Pituitary Stalk Stretch Predicts Postoperative Diabetes Insipidus After Pituitary Macroadenoma Transsphenoidal Resection

Alex Nguyen Hoang, MD*
Benjamin G. McGahan, MD‡
Santino Cua, MD§
Stephen T. Magill, MD, PhD||
Pratima Nayak, MD¶
Alaa S. Montaser, MD#
Luma Ghalib, MD¶
Luciano M. Prevedello, MD**
Douglas A. Hardesty, MD‡
Ricardo L. Carrau, MD††
Daniel M. Prevedello, MD‡

*Department of Neurological Surgery, Houston Methodist Hospital, Houston, Texas, USA; ‡Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; §The Ohio State University College of Medicine, Columbus, Ohio, USA; ||Department of Neurological Surgery, Northwestern University, Chicago, Illinois, USA; ¶Department of Endocrinology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; #Department of Neurological Surgery, Ain Shams University, Cairo, Egypt; **Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; ††Department of Otolaryngology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Correspondence:
Alex Nguyen Hoang, MD,
Department of Neurological Surgery,
Methodist Hospital,
6550 Fannin St Suite 489,
Houston, TX 77030 USA.
Email: nhoang01@gmail.com

Received, February 11, 2022.
Accepted, September 7, 2022.
Published Online, November 10, 2022.

BACKGROUND: Manipulation of the pituitary stalk, posterior pituitary gland, and hypothalamus during transsphenoidal pituitary adenoma resection can cause disruption of water electrolyte regulation leading to diabetes insipidus (DI).

OBJECTIVE: To determine whether pituitary stalk stretch is an independent risk factor for postoperative DI after pituitary adenoma resection.

METHODS: A retrospective review was performed of patients undergoing endoscopic endonasal resection of pituitary macroadenoma between July 2010 and December 2016 by a single neurosurgeon. We analyzed preoperative and postoperative imaging metrics to assess predictors for postoperative DI.

RESULTS: Of the 234 patients undergoing resection, 41 (17.5%) developed postoperative DI. DI was permanent in 10 (4.3%) and transient in 31 (13.2%). The pituitary stalk stretch, measured as the change in stalk length from preoperative to postoperative imaging, was greater in the DI compared with the non-DI group (10.1 mm vs 5.9 mm, $P < .0001$). The pituitary stalk stretch was associated with DI with significant difference in mean pituitary stalk stretch between non-DI group vs DI group (5.9 mm vs 10.1 mm, $P < .0001$). Multivariate analysis revealed that pituitary stalk stretch >10 mm was a significant independent predictor of postoperative DI [odds ratios = 2.56 (1.10-5.96), $P = .029$]. When stratified into transient and permanent DI, multivariable analysis showed that pituitary stalk stretch >10 mm was a significant independent predictor of transient DI [odds ratios = 2.71 (1.0-7.1), $P = .046$] but not permanent DI.

CONCLUSION: Postoperative pituitary stalk stretch after transsphenoidal pituitary adenoma surgery is an important factor for postoperative DI. We propose a reconstruction strategy to mitigate stalk stretch.

KEY WORDS: Pituitary, Pituitary stalk, Infundibulum, Endoscopic, Endonasal, Diabetes insipidus, Macroadenoma, Skull base, Adenoma

Operative Neurosurgery 24:248–255, 2023 https://doi.org/10.1227/ons.0000000000000501

Manipulation of the pituitary stalk, posterior pituitary gland, and hypothalamus during transsphenoidal pituitary adenoma resection can cause disruption of water electrolyte regulation through alterations in antidiuretic hormone (ADH) release, leading to transient or permanent diabetes insipidus (DI). The incidence of postoperative DI varies from 2% to 60%,[1-4] with permanent DI occurring less frequently in 2% to 10% of patients.[1,3,5] Postoperative DI contributes to increased morbidity and longer hospitalization stay.[6] Prompt clinical diagnosis is critical for fluid and sodium balance maintenance requiring close monitoring postoperatively.[7] Our group previously identified 3 preoperative imaging characteristics that significantly predicted postoperative DI.[8] Patients with a pituitary adenoma that has a large maximum diameter and extensive suprasellar encroachment with vision changes have a higher incidence of DI.

ABBREVIATIONS: ADH, antidiuretic hormone; **CM,** collagen matrix; **CSF,** cerebral spinal fluid; **DI,** diabetes insipidus; **TSH,** thyroid-stimulating hormone.

