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Original Research

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

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Introduction

- NFPA are the second most common pituitary tumor subtype after prolactinomas
- NFPA can cause hypopituitarism
- At diagnosis, 60%-85% of patients with macroadenoma have at least 1 pituitary hormone deficiency
- If there are indications for treatment, such as visual disturbances, the first-line treatment is transsphenoidal surgery
- Visual impairments frequently improve after surgery, while data regarding hypo-pituitarism are not consistent.

Introduction

- 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
- ACTH deficiency was associated with an increased relative risk of death.
- In Sweden, patients with pituitary tumors have been re- ported 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

- Is based on 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

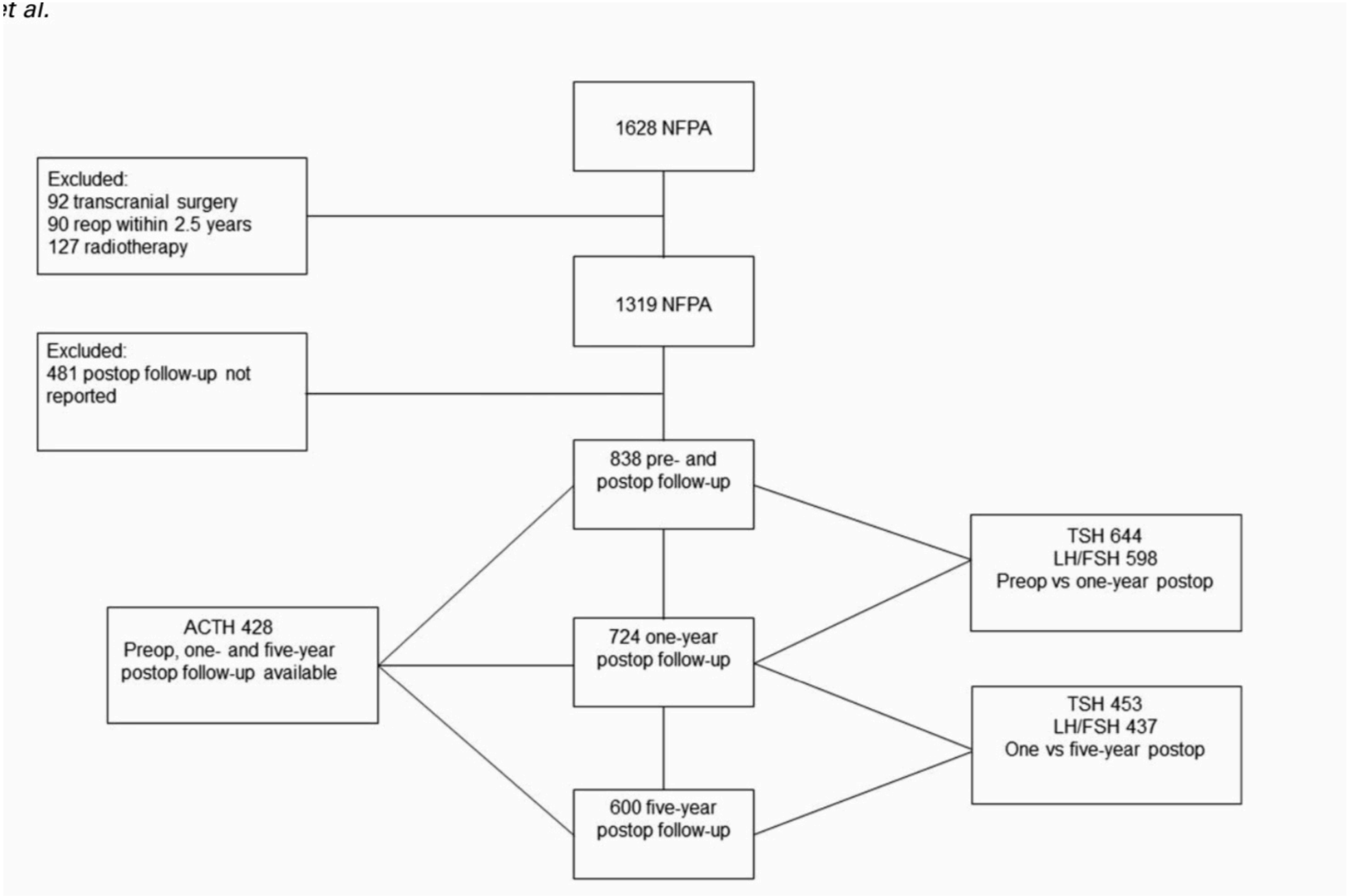
Study design

- Reported data on operated patients with NFPA diagnosed since 1991 were extracted from the SPR on February 26, 2018
- 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.

