# Intrasellar Pressure is Related to Endocrine Disturbances in Patients with Pituitary Tumors

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■ OBJECTIVE: **The aim of this study was to investigate the association between intraoperative intrasellar pressure (ISP) and pre- and postoperative endocrine disturbances with focus on hyperprolactinemia and hypopituitarism in patients with pituitary tumors.**

■ METHODS: **The study is a consecutive, retrospective study with ISP collected prospectively. One hundred patients operated with transsphenoidal surgery due to a pituitary tumor, who had their ISP measured intraoperatively, were included. Data on patient endocrine status preoperatively and from 3-month postoperative follow-up were collected from medical records.**

■ RESULTS: **The risk of preoperative hyperprolactinemia in patients with nonprolactinoma pituitary tumors increased with ISP (unit odds ratio 1.067, n = 70) ($P = 0.041$). Preoperative hyperprolactinemia was normalized at 3 months after surgery. Mean ISP was higher in patients with preoperative thyroid-stimulating hormone (TSH) deficiency (25.3 ± 9.2 mmHg, n = 37) than in patients with intact thyroid axis (21.6 ± 7.2 mmHg, n = 50) ($P = 0.041$). No significant difference in ISP was found between patients with and without adrenocorticotropic hormone(ACTH) deficiency. No association was found between ISP and postoperative hypopituitarism at 3 months after surgery.**

■ CONCLUSIONS: **In patients with pituitary tumors, preoperative hypothyroidism and hyperprolactinemia may be associated with higher ISP. This is in line with the theory of pituitary stalk compression, suggested to be mediated by an elevated ISP. ISP does not predict the risk of postoperative hypopituitarism 3 months after surgical treatment.**

## INTRODUCTION

The pituitary gland, located in the sella turcica at the base of the skull, has a key regulatory role in several endocrine systems affecting processes like growth, metabolism, and reproduction.[1] The endocrine functions of the pituitary gland are largely regulated by the hypothalamus via the hypothalamic-pituitary portal system.[2] The pituitary gland is surrounded by solid structures in multiple directions and space-occupying pituitary tumors have been reported to affect the intrasellar pressure (ISP), which could potentially alter the pituitary function.[3,4]

We have recently shown that ISP increases with larger pituitary tumor volume, and that lateral tumor growth into the cavernous sinus is associated with higher ISP.[5] Previous studies have indicated correlations between ISP elevation and pituitary function, both hyperprolactinaemia and hypopituitarism, in patients with nonfunctioning adenomas.[6-9] There is a documented risk of permanent hypopituitarism after pituitary surgery, and postoperative hypopituitarism has been associated with higher mortality due to adrenal crisis.[10] Evaluation of hormonal status after pituitary surgery is thus often performed 6–8 weeks postoperatively.[11] Findings of previous studies investigating pituitary function and endocrine recovery after surgery of nonfunctional pituitary adenoma have not been consistent.[12-14]

**Key words**
- Hyperprolactinemia
- Hypopituitarism
- Intrasellar pressure
- Pituitary adenoma

**Abbreviations and Acronyms**
ACTH: Adrenocorticotropic hormone
FSH: Follicle stimulating hormone
GH: Growth hormone
IGF-1: Insulin-like growth factor −1
ISP: Intrasellar pressure
LH: Luteinizing hormone
OR: Odds ratio
TSH: Thyroid stimulating hormone

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This justifies exploration of additional predictive factors for endocrine outcome after surgical treatment.

The aim of this study was to explore if there was an association between ISP at surgery and pre- and postoperative pituitary function, i.e., hypopituitarism and hyperprolactinemia, with the further question if intraoperative ISP measurement could be used to predict postoperative endocrine recovery. We hypothesized that higher ISP was associated with preoperative hypopituitarism and higher prolactin levels. We also hypothesized that high ISP was associated with pituitary damage and thus increased the risk of postoperative hypopituitarism.

