Elevated body mass index and risk of postoperative CSF leak following transsphenoidal surgery

Clinical article

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Object. Postoperative CSF leakage can be a serious complication after a transsphenoidal surgical approach. An elevated body mass index (BMI) is a significant risk factor for spontaneous CSF leaks. However, there is no evidence correlating BMI with postoperative CSF leak after transsphenoidal surgery. The authors hypothesized that patients with elevated BMI would have a higher incidence of CSF leakage complications following transsphenoidal surgery.

Methods. The authors conducted a retrospective review of 121 patients who, between August 2005 and March 2010, underwent endoscopic endonasal transsphenoidal surgeries for resection of primarily sellar masses. Patients requiring extended transsphenoidal approaches were excluded. A multivariate statistical analysis was performed to investigate the association of BMI and other risk factors with postoperative CSF leakage.

Results. In 92 patients, 96 endonasal endoscopic transsphenoidal surgeries were performed that met inclusion criteria. Thirteen postoperative leaks occurred and required subsequent treatment, including lumbar drainage and/or reoperation. The average BMI of patients with a postoperative CSF leak was significantly greater than that in patients with no postoperative CSF leak (39.2 vs 32.9 kg/m², p = 0.006). Multivariate analyses indicate that for every 5-kg/m² increase in BMI, patients undergoing a transsphenoidal approach for a primarily sellar mass have 1.61 times the odds (95% CI 1.10–2.29, p = 0.016, by multivariate logistic regression) of having a postoperative CSF leak.

Conclusions. Elevated BMI is an independent predictor of postoperative CSF leak after an endonasal endoscopic transsphenoidal approach. The authors recommend that patients with BMI greater than 30 kg/m² have meticulous sellar reconstruction at surgery and close monitoring postoperatively.

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Key Words • complication • craniopharyngioma • obesity • pituitary tumor • Rathke cleft cyst • rhinorrhea • pituitary surgery

The transsphenoidal approach to the sella allows access to and treatment of sellar masses including pituitary tumors, craniopharyngiomas, Rathke cleft cysts, and many other mass lesions that impinge upon the optic chiasm superiorly. However, this approach is not without risks. Cerebrospinal fluid leakage is a complication that can cause significant morbidity and long-term consequences due to meningitis and need for further invasive procedures. After mass resection and depending on intraoperative findings, sellar reconstruction is often important for prevention of postoperative CSF leaks. However, no reconstruction technique has been shown to be superior to another. In addition to proper sellar reconstruction, understanding the additional risk factors associated with postoperative CSF leakage is important for limiting this significant complication.

Obesity is an increasing public health problem in the US and is associated with significant morbidity. In 2007–2008, the prevalence of obesity was 32.2% among adult men and 35.5% among adult women, where “overweight” was defined as a BMI of 25.0 to 29.9 and “obese” was defined as a BMI of 30.0 or higher. Obesity places individuals at risk for a host of medical problems including cardiovascular disease, diabetes, and cancer. With regard to neurological/neurosurgical disorders, obesity is associated with both idiopathic intracranial hypertension and spontaneous CSF rhinorrhea. Recent studies

Abbreviations used in this paper: BMI = body mass index; ICP = intracranial pressure; IIH = idiopathic intracranial hypertension.
investigating the risk factors associated with spontaneous CSF leaks revealed that ICP elevation, an underlying diagnosis of idiopathic intracranial hypertension, and an elevated BMI are all significant risk factors.

Observation and anecdotal evidence from others suggest a plausible link between BMI and CSF leak after transsphenoidal surgery. However, to date there is no reported evidence correlating BMI with postoperative CSF leak after transsphenoidal surgery. Given the recent evidence associated with spontaneous CSF leaks, we hypothesized that patients with elevated BMI would have a higher incidence of CSF leak complications following transsphenoidal surgery. To test this hypothesis, we retrospectively examined all patients who underwent a transsphenoidal approach for pituitary mass resection at our institution to evaluate whether increased BMI correlated with increased rates of postoperative CSF leaks.

Methods

Patient Population

A total of 121 patients underwent endoscopic endonasal transsphenoidal surgeries between August 2005 and March 2010 at our institution. Only patients who underwent transsphenoidal approaches for resection of primarily sellar masses and had a minimum 4 weeks of follow-up were included. Patients requiring extended transsphenoidal approaches with large arachnoidal openings were excluded given the significant difference in surgical approach, sellar reconstruction, and the rate of postoperative CSF leakage.

