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Original Research

Pituitary function before and after surgery for nonfunctioning pituitary adenomas—data from the Swedish Pituitary Register

Nasrin Al-Shamkhi,[1,2,*] Katarina Berinder,[3] Henrik Borg,[4] Pia Burman,[5] Per Dahlqvist,[6] Charlotte Höybye,[3] Daniel S. Olsson,[7,8,9] Oskar Ragnarsson,[7,8,10] Bertil Ekman,[11] and Britt Edén Engström[12]

[1]Department of Internal Medicine, Örebro University Hospital and School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[2]Department of Endocrinology and Diabetology, Uppsala University Hospital, Uppsala, Sweden
[3]Department of Endocrinology, Karolinska University Hospital and Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[4]Department of Endocrinology, Skåne University Hospital, Lund University, Lund, Sweden
[5]Department of Endocrinology, Skåne University Hospital, Lund University, Malmö, Sweden
[6]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[7]Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden
[8]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[9]Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
[10]Wallenberg Center for Molecular and Translational Medicine, University of Gothenburg, Göteborg, Sweden
[11]Departments of Endocrinology in Linköping and Norrköping, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
[12]Department of Medical Sciences, Endocrinology and Mineral Metabolism, Uppsala University, Uppsala University Hospital, Uppsala, Sweden

*Corresponding author: Endokrin- och diabetesmottagningen, Akademiska sjukhuset, Uppsala 751 85, Sweden. Email: nasrin.al-shamkhi@oru.se

Abstract

Objective: Data on pre- and postoperative pituitary function in nonfunctioning pituitary adenomas (NFPA) are not consistent. We aimed to investigate pituitary function before and up to 5 years after transsphenoidal surgery with emphasis on the hypothalamic-pituitary-adrenal axis (HPA).

Design and methods: Data from the Swedish Pituitary Register was used to analyze anterior pituitary function in 838 patients with NFPA diagnosed between 1991 and 2014. Patients who were reoperated or had received radiotherapy were excluded.

Results: Preoperative ACTH, TSH, LH/FSH, and GH deficiencies were reported in 31% (236/755), 39% (300/769), 51% (378/742), and 28% (170/604) of the patients, respectively. Preoperative median tumor volume was 5.0 (2.4-9.0) cm^3. Among patients with preoperative, 1 year and 5 years postoperative data on the HPA axis ($n = 428$), 125 (29%) were ACTH-deficient preoperatively. One year postoperatively, 26% (32/125) of them had recovered ACTH function while 23% (70/303) patients had developed new ACTH deficiency. Thus, 1 year postoperatively, 163 (38%) patients were ACTH-deficient ($P < .001$ vs. preoperatively). No further increase was seen 5 years postoperatively (36%, $P = .096$). At 1 year postoperatively, recoveries in the TSH and LH/FSH axes were reported in 14% (33/241) and 15% (46/310), respectively, and new deficiencies in 22% (88/403) and 29% (83/288), respectively.

Conclusions: Adrenocorticotrophic hormone deficiency increased significantly at 1 year postoperatively. Even though not significant, some patients recovered from or developed new deficiency between 1 and 5 years postoperatively. This pattern was seen in all axes. Our study emphasizes that continuous individual evaluations are needed during longer follow-up of patients operated for NFPA.

Keywords: pituitary adenoma, transsphenoidal surgery, pituitary insufficiency, HPA axis, pituitary register

Significance

Although nonfunctioning pituitary adenomas are histologically benign, extensive growth or surgical treatment can give rise to pituitary failure including ACTH deficiency, which can be life-threatening. In this study, the proportion of anterior pituitary hormone deficiencies in macroadenomas, including ACTH deficiency, increased at 1 year postoperatively compared to preoperatively. This proportion did not change further between 1 and 5 years postoperatively, but some patients developed and others recovered from ACTH deficiency or other anterior hormone deficiencies, emphasizing that repeated evaluation of the anterior pituitary hormones is necessary.