We hypothesized that larger tumor size, suprasellar extension, and vision changes may be associated with increased displacement of the pituitary gland and stalk and a greater change in stalk length/stretch after surgery. Indeed, after

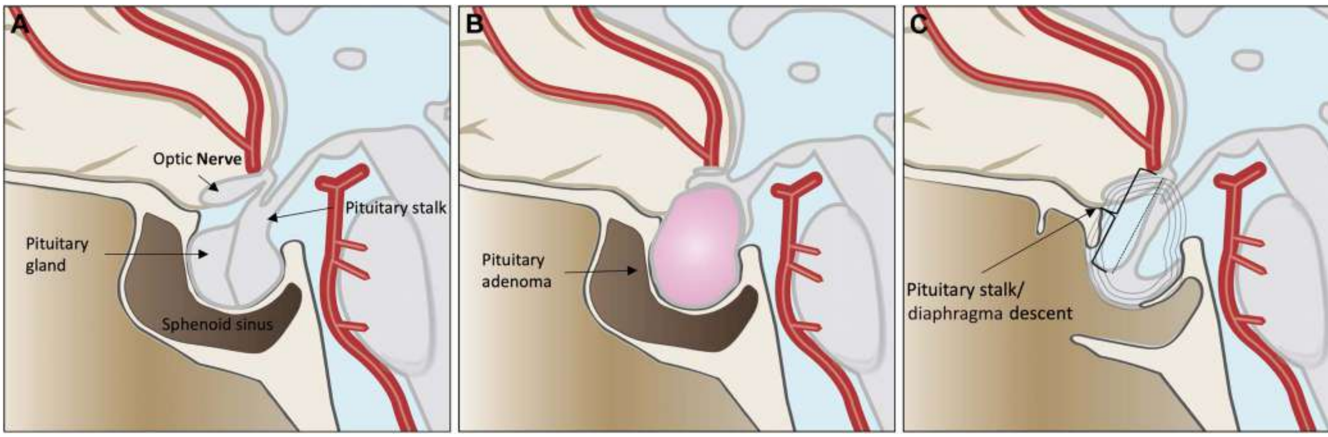


FIGURE 1. *Schematic of the pituitary stalk stretch after transsphenoidal pituitary adenoma resection.* **A**, *Schematic of the sella.* **B** *and* **C**, *Large pituitary adenomas with suprasellar extension can displace the optic nerve and pituitary gland upward causing visual symptoms and can lead to pituitary stalk stretch after resection. Pituitary stalk stretch is measured as the descent of the pituitary stalk/gland on* **B**, *preoperative and* **C**, *postoperative imaging.*

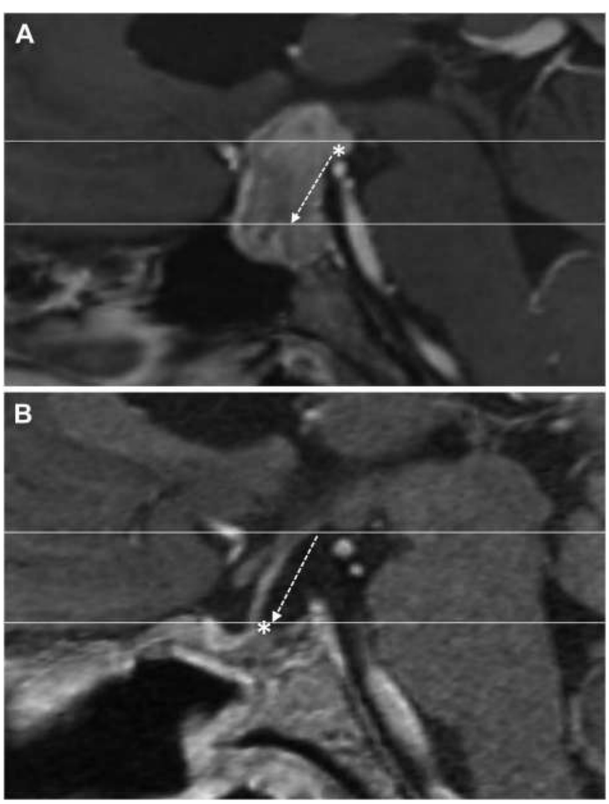


FIGURE 2. *Representative case of a patient with pituitary macroadenoma with* **A**, *preoperative MRI T1 with contrast and* **B**, *postoperative MR T1 with contrast. The descent of the pituitary gland and pituitary stretch is measured as displacement on the preoperative and postoperative position of the pituitary stalk/gland immediately after surgical resection.*

removal of the tumor, the stalk will then descend, leading to rapid stretching of the stalk that may contribute to DI. We defined a new parameter on MR imaging that we call pituitary stalk stretch, which is calculated by measuring the position of the stalk insertion into the posterior gland between preoperative and postoperative MRI with this displacement defined as the pituitary stalk stretch after resection. We hypothesized that increased stalk stretch may be related to increased incidence of DI and that reconstruction techniques that limit stalk stretch may decrease the rate of DI after transsphenoidal resection.

METHODS

This study was conducted after approval from Institutional Review Board, and patient consent was not required for this retrospective review. An electronic database was queried to identify 234 patients who underwent endoscopic endonasal surgery for pituitary macroadenoma performed by a single neurosurgeon between August 2010 and December 2016, before reconstruction technique changes to limit stalk stretch. Electronic medical records were reviewed to obtain preoperative characteristics that included demographic information, visual symptoms, anterior and posterior pituitary function, preoperative prolactin level, functional status of the tumor, and imaging metrics including maximal tumor diameter, tumor extension, suprasellar extension, and position of the pituitary stalk. Postoperative parameters collected include tumor pathology, intraoperative cerebral spinal fluid (CSF) exposure or leak, postoperative CSF leak, postoperative diagnosis of DI, and imaging metrics of pituitary stalk stretch.