All patients were treated by a single neurosurgeon (J.D.W.G.). After the study was approved by the University of Iowa Institutional Review Board, all inpatient and outpatient records were retrospectively reviewed, and the following information was recorded: patient age, sex, BMI at the time of surgery, histopathological diagnosis, presence of Cushing disease, tumor volume and type (primary or recurrent), sellar/suprasellar remnant, cavernous remnant, sphenoid packing, use of intraoperative lumbar drain or lumbar puncture, intraoperative CSF leakage, and postoperative CSF leakage. Intraoperative CSF leaks were determined using intraoperative records, and postoperative CSF leaks were determined by clinical evidence of CSF rhinorrhea.

Surgical Technique

All patients underwent an endonasal endoscopic transsphenoidal approach to the sella in which rigid endoscopes and instrumentation were used. In each case, the otolaryngology team provided access to the sphenoid sinus bilaterally. The middle turbinates were lateralized and not routinely resected. A posterior septectomy was created, removing mucosa and bone, and a sphenoidotomy was enlarged with a microdebrider. Typically, diamond burs were used to bur down the posterior septum, thin it out, and enlarge the sphenoidotomy. Through the sphenoidotomy, the back wall of the sphenoid sinus and both opticocarotid recesses were visualized. Frameless stereotaxy (Stealth, Medtronic, Inc.) was used to confirm the borders of the sella, including the carotid arteries laterally.

The anterior sella was opened with a high-speed drill and enlarged with rongeurs. A cruciate dural incision was made, and tumors were resected with suction and ring curettes. After tumor resection, the sella was reconstructed, typically using abdominal fat autograft sandwiched between two pieces of synthetic dura. In addition, some patients had their sphenoid sinus packed with bioresorbable sponges (Nasopore, Stryker, Inc.) to reinforce the sellar reconstruction.

Statistical Analysis

Descriptive statistics were calculated, and Wilcoxon rank-sum tests (continuous variables) and Fisher exact tests (dichotomous variables) were used to compare the 2 groups of patients—those with a postoperative CSF leak and those with no postoperative CSF leak. Logistic regression was used to assess predictors of postoperative CSF leakage, with exact (permutation-based) logistic regression used for dichotomous risk factors. Patient age, sex, BMI, the presence of Cushing disease, tumor type and volume/size, sellar/suprasellar remnant, cavernous remnant, sphenoid packing, intraoperative lumbar drain or lumbar puncture, and intraoperative CSF leak were initially examined in a series of univariate analyses followed by a multivariate regression analysis based on a stepwise approach including univariate analyses with p < 0.20 and p < 0.05 as the cutoff for inclusion in the final adjusted model. Statistical analyses were conducted with the help of SAS 9.2 software (SAS Institute, Inc.) and LogXact 8 (Cytel, Inc.).

Results

A total of 96 endonasal endoscopic transsphenoidal surgeries that met inclusion criteria were performed in 92 patients between August 2005 and March 2010 at our institution (Table 1). The average age of patients at surgery was 53 years (range 19.8–88.2 years). A total of 50 women and 46 men underwent surgery. A second transsphenoidal surgery for recurrent tumors was performed in 2 women and 2 men. Overall, 7 patients underwent recurrent pituitary adenoma resection. The sellar pathology consisted of the following: 88 pituitary adenomas, 3 Rathke cleft cysts, 1 metastatic lesion, and 4 others (for example, fibrous tissue or infection). Intraoperative CSF leaks were observed at time of surgery in 41 patients.

Thirteen (13.5%) of the 96 procedures were complicated by postoperative leaks and required subsequent treatment, including lumbar drainage and/or reoperation. In 1 patient with an intraoperative leak, a lumbar drain was placed during surgery. In 4 of these 13 patients, no intraoperative leak was evident at the time of initial surgery but delayed CSF rhinorrhea occurred on postoperative Days 1, 2, 6, and 7. One morbidly obese patient had surgery twice for a recurrence, and a postoperative leak developed on both occasions. The average length of hospital stay was twice as long for the patients with postoperative leaks (8 days) as for those with no leaks (4 days).