## METHOD

### Study Population

The study was a single-center, consecutive, retrospective, observational study with ISP data collected prospectively. We included patients operated for suspected pituitary adenoma at the Neurosurgical Department, Umeå University Hospital, Umeå, Sweden in 2009–2015. All of them, except patients with Cushing's disease, had their ISP measured intraoperatively. This resulted in a consecutively collected population of 100 patients.

### Surgery and ISP Measurements

The surgical approach was transsphenoidal tumour extirpation, either microscope-assisted through lateral rhinotomy or using the endoscopic transnasal-transsphenoidal approach. All procedures during these years (2009–2015) were performed with one neurosurgeon as the responsible main surgeon, and ISP measurements were included as part of the standardized surgical procedure at the clinic. Surgery was performed under standard neuroanaesthesia with oral intubation. Patients were normoventilated with $pCO_2$ levels at 4.6–5.5 kPa. ISP was measured before start of tumor resection using an intracranial pressure monitoring device (Codman MicroSensor, Codman & Shurtleff Inc, Raynham, MA USA).

This device's accuracy is well-documented, and it is used clinically as a standard method for intracranial pressure monitoring.[15-17] A minor bone opening, about 1.5 mm, was made with a high-speed drill, followed by a sharp cut of the capsule without allowing any tissue loss. After calibration, the sensor was inserted into the sellar room within the tumor, with extra attention paid to ensure no leakage of intrasellar content. ISP values were determined after pressure fluctuations had settled. After ISP measurement and removal of the Codman MicroSensor, the operation proceeded with further removal of bone from the sellar floor and intracapsular tumor resection.

### Data Collection

All patients were preoperatively investigated in accordance with the standardized procedure at our clinic. This included preoperative computed tomography of the brain and sella, and magnetic resonance imaging with and without gadolinium contrast enhancement. Volume calculations were performed using Automatic Sectra Volume Tool (Sectra Workstation, IDS7, ver 23.1). All patients had a preoperative endocrine evaluation and the decision to operate was made at a multidisciplinary treatment planning conference with a pituitary surgeon, an endocrinologist, and a neuroradiologist (and neuropathologist). Pituitary function was evaluated clinically and with laboratory tests before and 3 months after pituitary surgery.

Data, including symptoms, medications at the time of surgery, immunohistochemical diagnoses, and lab results, including hormone levels, were collected from patient medical records during the preoperative investigation. The endocrine evaluation was performed before the surgical decision was made, usually 1–12 weeks before the patient was admitted to the neurosurgical department. Preoperative patient status was collected from medical records, including both from preoperative endocrine evaluations and from the neurosurgical admission. In the case of repeated tests, the results closest in time to surgery were used.

Postoperative endocrine assessment test results, including need for pituitary hormone replacement therapy, were gathered from the medical records of the routine 3-month postoperative follow-up performed by an endocrinologist.

### Endocrine Assessment

Assessment of the pituitary axes included plasma or serum levels of prolactin, thyroid-stimulating hormone (TSH), free thyroxine (fT4), cortisol at 08:00–09:00 AM or peak cortisol after an adrenocorticotropic hormone (ACTH) test, testosterone or oestradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and insulin-like growth factor 1 (IGF-1). As data regarding hormone levels were gathered retrospectively over the course of several years in the catchment area in northern Sweden, serum or plasma hormone levels were analyzed with different methods and somewhat differing reference intervals, although always at accredited clinical laboratories. To adjust for these differences, levels of prolactin were divided by the upper limit of normal for the laboratory analysis method, and gonadotrophins, fT4, TSH and cortisol were categorized as within, below or above the reference interval for the specific method used. In the majority of the patients in this study, the cortisol axis was evaluated with an ACTH test, deemed normal if peak plasma cortisol was >500 nmol/L. In a few patients, the treating endocrinologist considered the cortisol axis normal based on a sufficiently high morning plasma cortisol level and thus no ACTH test needed to be performed. As IGF-1 reference values vary with age and sex, an IGF-1 standard deviation score (SDS) was calculated for each value, using the calculation evaluated in Chanson et al.[18] When assessing the hormonal axes, the endocrinologist's conclusion on whether or not replacement therapy was indicated was also considered.