Radiological Evaluation

Preoperative and postoperative radiological evaluation of pituitary adenomas was assessed on 1.5 or 3.0-T MRI scanner within 48 hours postoperatively. T1-weighted postgadolinium contrast and T2-weighted

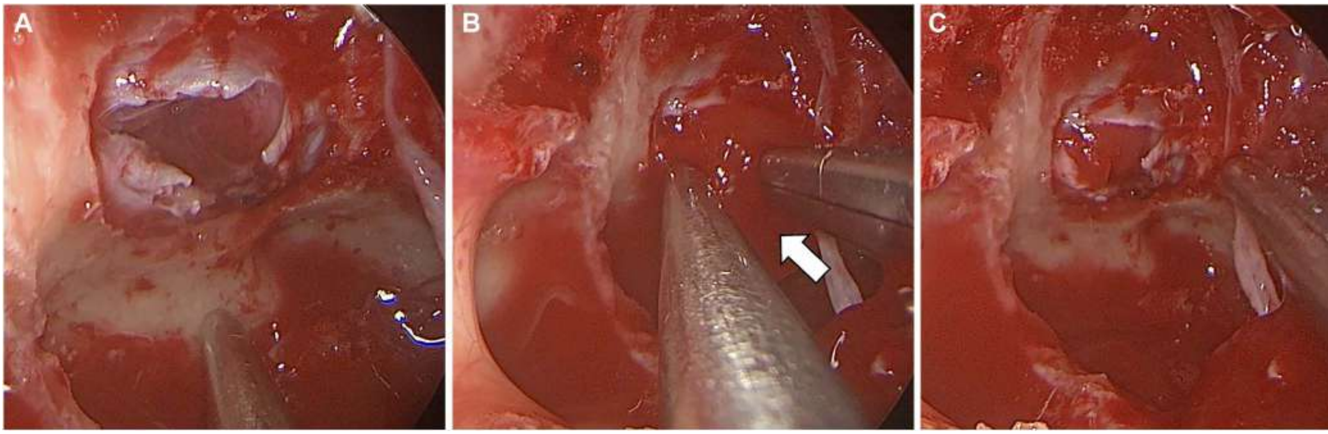


FIGURE 3. *Intraoperative placement of CM.* **A**, *The dural defect after removal of a pituitary adenoma.* **B**, *Placement of the CM (arrow) into the dural defect with a pituitary rongeur and suction.* **C**, *The dural defect after placement of the CM. CM, collagen matrix.*

imaging were reviewed in the coronal and sagittal planes. The extent of suprasellar extension was measured as tumor growth above the anterior skull base plane from the tuberculum to dorsum sellae on the sagittal MRI.

The pituitary stalk stretch was measured by the descent of the pituitary gland; this was measured as the displacement of the pituitary stalk and pituitary gland insertion point measured and overlayed on preoperative and postoperative MR imaging (Figures 1 and 2). For large adenomas, the

TABLE 1. Patient Demographics and Pituitary Macroadenoma Characteristics of Patients With and Without Postoperative DI

Variable	Postoperative DI (n = 41)	Non-postoperative DI (n = 193)	*P*
Age, y	54.5 (±13.7)	52.9 (±17.1)	
Sex			.931
Male	22 (53.7)	105 (54.4)	
Female	19 (46.3)	88 (45.6)	
Race			.092
White	27 (65.9)	155 (80.3)	
African American	10 (24.4)	28 (14.5)	
Hispanic	3 (7.3)	3 (1.6)	
Asian	0 (0.0)	3 (1.6)	
Others	1 (2.4)	4 (2.1)	
Clinical diagnosis			.946
Nonfunctioning	32 (78.0)	143 (74.1)	
Cushing disease	2 (4.9)	9 (4.7)	
Acromegaly	4 (9.8	20 (10.4)	
Prolactinoma	3 (7.3)	19 (9.8)	
TSH-oma	0 (0.0)	2 (1.0)	
Size and extension			
Giant macroadenoma	21 (51.2)	48 (23.8)	.001
Suprasellar extension	35 (85.4)	135 (69.9)	.051
Cavernous sinus extension	17 (41.5)	74 (38.3)	.71
Other extension	8 (19.5)	27 (14.0)	.368
Miscellaneous			
Visual abnormalities	22 (53.7)	61 (31.6)	.07
Panhypopituitarism	8 (19.5)	23 (11.9)	.22
Hyperprolactinemia	9 (22.0)	46 (23.8)	.533
Intraoperative CSF exposure	22(53.7)	77 (39.9)	.105
Postoperative CSF leak	3 (7.3)	8 (4.1)	.383

CSF, cerebral spinal fluid; DI, diabetes insipidus; TSH, thyroid-stimulating hormone.

stalk position on preoperative imaging may be deformed and is estimated as the midpoint of enhancement on MR T1-weighted. Measurements were made by the lead author under the supervision of a neuroradiologist blinded to clinical outcome of DI.