The average BMI of those patients who suffered a postoperative CSF leak was significantly greater than that of those with no leaks.
in patients with no postoperative CSF leaks (39.2 vs 32.9 kg/m², p = 0.006) (Table 2). Logistic regression results (Table 3) showed that increased BMI was associated with an increased risk of postoperative CSF leakage, both in unadjusted and adjusted analyses. We found that for every 5-kg/m² increase in BMI, patients undergoing a transsphenoidal approach for a primarily sellar mass have 1.61 times the odds (95% CI 1.10–2.29, p = 0.016) of having a postoperative CSF leak, adjusting for age and intraoperative leak status. None of the patients with a postoperative leak had a normal BMI. Eleven of the 13 patients with a postoperative leak met BMI criteria for obesity (> 30 kg/m²), and 9 of the 13 patients with a postoperative leak met BMI criteria for morbid obesity (> 35 kg/m²). The female/male ratio with postoperative leak was 10:3. However, no significant difference in postoperative CSF leakage was found between male and female patients. Among the patients with an intraoperative CSF leak, the female/male ratio was 22:19. Of the 13 patients with a postoperative leak, only 1 (7.7%) was diagnosed with Cushing disease. This is similar in comparison with 4 patients (4.8%) diagnosed with Cushing disease that did not result in a postoperative leak. There was no significant association of Cushing disease with postoperative CSF leak in our transsphenoidal series.

Additional risk factors beyond BMI that entered our final model (right column of Table 3) included younger age (p = 0.008) and intraoperative CSF leakage (p = 0.034) after adjusting for the additional factors. Although it did not enter into the final model, sphenoid sinus packing also approached significance (p = 0.055, adjusting for age and BMI, Table 3).

### Table 2: Demographic data stratified by presence or absence of postoperative CSF leak

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Postop CSF Leak (n = 83)</th>
<th>Postop CSF Leak (n = 13)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age in yrs (range)</td>
<td>54.6 (19.8–88.2)</td>
<td>42.9 (22.4–73.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>male sex</td>
<td>43 (51.8)</td>
<td>3 (23.1)</td>
<td>0.074</td>
</tr>
<tr>
<td>mean BMI in kg/m² (range)</td>
<td>32.9 (18.9–61.8)</td>
<td>39.2 (26.2–55.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pituitary adenoma</td>
<td>76 (91.6)</td>
<td>12 (92.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>connective tissue/infection</td>
<td>4 (4.8)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Rathke cleft cyst</td>
<td>2 (2.4)</td>
<td>1 (7.7)</td>
<td>0.357</td>
</tr>
<tr>
<td>metastatic lesion</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>4 (4.8)</td>
<td>1 (7.7)</td>
<td>0.525</td>
</tr>
<tr>
<td>mean mass vol in cm³ (range)</td>
<td>7.0 (0.0–57.6)</td>
<td>4.4 (0.0–17.2)</td>
<td>0.132</td>
</tr>
<tr>
<td>sella/suprasellar remnant</td>
<td>43 (51.8)</td>
<td>4 (30.7)</td>
<td>0.234</td>
</tr>
<tr>
<td>cavernous remnant</td>
<td>20 (24.1)</td>
<td>2 (15.4)</td>
<td>0.726</td>
</tr>
<tr>
<td>sphenoid packing</td>
<td>19 (22.9)</td>
<td>7 (53.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>intraop lumbar drain/puncture</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0.135</td>
</tr>
<tr>
<td>repeat transsphenoidal surgery</td>
<td>5 (6.0)</td>
<td>2 (15.4)</td>
<td>0.240</td>
</tr>
<tr>
<td>intraop leak</td>
<td>32 (38.6)</td>
<td>9 (69.2)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

* Wilcoxon rank-sum tests (continuous variables) and Fisher exact tests (dichotomous variables) were used to compare the no postoperative CSF leak group with the postoperative CSF leak group.
techniques, the risk of CSF rhinorrhea and meningitis was considerably reduced, and the transsphenoidal approach gained popularity again in the US in the 1970s.29

The use of the endoscope in neurosurgical procedures began in the early 1900s.13 However, it was not until the technical advances in the 1970s, 1980s, and 1990s that the endoscope became useful and effective as a neurosurgical tool.13 With better endoscopes providing better visualization for otorhinolaryngologists in the treatment of sinus disease, neurosurgeons adopted this instrument for the transsphenoidal approach and pituitary tumor resection.20 Now, the endonasal endoscopic transsphenoidal approach for resection of sellar and parasellar lesions is commonplace.

Even with advances in antibiotics, endoscopic visualization, and operative techniques, the risk of a CSF leak remains,8 and the possibility of meningitis can lead to significant morbidity and mortality. A better understanding of the risk factors associated with postoperative CSF rhinorrhea may help to lessen this surgical complication. We observed a greater prevalence of postoperative CSF leakage in our patient population treated with transsphenoidal surgeries than has been reported in the literature. This provided the impetus for analyzing unexplored risk factors that may be unique in our patient population.

