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Increased Whole-Body and Sustained Liver Cortisol Regeneration by 11β-Hydroxysteroid Dehydrogenase Type 1 in Obese Men With Type 2 Diabetes Provides a Target for Enzyme Inhibition

Roland H. Stimson,1 Ruth Andrew,1 Norma C. McAvoy,2 Dhiraj Tripathi,2 Peter C. Hayes,2 and Brian R. Walker1

OBJECTIVE—The cortisol-regenerating enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) amplifies glucocorticoid levels in liver and adipose tissue. 11β-HSD1 inhibitors are being developed to treat type 2 diabetes. In obesity, 11β-HSD1 is increased in adipose tissue but decreased in liver. The benefits of pharmacological inhibition may be reduced if hepatic 11β-HSD1 is similarly decreased in obese patients with type 2 diabetes. To examine this, we quantified in vivo whole-body, splanchnic, and hepatic 11β-HSD1 activity in obese type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS—Ten obese men with type 2 diabetes and seven normal-weight control subjects were infused with 9,11,12,12-[2H4]cortisol (40%) and cortisol (60%) at 1.74 nmol/min. Adrenal cortisol secretion was suppressed with dexamethasone. Samples were obtained from the hepatic vein and an arterialized hand vein at steady state and after oral administration of cortisone (5 mg) to estimate whole-body and liver 11β-HSD1 activity using tracer dilution.

RESULTS—In obese type 2 diabetic subjects, the appearance rate of 9,12,12-[2H4]cortisol in arterialized blood was increased (35 ± 2 vs. 20 ± 1 nmol/min; P < 0.05), splanchic 9,12,12-[2H4]cortisol production was not reduced (29 ± 6 vs. 29 ± 6 nmol/min), and cortisol appearance in the hepatic vein after oral cortisone was unchanged.

CONCLUSIONS—Whole-body 11β-HSD1 activity is increased in obese men with type 2 diabetes, whereas liver 11β-HSD1 activity is sustained, unlike in euglycemic obesity. This supports the concept that inhibitors of 11β-HSD1 are likely to be most effective in obese type 2 diabetic subjects. Diabetes 60:720–725, 2011

Cortisol is an important regulator of energy homeostasis, particularly in the liver and adipose tissue (1). Cortisol levels in these tissues are amplified by the 11β-reductase activity of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which regenerates cortisol from inert cortisone (2). In rodents, 11β-HSD1 is a powerful determinant of metabolic health. For example, transgenic mice selectively overexpressing 11β-HSD1 in adipose tissue develop obesity, insulin resistance, hypertension, and dyslipidemia (3,4). Similarly, mice overexpressing 11β-HSD1 in the liver develop adverse metabolic features but do not become obese (5). Obese rodents exhibit tissue-specific dysregulation of 11β-HSD1, usually with upregulation in adipose tissue and downregulation in liver (6,7). Selective 11β-HSD1 inhibitors are efficacious in several rodent models of diabetes (8–11).

In humans, 11β-HSD1 also may be important to metabolic health, and selective 11β-HSD1 inhibitors are in development (11). Enzyme activity has been quantified using a stable isotope tracer, 9,11,12,12-[2H4]cortisol (d4-cortisol), from which the 11-deuterium is removed during interconversion with cortisone, allowing quantification of dilution of d4-cortisol by d3-cortisol and hence of 11β-HSD1 activity, independently from the influence of other cortisol-metabolizing enzymes (12). Substantial extra-adrenal regeneration of cortisol by 11β-HSD1 has been detected in the splanchnic circulation (13,14), arising mainly from liver (15,16), and in subcutaneous adipose tissue (15). In euglycemic obesity, numerous studies (17–19) have shown that 11β-HSD1 mRNA and activity in subcutaneous adipose tissue is increased, which has been corroborated in vivo using microdialysis (20). Conversely, hepatic 11β-HSD1 activity, assessed by measuring plasma cortisol after oral administration of cortisone, is reduced in obesity (17,19,21), although it is uncertain whether increased inactivation of cortisone and cortisol by A-ring reductases in the liver (22) contributes to the difference in plasma cortisol. Increased cortisol clearance most likely explains why morning cortisol levels are not elevated in obesity despite increased cortisol secretion rates, as measured by urinary cortisol metabolite excretion (19,23,24).

