Cushing’s disease (CD) is a state of excess glucocorticoid production resulting from an adrenocorticotropic hormone (ACTH)–secreting pituitary adenoma. The gold-standard treatment for CD is transsphenoidal adenomectomy. In the hands of an experienced neurosurgeon, gross-total resection is possible in the majority of ACTH-secreting pituitary adenomas, with early postoperative remission rates ranging from 67% to 95%. In contrast to the strong data in support of resection, the clinical course of postsurgical persistent or recurrent disease remains unclear. There is significant variability in recurrence rates, with reports as high as 36% with a mean time to recurrence of 15–50 months. It is therefore important to develop biochemical criteria that define postsurgical remission and that may provide prognosis for long-term recurrence. Despite the use of a number of biochemical assessments, there is debate regarding the accuracy of these tests in predicting recurrence. Here, the authors review the various biochemical criteria and assess their utility in predicting CD recurrence after resection.

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KEY WORDS Cushing’s disease; postsurgical recurrence; cortisol; ACTH
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geon are associated with lower rates of recurrence.\textsuperscript{2,23,30,35} However, a recent meta-analysis demonstrated that age, sex, tumor size, and macroscopic invasion were not reliable predictors of recurrence.\textsuperscript{48}

Attention has therefore turned toward establishing biochemical criteria for disease remission and recurrence risk. These criteria center on the goal of transsphenoidal adenomectomy—to induce postoperative hypocortisolism after removal of a pituitary adenoma. The degree of adrenal insufficiency can be assessed as a static variable or as a dynamic test. Here, we review the various biochemical criteria and assess their utility in predicting CD recurrence after resection.

**Postoperative Adrenal Insufficiency**

In CD, the corticotroph adenoma hypersекretes ACTH, leading to hypercortisolism and subsequent downregulation of endogenous pituitary corticotrophs through negative feedback. After resection of an ACTH-secreting adenoma, serum ACTH levels decline. However, the normal corticotrophs remain suppressed and thereby give rise to a characteristic hypocortisolism that has been widely used to define initial postoperative remission. The degree of adrenal insufficiency can be assessed as a static variable or as a dynamic test. Here, we review the various biochemical criteria and assess their utility in predicting CD recurrence after resection.

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The hypothalamic-pituitary-adrenal (HPA) axis has been studied extensively in the early postoperative period to evaluate the degree of corticotroph suppression and adrenal insufficiency following resection of an ACTH-secreting pituitary adenoma. Serum cortisol and urinary free cortisol (UFC) have been used as biochemical markers to classify initial remission and to predict long-term recurrence. One complicating factor in interpreting these tests, however, is the lack of standardization in postoperative administration of glucocorticoid therapy. Some groups routinely administer perioperative steroid therapy followed by rapid taper while others hold all glucocorticoid therapy until a diagnosis of adrenal insufficiency—either biochemical or clinical—is identified.\textsuperscript{1,10,57}

**The Impact of Postoperative Management on Biochemical Testing Results**

We have separated the biochemical assessments into those that require random or timed hormone measurements versus those that require dynamic testing. The postoperative protocol for glucocorticoid administration plays a key role in interpretation of these data. Cortisol levels following immediate postoperative administration of stress dose steroids followed by rapid taper may be different from assessments in which glucocorticoids are withheld. Cortisol can be measured sooner after surgery when glucocorticoids are withheld, so the postoperative management may affect the timing of measurements and the cortisol levels themselves.

**Static Biochemical Tests**

**Postoperative Cortisol Measurements**

The degree of hypocortisolism in the postoperative period has been suggested as a potential predictor of long-term recurrence of CD. Numerous studies have demonstrated a lower rate of recurrence in patients with subnormal postoperative cortisol levels than in patients with normal or supranormal levels.\textsuperscript{10,30,34,44,48,59} However, the “normal range” of serum cortisol level used as a criterion for surgical success varies significantly in the literature.\textsuperscript{2,8} Esposito et al. reported that patients who go on to achieve sustained remission following resection have lower mean nadir cortisol levels than patients who eventually develop recurrent disease.\textsuperscript{23} Yap et al. stratified patients into those with detectable versus those with undetectable postoperative cortisol levels and determined that undetectable postoperative serum cortisol level is associated with a lower