Obesity and Increased Risk of Spontaneous CSF Leaks

Obesity is a major cause of morbidity and mortality in the US and is a growing problem, as the rates of obesity have doubled in adults and tripled in children since 1980.28 Various studies have demonstrated that patients with spontaneous CSF leaks have an elevated BMI. A study examining risk factors for spontaneous CSF leaks showed that 14 of 15 patients with spontaneous CSF leaks were noted to have an elevated BMI with 5 of those patients being overweight (BMI > 24.9) and 9 being obese (BMI > 30).8 Lindstrom and associates28 noted that patients with spontaneous CSF rhinorrhea had a BMI of 33 compared with patients with iatrogenic CSF rhinorrhea who had a BMI of 29.8. Similarly, Banks et al.4 found that patients with spontaneous CSF leaks had a BMI of 35 or greater. In our study, 4 of the 13 patients with postoperative CSF leaks did not have an observed intraoperative leak but had a significantly elevated BMI; in 2 of the 4 patients a CSF leak was observed on postoperative Days 6

### TABLE 3: Risk factor analysis for postoperative CSF leak using logistic regression analysis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Patients</th>
<th>Postoperative CSF Leak (n = 13)</th>
<th>No. (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age in yrs, continuous</td>
<td>0.94 (0.89–0.98)</td>
<td>0.93 (0.88–0.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>50</td>
<td>10 (20)</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>46</td>
<td>3 (6.5)</td>
<td>0.28 (0.05–1.20)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>BMI in kg/m², continuous†</td>
<td></td>
<td>1.47 (1.05–2.01)</td>
<td>1.61 (1.10–2.29)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>mass vol in cm³, continuous</td>
<td></td>
<td>0.94 (0.84–1.06)</td>
<td></td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>sella/suprasellar remnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>no</td>
<td>49</td>
<td>9 (18.4)</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>47</td>
<td>4 (7.8)</td>
<td>0.42 (0.09–1.64)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>cavernous remnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>74</td>
<td>11 (14.9)</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>22</td>
<td>2 (9.1)</td>
<td>0.58 (0.06–2.99)</td>
<td>—</td>
<td></td>
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<tr>
<td>sphenoid packing</td>
<td></td>
<td></td>
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<tr>
<td>no</td>
<td>70</td>
<td>4 (5.7)</td>
<td>1.0</td>
<td>—</td>
<td></td>
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<tr>
<td>yes</td>
<td>26</td>
<td>7 (26.9)</td>
<td>3.86 (0.98–15.8)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>intraop lumbar drain/puncture</td>
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<td></td>
<td></td>
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<tr>
<td>no</td>
<td>0</td>
<td>12 (12.6)</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1</td>
<td>1 (100)</td>
<td>6.39 (0.16–infinity)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>repeat transsphenoidal surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>89</td>
<td>11 (12.4)</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>7</td>
<td>2 (28.6)</td>
<td>2.80 (0.24–19.88)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>intraop leak</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>55</td>
<td>4 (7.3)</td>
<td>1.0</td>
<td>1.0</td>
<td>5.66 (1.10–47.95)</td>
</tr>
<tr>
<td>yes</td>
<td>41</td>
<td>9 (21.9)</td>
<td>3.54 (0.89–17.06)</td>
<td>5.66 (1.10–47.95)</td>
<td></td>
</tr>
</tbody>
</table>

* Unadjusted odds ratios were determined with univariate logistic regression analysis and adjusted odds ratios were determined using multivariate logistic regression analysis.
† For every 5-kg/m² increase in BMI.
Body mass index and post-transsphenoidal CSF leak

and 7, possibly due to a prolonged sustained elevated ICP, which caused a dehiscence in the sellar reconstruction.

**Obesity and Increased ICP**

The pathophysiology of IIH is unclear, and different hypothesized mechanisms exist. Obesity is a notable risk factor for IIH, and several factors likely contribute to this phenomenon. Elevated intraabdominal pressure secondary to visceral obesity has been demonstrated to increase central venous pressure. Sugerman et al. suggest that this increase in pleural pressure and cardiac filling pressure may impede venous return from the brain, leading to increased intracranial venous pressure and increased ICP associated with IIH. In addition, other studies show that various metabolic alterations in obesity increase ICP associated with IIH. In addition, other studies show that various metabolic alterations in obesity increase ICP associated with IIH. In addition, other studies show that various metabolic alterations in obesity increase ICP associated with IIH. In addition, other studies show that various metabolic alterations in obesity increase ICP associated with IIH. In addition, other studies show that various metabolic alterations in obesity increase ICP associated with IIH.