Study design

- Baseline Data 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 followup (defined as 2.5 years to 7.5 years after surgery)
- pituitary function of each axis was reported as **deficient**, **sufficient**, or undeterminable by the treating clinician

- 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 **pre- operative 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).


1628 NFPA
Excluded:
92 transcranial surgery
90 reop witihin 2.5 years
127 radiotherapy
1319 NFPA
Excluded:
481 postop follow-up not reported
838 pre- and postop follow-up
ACTH 428
Preop, one- and five-year postop follow-up available
724 one-year postop follow-up
600 five-year postop follow-up
TSH 644
LH/FSH 598
Preop vs one-year postop
TSH 453
LH/FSH 437
One vs five-year postop

Methods

Definitions of pituitary deficiencies

- 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

Definitions of pituitary deficiencies

- 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 de fined 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(**IGF-1) values below r**eference range for age since stimulation tests were usually not performed before surgery
- To confirm GH deficiency, insulin tolerance test (**ITT**) or(**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 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

Results

- 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
- Postoperative evaluations were available for 838 patients, 724 patients at 1 year, and 600 patients at 5 years
- 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

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.

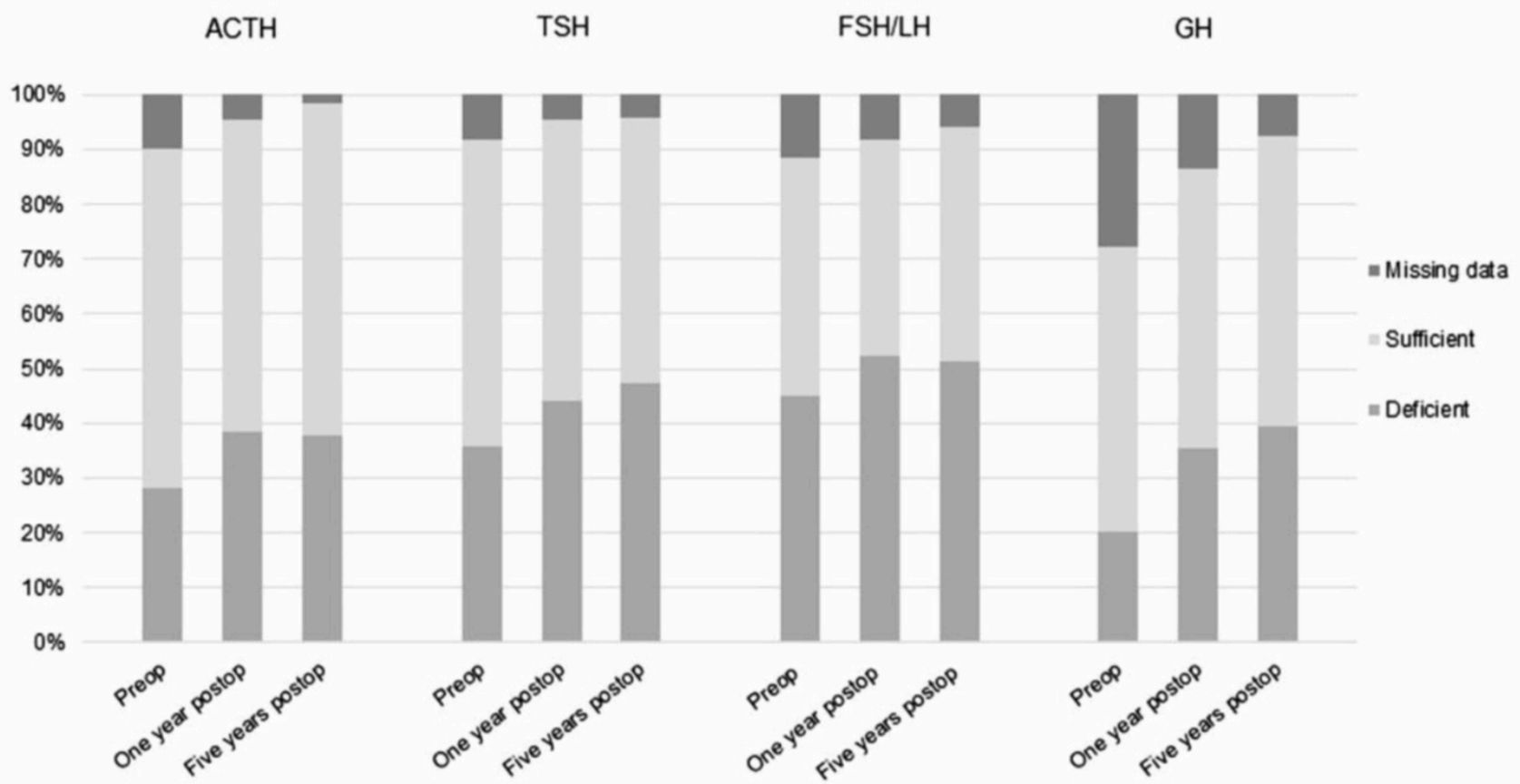


Figure 2. Proportions of patients with reported deficiencies in the HPA, TSH, LH/FSH, and GH axes preoperatively ($n = 838$) and at the 1-year ($n = 724$) and 5-year postoperative follow-ups ($n = 600$).

Results

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
- Tumor volume before surgery in patients with (median 5.5 cm3, IQR 3.0-9.4, n = 102) and without ACTH deficiency (median 4.8 cm3, 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**

Results

The HPA axis in patients with complete longitudinal follow-up

- 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) 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
- **More men** than women had ACTH deficiency at all time points (Figure 4)

