The low-dose (1 μg) adrenocorticotropin stimulation test in kidney and kidney–pancreas transplant patients: a potential guideline for steroid withdrawal


Abstract: Chronic steroid treatment is known to impair the hypothalamic–pituitary–adrenal axis (HPA) but the need to assess HPA function prior to withdrawal of steroid therapy in post-transplant patients has not been uniformly accepted. We evaluated the status of the HPA axis in 48 kidney or kidney–pancreas transplant patients who were considered for possible discontinuation of glucocorticoid therapy using a recently validated dynamic test of HPA integrity, the low-dose (1 μg) adrenocorticotropin (ACTH) test. HPA suppression was detected in 29 (60%) of the patients, four of which had severe hypoadrenalism prohibitive of steroid withdrawal. Neither the duration of steroid treatment nor 8:00 AM serum cortisol was a useful marker of hypoadrenalism. 8:00 AM cortisol in subjects with normal HPA reserve and subjects with partial hypoadrenalism overlapped considerably but levels < 5 μg/dL were indicative of severe hypoadrenalism. Pre-withdrawal diagnosis of partial hypoadrenalism allowed the identification of subjects requiring no further steroid replacement under regular daily circumstances. However glucocorticoid supplementation was prescribed in the event of stress such as infection, exceptional effort, trauma or surgery. Individuals with partial HPA impairment, but not patients with severe HPA suppression, improved upon retesting 3 months later. Patients exhibiting normal response to 1 mcg ACTH enjoyed an uneventful course following steroid withdrawal. Since hypoadrenalism is extremely common in post-transplant patients, we recommend the use of the low-dose ACTH test as a convenient method to identify patients with various degrees of hypoadrenalism prior to steroid withdrawal.

Key words: adrenocorticotropin test – kidney/kidney–pancreas transplantation – steroid withdrawal

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Accepted for publication 29 July 2005

Long-term treatment with corticosteroids may suppress normal pituitary–adrenal axis function and expose the patient to risk if corticosteroids are withdrawn, especially under stressful conditions such as surgery or severe infection. Corticosteroids have been a part of anti-rejection treatment since the beginning of solid organ transplantation. To minimize unfavorable metabolic side effects with long-term treatment, multiple protocols have been proposed for the withdrawal of corticosteroids at various intervals after transplantation (1–7).

The adrenocorticotropin (ACTH) test is used to assess hypothalamic–pituitary–adrenal (HPA) reserve. Traditionally, this test was based on the use of a high dose of ACTH (250 μg). Following the intravenous administration of this dose, circulating ACTH levels increase much above the concentrations of endogenous ACTH observed under
stressful conditions or in response to the ‘gold standard’ test of assessing the integrity of the HPA axis, i.e., insulin induced hypoglycemia (8). As the traditional high dose ACTH test provides a supraphysiologic stimulus to the adrenal cortex it could overcome partial impairment in the HPA reserve and elicit a falsely ‘normal’ response. Indeed, there is substantial evidence that, despite its simplicity and worldwide acceptance, the traditional high dose ACTH test misses up to 30–50% of patients with well-documented secondary hypoadrenalism (9,10), most of whom are afflicted with partial impairment but some with severe, occasionally life threatening cortisol deficiency. Based on these considerations, the use of the ‘low-dose’ of ACTH (mostly 1 μg) has been introduced into clinical endocrine testing in recent years (11–15). Further, several studies have demonstrated that this test detects impairment in the function of the HPA axis in patients subjected to various forms of glucocorticoid therapy (14–16).

Previous studies have tested the pituitary adrenal axis in kidney-transplant patients using the 250 μg ACTH test. These reports have focused on kidney-transplant patients returning to hemodyalysis (17–19), or after a stressful event (20). One study addressed the elective process of steroid withdrawal in stable post-transplant patients employing the 1 μg ACTH test to assess adrenal response (21).

Our study assessed the prevalence of adrenal suppression in stable kidney transplant patients and the usefulness of the 1 μg ACTH test as guidance before steroid withdrawal, and suggests a cutoff point predictive of expected consequences of steroid withdrawal.