Diagnostic Criteria

A standardized inpatient monitoring protocol was used in all post-operative patients that included laboratory testing of urine osmolality, urine specific gravity, and serum sodium every 6 hours for 48 hours after surgery. The diagnostic criteria for DI were from the intake and output record showing >250 cc of urine output per hour for at least 2 hours, urine osmolality of <200 mOsm/kg, and urine specific gravity <1.005 or a serum sodium >143 mmol/L. Transient DI is defined as patients who required symptomatic DI treatment for <3 months from the day of surgery. Permanent DI is defined as treatment requiring desmopressin for >3 months from surgery.[8]

Statistical Analysis

Statistical analysis was performed with SPSS version 27. Independent *t* test was used to evaluate differences between 2 continuous independent groups with parametric data. The Pearson χ^2 test was used to evaluate for intergroup differences, including demographic and outcome nominal variables. Two-sided *P* values were reported, and a value less than 0.05 was considered to be statistically significant. Ordinary one-way analysis of variance was used to assess differences among groups with extent of suprasellar extension, descent of diaphragma, and maximum tumor diameter. To identify independent risk factors for postoperative DI, variables were included in the univariate and then multivariable model if the *P* value was ≤.05 in logistic regression analysis. Odds ratios (ORs) were computed using logistic regression analysis including the independent predictors of postoperative DI. Variance inflation factor values were used to measure multicollinearity among the variables that were statistically significant in the univariate analyses ($P < .05$). Variables with variance inflation factor of >2 were excluded from the logistic regression model.

Sellar Floor Buttress With CM Reconstruction Technique

We have adopted a strategy[9] of buttressing the pituitary gland and reconstructing the sella floor and tumor cavity with collagen matrix (CM) (DuraGenR Plus Matrix, Integra LifeSciences Corporation) to prevent pituitary stalk stretch. CM were cut to the appropriate sizes and placed into the sellar cavity to fill the resultant dead space after resection. CM is placed until there is slight herniation of the CM out of the dural defect signifying adequate buttressing of the arachnoid, diaphragma, and pituitary stalk. Intraoperative pictures demonstrating placement of the CM are shown in Figure 3A-3C.

RESULTS

Of the 234 patients with pituitary macroadenoma who underwent a transsphenoidal endoscopic endonasal approach for resection, 41 (17.5%) developed postoperative DI. Of these

