients than C-HT patients. Individual C-DM patients tended more often to have increases in disposition index than C-HT patients ( $3.079 \pm 4.387$  vs.  $-1.739 \pm 5.444$ ,  $P = 0.063$ , respectively). Adiponectin levels increased from baseline to week 24 in C-HT subjects only in a temporal pattern that closely followed changes in WT and WC.

These findings suggest that rapid improvements in insulin sensitivity occurred due to direct effects of glucocorticoid blockade and longer-term improvements resulted from weight loss. Our data suggest that CS patients without underlying IGT or diabetes experience appropriate reductions in  $\beta$ -cell secretory response in

Table 1—Insulin sensitivity and secretory parameters in CS patients (C-DM and C-HT) treated with mifepristone

|                                      | Baseline                   | Week 6                     | Week 10                   | Week 16                    | Week 24                    |
|--------------------------------------|----------------------------|----------------------------|---------------------------|----------------------------|----------------------------|
| Overall (C-DM and C-HT), n = 19      |                            |                            |                           |                            |                            |
| Weight (kg)                          | 98.2 (23.2)                | 97.0 (23.0)                | 95.3 (22.4) <sup>b</sup>  | 93.4 (22.9) <sup>c</sup>   | 90.5 (22.2) <sup>d</sup>   |
| Waist circumference (cm)             | 117.5 (19.0)               | 115.9 (18.4)               | 113.2 (18.4) <sup>d</sup> | 110.8 (19.1) <sup>d</sup>  | 108.5 (18.8) <sup>d</sup>  |
| Matsuda index insulin sensitivity    | 2.64 (1.96)                | 3.46 (2.17) <sup>a</sup>   | 3.58 (1.96) <sup>c</sup>  | 4.00 (2.14) <sup>c</sup>   | 4.20 (1.95) <sup>d</sup>   |
| Insulinogenic index <sub>0–30</sub>  | 1.117 (1.164)              | 1.001 (0.930)              | 1.027 (0.856)             | 1.542 (1.740)              | 1.022 (0.777)              |
| Insulinogenic index <sub>0–120</sub> | 1.294 (1.221)              | 1.402 (1.040)              | 0.995 (0.906)             | 0.956 (0.796)              | 0.990 (0.506)              |
| HOMA- $\beta$                        | 253.5 (162.2)              | 199.3 (157.6)              | 206.4 (144.4)             | 185.8 (75.7) <sup>a</sup>  | 195.9 (78.8)               |
| Disposition index                    | 3.909 (5.753)              | 4.733 (3.624)              | 3.390 (3.300)             | 3.410 (2.915)              | 4.199 (3.220)              |
| Total adiponectin ( $\mu$ g/mL)      | 11.3 (5.7)                 | 12.5 (5.6)                 | 13.9 (7.3)                | 14.1 (5.4)                 | 16.9 (7.5) <sup>c</sup>    |
| C-DM cohort, n = 8                   |                            |                            |                           |                            |                            |
| Matsuda index insulin sensitivity    | 1.63 (1.04)                | 2.26 (0.90)                | 2.70 (1.05) <sup>b</sup>  | 2.72 (1.17)                | 3.48 (1.91) <sup>c</sup>   |
| Insulinogenic index <sub>0–30</sub>  | 0.348 (0.261) <sup>‡</sup> | 0.669 (0.537)              | 0.920 (0.737)             | 1.236 (1.522)              | 1.055 (0.928)              |
| Insulinogenic index <sub>0–120</sub> | 0.429 (0.278) <sup>‡</sup> | 1.071 (0.872)              | 0.788 (0.504)             | 0.935 (0.861)              | 0.952 (0.664)              |
| HOMA- $\beta$                        | 164.2 (115.4) <sup>†</sup> | 158.0 (98.0)               | 172.5 (80.9)              | 193.3 (62.6)               | 204.0 (71.9)               |
| Disposition index                    | 0.655 (0.570) <sup>†</sup> | 2.729 (3.134)              | 2.306 (2.043)             | 2.811 (3.425)              | 3.734 (4.505)              |
| Total adiponectin ( $\mu$ g/mL)      | 12.4 (8.4)                 | 11.1 (5.7)                 | 10.9 (4.9)                | 11.9 (4.5)                 | 14.1 (4.5)                 |
| C-HT cohort, n = 11                  |                            |                            |                           |                            |                            |
| Matsuda index insulin sensitivity    | 3.38 (2.18)                | 4.34 (2.43)                | 4.23 (2.25) <sup>b</sup>  | 4.92 (2.25) <sup>c</sup>   | 4.72 (1.90) <sup>c</sup>   |
| Insulinogenic index <sub>0–30</sub>  | 1.677 (1.254)              | 1.242 (1.097)              | 1.106 (0.960)             | 1.764 (1.924)              | 0.997 (0.694) <sup>a</sup> |
| Insulinogenic index <sub>0–120</sub> | 1.923 (1.263)              | 1.643 (1.123)              | 1.147 (1.114)             | 0.972 (0.787) <sup>b</sup> | 1.018 (0.387) <sup>b</sup> |
| HOMA- $\beta$                        | 318.5 (164.3)              | 229.2 (188.8) <sup>a</sup> | 231.0 (177.1)             | 180.4 (86.5) <sup>c</sup>  | 189.9 (86.4) <sup>c</sup>  |
| Disposition index                    | 6.276 (6.686)              | 6.189 (3.349)              | 4.179 (3.880)             | 3.846 (2.566)              | 4.537 (2.037)              |
| Total adiponectin ( $\mu$ g/mL)      | 10.5 (2.9)                 | 13.5 (5.5) <sup>a</sup>    | 16.1 (8.2) <sup>a</sup>   | 15.7 (5.6) <sup>b</sup>    | 18.9 (8.3) <sup>c</sup>    |

Results are mean (SD). <sup>a</sup>*P* vs. baseline (ANOVA within group): <0.05. <sup>b</sup>*P* vs. baseline (ANOVA within group): <0.02. <sup>c</sup>*P* vs. baseline (ANOVA within group):  $\leq 0.01$ . <sup>d</sup>*P* vs. baseline (ANOVA within group): <0.001. <sup>†</sup>*P* for C-DM vs. C-HT at baseline (unpaired Student *t* test): <0.05. <sup>‡</sup>*P* for C-DM vs. C-HT at baseline (unpaired Student *t* test):  $\leq 0.01$ .

proportion to their improved insulin sensitivity with insulin secretion decreasing in parallel (minimal change in disposition index). However, CS patients with IGT or diabetes manifest a baseline defect in  $\beta$ -cell secretory responsiveness that is partially retrievable along with improvement in insulin sensitivity (increase trend in disposition index) with mifepristone treatment. Adiponectin levels significantly increased with mifepristone throughout the course of treatment, particularly in patients without diabetes/IGT.

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