Patients and methods

Kidney and kidney–pancreas transplant patients were selected from January 2001 to December 2002 as candidates for steroid withdrawal using the following criteria: no evidence of acute rejection 3–6 months after transplantation; stable serum creatinine for at least 6 months; triple drug immunosuppression prior to steroid withdrawal. At that point all patients were already on a low-dose of prednisone (5 mg/d) combined with a calcineurine inhibitor (cyclosporine or tacrolimus) and an antimetabolic drug (azathioprine or mycophenolate mofetil). We measured 8:00 AM serum cortisol level in all patients before taking their daily prednisone tablets. In patients in whom cortisol level was ≥ 15 μg/dL we proceeded with withdrawal of prednisone. If 8:00 AM cortisol level was < 15 μg/dL patients were scheduled to undergo the low-dose ACTH test. During the test, 1 μg of synacten (synthetic 1–34 ACTH) was injected intravenously.

Serum cortisol level was measured just before and as well as 20, 30 and 40 min after the administration of synacten. Based on the results of the test patients were classified into three groups: (i) Normal responders, in whom peak stimulated cortisol level was ≥ 18 μg/dL (12,13); (ii) Borderline responders, whose peak stimulated cortisol level was < 18 μg/dL, but whose 8:00 AM cortisol level was > 5 μg/dL; (iii) Abnormal responders in whom 8:00 AM cortisol level was < 5 μg/dL and stimulated cortisol level was < 18 μg/dL. Patients exhibiting a normal response were taken off steroid therapy. In patients with borderline test prednisone treatment was also withdrawn. However, these subjects were closely monitored for symptoms of steroid deficiency. Patients with an abnormal test continued to receive a maintenance dose of prednisone (5–7.5 mg/d). Patients underwent physical examination, blood tests and 24 urine collections for creatinine clearance before as well as 3 months after steroid withdrawal. Serum creatinine level was measured every 1–2 wk during the first month after steroid withdrawal and at monthly intervals thereafter. In patients with borderline response the ACTH test was repeated 3 months after steroid withdrawal.

Statistical analysis

We used Paired t-test and the Wilcoxon non-parametric test to compare various parameters after 3 months of steroid withdrawal with baseline levels. Analysis of variance was performed to examine the association between length of steroid treatment and the results of the 1 μg ACTH test. Statistical significance level was set to 0.05. The SPSS software (version 10.0, SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

HPA assessment with the 1 μg ACTH test was performed in 48 kidney and kidney–pancreas transplant patients included in our study. In the process of evaluation, 17 patients were deemed inappropriate for steroid withdrawal for reasons unrelated to the results of this test but were included in the overall analysis. There were 20 females and 28 males, 37 with kidney transplant and 11 with kidney–pancreas transplant. From these, the cohort organs were harvested from 29 cadaver donors and 19 living-related donors. In 40 of the patients included in this series this was the first transplantation whereas for eight patients the present procedure was the second transplantation. The patients’ age at the time of transplantation was 43.3 ± 11.8 yr (range, 16–70 yr). The primary causes of end stage kidney disease
were diabetes mellitus (type 1 diabetes – 11 patients; type 2 diabetes – two patients), polycystic kidneys (seven patients), chronic glomerulonephritis (eight patients), and hypertension (four patients). Less common underlying diseases were chronic pyelonephritis (two patients), interstitial nephritis (three patients), Alport’s disease (two patients), nephrolithiasis (two patients) and reflux, oxaluria, and cystinuria (one patient each). In 4 patients the cause of kidney failure remained unknown.

The mean duration of steroid treatment prior to performing the ACTH test was 78 ± 75 wk. The results of the 1 µg ACTH test were normal in 19 patients, borderline in 25 patients and abnormal in four patients (Figs 1–3). There was no correlation between the duration of steroid treatment and the results of the test.

Four patients had a grossly abnormal cortisol response profile, with 8:00 AM cortisol levels ranging at 0.65–4.1 µg/dL and peak ACTH stimulated cortisol levels of 3.1–6.4 µg/dL (Fig. 3). These individuals who fulfilled standard criteria for overt hypoadrenalism, were the only patients in the present series whose 8:00AM cortisol levels were <5 µg/dL. All patients but one from whom steroids were withdrawn, did not experience any symptoms of steroid withdrawal. One patient with a borderline results (8:00 AM cortisol of 7 µg/dL and peak stimulated cortisol of 10.4 µg/dL) developed severe weakness upon prednisone withdrawal necessitating the re-administration of a maintenance dose. In three patients steroid treatment was renewed because of a rise in creatinine level: in one patient 1 week following the withdrawal of prednisone; in the two other patients 10 and 12 months after the discontinuation of glucocorticoid therapy.