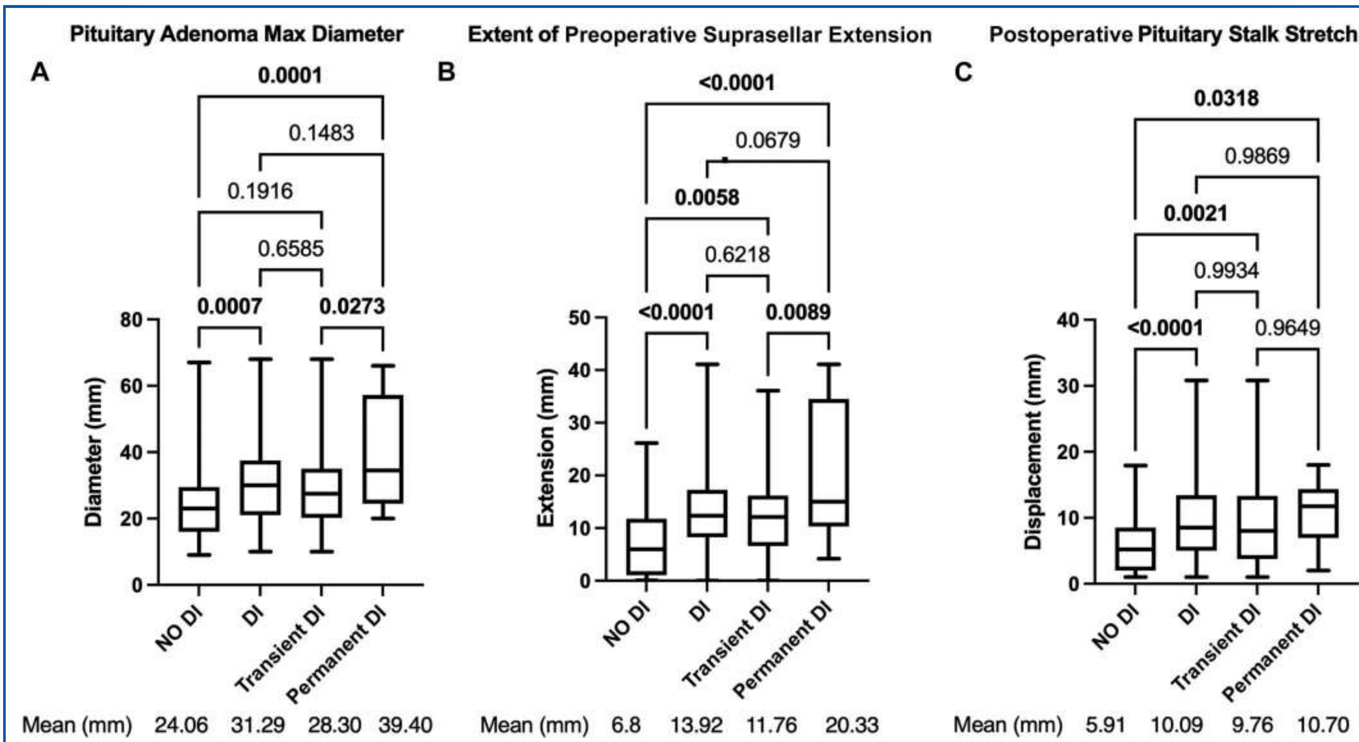


FIGURE 4. *Preoperative and postoperative MRI measurements within the patient cohort.* **A**, *Comparison of pituitary maximum diameters among patients with no DI, transient DI, permanent DI, and combined transient and permanent DI.* **B**, *Comparison of preoperative suprasellar extension among patients with and without DI.* **C**, *Comparison of the pituitary stalk stretch among patients with and without DI. DI, diabetes insipidus.*

TABLE 2. Predictive Risk Factors for Postoperative DI (total, transient, and permanent)

Variable	B	Odds ratio for postoperative total DI Univariate	95% CI	*P* value	B	Odds ratio for postoperative total DI Multivariate	95% CI	*P* value	B	Odds ratio for postoperative transient DI Multivariate	95% CI	*P* value	B	Odds ratio for postoperative permanent DI Multivariate	95% CI	*P* value
Size and extension																
Giant macroadenoma	1.15	3.17	1.58-6.35	.001	0.73	2.07	0.94-4.58	.071	0.26	1.30	0.47-3.58	.610	1.42	4.13	0.74-23.19	.107
Suprasellar extension	0.89	2.44	0.97-6.13	.057	0.24	1.27	0.46-3.46	.646	0.28	1.31	0.43-3.94	.630	0.09	1.1	0.11-10.79	.930
Cavernous sinus extension	0.13	1.14	0.57-2.26	.710												
Other extension	0.39	1.49	0.62-3.57	.370												
Miscellaneous																
Visual abnormalities	0.92	2.51	1.26-4.97	.009	0.55	1.74	0.81-3.72	.156	0.37	1.45	0.61-3.47	.390	1.00	2.73	0.53-14.18	.230
Panhypopituitarism	0.55	1.73	0.71-4.20	.227												
Hyperprolactinemia	−0.26	0.76	0.34-1.76	.533												
Intraoperative CSF exposure	0.56	1.75	0.88-3.44	.108												
Postoperative CSF leak	0.6	1.83	0.47-7.20	.390												
Pituitary stalk stretch >10 mm	1.46	4.3	2.08-8.89	.0001	0.94	2.57	1.10-5.96	.029	0.99	2.71	1.0-7.14	.046	0.841	2.32	0.45-11.89	.310

CSF, cerebral spinal fluid; DI, diabetes insipidus.
Logistic regression analysis of predictive variables for postoperative DI, transient DI, and permanent DI.

patients, 10 patients experienced permanent DI (4.3%). 31 patients (13.2%) had transient DI that was treated symptomatically and weaned off desmopressin within 3 months of discharge. There was no significant difference between patients who experienced postoperative DI for age, sex, race, or pituitary adenoma pathologic diagnosis (Table 1).

Both tumor size and tumor extension contributed to differences in the development of postoperative transient and permanent DI (Table 1). Giant macroadenomas (>4cm) were more common in patients who developed postoperative DI, 51.2%, compared with 23.8% in patients who did not develop DI (P = .001). There was a significant difference in suprasellar extension between postoperative DI and non-DI groups, 85.4% vs 69.9%, respectively, P = .05. Lateral cavernous sinus and inferior clival tumor extension was not significant between groups. Presurgical complaints of visual abnormalities were evaluated as a clinical marker for suprasellar extension and pituitary stalk compression. Patients with visual complaints at presentation had a significantly higher incidence of postoperative DI (53.7% vs 31.6%; P = .007). Presurgical pituitary dysfunction characterized by panhypopitutarism and hyperprolactinemia was not associated with postoperative DI among groups. Intraoperative or postoperative CSF leak was not associated with DI (P = .105).

Given the association of tumor size and suprasellar extension with postoperative DI, the radiographic tumor dimensions and extension were assessed (Figure 4). Larger maximum tumor diameter was associated with any postoperative DI and increased risk of permanent DI (Figure 3A). There was a significant difference between maximum diameter in the non-DI group vs DI group (24.1 mm vs 39.4 mm, P = .0007), non-DI and permanent DI group (24.1 mm vs 39.4 mm, P = .0001), and transient DI vs permanent DI group (28.3 mm vs 39.4 mm, P = .027). Similarly, suprasellar extension was significantly associated with the risk of any DI and permanent DI (Figure 4B). There was a significant difference in mean suprasellar extension between the non-DI group vs DI group (6.8 mm vs 13.9 mm, P < .0001), non-DI and permanent DI group (6.8 mm vs 20.3 mm, P < .0001), and transient DI vs permanent DI group (11.7 mm vs 20.3 mm, P = .008).