In obesity, a balance between 11β-HSD1 upregulation in adipose tissue and downregulation in liver likely explains the lack of consistent changes in urinary cortisol–cortisone metabolite ratios (25) or in whole-body cortisol regeneration measured during d4-cortisol tracer infusion (20,26). Whether such tissue-specific dysregulation occurs in obese patients with type 2 diabetes is uncertain. This is important, in particular because 11β-HSD1 inhibitors have shown inconsistent efficacy in Phase II clinical studies in patients with type 2 diabetes (11). If downregulation of hepatic 11β-HSD1 occurs in type 2 diabetes, as it does in euglycemic obesity, this may render type 2 diabetic patients insensitive to enzyme inhibition. Indeed, this might explain earlier observations that carbemoxolone, a non-selective “prototype” 11β-HSD inhibitor, enhances insulin sensitivity in healthy volunteers (27) and in lean patients with type 2 diabetes (28) but not in obese patients (20).
Surprisingly, few investigations of 11β-HSD1 have been performed to date in obese patients with type 2 diabetes, the likely target patient group for treatment with selective 11β-HSD1 inhibitors. Subcutaneous adipose tissue biopsies suggest that 11β-HSD1 expression is increased in parallel with the degree of obesity (29–32). Only one report (29) describes hepatic 11β-HSD1 measured with the oral cortisone test in type 2 diabetes in an unusual group of patients who were not obese; although the area under the curve was reduced, the initial rate of appearance of cortisol was unchanged. Urinary cortisol–to–cortisone metabolite ratios also are unchanged in type 2 diabetes (29,33), as they can be in euglycemic obesity. The only study (26) using deuterated cortisol tracer in type 2 diabetes found that whole-body and splanchic 11β-HSD1 were unaltered, although, again, this group was not particularly obese (mean BMI 30 kg/m²); comprised a mixture of men and women (34); and liver 11β-HSD1 activity was not measured specifically.

To resolve the question of whether obese patients with type 2 diabetes have reduced 11β-HSD1 in the liver, we examined whole-body, splanchic, and liver 11β-HSD1 activity by sampling from the hepatic vein during infusions of 9,11,12,12-[^3]H_2_cortisol tracer (12) in steady state and after oral administration of cortisone.

### RESEARCH DESIGN AND METHODS

Participants were male, aged 20–70 years, with normal full blood count and normal renal, liver, and thyroid function. Subjects had no history of glucocorticoid therapy in the past year and an alcohol intake of <21 units per week. Two groups were recruited: healthy control subjects (BMI 20–26 kg/m²) with no significant medical history or current use of any medication and men with diet- or tablet-treated type 2 diabetes (BMI 30–40 kg/m²). Local ethical approval and written informed consent were obtained.

Subjects were given 1 mg oral dexamethasone at 2300 h and fasted until they attended the clinical research facility at 0730 h the following morning. Measurements of blood pressure, height, weight, and waist and hip circumference were taken. Abdominal subcutaneous and visceral adipose content was quantified by magnetic resonance imaging (MRI) using a 1.5T Gyroscan Intera scanner (Philips Medical Systems, Shelton, CT), comprising 24 standardized slices centered on the fourth/fifth lumbar vertebrae encompassing L3–5. Cannulae (21G) were sited in the antecubital fossa of the right arm for infusion of 11β-HSD1 inhibitors and measurements in 7 control subjects and 10 obese type 2 diabetes (BMI 30–40 kg/m²). Local ethical approval and written informed consent were obtained.