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Introduction

Nonfunctioning pituitary adenomas (NFPA) are the second most common pituitary tumor subtype after prolactinomas,[1–5] with a reported prevalence between 21 and 26/100 000[1,2,4] and in a Swedish study a standard incidence rate of 1.8/100 000.[6]

It is known that NFPA can cause hypopituitarism.[7,8] At diagnosis, 60%-85% of patients with macroadenoma have at least 1 pituitary hormone deficiency.[9] If there are indications for treatment, such as visual disturbances, the first-line treatment is transsphenoidal surgery.[10] Visual impairments frequently improve after surgery, while data regarding hypopituitarism are not consistent.[7,11–13] In a single-center study with 466 surgically treated NFPA, an increase in pituitary deficiencies of 3.5% in the hypothalamic-pituitary-adrenal (HPA) axis, 4.1% in the thyroid stimulating hormone (TSH) axis, and 3.3% in the luteinizing hormone/follicle stimulating hormone (LH/FSH) axis was observed, but some of the patients had been treated with radiotherapy or multiple surgeries.[14] In a recent study from 2 surgical centers, deficiency of at least 1 pituitary axis was reported in 80% (197/246) of the patients at baseline, which dropped to 61% 1 year postoperatively, the improvement was more pronounced for the LH/FSH and TSH axes than for the HPA axis.[15] This is of great importance since adrenocorticotrophic hormone (ACTH) deficiency can be life-threatening, which was shown in a Swedish study of 1286 patients with hypopituitarism where ACTH deficiency was associated with excess mortality due to adrenal crisis.[16] In another European study of 519 patients with NFPA, ACTH deficiency was associated with an increased relative risk of death.[17]

In Sweden, patients with pituitary tumors have been reported to the Swedish Pituitary Register (SPR) since 1991. The aim of the present study was to evaluate anterior pituitary function with emphasis on the HPA axis before and after transsphenoidal surgery in patients with NFPA diagnosed and reported to the SPR between 1991 and 2014.

Subjects and methods

The Swedish Pituitary Register

The SPR is based on the national Information Network for Cancer treatment IT platform located in the Regional Cancer Center (RCC) Stockholm-Gotland and is financially supported by the Swedish government. The SPR is organized by endocrinologists, neurosurgeons, oncologists, pathologists, ophthalmologists, neuroradiologists, and endocrine nurses from all 6 health care regions in Sweden.

Study design

Reported data on operated patients with NFPA diagnosed since 1991 were extracted from the SPR on February 26, 2018. Missing data were obtained retrospectively from medical records when available. The study aimed for a postoperative follow-up time of at least 2.5 years, so only patients who had undergone transsphenoidal surgery for NFPA before December 31, 2014 were included. Patients who had undergone reoperation or received radiotherapy within 2.5 years after the first surgery were excluded. Data from baseline, defined as the time of diagnosis (before surgery), such as age, sex, adenoma size, and anterior pituitary function, were gathered. Data on pituitary function were also gathered from the 1-year postoperative follow-up (defined as 6 months to 2.5 years after surgery), as well as the 5-year postoperative follow-up (defined as 2.5 years to 7.5 years after surgery). The pituitary function of each axis was reported as deficient, sufficient, or undeterminable by the treating clinician. Furthermore, we confirmed the reported data in the SPR regarding the pituitary function of 180 patients who had recovered from a preoperative pituitary deficiency in the HPA axis by either 1 year or 5 years postoperatively or had become deficient at 5 years postoperatively by rechecking the medical records.

For the whole study cohort, a cross-sectional analysis was performed for all axes [HPA, TSH, LH/FSH, and growth hormone (GH)] before surgery and at 1 and 5 years after surgery. Patients with complete preoperative, 1- and 5-year postoperative data regarding the HPA axis were analyzed as 1 longitudinal group (Figure 1). We also constituted 2 groups for each of the TSH and LH/FSH axes, 1 group consisting of patients who had preoperative and 1-year postoperative follow-up and one consisting of patients who had 1- and 5-year postoperative follow-up, and analyzed change over time of each axis separately (Figure 1).

Methods

Definitions of pituitary deficiencies

The classification of anterior pituitary function in the study was based on reported data in the SPR (deficiency Yes or No). The responsible clinician's evaluation of the anterior pituitary function was based on current national and international clinical guidelines. Different cutoff values were used depending on which analysis method was used at the actual time for testing during the study period.

If morning S-cortisol <400-450 (before 2018) or <300-350 (from 2018) nmol/L in combination with clinical signs and symptoms, Synacthen stimulation test (low-dose 1 μg iv. or 250 μg iv.) or ITT (Insulin Tolerance Test, 0.1 U insulin/kg bodyweight, adequate hypoglycemia) was performed to confirm ACTH deficiency. Preoperatively, some patients may have received hydrocortisone replacement based on morning S-cortisol <100 nmol/L and clinical signs and symptoms of hypocortisolism before a more rigorous evaluation with a stimulation test was done postoperatively.