**Obesity and Transsphenoidal CSF Leak**

The reported incidence of postoperative CSF leak after transsphenoidal surgery in the literature ranges from 1.5% to 10.3%. The national average of transsphenoidal postoperative CSF leakage is thought to be 2%—3%. We noted a greater prevalence of postoperative CSF leaks in our patient population than has been reported in the literature. No study to date has examined BMI as a risk factor in the incidence of transsphenoidal postoperative CSF leakage. What prompted us to examine risk factors in our patients were the reported risks of elevated BMI and spontaneous CSF leakage in other studies, and the suspected elevated BMI in our population. We statistically demonstrated a greater average BMI in our patients with CSF leaks than in our patients with no CSF leaks. It is possible that our cohort had a larger percentage of patients with an elevated BMI compared with others, contributing to our greater postoperative CSF leakage rate (39.2 kg/m^2 [with CSF leakage] vs 32.9 kg/m^2 [no leakage]). The pathophysiology behind this association is only hypothetical, but one can speculate that a similar pathogenesis is associated with elevated BMI and spontaneous CSF leaks and that IIH may play a role. As with IIH, for which elevated BMI is a risk factor, increased ICP may lead to dehiscence of the sellar reconstruction. Patients with IIH can have markedly elevated ICP on a chronic basis, yet exhibit few symptoms.

In our multivariate analysis, younger age also conferred risk for postoperative CSF leakage in our patients. Interestingly, patients that present with IIH are of a younger age as well. Although the significance is unknown, we can speculate that younger age may also play a role in altering the ICP. Additionally, intraoperative CSF leakage conferred a risk for postoperative CSF leakage. This is not a surprising observation and is consistent with previous reports after transsphenoidal surgery.

**Sellar Reconstruction**

There are many ways to reconstruct the sella, including “tiered” repairs based on intraoperative findings. For our typical transsphenoidal approach, we use a fat graft sandwiched between 2 layers of synthetic dura. We position the fat graft so that it partially resides within the sella and protrudes into the sphenoid sinus. Other groups use a variety of fat, fascia, and muscle in addition to other types of synthetic materials to reconstruct the sella. Some have used a dural suture for closure of the sella as well as various other techniques, including incorporation of rigid buttresses such as titanium, bone, or cartilage to hold the sellar packing in place. For larger sellar defects, some have encountered after extended transsphenoidal approaches, Hadad et al. used the combination of fascia lata, abdominal fat, mucoperiosteum, and fibrin sealants followed by a vascularized nasal septal mucosal flap as a final layer, with reinforcement of this construct via an inflated Foley catheter balloon. To date, there is no good evidence showing that one reconstruction technique is superior to another.

Our sellar repair has evolved over time, and earlier patients in the series did not routinely undergo sphenoid sinus packing, whereas in recent patients the sinus is typically filled with synthetic, bioresorbable sponges. Additionally, in some patients without intraoperative leaks early in the series we did not use fat autografts. Our practice now is that every patient with a BMI over 25 kg/m^2 undergoes fat grafting as part of the reconstruction. We do not routinely use dural sealants. As noted, comparisons of variations in sellar repair are lacking.

**Study Limitations**

As with all retrospective studies, there is an inherent bias compared with prospective studies. Additionally, the cohort is small in size, which may lead to an inability to demonstrate additional risk factors in a subgroup analysis. If anything, our study may provide impetus for larger studies and further investigation into the question of elevated BMI and transsphenoidal CSF leak.

**Conclusions**

There is a significant association between elevated BMI and postoperative transsphenoidal CSF leakage, and an elevated BMI is an independent predictor of a postoperative CSF leak. We propose certain recommendations that we adopted in our clinical setting to address the risk of elevated BMI and the transsphenoidal approach. We recommend that patients with BMI exceeding 30 kg/m^2 undergo appropriate preoperative counseling, meticulous
sellar reconstruction at surgery, and close monitoring postoperatively.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Greenlee, Dlouhy, Madhavan, O’Brien. Acquisition of data: Dlouhy, Madhavan, Clinger, Reddy. Analysis and interpretation of data: Dlouhy, O’Brien, Chang, Graham. Drafting the article: Dlouhy. 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. Greenlee. Statistical analysis: Dlouhy, Dawson. Administrative/technical/material support: O’Brien. Study supervision: Greenlee, Dlouhy.

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