**Variables currently taken by the diabetic patients include metformin (n = 8), a statin (n = 7), a sulphonylurea (n = 3), an ACE inhibitor (n = 3), a thiazide diuretic (n = 3), a calcium channel blocker (n = 2), a β-blocker (n = 2), aspirin (n = 2), an angiotensin 2 receptor antagonist (n = 1), an α agonist (n = 1), and an α agonist (n = 1).**

**Kinetic analyses.** Kinetic analysis in each subject was performed using the mean of the seven samples obtained in steady state (ss) (t = +180–210 min). Whole-body 11β-HSD1 activity was calculated from measurements in arterialized (A) samples as previously described using Eqs. 1 and 2 (12):

\[
\text{Rate of appearance of cortisol} = \frac{d\text{4-cortisol infusion rate}}{d\text{4-cortisol/cortisolA}_{ss}} - \text{cortisol infusion rate} \tag{1}
\]

\[
\text{Rate of appearance of d3-cortisol} = \frac{d\text{4-cortisol infusion rate}}{d\text{4-cortisol/d3-cortisolA}_{ss}} \tag{2}
\]

Clearance of d4-cortisol was determined by dividing the rate of infusion of d4-cortisol by the arterialized d4-cortisol concentration (12). Hepatic blood flow was calculated as previously described (15). Splanchnic arterio-venous (AV) cortisol and d3-cortisol appearance were calculated using the principle that tissue appearance = total appearance – arterial delivery to tissue (35). The respective components were calculated as follows:

\[
\text{total appearance} = \text{tissue blood flow}_{ss} \times \frac{\text{traceeA}_{ss}}{\text{tracer/tracee}_{ss}} \times \frac{\text{tracer/tracee}_{ss}}{\text{traceeV}_{ss}} \tag{3}
\]

\[
\text{arterial delivery} = \text{tissue blood flow}_{ss} \times \frac{\text{traceeA}_{ss}}{\text{tracer/tracee}_{ss}} \tag{4}
\]

By substituting d4-cortisol as the tracer and either cortisol or d3-cortisol as the respective tracer, we derived equations to determine splanchic (visceral tissues and liver) 11β-HSD1 measured in arterialized and hepatic vein (HV) samples using Eqs. 5 and 6 (14):

\[
\text{Splanchnic cortisol production} = \left(\frac{\text{HBF}_{ss} \times \text{[cortisolA]}_{ss}}{\text{[d4-cortisol/cortisolA]}_{ss}} - \frac{\text{HBF}_{ss} \times \text{[cortisolA]}_{ss}}{\text{[d4-cortisol/d4-cortisolA]}_{ss}}\right) \tag{5}
\]

\[
\text{Splanchnic d3-cortisol production} = \left(\frac{\text{HBF}_{ss} \times \text{[d3-cortisolA]}_{ss}}{\text{[d4-cortisol/d3-cortisolA]}_{ss}} - \frac{\text{HBF}_{ss} \times \text{[d3-cortisolA]}_{ss}}{\text{[d4-cortisol/d3-cortisolA]}_{ss}}\right) \tag{6}
\]

Hepatic 11β-HSD1 activity in the non–steady state was estimated from the conversion of orally administered cortisol to cortisol during the d4-cortisol infusion by examining the enrichment of cortisol with d4-cortisol in the hepatic vein from t = +210 min onwards. The change in cortisol concentrations in the artery and hepatic vein after oral cortisol also was used as an index of hepatic 11β-HSD1 activity.

**Statistical analysis.** All statistical analyses were performed using SPSS version 14. All data were normally distributed on Kolmogorov-Smirnov tests. Single measurements between groups were compared using unpaired t tests, and measurements within individuals were compared using paired t tests. Differences after cortisone administration were compared by two-way repeated-measures ANOVA to examine changes with time and differences between groups (control or obese type 2 diabetic subjects), with Bonferroni post hoc testing as appropriate. P < 0.05 was considered significant. Data are presented as means ± SEM. The study has 84% power to detect a 10% difference in the whole-body rate of appearance of d3-cortisol, based on previous measurements (15).