Free thyroxine (fT4) and free triiodothyronine (fT3) under reference range in combination with not adequately increased TSH concentration was indicative of TSH deficiency.

Deficiency in the LH/FSH axis was suggested in premenopausal women with low estradiol and low LH/FSH in combination with amenorrhea or irregular menstrual bleeding, and in postmenopausal women with low estradiol without a compensatory increase in LH/FSH. In men, hypogonadism was defined by testosterone under reference range for age and low LH/FSH in combination with clinical signs and symptoms.

Preoperative data on the GH axis were in the vast majority of cases based on insulin-like growth factor 1 (IGF-1) values below reference range for age since stimulation tests were usually not performed before surgery. To confirm GH deficiency, insulin tolerance test (ITT) or growth hormone releasing hormone (GHRH)-arginine test was performed postoperatively. In selected cases, IGF-1 below reference range for age in combination with at least 3 other pituitary deficiencies could define GH deficiency.

Statistical analyses

The changes over time in the pituitary axes were compared with a 2-tailed exact McNemar test. Sensitivity analyses

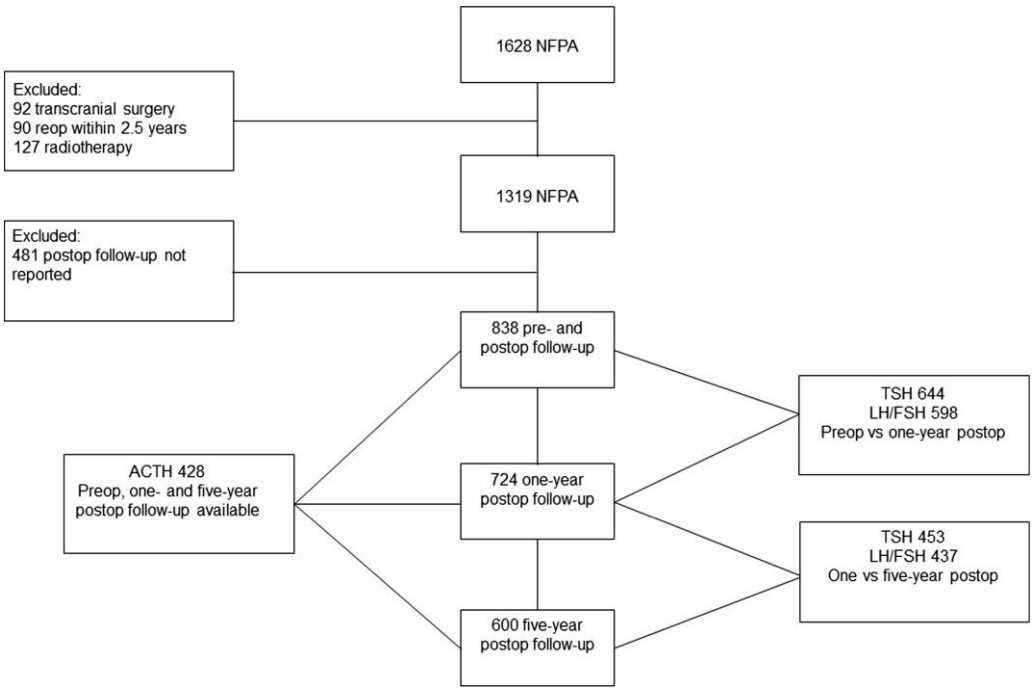

Figure 1. In the SPR, 1319 patients who fulfilled the inclusion criteria were identified, and 838 patients had postoperative follow-ups. At 1 year postoperatively 644 patients had preoperative and 1-year postoperative data regarding the TSH axis and 598 patients regarding the LH/FSH axis. Of 600 patients at 5 years, 453 patients had both 1- and 5-year postoperative data regarding the TSH axis and 437 patients regarding the LH/FSH axis. Data regarding the HPA axis were available for 428 patients at all time points.

comparing baseline data between the group of patients who had postoperative evaluations and the group who did not, as well as the age and sex within the group with longitudinal data regarding the HPA axis, were compared statistically with Fisher's exact test or the Mann-Whitney U test. $P < .05$ was considered significant. IBM SPSS Statistics version 27 was used for all statistical analyses in this study.