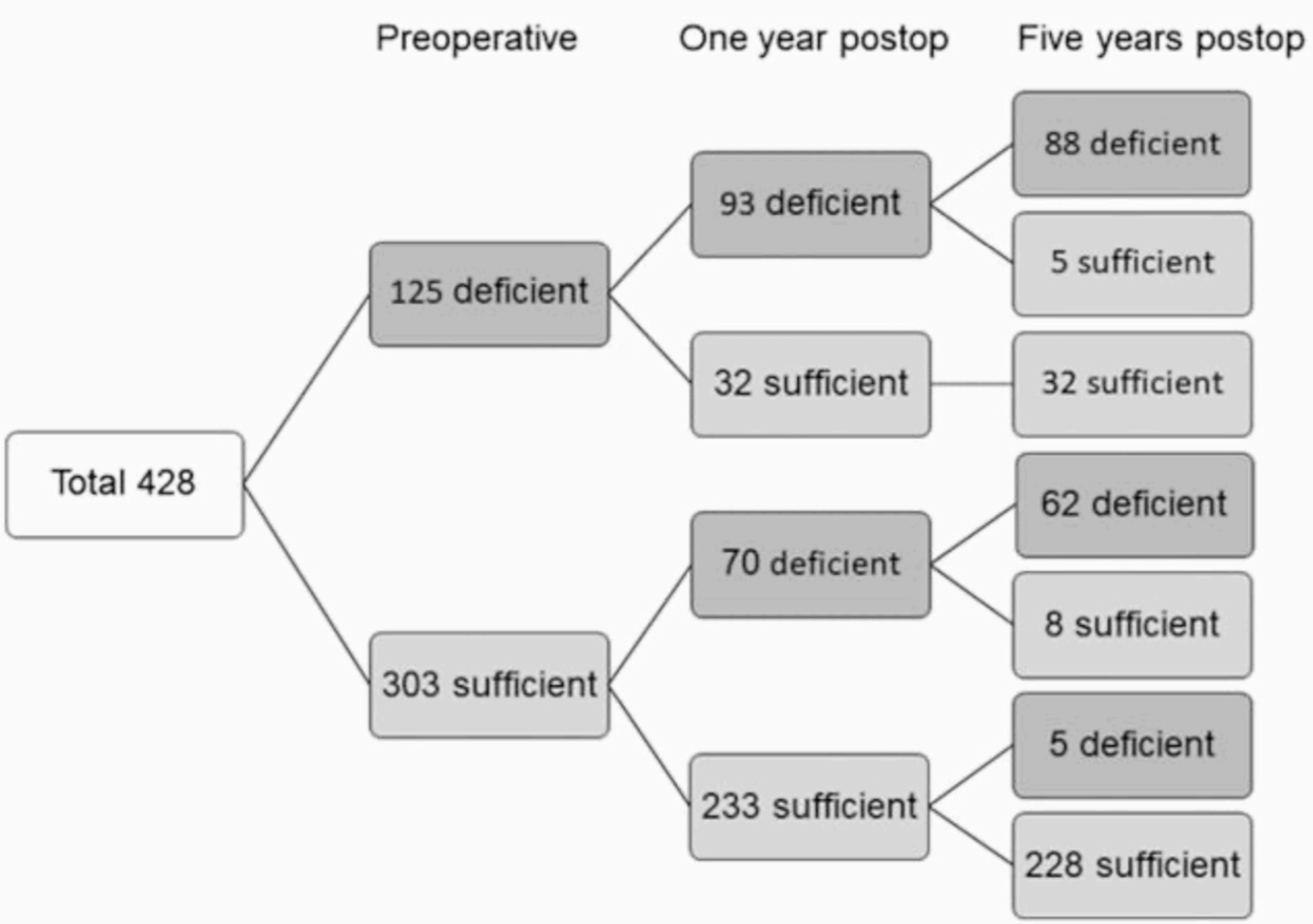


Figure 3. The development of the HPA axis in 428 patients with longitudinal follow-up. Eighty-eight patients were ACTH-deficient throughout the entire follow-up period, and 228 were never ACTH-deficient. At 1 year postoperatively, 163 patients were ACTH-deficient, and 265 were sufficient; at 5 years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