Hypopituitarism was defined as hormonal deficiency in one or multiple pituitary endocrine axes. In the current study, the definitions of deficiency in the separate axes after endocrine evaluation were: Cortisol axis—ACTH test with a peak plasma cortisol <500 nmol/L and/or initiation/continuation of cortisol replacement therapy. Patients with sufficient morning plasma cortisol levels (>450 nmol/L) were considered nondeficient. Thyroid axis—plasma fT4 below lower limit of normal with low or normal plasma TSH and/or initiation/continuation of thyroid hormone replacement therapy. Gonadotrophin axis—for males: testosterone below the lower limit of normal with plasma LH not exceeding the upper limit of normal and/or initiation/continuation of testosterone replacement therapy; for postmenopausal females: plasma LH and/or FSH below lower limit of normal for postmenopausal

females and/or initiation/continuation of hormone replacement therapy (premenopausal females were excluded from this analysis as menstrual history data was not available for many patients). GH-IGF-1 axis—IGF-1 SDS <2.0 for the patient's age and sex.

### Exclusions and Group Analyses

Exclusions are illustrated in Figure 1.

One subject was excluded from all analyses as the sellar walls were intraoperatively considered too damaged for reliable measurement of ISP.

Two subjects with very high ISP (>50 mmHg) were considered to be extreme outliers and therefore also excluded from statistical analysis.

Patients with hormone-producing adenomas were excluded from analyses of hormone deficiency in that axis, i.e., patients with acromegaly were excluded from GH axis analyses. A few cases which were immunohistochemically positive for ACTH (n = 2), TSH (n = 1) or prolactin (n = 1) were excluded from analysis of the relevant axis, although no clinical or biochemical signs of hormonal overproduction were found.

Another 8 patients were excluded from the analyses on pre- and postoperative hormone deficiency because they had previously been diagnosed with a disease causing a hormone deficiency and/or need for hormone replacement therapy. This included 4 patients on hormone replacement therapy after previous pituitary surgery and 4 subjects on levothyroxine for hypothyroidism. Thus, after exclusions, all patients in the study population underwent their first pituitary surgery.

Several medications are known to affect serum prolactin levels, including antipsychotics, antidepressants, hormonal replacements, antiemetics, cabergoline, L-Dopa, and dopamine.[19,20] For this reason, all analyses regarding prolactin levels were made after exclusion of patients on any medication that could potentially affect prolactin levels (n = 15).

### Statistics

Independent t-tests were used for comparisons of mean ISP between 2 groups. Results are reported as mean ± standard deviation. Logistic regression analysis with ISP as the independent variable was used to analyze prediction (unit odds ratio (OR)) of hormonal deficiency pre- and postoperatively. JMP Statistics version 14.2 was used for statistical analysis of the laboratory data. A *P*-value of ≤ 0.05 was considered significant.

### Ethics

The study was approved by the Regional Ethics Review Board. It was conducted in accordance with the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

## RESULTS

### Characteristics

After initial exclusions, the study population consisted of 97 subjects, 53 males and 44 females, mean age 60.2 ± 14.8 yrs. The mean tumor volume was 6.1 $cm^3$, the mean maximal tumor