Pituitary stalk stretch was measured by the descent of the infundibular insertion into the posterior pituitary gland between preoperative and postoperative MRI (Figures 1 and 2). This variable assessed the degree of stretching of the axonal outflow fibers that connect the median eminence to the neurohypophysis through the infundibulum. The pituitary stalk stretch was significantly associated with postoperative DI (Figure 4C). There was a significant difference in mean pituitary stalk stretch between the non-DI group vs DI group (5.9 mm vs 10.1 mm, P < .0001), non-DI and transient DI group (5.9 mm vs 9.7 mm, $P \leq$ .002), and non-DI vs permanent DI group (5.9 mm vs 10.7 mm, P = .032).

Logistic regression for significant predictors for postoperative DI was assessed. Table 2 lists possible predictors based on size, extension, clinical characteristics, and pituitary stalk stretch. The pituitary stretch threshold of 10 mm was chosen as the mean displacement of the pituitary stalk that contributed to development of DI postoperatively (Figure 4C).

Univariate analysis showed that giant macroadenoma [OR = 3.17 (1.58-6.35), P = .001], suprasellar extension [OR = 2.44 (0.97-6.13), P = .050], visual abnormalities at presentation [OR = 2.51 (1.26-4.97), P = .009], and a pituitary stalk stretch >10 mm [OR = 4.3 (2.08-8.89), P = .0001] were significant predictors of postoperative DI. Multivariable analysis showed that a pituitary stalk stretch >10 mm was a significant independent predictor of postop DI [OR = 2.56 (1.10-5.96), P = .029]. When stratified into transient and permanent DI, multivariable analysis showed that pituitary stalk stretch >10 mm was a significant independent predictor of transient DI [OR = 2.71 (1.0-7.1), P = .046] but not permanent DI.

DISCUSSION

We previously identified 3 risk factors for postoperative DI that included visual abnormalities, large maximum tumor diameter, and suprasellar extension[8] which as a whole are clinical and radiological markers for compression of the neurohypophysis and pituitary stalk. Schreckinger et al[6] evaluated 172 endoscopic transsphenoidal surgeries and found that tumor volume and histopathology of the Rathke cleft cyst and craniopharyngioma were statistically significant independent risk factors for DI. Similarly, Chohan et al[11] assessed surgical outcomes after resection of giant pituitary adenomas. They showed a higher incidence of permanent DI among giant pituitary adenomas (18%) and that preoperative transverse diameters measuring >4 cm predicted development of postoperative DI on multivariable analysis.[10,11] Similarly, Araujo-Castro et al[12] in a series of 241 patients undergoing transsphenoidal pituitary resection found that the risk for postoperative DI was higher in patients younger than 65 years with gross total tumoral resection and diaphragma opening during pituitary resection. Once postoperative DI developed, the risk of permanent DI increased in those patients with larger pituitary adenoma diameter, especially in those greater than 30 mm. Moreover, diaphragma opening during surgery predicted long-term DI, independent of pituitary tumor size.[12] Krogh et al[13] looked at readmission after transsphenoidal surgery because of delayed hyponatremia. The risk of hyponatremia 1 week postsurgery was increased in patients with a tumor with suprasellar extension abutting the optic chiasm.[13] A mechanistic model of DI and hyponatremia remains unclear, but it appears that tumors that are large and extend into the suprasellar space compressing the neurohypophysis, pituitary stalk, and hypothalamus may contribute in some degree to postoperative DI.

Compression of these structures may not contribute itself to preoperative pituitary dysfunction, but we hypothesize that it does prime the neurohypophysis for dysfunction postoperatively because of subsequent involution of the gland that contributes to stretching of the axonal pathways in the pituitary stalk.

Within our cohort, we found that significant sinking of the infundibular stem as it inserts into the posterior gland is an independent risk factor for postoperative DI. We found a significant difference in mean pituitary stalk stretch between the non-DI group vs DI group (5.9 mm vs 10.1 mm, $P < .0001$). Using the mean of 10 mm as a threshold, logistic regression showed that a displacement greater than 10 mm was an independent risk factor for postoperative DI (Table 2).[14] This risk holds true for transient DI only, and we hypothesized that stalk stretch is a transitory phenomenon in the perioperative period where stretching may lead to the disruption of the neurohypophysial tract disturbing the axonal outflow from the magnocellular neurons of the supraoptic and paraventricular nuclei terminating through the infundibular stem to the neurohypophysis. It is important to note that stalk stretch does not contribute to permanent stalk injury leading to permanent DI. While fleeting, transient DI still contributes to significant morbidity and length of hospital stay.