When the 1 µg ACTH test was repeated 3 months after steroid withdrawal (n = 13), the cortisol response improved, though it did not necessarily normalize, in all patients with borderline results (data not shown) except for the patient who developed severe weakness following the attempted withdrawal of steroids. Normalization was observed in 5/9 subjects with initial borderline results, but not in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>Mean % change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>75.0 ± 22.8</td>
<td>76.4 ± 23.5</td>
<td>+2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 7.0</td>
<td>26.6 ± 7.1</td>
<td>+2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 ± 16</td>
<td>125 ± 18</td>
<td>-5</td>
<td>0.02</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>76 ± 14</td>
<td>74 ± 11</td>
<td>+3</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>107 ± 33</td>
<td>104 ± 24</td>
<td>+0.1</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)*</td>
<td>5.7 ± 0.8</td>
<td>5.7 ± 0.6</td>
<td>+1</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>198 ± 42</td>
<td>181 ± 43</td>
<td>-8</td>
<td>0.02</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>153 ± 89</td>
<td>134 ± 63</td>
<td>-4</td>
<td>NS</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>41 ± 11</td>
<td>43 ± 11</td>
<td>+6</td>
<td>NS</td>
</tr>
<tr>
<td>LDL (mg/dL)*</td>
<td>131 ± 34</td>
<td>117 ± 36</td>
<td>-8</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5 ± 0.5</td>
<td>1.5 ± 0.6</td>
<td>+6</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>58 ± 23</td>
<td>55 ± 24</td>
<td>-0.3</td>
<td>NS</td>
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<tr>
<td>Na (meq/L)</td>
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<td>137 ± 2</td>
<td>-0.3</td>
<td>NS</td>
</tr>
<tr>
<td>K (meq/L)</td>
<td>4.6 ± 0.5</td>
<td>4.7 ± 0.4</td>
<td>+3</td>
<td>NS</td>
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</table>

* HbA1c was available only in 12 patients, LDL-cholesterol only in 15 patients and creatinine clearance only in 13 of 25 patients.
any of the four patients with severe depression of the pituitary-adrenal axis upon the initial testing.

Table 1 depicts several anthropometric, clinical and biochemical parameters recorded before as well as 3 months after steroid withdrawal. As shown, significant reductions were noted in systolic blood pressure and total cholesterol but not in any of the other parameters listed. Because of an unexpected trend for body mass index (BMI) elevation after the withdrawal of steroids, we reanalyzed the change in BMI according to pre-withdrawal BMI. Patients were divided into standard weights, normal weight (BMI ≤ 25), overweight (25 < BMI < 30), and obese (BMI ≥ 30). As shown in Table 2, the main increase in BMI was seen in the group of normal weight patients and not in the obese patients.

**Table 2. The changes in body mass index (BMI) according to pre-withdrawal BMI**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Number of patients</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≤ 25</td>
<td>13</td>
<td>+4.5</td>
</tr>
<tr>
<td>25 &lt; BMI &lt; 30</td>
<td>6</td>
<td>+1.3</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>6</td>
<td>−1.9</td>
</tr>
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**Discussion**

The 1 μg ACTH test was used in this study to evaluate its use for the detection of HPA dysfunction in kidney and kidney–pancreas transplant patients in whom steroid withdrawal is being considered in light of an apparent favorable status of the transplant itself. Several findings in the present analysis could apply well to the daily care of such patients.