Ethics

The SPR was approved by the Ethics Committee at Karolinska Institute (Stockholm, Sweden), 2003 (Dnr 515/03) and 2012 (Dnr 2012/915-32). Since the SPR is a national quality register supported by the government, written approval for inclusion in the register is not needed, but the patients are informed, with an opt-out possibility, either orally or in writing. This study is in accordance with the Declaration of Helsinki.

Results

A total of 1628 patients diagnosed with NFPA 1991-2014 who underwent surgery before December 31, 2014 were reported in the SPR. Ninety-two of those had undergone transcranial surgery, 127 had received radiotherapy, and 90 had been reoperated within 2.5 years after the first surgery. Of the remaining 1319 patients, 481 had no postoperative evaluation reported in the SPR (Figure 1). These patients were significantly older than those with registered follow-up visits, but no other significant differences were found at NFPA diagnosis (Table 1). Postoperative evaluations were available for 838 patients, 724 patients at 1 year, and 600 patients at 5 years. The median follow-up times were 1.1 years (IQR 0.87-1.56) and 5.0 years (IQR 4.27-6.11), respectively. Seventy-six of the 838 patients were reoperated more than 2.5 years after the first surgery, of those, 64.5% (49/76) were men, median age was 53 years (IQR 45.3-60.8), and median tumor volume at diagnosis was 7.6 cm^3 (IQR 5.0-12.0). Data after the reoperation were not included in the analyses. At the time of diagnosis, 58% (490/838) of the patients who had postoperative evaluations were reported to be deficient in at least 1 pituitary axis. The proportions of patients with ACTH, TSH, LH/FSH, and GH deficiencies before and after surgery are shown in Figure 2.

The HPA axis in patients with complete longitudinal follow-up

Complete pre- and postoperative data at both the 1- and 5-year follow-ups regarding the HPA axis were available for 428 patients. These patients were analyzed as a separate longitudinal group. There were no significant differences regarding sex or age at diagnosis compared to the 410 patients who did not have complete follow-up data regarding the HPA axis.

Tumor volume before surgery in patients with (median 5.5 cm^3, IQR 3.0-9.4, $n = 102$) and without ACTH deficiency (median 4.8 cm^3, IQR 2.3-8.4, $n = 250$) was not significantly different $P = .07$.

The proportion of ACTH-deficient patients increased significantly from 29% (125/428) preoperatively to 38% (163/428) 1 year postoperatively ($P < .001$), with no further change at 5 years, 36% (155/428). Among the patients with preoperative ACTH deficiency, 70% (88/125) remained deficient throughout the study period, whereas 26% (32/125) had recovered 1 year postoperatively. Another 4% (5/125) recovered ACTH function between 1 and 5 years postoperatively (Figures 3 and 4).

Preoperatively, 71% (303/428) were ACTH-sufficient, and 75% of these (228/303) remained sufficient during the entire follow-up period. One year postoperatively, 23% (70/303)

Table 1. Preoperative characteristics of patients with and without postoperative follow-up.

	Total ($n = 1319$)	Patients with follow-up ($n = 838$)	Patients without follow-up ($n = 481$)	*P*-value
Gender				.13
Men, % (n)	60 (788)	61 (514)	57 (274)	
Women, % (n)	40 (531)	39 (324)	43 (207)	
Age, years median (IQR)	61 (50-70)	60 (49-69)	64 (52-72)	<.001
Men, median (IQR)		60 (50-69)	65 (54-73)	<.001
Women, median (IQR)		59 (45-69)	63 (50-71)	.02
Adenoma volume, cm^3, median (IQR)	4.8 (2.4-8.7)	5.0 (2.4-9.0)	4.4 (2.4-8.2)	.14
Men, median (IQR)		5.1 (2.7-9.6)	4.7 (2.9-8.7)	
Women, median (IQR)		4.8 (2.3-7.8)	3.8 (1.8-7.5)	
ACTH deficiency, % (n)	31 (366)	31 (236)	30 (130)	.74
Men, % (n)		39 (178)	36 (89)	
Women, % (n)		20 (58)	23 (41)	
TSH deficiency, % (n)	38 (464)	39 (300)	37 (164)	.58
Men, % (n)		46 (216)	45 (115)	
Women, % (n)		28 (84)	27 (49)	
LH/FSH deficiency, % (n)	51 (586)	51 (378)	50 (208)	.76
Men, % (n)		62 (285)	60 (147)	
Women, % (n)		33 (93)	35 (61)	

Among patients with follow-up ($n = 838$), adenoma volume was reported for 670 (80%), 256 women and 414 men, and among patients without follow-up ($n = 481$), adenoma volume was reported for 335 (70%), 143 women and 192 men. In the group with follow-up, ACTH, TSH, and LH/FSH axes were reported for 755, 769, and 742 patients, respectively. In the group followed up, the men had more pituitary deficiencies in all axes ($P < .001$) than the women but there was no difference in age or adenoma size between men and women.