**RESULTS**

**Subject characteristics.** Anthropometric and biochemical measurements in 7 control subjects and 10 obese type 2 diabetic patients are detailed in Table 1. Medications currently taken by the diabetic patients include metformin (n = 8), a statin (n = 7), a sulphonylurea (n = 3), an ACE inhibitor (n = 3), a thiazide diuretic (n = 3), a calcium channel blocker (n = 2), a β-blocker (n = 2), aspirin (n = 2), an angiotensin 2 receptor antagonist (n = 1), an α agonist (n = 1), and an α agonist (n = 1).
TABLE 1
Anthropometry and biochemistry

<table>
<thead>
<tr>
<th></th>
<th>Lean control subjects</th>
<th>Obese type 2 diabetic subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.5 ± 6.0</td>
<td>52.3 ± 2.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 3.5</td>
<td>109.7 ± 3.6*</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.80 ± 0.02</td>
<td>1.77 ± 0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 1.1</td>
<td>35.0 ± 1.0*</td>
</tr>
<tr>
<td>Subcutaneous abdominal adipose tissue volume (L)</td>
<td>1.69 ± 0.27</td>
<td>4.27 ± 0.34*</td>
</tr>
<tr>
<td>Visceral abdominal adipose tissue volume (L)</td>
<td>0.94 ± 0.13</td>
<td>2.96 ± 0.28*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133 ± 4</td>
<td>151 ± 5*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 2</td>
<td>87 ± 2†</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.3 ± 0.3</td>
<td>8.4 ± 0.5*</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.3 ± 0.1</td>
<td>7.2 ± 0.3*</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.3 ± 0.3</td>
<td>4.7 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.5 ± 0.1</td>
<td>1.2 ± 0.1†</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.8 ± 0.1</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>4.4 ± 0</td>
<td>44 ± 1</td>
</tr>
<tr>
<td>Corticosteroid-binding globulin (mg/L)</td>
<td>45 ± 2</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>Alkaline phosphatase (units/L)</td>
<td>76 ± 6</td>
<td>70 ± 6</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (units/L)</td>
<td>23 ± 5</td>
<td>45 ± 5*</td>
</tr>
<tr>
<td>Alanine aminotransferase (units/L)</td>
<td>23 ± 4</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
</tr>
</tbody>
</table>

Data are means ± SEM for lean control subjects (n = 7) and obese men with type 2 diabetes (n = 10). *P < 0.001; †P < 0.05; ‡P < 0.01 vs. lean control subjects.

and a fibrate (n = 1). The obese type 2 diabetic group had higher systolic and diastolic blood pressure, fasting A1C, plasma glucose, and γ-glutamyltransferase concentrations; lower HDL cholesterol; and increased subcutaneous and visceral abdominal adipose tissue volume on MRI scanning. Neither albumin nor CBG differed between groups. Fasting plasma cortisol was similarly suppressed following dexamethasone in both control and obese type 2 diabetic groups (24 ± 5 vs. 30 ± 3 nmol/L), as was plasma cortisone (5 ± 1 vs. 8 ± 1 nmol/L). The hepatic vein could not be cannulated in one participant from the obese type 2 diabetic group; therefore, only data from the arterialized samples in this individual were used for analysis.

Cortisol concentrations and kinetics in steady state.

Steady-state tracer concentrations and enrichments were achieved after 180 min of d4-cortisol infusion (Fig. 1). At steady state, plasma cortisol concentrations were similar in the artery and hepatic vein in both groups (Table 2). d4-Cortisol concentrations were lower in the hepatic vein than the artery, in keeping with d4-cortisol metabolism across the splanchnic tissues. d3-Cortisol was higher and cortisol and d3-cortisone levels substantially lower in the hepatic vein than in arterialized blood in both groups, consistent with splanchnic 11β-HSD1 activity. There were no differences in steady-state steroid concentrations between control and obese type 2 diabetic patients.

Compared with control subjects, obese type 2 diabetic patients had a similar steady-state whole-body rate of appearance of cortisol (70 ± 6 vs. 60 ± 12 nmol/min, P = 0.14) but a higher rate of appearance of d3-cortisol (35 ± 2 vs. 29 ± 1 nmol/min, P < 0.05) (Fig. 2) and also a trend for increased d4-cortisol clearance (0.60 ± 0.02 vs. 0.50 ± 0.05 L/min, P = 0.05).