In this series of consecutive and unselected 48 transplant patients subjected to glucocorticoid therapy for a rather variable duration, only 40% (19 patients) had an entirely normal test, whereas 60% responded abnormally: 25 (52%) had partial impairment of the HPA axis and 4 (8%) had severe depression of HPA. The distinction between ‘borderline’ and ‘abnormal’ results is clearly arbitrary as best exemplified by the patient with a ‘borderline’ response who required resumption of prednisone therapy shortly after withdrawal. Indeed, current criteria for the diagnosis of HPA suppression do not address the distinction between partial and complete hypoadrenalism but rather between normal and subnormal results. Hence, while the precise definition of ‘borderline’ or partial impairment of the HPA axis following glucocorticoid therapy awaits further refinement, the protocol followed by us proved fairly useful, as withdrawal from steroids based on the results of the 1 μg ACTH test was without symptoms of cortisol deficiency in all subjects but one. Overall, the high rate of diagnosed hypoadrenalism in our study is in agreement with four previous reports in which HPA suppression, diagnosed by the more traditional 250 μg ACTH test, was observed in 44% to 66% of kidney transplant patients (17–20). Based on the reported higher sensitivity of the 1 μg ACTH test, one might have expected that it would yield a higher rate of abnormal results than the 250 μg test. One possible explanation for the apparent lack of such difference between our study and previous reports utilizing the high dose test may be the longer duration of steroid therapy in the other studies. Particularly in the article reporting the highest rate of HPA axis impairment, where subnormal response to ACTH was detected in 66% of patients, nine of 21 patients received steroids for periods exceeding 302 wk (18), which was the longest period of steroid treatment in our study (applied only in one of 48 patients). While no correlation between the length of treatment and the appearance of hyoadrenalism was found in our patients, it is plausible that this applies to short to medium treatment periods only, whereas following extremely long steroid therapy, such as reported by Rodger et al. (18), suppression of the HPA axis may be more common.

A recently reported study (21), used a more stringent cutoff level of 20 μg/dL instead of 18 μg/dL and yet 69% of their patients had normal ACTH test results, which is about double of ours, and double the results of other studies (17–20) that used the much higher ACTH dose (250 μg/dL). Moreover, the mean duration of steroid treatment in that study was about double (36 months) of ours, inviting more and not less adrenal axis impairment. Separately, that study’s 8:00 AM cortisol levels unexpectedly decreased after steroid withdrawal, all which may suggest some difference in methods.

The 8:00 AM serum cortisol per se is clearly insufficient to correctly identify glucocorticoid treated transplant patients with HPA axis impairment. As shown in Figs 1–3, only subjects with severe HPA suppression can be singled out based on 8:00 AM cortisol levels. In contrast, baseline serum cortisol levels >5 μg/dL provide no specific information as concentrations in normal subjects and in patients with partial secondary hypoadrenalism overlap considerably.

Based on the first 3 months of follow-up, all subjects considered normal by the cortisol response to 1 μg ACTH, indeed enjoyed an uneventful course in terms of their adrenal reserve. Resumption of steroid treatment, when indicated, was dictated by the status of the transplant (i.e. a rising serum creatinine), not by the HPA status.
The identification of a ‘borderline’ cortisol response to 1 μg ACTH may be a good predictor of further improvement upon repeat testing within 3 months, whereas a grossly abnormal response appears to be associated with protracted hypothalamic–pituitary–adrenal suppression within the same time frame. This would suggest that repeat ACTH testing in transplant patients with grossly suppressed adrenal function due to steroid treatment should be considered only after time intervals exceeding 3 months. A reasonable practice, (though presently not supported by specific evidence) would be to defer repeat testing in these patients until the 8:00 AM serum cortisol rises above 5 μg/dL.

The significant reduction in systolic blood pressure and total cholesterol 3 months after steroid withdrawal suggests that even at low ‘maintenance’ doses may have deleterious metabolic effects. Similarly, Hricik et al. (4) observed significant reduction in blood pressure, cholesterol level, and glycohemoglobin following steroid withdrawal. Fabrega et al. (2) reported favorable effect of steroid withdrawal on glucose homeostasis, body weight and hypertension in post-kidney-transplant diabetic patients. In contrast, Sivaraman et al. (6) reported that metabolic benefits were noted when prednisone was tapered down from 10 mg/d to 10 mg every other day, with no further improvement upon discontinuation of steroid treatment. Further, as our patients were closely followed and aggressively treated for hypertension, diabetes, hyperlipidemia and other cardiovascular risk factors before and as well as during the 3 months of follow-up, this type of intervention could have obscured even larger benefits that might have resulted from steroid withdrawal per se.

In conclusion our work shows that a significant percentage of kidney/kidney–pancreas transplant patients have depressed adrenal reserve that cannot be predicted by either the length of prior steroid treatment or by 8:00 AM serum cortisol. The 1 μg ACTH test is easy to perform and provides useful information, which facilitates rational treatment of these complex patients. We recommended its routine use before the elective process of steroid withdrawal.

References


Low-dose ACTH test in kidney transplant patients