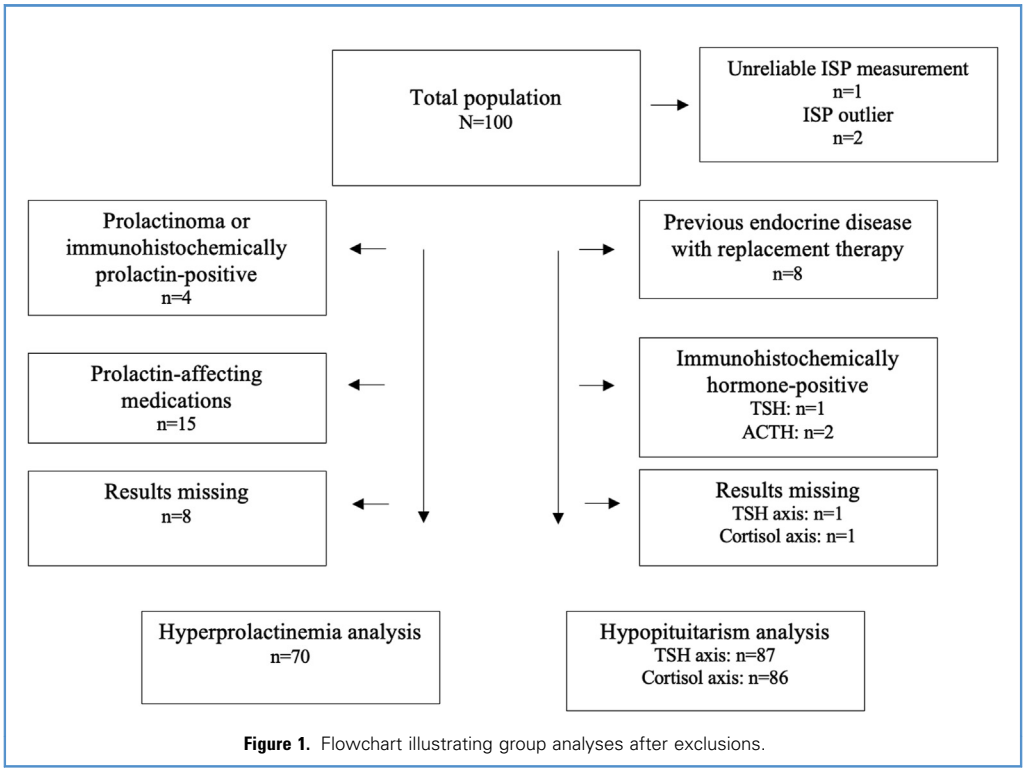


**Figure 1.** Flowchart illustrating group analyses after exclusions.

diameter 23.3 mm, and the population included 2 microadenomas and 95 macroadenomas. Tumors were classified according to the Hardy-classification, see Table 1.[21,22] The mean ISP was 22.9 ± 8.0 mmHg (95% CI 21.3–24.5), higher in males (24.6 ± 1.1 mmHg) than females (21.0 ± 1.2) (P = 0.0253). There was no correlation between ISP and age and there were no differences in mean age or sex between the groups with and without preoperative hyperprolactinemia or pre- and postoperative hypopituitarism. Five subjects were shown to have a histopathological diagnosis other than pituitary adenoma (2 subjects with benign cysts, 2 with pituitary inflammatory lesions, one with adenocarcinoma metastasis). The clinical diagnoses of the pituitary adenomas are presented in Table 2. In the histopathology with immunohistochemical analyses 2 silent corticotroph adenomas and one silent TSH-positive adenoma were found. Additionally, one nonprolactinoma tumor was immunopositive for prolactin at histopathology.

## ISP and Hyperprolactinemia

Among the 89 patients with documented preoperative prolactin levels, 19 were excluded: 4 were positive for prolactin biochemically and/or immunohistochemically, and another 15 used medications that could potentially affect prolactin levels. Of the remaining 70 patients, 34 (48%) had preoperative prolactin levels above the upper limit of normal, and a logistic regression analysis showed that the risk of preoperative hyperprolactinemia in this group increased with ISP (unit OR 1.067 [95% CI 1.005–1.130], P = 0.041). Accordingly, we found that mean ISP was higher in subjects with preoperative hyperprolactinemia (25.0 ± 9.0 mmHg, n = 34), compared with those without hyperprolactinemia (20.9 ± 7.0 mmHg, n = 36) (P = 0.037) (Figure 2). A sensitivity analysis re-including patients with medications potentially affecting prolactin levels did not alter these findings (unit OR 1.076 [95% CI 1.013–1.139], P = 0.022, n = 85). There was no difference in the occurrence of preoperative hyperprolactinemia between males and females.