Hepatic blood flow (1.0 ± 0.1 vs. 1.1 ± 0.2 L/min), steady-state splanchnic cortisol release (50 ± 6 vs. 58 ± 13 nmol/min), and splanchnic d3-cortisol release (29 ± 6 vs. 29 ± 6 nmol/min) were not significantly different between control and obese type 2 diabetic subjects (Fig. 2).

Change in cortisol concentrations and d4-cortisol enrichment after oral cortisone. After oral cortisone, cortisol concentrations increased in the hepatic vein and, to a lesser degree, in arterialized blood (Fig. 1A). There was dilution of d4-cortisol by cortisone (P < 0.001) (Fig. 1B) but no dilution of d4-cortisol by d3-cortisol; in fact, the dilution by d3-cortisol decreased in both groups in arterialized and hepatic vein samples from 20 min after oral cortisone (Fig. 1C). However, there was no significant difference in any of these variables between control and obese type 2 diabetic groups and no interaction between group and time in repeated-measures ANOVAs (all P > 0.1).

DISCUSSION

These data show that whole-body cortisol regeneration by 11β-HSD1 is increased (by ~20%) in obese men with type 2 diabetes compared with lean control subjects. Splanchnic 11β-HSD1, measured as cortisol and d3-cortisol release into hepatic vein in the steady state, was not different between groups, while first-pass conversion of cortisone to cortisol in liver was similarly unchanged. We conclude that, unlike in euglycemic obesity where liver 11β-HSD1 is downregulated (17,19,21), in obese men with type 2 diabetes liver 11β-HSD1 is sustained. These observations support the concept, inferred from earlier observations of urinary cortisol–to-cortisone metabolite ratios (33), that obese patients with type 2 diabetes lack compensatory downregulation of 11β-HSD1 in liver and suggest that intact pancreatic β-cell function is important in mediating this compensatory response in euglycemic obesity. Moreover, these data suggest that there is plentiful 11β-HSD1 activity in liver as a target for selective 11β-HSD1 inhibition in obese hyperglycemic men.

Previous studies (17,19,21,29) examining liver 11β-HSD1 activity in vivo have relied on measurement of peripheral plasma cortisol after oral administration of cortisone. Using this technique for total concentration, differences in inactivation and clearance of cortisol may obscure differences in cortisol appearance; cortisol clearance tended to be higher in the obese type 2 diabetic group in the current study and has previously been shown to be increased in obesity (23,36). The only previous report of plasma cortisol after oral cortisone administration in type 2 diabetes, albeit in unusually lean patients, found that peripheral cortisol was not different during the early time points after cortisone ingestion, whereas cortisol concentrations were lower in type 2 diabetes at later time points (29), consistent with increased cortisol metabolism by other enzymes. To minimize this confounding effect, we measured dilution of d4-cortisol by cortisol in the hepatic vein. We also used a lower dose of cortisone (5 mg) than previously (25 mg) in order to avoid excessive dilution of tracer in the hepatic vein. After correcting for baseline (steady state) differences by ANOVA, we found no differences between groups in the appearance of cortisol in the hepatic vein or the arterial circulation. As an aside, we also observed that the ratio of d4-cortisol to d3-cortisol increased after oral cortisone administration (Fig. 1C), secondary to a reduction in
plasma d3-cortisol concentrations without any significant change in d4-cortisol concentrations. This is most likely attributed to substrate competition between orally administered cortisone and d3-cortisone for 11β-HSD1, leading to a lower rate of appearance of d3-cortisol.