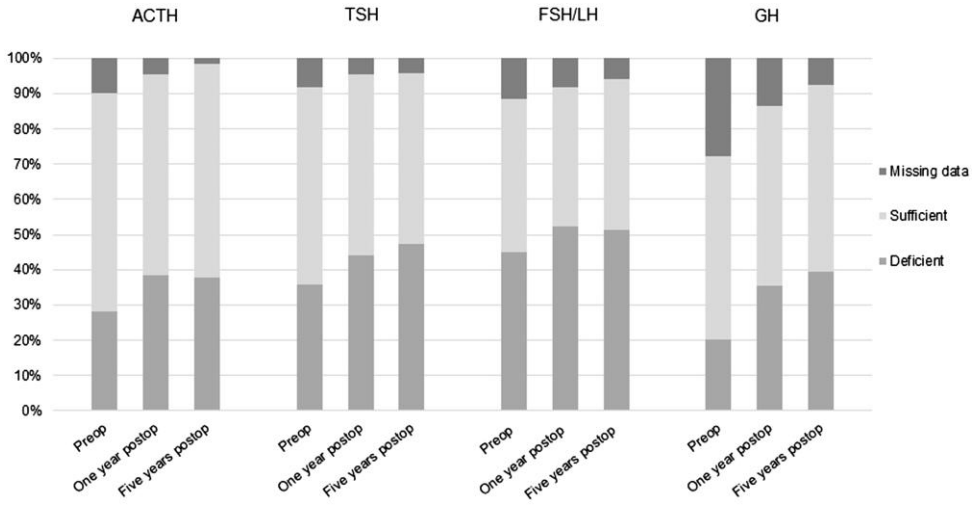

Figure 2. Proportions of patients with reported deficiencies in the HPA, TSH, LH/FSH, and GH axes preoperatively ($n = 838$) and at the 1-year ($n = 724$) and 5-year postoperative follow-ups ($n = 600$).

of the preoperatively ACTH-sufficient patients had developed ACTH deficiency, 11% (8/70) were deficient at only 1 year postoperatively, while the rest continued to be deficient throughout the follow-up period, and another 2% (5/303) became ACTH-deficient between 1 and 5 years postoperatively (Figures 3 and 4).

More men than women had ACTH deficiency at all time points (Figure 4). There were no significant differences in age or sex between those who recovered and those who did not or between those who developed a new deficiency and those who did not at 1 year postoperatively. Patients ($n = 30$) who recovered from an ACTH deficiency 1 year postoperatively had a smaller tumor volume at diagnosis (median 3.3 cm^3, IQR 2.6-6.1) than those ($n = 72$) who remained deficient (median 7.4 cm^3, IQR 3.8-11.7) ($P = .001$), and those ($n = 57$) who developed a deficiency 1 year postoperatively had a larger tumor volume (median 7.1 cm^3, IQR 3.8-11.9) than those ($n = 193$) who remained sufficient (median 4.1 cm^3, IQR 2.1-7.7) ($P = .002$).

TSH axis

Data regarding the TSH axis were missing or undeterminable in 8% (69/838) preoperatively, 5% (33/724) 1 year postoperatively, and 4% (26/600) 5 years postoperatively. Preoperatively 39% (300/769) of the patients had TSH deficiency. In 644 patients with both preoperative and 1-year postoperative data, 22% (88/403) developed postoperative TSH deficiency, while 14% (33/241) recovered from preoperative TSH deficiency. Among the 453 patients with both 1- and 5-year postoperative data, 8.4% (21/250) had developed postoperative TSH deficiency between 1 and 5 years postoperatively, while 4.4% (9/203) had recovered function of the TSH axis (Tables 2 and 3).

LH/FSH axis

Data regarding the LH/FSH axis were missing or undeterminable in 11% (96/838) preoperatively, 8% (60/724) 1 year postoperatively, and 6% (36/600) 5 years postoperatively. Preoperatively 51% (378/742) of the patients were reported to have LH/FSH deficiency. In 598 patients with both preoperative and 1-year postoperative data, 29% (83/288) developed postoperative LH/FSH deficiency, while 15% (46/310) recovered function in the LH/FSH axis. Among 437 patients with both 1- and 5-year postoperative data for the LH/FSH axis, 11% (21/191) developed LH/FSH deficiency between 1 and 5 years postoperatively, while 10% (25/246) had recovered function in the LH/FSH axis in this period (Tables 2 and 3).