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**TABLE 1. Summary of series reporting postoperative cortisol values and long-term recurrence rates after surgical treatment of CD**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Periop Steroids</th>
<th>Cortisol Cutoff (μg/dl)</th>
<th>Recurrence Rate (%)</th>
<th>Mean Follow-Up in Mos (range, if available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trainer et al., 1993</td>
<td>48</td>
<td>Yes</td>
<td>1.8</td>
<td>0</td>
<td>40 (15–70)</td>
</tr>
<tr>
<td>McCance et al., 1993</td>
<td>19</td>
<td>Yes</td>
<td>1.8</td>
<td>0</td>
<td>30 (6–72)</td>
</tr>
<tr>
<td>Bochicchio et al., 1995</td>
<td>94</td>
<td>Yes</td>
<td>“Undetectable”</td>
<td>4.3</td>
<td>40 (6–104)</td>
</tr>
<tr>
<td>Chee et al., 2001</td>
<td>48</td>
<td>Yes</td>
<td>3.6</td>
<td>14.5</td>
<td>76 (22–158)</td>
</tr>
<tr>
<td>Simmons et al., 2001</td>
<td>21</td>
<td>No</td>
<td>10</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Rees et al., 2002</td>
<td>53</td>
<td>Yes</td>
<td>1.8</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Yap et al., 2002</td>
<td>97</td>
<td>Yes</td>
<td>1.8</td>
<td>11.5</td>
<td>92 (6–348)</td>
</tr>
<tr>
<td>Rollin et al., 2004</td>
<td>42</td>
<td>Yes</td>
<td>3.2</td>
<td>4.7</td>
<td>59 (4–170)</td>
</tr>
<tr>
<td>Atkinson et al., 2005</td>
<td>45</td>
<td>Yes</td>
<td>10</td>
<td>22</td>
<td>108</td>
</tr>
<tr>
<td>Esposito et al., 2006</td>
<td>32</td>
<td>No</td>
<td>5</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Patil et al., 2008</td>
<td>97</td>
<td>No</td>
<td>2</td>
<td>20.6</td>
<td>5-yr actuarial occurrence</td>
</tr>
<tr>
<td>Sughrue et al., 2010</td>
<td>32</td>
<td>Yes</td>
<td>8</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>Lindsay et al., 2011</td>
<td>295</td>
<td>Yes</td>
<td>2</td>
<td>9.5</td>
<td>132 (12–275)</td>
</tr>
<tr>
<td>Hameed et al., 2013</td>
<td>19</td>
<td>No</td>
<td>5</td>
<td>0</td>
<td>23</td>
</tr>
</tbody>
</table>
rate of disease recurrence, although recurrence still occurred in 11.5% of patients with undetectable levels. A retrospective study of 30 patients with CD reported a recurrence rate of 60% (3 of 5 patients) when postoperative serum cortisol was greater than 2 μg/dl, but only 4% (1 of 25 patients) when postoperative cortisol was less than 2 μg/dl. Similarly, in a retrospective review of 215 patients, those patients with a postoperative serum cortisol level higher than 2 μg/ml had 2.5 times the risk of recurrence compared with patients with postoperative serum cortisol levels less than 2 μg/ml. Interestingly, Lindsay et al. found that rates of recurrence were similar between patients with nadir serum cortisol levels less than 2 μg/dl and those with levels less than 5 μg/dl. Based on these studies, a consensus statement published by an international cohort of 32 leading clinicians with extensive experience in management of CD recommends immediate reevaluation of patients with persistent serum cortisol levels greater than 5 μg/dl, and careful observation of those patients with cortisol levels between 2 and 5 μg/dl. In a recently published retrospective review of a prospective database of 61 patients with CD who underwent endoscopic transphenoidal tumor resection, a postoperative serum cortisol level less than 5.7 μg/dl was the best predictor of postoperative remission (sensitivity 88.6%, specificity 83.3%). Furthermore, when measured as a continuous variable, the postoperative serum cortisol level is directly correlated with the subsequent rate of CD recurrence. It is important to emphasize, however, that disease recurrence does still occur in approximately 10% of patients with low (< 2 μg/dl) or even undetectable postoperative serum cortisol levels, necessitating long-term follow-up in all CD patients. In other words, there is no clear cutoff value that unequivocally excludes the risk of recurrence, and likewise, some patients with elevated postoperative serum cortisol go on to achieve sustained long-term remission. Urinary free cortisol excretion has also been evaluated as a predictor of CD remission, and while there is a trend toward lower rates of recurrence in patients with low UFC levels, this difference does not reach statistical significance until 6 weeks after surgery. Thus, despite the simplicity of urinary sample collection, current recommendations indicate that UFC measurements should only be used when serum cortisol levels are equivocal. In this case, UFC levels of less than 20 μg/24 hours are suggestive of surgical remission, normal UFC levels (range 20–100 μg/24 hours) are equivocal, and elevated values suggest remaining tumor.

Nighttime salivary cortisol testing also benefits from the same advantages as urine testing and has been shown to have high sensitivity and specificity for detecting surgical failure and recurrence in CD. Furthermore, nighttime salivary cortisol has lower intrasubject variability than UFC. Nonetheless, given the variability of the available salivary cortisol assays and lack of a clear cutoff value, the late-night salivary cortisol has not been sufficiently validated as a useful predictor of long-term recurrence.

Postoperative ACTH

Adrenocorticotropin-releasing hormone (CRH) from the hypothalamus. The setting of CD, ACTH is secreted autonomously from neoplastic corticotrophs. The pattern of serum ACTH levels in the postoperative period following resection of ACTH-secreting pituitary adenomas has been studied. Similar to serum cortisol, higher serum ACTH levels correlate with an increased incidence of CD recurrence, whereas low serum ACTH levels correlate with sustained disease remission. Interestingly, subnormal serum ACTH is significantly less sensitive for sustained disease remission but also more specific for long-term disease remission than subnormal serum cortisol. However, an ACTH value that may predict long-term recurrence has not been determined.