The oral cortisone administration was performed to determine whether the hepatic component of splanchnic activity was decreased in obese type 2 diabetic patients, since we have previously suggested that visceral adipose tissue may contribute a significant proportion (approximately one-third) of splanchnic 11β-HSD1 activity (14) and that increased visceral adipose activity could be balanced by decreased hepatic 11β-HSD1 activity in obesity. However, in two recent studies (15,16) involving portal vein cannulation there was no evidence of extrahepatic splanchnic 11β-HSD1 activity. Consistent with these data, we found no discrepancy between hepatic (non–steady-state) or splanchnic (steady-state) results. In our earlier study, we modeled the data obtained from hepatic vein samples after oral cortisone to derive estimates of the contribution of liver and visceral adipose tissue to the total splanchnic 11β-HSD1 activity (14). However, this model relied on assumptions about portal vein concentrations of cortisone, which subsequent portal vein sampling showed to be incorrect because of 11β-HSD2 activity in the gastrointestinal tract (15,16). For this reason, we have not attempted to apply this model to the current data.
Cortisol (nmol/L) 222 ± 19 210 ± 24 213 ± 9 213 ± 10

Obese type 2 diabetic subjects

Artery 59 ± 4 66 ± 5†
Hepatic vein 54 ± 2 42 ± 2†

TABLE 2
Plasma concentrations during steady state

---

Our finding that whole-body 11β-HSD1 cortisol regeneration is increased in type 2 diabetes is at odds with the normal values reported in one previously published article (26). In the previous study, splanchic steady-state d3-cortisol and cortisol release also were unaltered, as in our data. However, the patients were not particularly obese, with a mean BMI of 30 kg/m², whereas our subjects had a higher mean BMI of 35 kg/m². This additional adiposity may be important in that it may contribute additional extrasplanchnic d3-cortisol generation from adipose tissue, which may be sufficient to increase whole-body regeneration rates. Indeed, we have previously shown that subcutaneous adipose tissue significantly contributes to total 11β-HSD1 activity in euglycemic obesity (15), making this depot the most likely source of the increased whole-body 11β-HSD1 in obese type 2 diabetic subjects. Other tissues might also contribute to extrasplanchnic cortisol release, including skeletal muscle (37), although previous work (26) found no significant d3-cortisol release across the leg in type 2 diabetes.

We have previously suggested that chronic hyperinsulinemia is responsible for the decreased hepatic 11β-HSD1 in euglycemic obesity. Insulin decreases 11β-HSD1 in hepatocytes in vitro (38), while a low-carbohydrate diet reduces fasting insulin concentrations and increases hepatic 11β-HSD1 activity (39). Type 2 diabetes is a disorder of relative insulin deficiency, which may account for lack of downregulation of hepatic 11β-HSD1 in obese type 2 diabetic subjects. This appears to be at odds with previous data (40,41) in humans showing that either an insulin infusion or a mixed meal increases whole-body 11β-HSD1 activity, but this acute effect may operate primarily in adipose tissue and may be posttranscriptional. Downregulation of 11β-HSD1 in the liver in euglycemic obesity can be viewed as an adaptive process to decrease intrahepatic glucocorticoid concentrations (33); failure to decrease 11β-HSD1 in type 2 diabetes may result in increased intrahepatic cortisol levels, which exacerbate the adverse metabolic phenotype. Indeed, hepatic 11β-HSD1 mRNA levels have been shown to correlate positively with serum glucose concentrations in morbidly obese patients (42). Obese type 2 diabetic patients in this study were taking a variety of medications. None of these is known to alter hepatic 11β-HSD1, and prescriptions varied widely among our participants, but this remains a possible confounder. Another potential confounder might arise if there were differences between groups in the proportion of free and protein-bound cortisol in plasma (43). There is evidence that turnover of cortisol in the free pool is different from that in the total plasma pool (44). However, serum CBG and albumin concentrations were not different between groups, indicating that the free cortisol pools are likely to be similar in control and obese type 2 diabetic men.

To conclude, we have shown that obese men with type 2 diabetes, unlike euglycemic men (20,26), have increased whole-body regeneration of cortisol by 11β-HSD1 and sustained liver 11β-HSD1. Thus, it is justified to test the efficacy of selective 11β-HSD1 inhibitors in this group of patients.

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R.H.S. researched data, contributed to discussion, and wrote the manuscript. R.A. contributed to discussion and reviewed and edited the manuscript. N.C.M., D.T., and P.C.H. researched data and reviewed and edited the manuscript. B.R.W. contributed to discussion and reviewed and edited the manuscript.
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