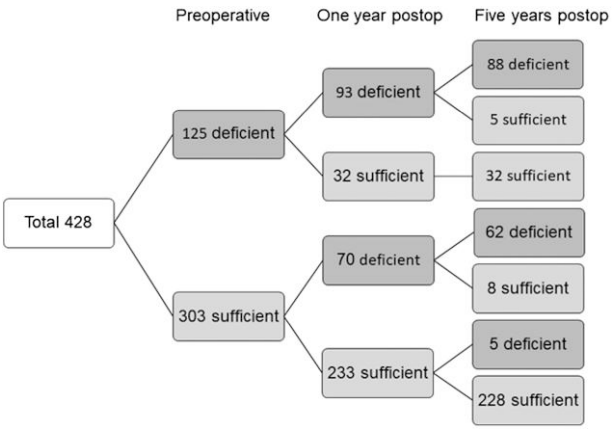

Figure 3. The development of the HPA axis in 428 patients with longitudinal follow-up. Eighty-eight patients were ACTH-deficient throughout the entire follow-up period, and 228 were never ACTH-deficient. At 1 year postoperatively, 163 patients were ACTH-deficient, and 265 were sufficient; at 5 years postoperatively, 155 patients were ACTH-deficient, and 273 were sufficient, compared to 125 and 303, respectively, at diagnosis.

GH axis

Data regarding the GH axis were missing or undeterminable in 28% (234/838) preoperatively, 13% (97/724) 1 year postoperatively, and 7.5% (45/600) 5 years postoperatively. At diagnosis, 28% (170/604) of the patients were reported to have GH deficiency primarily based on low IGF-1 values. At 1 year postoperatively, 41% (257/627) were reported as GH-deficient, while 34% (88/257) of them were receiving GH replacement. At 5 years, 43% (236/555) were reported as GH-deficient and 69% (163/236) of them were receiving replacement; 55 of those were new deficiencies, and 46 lacked prior information on the GH axis.

Patients who were on GH replacement therapy were younger than those without (median 56 vs. 64 years, $P = .004$, at 1-year postoperative follow-up, and median 55 vs. 60 years at 5-year follow-up, $P = .001$). There was no sex difference among patients receiving or not receiving GH replacement.

Table 2. Preoperative and 1 year postoperative TSH and LH/FSH deficiency.

	Preoperative deficiency	One year postoperative deficiency	*P*-value
TSH, % (*n*)	37 (241/644)	46 (296/644)	<.001
Men, % (*n*)	44 (117/403)	50 (202/403)	
Women, % (*n*)	27 (64/241)	40 (94/241)	
LH/FSH, % (*n*)	52 (310/598)	58 (347/598)	.001
Men, % (*n*)	62 (236/382)	66 (254/382)	
Women, % (*n*)	34 (74/216)	43 (93/216)	

There was an increase in TSH and LH/FSH deficiency at 1 year postoperatively vs. preoperatively. Men had more TSH deficiency both preoperatively ($P < .001$) and 1 year postoperatively ($P = .007$) than women. Men also had more LH/FSH deficiency at these time points, $P < .001$. At 1 year, 80% (202/254) of the deficient men were receiving hormone replacement therapy, while 23% (21/93) of the deficient women were on hormone replacement.