**Table 1.** Shows the Anatomical Description of the Tumors in the Study Population, Including Both Tumour Volume and Diameter, and How the Tumors Were Classified According to the Hardy Classification

| Anatomical Description of Pituitary Tumors | | | | | | |
|---|---|---|---|---|---|---|
| | | | Mean | 95% CI | Max | Min |
| Tumor volume ($mm^3$) | | | 6.1 | 5.0–7.2 | 30.4 | 0.677 |
| Tumor maximal diameter (mm) | | | 23.3 | 21.8–24.7 | 49.0 | 7.5 |
| **Hardy Grade** | **I** | **II** | **III** | **IV** | **Missing/Inconclusive** | |
| N | 1 | 56 | 29 | 9 | 2 | |
| **Hardy Class** | **A** | **B** | **C** | **D** | **E** | **Missing/Inconclusive** |
| N | 18 | 19 | 10 | 6 | 41 | 3 |

**Table 2.** Distribution of Clinical Diagnoses of Pituitary Tumor in the Study Population (n = 97). The Group Non-adenoma Included 2 Subjects with Benign Cysts, 2 Subjects with Inflammatory Pituitary Mass Lesion and One Subject with Adenocarcinoma Metastasis

| Clinical Diagnosis of Pituitary Tumor | |
|---|---|
| **Diagnosis** | **Number of Patients** |
| Acromegaly | 9 |
| Gonadotropin-producing tumour | 1 |
| Prolactinoma | 3 |
| TSH-producing tumour | 0 |
| Clinically non-functioning tumour | 79 |
| Non-adenoma | 5 |
| Total | 97 |

At the 3-month postoperative follow-up, none of the included patients with available test results (n = 68) had elevated prolactin levels.

## ISP and Hypopituitarism

After exclusions, 87 patients had available preoperative evaluations of the thyroid axis and 86 patients of the cortisol axis, respectively.

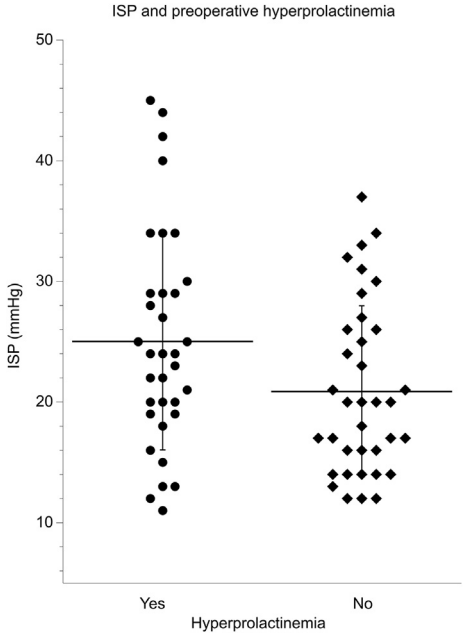


**Figure 2.** Mean intrasellar pressure (ISP) was higher in patients with preoperative hyperprolactinemia (25.0 ± 9.0 mmHg) than in patients with normal preoperative prolactin (20.9 ± 7.0 mmHg) (*P* = 0.037).

Of these, 37 (43%) were TSH-deficient and 25 (29%) were ACTH-deficient (Table 3). As preoperative evaluation of the GH axis (at least S/P-IGF-1) was missing in 28 (31%) and evaluation of the gonadal axis was missing in 54 (61%), preoperative deficiencies in these hormonal axes were not evaluated in relation to ISP.

Mean ISP was higher in patients with preoperative TSH deficiency (25.3 ± 9.2 mmHg) than in those with an intact thyroid axis (21.6 ± 7.2 mmHg) ($P = 0.041$) (Figure 3). In line with this, the risk of preoperative thyroid insufficiency increased with ISP (unit OR=1.057 [95% CI 1.003–1.112], $P = 0.045$, n = 87). The distribution of deficiency in the thyroid axis was not correlated with sex or age. No differences in ISP were found between those with or without deficiency in the cortisol axis (Table 3).