Dynamic Biochemical Assessments

There are several well-known synthetic and naturally occurring effectors of the HPA axis that have predictable biochemical responses in CD. Several of these have been used in the perioperative period of CD to confirm initial remission and to predict long-term recurrence with dynamic stimulation of the HPA axis.

CRH Stimulation

In patients with CD, administration of CRH results in a disproportionate increase in ACTH and cortisol. There have been several reports of using the CRH test in the postoperative setting to assess adrenal reserve and determine surgical efficacy. Invitti et al. first demonstrated that an increase of more than 50% of plasma ACTH and serum cortisol after CRH administration was significantly correlated with the risk of postsurgical recurrence; this finding has been verified by several follow-up studies. However, there have also been less than reliable rates of recurrence reported with normal or even supranormal responses to CRH stimulation. Several studies have also shown significant rates of overlap in recurrence between patients who exhibited positive response and those who exhibited no response to CRH stimulation. A number of different protocols utilizing both human and animal CRH stimulation with a wide range of diagnostic cutoff points and clinical follow-up periods have been published, although small sample sizes and short duration of follow-up have limited the wider applicability of these varied CRH stimulation strategies. In the most recent large retrospective study with adequate long-term follow-up, ACTH and cortisol levels following CRH stimulation were higher in the group of CD patients who eventually experienced recurrence, but there were no identifiable basal or stimulated CRH cutoff values that could capture all of these recurrences. Finally, studies of dynamic CRH testing in other clinical situations of hypothalamic-pituitary insufficiency (i.e., not postoperative) have also reported contradictory results with regard to CRH response rates.

In general, results have been highly variable in determining useful criteria for evaluating CRH stimulation data, and there has been no established added benefit over measurement of static serum cortisol levels.
Desmopressin Stimulation

Desmopressin is a synthetic analog of vasopressin. Administration in healthy individuals does not result in any perceptible change in plasma ACTH or cortisol levels, but in patients with CD or subtotal resection of an ACTH-secreting pituitary adenoma, desmopressin stimulation results in a significant increase in both ACTH and cortisol levels. Because desmopressin administration elicits a positive ACTH and cortisol response in patients who have undergone subtotal resection and/or experienced late recurrence, and an absent response in subjects with full resection, desmopressin stimulation has been proposed as a postoperative functional measure of extent of resection. In a series of more than 100 patients with CD, Losa et al. demonstrated that 50 of 87 patients had a complete disappearance of the preoperative positive desmopressin response. In patients with recurrent CD, Losa et al. demonstrated that 50 of 87 patients had a complete disappearance of the preoperative positive desmopressin response. In summary, there has been reports of postoperative relapse despite complete disappearance of the preoperative positive desmopressin response. In a series of more than 100 patients with CD, Losa et al. demonstrated that 50 of 87 patients had a complete disappearance of the preoperative positive desmopressin response. In summary, there has been reports of postoperative relapse despite complete disappearance of the preoperative positive desmopressin response.

Metyrapone Stimulation

Metyrapone is a competitive 11β-hydroxylase inhibitor. When this substrate is blocked in the adrenal cortex, cortisol synthesis is disrupted, and ACTH secretion is thereby increased. Stimulation of ACTH following metyrapone leads to buildup of cortisol precursors such as 11-deoxycortisol and provides a dynamic measurement of HPA axis integrity. In this way, response to metyrapone may be a surrogate measurement for continued pituitary activity after pituitary surgery for CD and has been correlated with surgical outcome. It has been suggested that patients with persistent CD after resection would have increased 11-deoxycortisol levels compared with those in sustained remission. Van Aken et al. demonstrated 100% sensitivity of postoperative metyrapone testing to predict CD recurrence. However, the specificity of this test has been questioned in the setting of several follow-up reports of patients with recurrent CD with a wide range of 11-deoxycortisol values. Consequently, the use of the metyrapone stimulation test for predicting CD recurrence has been limited.

Conclusions

The postsurgical management and prediction of long-term disease remission in patients with CD presents an exceedingly complicated problem. Given the lack of standardization of postoperative glucocorticoid protocols as well as clear criteria for determining long-term remission, there is no consensus on the appropriate testing that can predict permanence of remission. Dynamic tests do not appear to offer an advantage over serum cortisol measurements, and therefore a role for dynamic tests has not been firmly established. Demonstration of hypocortisolism remains the standard assessment following CD surgery, and the degree of hypocortisolism likely is the most valuable tool for predicting recurrence. Further studies that can define these tests further or determine other biomarkers of tumor activity are necessary to further our understanding of how to prognosticate outcome in patients with CD.

References


**Author Contributions**

Drafting the article: Pendharkar, Sussman, Ho, Katzenelson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pendharkar.

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