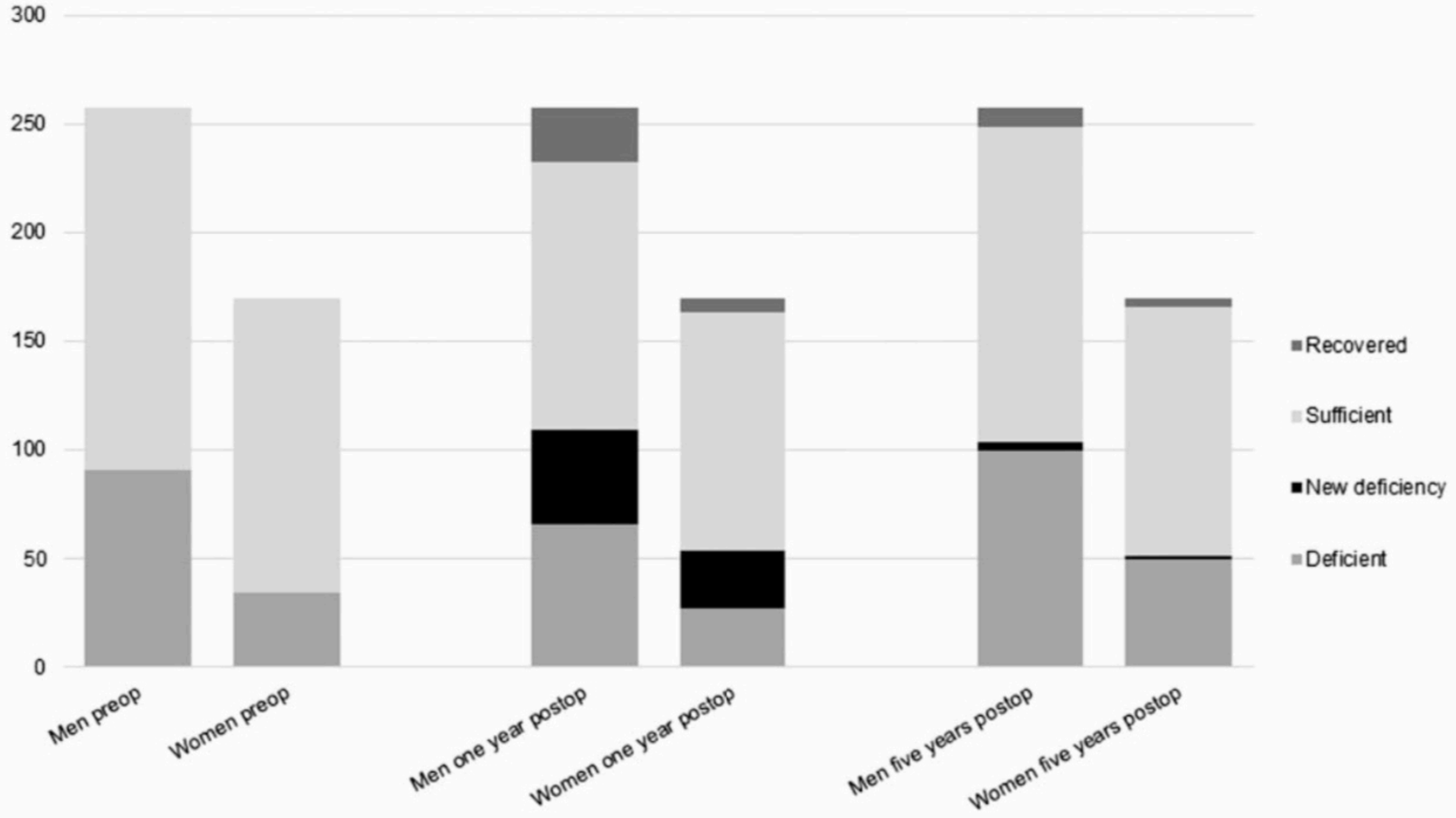


Figure 4. The development of ACTH deficiency in 428 patients, including 258 men and 170 women, with longitudinal follow-up. At 1 year postoperatively, 23% (70/303) of the patients had developed postoperative ACTH deficiency, while 26% (32/125) had recovered from preoperative deficiency. $P < .001$. At 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 ($P = .03$).

- Patients (n = 30) who **recovered** from an ACTH deficiency 1 year postoperatively had a **smaller tumor volume** at diagnosis (median 3.3 cm3, IQR 2.6-6.1) than those (n = 72) who remained deficient (median 7.4 cm3, 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 cm3, IQR 3.8-11.9) than those (n = 193) who remained sufficient (median 4.1 cm3, IQR 2.1-7.7) (P = .002).

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.

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

- 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
- **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.
- **other anterior pituitary axes showed the same patterns** with an overall significant increase in anterior hormone deficiencies, despite a few recoveries.

- The proportion of patients with **preoperative ACTH deficiency** in the present study was **in accordance with some earlier studies** as well as the **degree of recovery** from preoperative ACTH deficiency
- Fatemi et al. 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.

- have **not** found **age** to be a predictor of postoperative recovery or no difference in pre- or post- operative deficiencies according to age which is in line with our study
- 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
- Since unnecessary treatment with glucocorticoids should be avoided, the **clinician should be aware of possible late changes in pituitary function requiring retesting**
-

- men had more pre- and postoperative deficiencies than women in the HPA, TSH, and LH/FSH axes
- Further studies are needed to clarify the gender differences in pituitary deficiency

strengths

- **large** population size and the **long follow-up tim**e, particularly the 428 patients who were followed longitudinally with complete data about the HPA axis up to 5 years postoperatively
- we made efforts to study a **homogenous** group of patients with NFPA and effect of 1 transsphenoidal surgery by excluding patients that were operated transcranially, had more than 1 transsphenoidal surgery, or received radiotherapy

- assessment of some of the anterior pituitary axes can be difficult, especially the evaluation of the function over time
- evaluation of the **TSH axis** was **limited** 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.

conclusion

- 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.