At the 3-month follow up, 61% of the patients were considered to have at least one remaining pituitary hormone deficiency in need of replacement therapy. The distribution of postoperative insufficiencies is listed in Table 4. Intraoperative ISP was not significantly different in patients with versus without deficiency in any of the hormonal axes at 3 months after surgery. Among patients with preoperative deficiency in the thyroid and cortisol axes, recovery of function was seen in 8/37 (22%) and 7/25 (28%) respectively. Among patients without preoperative deficiency in the thyroid axis 5/50 (10%) had developed a need for replacement therapy at 3 months postoperatively, the corresponding figure for the cortisol axis was 20/62 (32%). We found no differences in ISP between patients who recovered from a hormone deficiency in the thyroid or cortisol axes or who developed a new deficiency postoperatively, and those who did not.

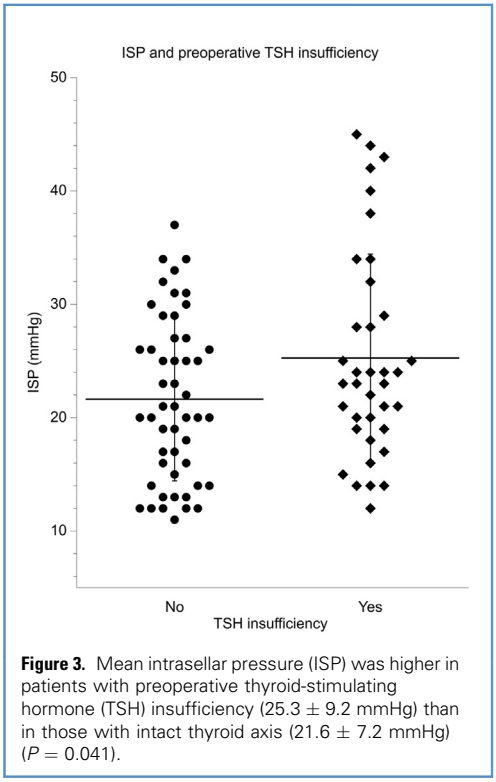


**Figure 3.** Mean intrasellar pressure (ISP) was higher in patients with preoperative thyroid-stimulating hormone (TSH) insufficiency (25.3 ± 9.2 mmHg) than in those with intact thyroid axis (21.6 ± 7.2 mmHg) ($P = 0.041$).

**Table 3.** Intrasellar Pressure (ISP) in Patients with and without Preoperative Deficiency in Thyroid and Cortisol Axes, respectively. ISP is Presented as Mean ± Standard Deviation. T-Tests Were Performed to Analyse the Differences in Mean ISP Between Patients with and without Hormone Deficiency in the 2 Axes

| Preoperative Hormone Deficiency | | | | |
|---|---|---|---|---|
| | Thyroid | | Cortisol | |
| Hormone deficiency | n | ISP (mmHg) | n | ISP (mmHg) |
| Yes | 37 | 25.3 ± 9.2 | 25 | 25.6 ± 9.5 |
| No | 50 | 21.6 ± 7.2 | 61 | 22.6 ± 7.5 |
| T-test | | $P = 0.041$ | | $P = 0.12$ |

The 2 outliers that were excluded from statistical analysis due to very high ISP (51 mmHg and 54 mmHg, respectively) both had panhypopituitarism (one of these subjects also had very low prolactin levels). One was diagnosed with a malignant sarcoma and one with an adenoma with atypical morphology.

## DISCUSSION

The main findings of this study were that preoperative hyperprolactinemia and preoperative thyroid insufficiency were associated with higher ISP at surgery. We found no association between intraoperative ISP and the risk of postoperative pituitary insufficiency.

We have recently shown a correlation between ISP and anatomical features, i.e., tumor volume and laterally invasive growth pattern.[5] In this study, we aimed to further increase the understanding of pathophysiological mechanisms underlying hormonal disturbances in patients with intrasellar tumors. The results strengthen the hypothesis that ISP is a factor that may affect pituitary function in patients with intrasellar mass lesions.

A novel approach in this study compared with in previous studies on ISP was to include the 3-month postoperative follow-up to explore ISP as a predictor of postoperative endocrine outcome. It has been suggested that, for example, younger age and mild preoperative hormonal deficit are associated with more favorable endocrine recovery.[23] We cannot, based on this study, conclude that ISP is a significant predictive factor for endocrine outcome after pituitary tumor surgery.