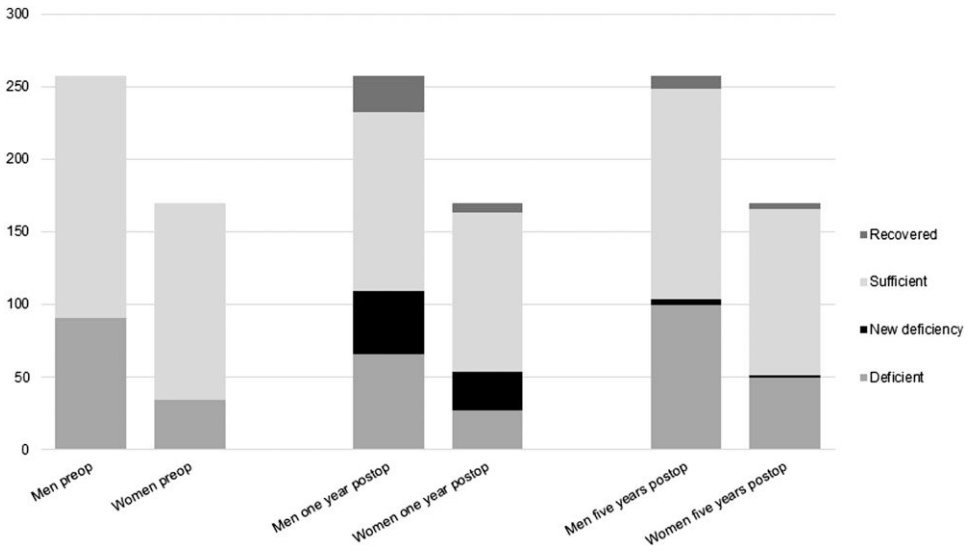

Figure 4. The development of ACTH deficiency in 428 patients, including 258 men and 170 women, with longitudinal follow-up. At 1 year postoperatively, 23% (70/303) of the patients had developed postoperative ACTH deficiency, while 26% (32/125) had recovered from preoperative deficiency. $P < .001$. At 5 years postoperatively, another 5 patients had developed postoperative ACTH deficiency, and 5 patients had recovered from preoperative ACTH deficiency. Eight out of the 70 patients who developed postoperative ACTH deficiency 1 year postoperatively also regained function in the HPA axis at 5 years postoperatively. At all time points, more men than women had ACTH deficiency, 35% (91/258) and 20% (34/170) preoperatively ($P < .001$), 42% (109/258) and 32% (54/170) at 1 year ($P = .03$), and 40% (104/258) and 30% (51/170) at 5 years ($P = .03$).

Table 3. One year and 5 years postoperative TSH and LH/FSH deficiency.

	One year postoperative deficiency	Five years postoperative deficiency	*P*-value
TSH, % (*n*)	45 (203/453)	48 (215/453)	.04
Men, % (*n*)	49 (138/281)	51 (142/281)	
Women, % (*n*)	38 (65/172)	42 (73/172)	
LH/FSH, % (*n*)	56 (246/437)	55 (242/437)	.70
Men, % (*n*)	66 (180/272)	65 (177/272)	
Women, % (*n*)	40 (66/165)	39 (65/165)	

At 5 years, there was a small but significant increase in TSH deficiency and no increase in LH/FSH deficiency vs. 1 year postoperatively. Men had more TSH deficiency at 1 year ($P = .02$) but not at 5 years ($P = .1$), while men had more LH/FSH deficiency at both time points ($P < .001$). At 5 years, 89% (158/177) of the deficient men and 20% (13/65) of the deficient women received hormone replacement therapy.

Discussion

This national register-based study of pituitary function before and after transsphenoidal surgery in patients with NFPA, preoperative median tumor volume 5.0 (2.4-9.0) cm^3, focused mainly on the HPA axis. The proportion of ACTH-deficient patients increased from 29% preoperatively to 38% 1 year postoperatively. Although a few patients recovered from a preoperative ACTH deficiency, considerably more developed a new ACTH deficiency. Even if no significant further increase in ACTH deficiencies was seen at 5 years postoperatively, some patients recovered and some patients developed new deficiencies between 1 and 5 years postoperatively. Furthermore, the other anterior pituitary axes showed the same patterns with an overall significant increase in anterior hormone deficiencies, despite a few recoveries. In total, at 5 years postoperatively recoveries from ACTH, TSH, and LH/FSH deficiency were reported in 45, 42, and 71 patients, respectively, while 67, 109, and 104 had developed new deficiencies, respectively.

The proportion of patients with preoperative ACTH deficiency in the present study was in accordance with some earlier studies[8,14] regarding NFPA as well as the degree of recovery from preoperative ACTH deficiency.[13,18] Other studies have shown a degree of recovery ranging from 16%-45%[19–21] and new postoperative ACTH deficiencies ranging from 3%-13%.[14,18–21] Different criteria for ACTH deficiency have been used in different studies which might have affected the reported outcomes.[14,18–20]

Fatemi et al.[21] reported in 223 patients with NFPA that tumor size was the strongest predictor of new deficiencies, which is in line with our data where patients who developed a new deficiency had larger tumor volumes preoperatively than those who remained sufficient. In contrast, patients who recovered had a smaller tumor volume preoperatively, which was not found in the Fatemi study. One study of 601 patients with NFPA described younger age as a predictor of postoperative recovery.[22] Other studies have not found age to be a predictor of postoperative recovery or no difference in pre- or postoperative deficiencies according to age,[18,23] which is in line with our study.