Pituitary stalk stretch may be a factor that contributes to the varying clinical presentations of water and electrolyte disturbance that is not entirely explained by mechanical injury from the loss of ADH secretion after manipulation of the neurohypophysis or ADH leakage from disrupted axons. Recently, Lin et al[14] published on this phenomenon of pituitary stretch independently of our group. They assessed the effect of diaphragma sellae sinking on postoperative hyponatremia after transsphenoidal surgery. Diaphragma sellae sinking along with large pituitary stalk deviation angle difference and longer length of pituitary stalk postoperatively was associated with the risk of hyponatremia. Although the sinking of the diaphragma sellae is a marker for pituitary stretch, this is not synonymous because there can be descent of the diaphragma without sinking of the pituitary stalk; this is seen when we observe the stalk at a position that is posterior to the tumor and not displaced superiorly preoperatively.

Sellar Floor Buttress With CM Reconstruction Technique

The routine use of intrasellar packing has been argued to be unnecessary, except, in the presence of intraoperative CSF leak because of the anecdotally low risk of symptomatic empty sella syndrome and its associated endocrinopathies.[15] We have found that stretching of the pituitary stalk from an acute loss of the sella floor can contribute to postoperative DI, and careful sellar reconstruction to prevent this phenomenon may be important. The descent of the posterior gland and resultant pituitary stalk stretch is a modifiable factor that is easily mitigated at the time of closure to prevent postoperative DI.

Different sellar reconstruction strategies have been described that include the use of autologous graft (fat, fascia, and mucoperiosteum), CM, hemostatic agents (gelatin foam, oxidized cellulose, and fibrin glue), and other packing materials to reconstruct the sellar floor.

We have adopted the strategy of buttressing the pituitary gland and reconstructing the sella and tumor cavity with CM (DuraGenR Plus Matrix, Integra LifeSciences Corporation) to prevent pituitary stalk stretch. Intraoperative pictures demonstrating placement of the CM are shown in Figure 3. The use of CM slows the pituitary stalks descent and provides several advantages over autologous fat graft which can cause infection, interfere with MRI interpretation postoperatively, lead to cranial nerve palsy, and increase operative time by requiring a separate incision.[16,17] Further prospective study to assess whether sellar reconstruction can affect postoperative DI will need to be performed.

Limitations

This is a retrospective, single-institution, and single-surgeon cohort and has the inherent limitations to this study design. The findings that postoperative DI is associated with postoperative pituitary stalk stretch may be improved with a prospective analysis of intrasellar packing to slow the descent of the gland after surgical resection.

CONCLUSION

Pituitary stalk stretch may be a mechanism that contributes to the varying clinical presentations of water electrolyte disturbances not entirely explained by mechanical injury alone. Pituitary stalk stretch is not a useful measurement done postoperatively. Its usefulness lies with the knowledge that in large pituitary macroadenomas where resection would lead to this stretching phenomenon; appropriate methods of intrasellar packing and perioperative surveillance of electrolyte abnormalities could prevent DI and its morbidity. Future studies are needed to determine whether reconstruction strategies with buttressing of the tumor cavity using CM will prevent pituitary stalk stretch.

Funding

This study did not receive any funding or financial support.

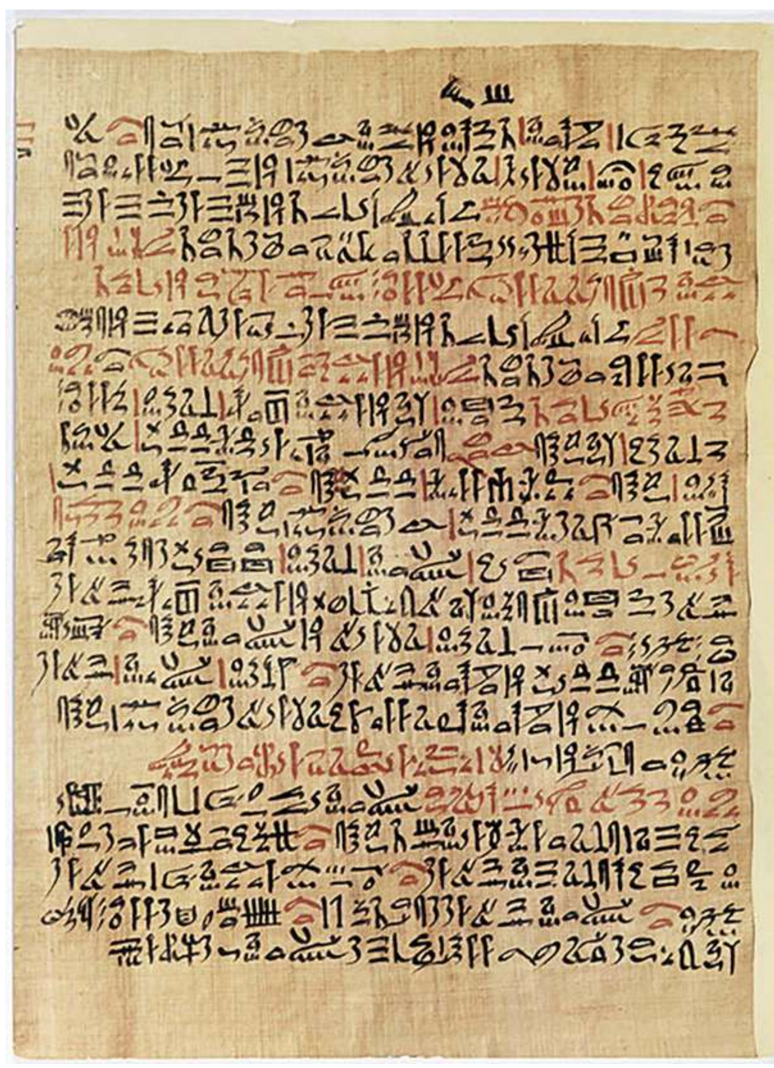
Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Prevedello has financial relationships with Stryker, Integra, and BK Medical and receives royalties from Mizuho, KLS Martin, and ACE Medical.