The finding that higher ISP is related to hypopituitarism and hyperprolactinemia in nonprolactinoma pituitary tumors, are in line with the results of previous studies.[4,8,9] However, these did not clearly consider or exclude other factors influencing prolactin levels, such as medication. The series performed on 49 patients by Arafah et al. in 2000[6] was the first study which presented robust results suggesting ISP to be the mechanism involved in endocrine imbalances by revealing a positive correlation between prolactin levels and ISP.

Our ISP values harmonize well with earlier data on ISP in this patient category.[3,8,9,24] For understandable reasons, 'normal' ISP

**Table 4.** Intrasellar Pressure (ISP) in Patients with and without Hormone Deficiency in the Thyroid, Cortisol, Growth Hormone (GH) or Gonadotrophin Axis at the 3-Month Postoperative Follow-up. ISP is Presented as Mean ± Standard Deviation. T-Tests Were Performed to Analyse the Differences in Mean ISP Between Patients with and without Hormone Deficiency in the 4 Axes

| Hormone Deficiency at 3-month Postoperative Follow-up | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Thyroid | | Cortisol | | GH | | Gonadotrophin | |
| Hormone Deficiency | n | ISP (mmHg) | n | ISP (mmHg) | n | ISP (mmHg) | n | ISP (mmHg) |
| Yes | 34 | 22.0 ± 7.3 | 38 | 23.3 ± 8.9 | 21 | 22.0 ± 8.0 | 18 | 25.2 ± 10.1 |
| No | 54 | 24.8 ± 9.1 | 50 | 22.9 ± 7.6 | 63 | 23.5 ± 7.9 | 69 | 22.5 ± 7.3 |
| t-test | | $P = 0.13$ | | $P = 0.81$ | | $P = 0.45$ | | $P = 0.34$ |

in people without intrasellar disease has never been explored, but is believed to be similar to the normal intracranial pressure,[8] which means that ISP in patients with a pituitary tumor seems to be elevated beyond normal intracranial pressure levels.[5] The rather interesting finding that males with pituitary tumors showed higher mean ISP than females was discussed in our previous publication based on the same population. No similar differences in ISP between sexes have been seen in earlier studies on ISP and no clear explanation for this has been found.[5,25,26] However, analyses have not shown any differences in the distribution of endocrine disturbances in relation to sex in this population, minimizing the risk of confounding.

The frequency of hyperprolactinemia, 48%, in patients with nonprolactinoma pituitary tumors after exclusion of subjects with prolactin-affecting medications, is in line with previous reports,[7,27] though it has been observed in up to 70% of these patients.[28,29] Compared with publications from much larger patient materials, we found a somewhat higher incidence of both preoperative TSH and ACTH insufficiency when the axes were analyzed separately.[23,30] However, looking at earlier studies on ISP, the incidence of preoperative deficiency in at least one axis is reported to be up to 67%, and it was up to 81% (TSH) and 62% (ACTH) in a population with large adenomas.[6,31] The rate of postoperative ACTH-deficiency in this series are somewhat high compared to what is reported.[23] This may be explained by the fact that the study mostly included large tumors and consequently higher rate of deficiencies. Another explanation could be that we used somewhat broader criteria to classify a patient as ACTH-deficient by including all patients continuing with replacement therapy after 3 months in this group.