Keeping in mind the inherent limitations of register-based studies, our results suggest that in some patients, the function of the HPA axis continues to change postoperatively, even without radiotherapy. This has been described before; in a study with a median follow-up time of 20 months (range 8-51), where recovery was seen in the NFPA subgroup in 4 out of 23 patients.[24] Pofi et al.[25] reported that a combination of the stimulated cortisol level preoperatively, early postoperative cortisol level and a 6-week 9 AM cortisol level could predict which patients should be tested for later recovery of the HPA axis. Since unnecessary treatment with glucocorticoids should be avoided, the clinician should be aware of possible late changes in pituitary function requiring retesting.

Interestingly, men had more pre- and postoperative deficiencies than women in the HPA, TSH, and LH/FSH axes. A gender difference in the HPA and TSH axes has recently been described in an Italian study in 73 NFPA patients[26] where a larger tumor volume in men could explain the gender difference. In contrast to our study, no gender difference was seen regarding the LH/FSH axis in the Italian study, possibly because of a younger age in the women compared to the men which made a gonadotropic deficiency more relevant to diagnose and replace. In a study of 218 patients with NFPA, an association was seen between ACTH deficiency and tumors that did not invade the cavernous sinus walls but compressed them, which are more common in men,[27] while another study of 122 patients with NFPA was not able to demonstrate an association between more multiple hormone deficiencies in men and tumor size or invasion at presentation.[28] In the present study, men did not have a larger preoperative tumor volume than women. Further studies are needed to clarify the gender differences in pituitary deficiencies.

In a recent systematic review and meta-analysis, a large number of studies were excluded due to an insufficient follow-up period or that data on NFPA or transsphenoidal surgery were not specifically reported.[29] The strengths of this national study are the large population size and the long follow-up time, particularly the 428 patients who were followed longitudinally with complete data about the HPA axis up to 5 years postoperatively. Furthermore, data on 180 patients who recovered from preoperative ACTH deficiency at 1 or 5 years postoperatively or developed postoperative ACTH deficiency at 5 years were confirmed by rechecking the patients' medical records. Another strength is that data in the SPR represent patients from all Swedish health care regions; hence, all centers that conducted pituitary surgery were represented. Finally, we made efforts to study a homogenous group of patients with NFPA and the effect of 1 transsphenoidal surgery by excluding patients that were operated transcranially, had more than 1 transsphenoidal surgery, or received radiotherapy.

The included patients have undergone transsphenoidal surgery between 1991 and 2014. Any developments in MRI-imaging or surgical techniques during the last decades were not reflected in the study data which might be a limitation since these developments could have affected the degree of postoperative pituitary deficiencies.

The assessment of some of the anterior pituitary axes can be difficult, especially the evaluation of the function over time. The evaluation of the TSH axis was limited by the fact that levothyroxine is usually not routinely withdrawn postoperatively and in the clinical routine, it can be hard to differentiate between primary and secondary hypothyroidism, especially if the patient is already treated with levothyroxine at time of diagnosis of the NFPA. Preoperatively, the GH axis is not routinely evaluated with provocative testing. Register data regarding preoperative GH deficiency were therefore mainly based on low IGF-1 values and should therefore be interpreted cautiously. This also limited the possibility of investigating whether the proportion of

GH-deficient patients was altered postoperatively. Not all patients undergo provocative testing regarding the GH axis, and not all patients with a confirmed deficiency are treated with GH replacement due to the patient's own wishes, comorbidities, age, tumor not in remission, or other reasons. The larger proportion of patients on GH replacement at 5 years compared to 1 year postoperatively, in the present study, was probably due to GH being the last axis to be fully evaluated and, if indicated, treated with hormonal replacement.

In conclusion, in this large national register study of patients operated once for NFPA, the proportion of patients with ACTH deficiency increased significantly after surgery. The same pattern was seen for the other anterior pituitary axes. Even though there was no significant difference regarding ACTH deficiency between 1 and 5 years postoperatively, some patients recovered from or developed ACTH deficiency between these 2 time points, indicating a need for later retesting in patients operated for NFPA. Prospective studies with a standardized evaluation of pituitary function before and after surgery might clarify the changes of the pituitary axes.

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Data availability

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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