REFERENCES

1. Sorba EL, Staartjes VE, Voglis S, et al. Diabetes insipidus and syndrome of inappropriate antidiuresis (SIADH) after pituitary surgery: incidence and risk factors. *Neurosurg Rev.* 2021;44(3):1503-1511.
2. Qari FA, AbuDaood EA, Nasser TA. Diabetes insipidus following neurosurgery at a university hospital in Western Saudi Arabia. *Saudi Med J.* 2016;37(2):156-160.
3. Nemergut EC, Zuo Z, Jane JA, Laws ER. Predictors of diabetes insipidus after transsphenoidal surgery: a review of 881 patients. *J Neurosurg.* 2005;103(3):448-454.
4. Sigounas DG, Sharpless JL, Cheng DML, Johnson TG, Senior BA, Ewend MG. Predictors and incidence of central diabetes insipidus after endoscopic pituitary surgery. *Neurosurgery.* 2008;62(1):71-79.
5. Ajlan A, Abdulqader S, Achrol A, et al. Diabetes insipidus following endoscopic transsphenoidal surgery for pituitary adenoma. *J Neurol Surg B Skull Base.* 2017;79(2):117-122.
6. Schreckinger M, Walker B, Knepper J, et al. Post-operative diabetes insipidus after endoscopic transsphenoidal surgery. *Pituitary.* 2013;16(4):445-451.
7. Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. *Ther Adv Endocrinol Metab.* 2016;8(3):33-48.

8. Nayak P, Montaser AS, Hu J, Prevedello DM, Kirschner LS, Ghalib L. Predictors of post-operative diabete insipidus following endoscopic endonasal resection of pituitary adenoma. *J Endocr Soc.* 2018;2(9):1010-1019.
9. Shahein M, Montaser AS, Barbero JMR, et al. Collagen matrix with mucoperiosteum graft as an effective fatless flapless reconstruction after endoscopic pituitary adenoma resection. *Oper Neurosurg.* 2020;19(6):E573-E580.
10. Lobatto DJ, de Vries F, Najafabadi AHZ, et al. Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review. *Pituitary.* 2018;21(1):84-97.
11. Chohan MO, Levin AM, Singh R, et al. Three-dimensional volumetric measurements in defining endoscope-guided giant adenoma surgery outcomes. *Pituitary.* 2016;19(3):311-321.
12. Araujo-Castro M, Mariño-Sánchez F, Cancela AA, Fernández AG, Duque SG, Berrocal VR. Is it possible to predict the development of diabetes insipidus after pituitary surgery? Study of 241 endoscopic transsphenoidal pituitary surgeries. *J Endocrinol Invest.* 2021;44(7):1457-1464.
13. Krogh J, Kistorp CN, Jafar-Mohammadi B, Pal A, Cudlip S, Grossman A. Transsphenoidal surgery for pituitary tumours: frequency and predictors of delayed hyponatraemia and their relationship to early readmission. *Eur J Endocrinol.* 2018; 178(3):247-253.
14. Lin K, Li J, Lu L, et al. Diaphragma sellae sinking can predict the onset of hyponatremia after transsphenoidal surgery for pituitary adenomas. *J Endocrinol Invest.* 2021;44(11):2511-2520.
15. Couldwell WT, Kan P, Weiss MH. Simple closure following transsphenoidal surgery: technical note. *Neurosurg Focus.* 2006;20(3):1-3.
16. Kremer P, Forsting M, Ranaei G, et al. Magnetic resonance imaging after transsphenoidal surgery of clinically non-functional pituitary macroadenomas and its impact on detecting residual adenoma. *Acta Neurochir.* 2002;144(5):433-443.
17. Kong DS, Kim HY, Kim SH, et al. Challenging reconstructive techniques for skull base defect following endoscopic endonasal approaches. *Acta Neurochir.* 2011; 153(4):807-813.



Ebers papyrus, an Egyptian medical papyrus of herbal knowledge dating to c. 1550 BCE. The treatment for asthma suggested in the Ebers papyrus is a mixture of herbs heated on a brick so that the patient could inhale their fumes. By Unknown scribe. This faithful reproduction is in the public domain. Image from https://egypt-museum.com/the-ebers-papyrus.