The main theory to explain the development of hyperprolactinemia in patients with nonprolactinoma tumours is the so-called 'stalk compression syndrome', which involves compression of the pituitary stalk that inhibits the control of pituitary cells mediated by the hypothalamus via the hypothalamic-hypophyseal portal venous system. Excess secretion of prolactin from the pituitary gland is explained as the result of a decrease in dopamine inhibition from hypothalamic neurons.[6,32,33] With a pituitary tumor, ISP has been shown to be potentially elevated above the expected normal intrasellar and intracranial pressure (<15 mmHg), and hence the venous pressure of the portal system, which would suggest that portal compression could theoretically be caused by ISP elevation.[6,8,9] Antunes et al. demonstrated that an arrest in blood flow in long portal veins in Rhesus monkeys could be reached with a positive airway pressure of as little as 22 mmHg.[34] It has also been reported that an elevation of ISP in humans during intrasellar surgery leads to a sharp decrease in pituitary blood flow.[35] Thus, there are reasons to believe that a loss of regulating hormones followed by a decline in venous blood flow to the anterior pituitary could be one of the mechanisms behind the hormonal disturbances seen in association to ISP. An alternative to the stalk compression hypothesis is the occurrence of co-existing functional microtumours in the remnant pituitary gland,[36,37] which could explain the hormone overproduction seen in adenomas classified as non-functional.[32] Though, this theory does not give a satisfactory answer to the question of why overproduction is seen only in the prolactin axis. Another possible theoretical mechanism behind hyperprolactinemia and hypopituitarism seen in non-functional pituitary tumors could be angulation or breakage of the pituitary stalk secondary to a growing macrotumor, a hypothesis not yet confirmed with studies.

However, what further strengthens the stalk compression theory is the fact that we saw a normalization of prolactin levels in every nonprolactinoma patient after surgical decompression. This outcome is in accordance with earlier reports of normalization of prolactin levels and recovery of other anterior pituitary axes in many cases.[6,7,38,39] This is noteworthy, as a hypothesized development of ischemic necrosis of pituitary cells secondary to compromised blood flow has been discussed as a possible explanation to the hormone deficiency seen in patients with large intrasellar tumors with confirmed or expected high ISP.

Two cases with extremely high intraoperative ISP (>50 mmHg) were excluded before analysis as these were obvious outliers. One of these had a malignant sarcoma and one had an atypical adenoma. The reason for the very high ISP can only be speculated about. One reason may be due to the speed of growth resulting in reduced compensatory mechanisms or due to tissue ischemia.

Strengths with this study are the facts that it is performed at a single center and constitutes one of the largest consecutive patient materials in the field. The ISP values were collected prospectively,

and a single responsible neurosurgeon was involved in the intraoperative ISP measurement, maximizing the uniformity of the procedure. The accuracy of the pressure monitoring device is satisfactory, and the method used is analogous to those previously described. It is important to point out that the actual dura opening was only large enough to insert the monitoring device. In addition, special attention was paid to confirm that no intrasellar components leaked out during the pressure monitoring. Unfortunately, since hormone levels were analyzed with different methods during the study, we could not compare absolute hormone levels as continuous variables in direct correlation to ISP. However, presenting hormonal levels as ordinal data strengthens the comparability and validity of our results. We studied all patient records carefully to make sure that all subjects with medications potentially affecting hormone levels were found, enabling exclusion of this known confounder. Comparability of laboratory methods as well as medications with known effect on hormone levels are both examples of important issues which, interestingly, are seldom addressed in previous publications in this field. In assessing the frequency of hormone deficiency, we focused on the thyroid and cortisol axes, as the GH and gonad axes were not routinely evaluated preoperatively in all patients during the study period.

As the majority of pituitary tumors are benign, long-term postoperative results, including both endocrine deficiencies and other postoperative squeal, remain important. This should encourage further investigations with the aim of exploring factors that can predict endocrine outcome after surgical treatment.

## CONCLUSION

We conclude that the hyperprolactinemia commonly seen in patients with nonprolactinoma pituitary tumors is associated with ISP and usually normalized after tumor resection, likely to be explained by compression of the pituitary stalk caused by ISP elevation and postoperative relief of the stalk pressure. We found an association between preoperative hypothyroidism and ISP elevation in our patients. The risk of postoperative hypopituitarism at 3 months after surgery could not be predicted based on intraoperative ISP. Extremely high ISP values should be handled with care as they seem not to follow the anticipated physiological hormonal response.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

LOK contributed to the study conceptualization and design, and LOK, POE, PL, GS, and LO contributed to data collection. Data analysis was performed by GS, PD, and LOK. The manuscript was written by GS. All authors have read, commented on and approved the final manuscript.

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