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ORIGINAL ARTICLE

Sexual Function

Risk factors and the prognosis of sexual dysfunction in male patients with pituitary adenomas: a multivariate analysis

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The impact of sexual dysfunction (SD) is distressing to many male patients with pituitary adenomas which affect both physical and psychological health. The research explored to identify risk factors affecting sexual function and the prognosis of male patients with pituitary adenomas. Two hundred and fifty-four male patients, who aged between 18 and 60 (mean \pm s.d.: 44.16 \pm 10.14) years and diagnosed with pituitary adenomas, were retrospectively analyzed. One hundred and fifty-nine patients (62.6%) complained of SD prior to surgery. The mean International Index of Erectile Function (IIEF-5) in patients with giant adenomas was 16.13 \pm 2.51, much smaller than those with microadenomas or macroadenomas ($P < 0.05$). All the patients showed significant improvement in terms of erectile dysfunction (ED) following surgery ($P < 0.05$). In addition, complete resection achieved a higher degree of SD relief than partial resection. The incidence of SD in functioning pituitary adenomas (FPAs) was much higher than that in nonfunctioning pituitary adenomas (NFPAs) ($P < 0.05$). In addition, compared with NFPAs, males with prolactinomas (82.8%) had the higher prevalence of SD and significantly improvement following surgical intervention ($P < 0.05$). An inverse relationship was identified between decreasing testosterone levels and increasing incidence of SD before surgery ($P < 0.05$). There was no significant difference between 6 months and 12 months after surgery in serum testosterone level ($P > 0.05$). Our results indicated that surgical therapy could be optimized for improvements in SD and that testosterone levels can be used as a sensitive indicator to predict the recovery rate of sexual function in patients with pituitary adenomas following surgery and the serum testosterone level will stay stable in 6 months after surgery.

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INTRODUCTION

Pituitary adenomas are usually benign tumors, account for 15% of all intracranial neoplasms, and represent the third most frequent type of tumor after meningiomas and gliomas.¹ Although considered as benign, as many as 25%–55% of pituitary adenomas are invasive^{2–4} and some exhibit clinically aggressive behavior.^{5–7} In addition, different pathological types of pituitary adenomas can result in different prognoses. One of the most common symptoms in male patients with prolactinomas is sexual dysfunction (SD), of which erectile dysfunction (ED) is the major revealing symptom.⁸ ED (once known as male impotence) is defined as the inability of a man to achieve and maintain an erection sufficient for mutually satisfactory intercourse with his partner, causing stress and relationship problems and affecting male self-confidence.⁹ Recent studies, involving large cohorts, have demonstrated that many aging men and women engaged in sex with approximately 50% of this population, indicating that sex is also important in their life. Indeed, 26%–90% of men and women aged between 70 and 90 years are reported to engage in some forms of

sexual activity and 18% of them declaring one or more incidences of sexual intercourse per week.¹⁰ Notably, the most common sexual problem in men residing in the USA is erectile difficulties, accounting for 43% of the population of men reporting SD.^{11,12} Nicolosi *et al.*¹³ used a standard questionnaire to identify the most common sexual problems in 27 500 men and women aged between 40 and 80 years from 29 countries. They found that the most commonly reported problems among the male population were premature ejaculation (14%) and erectile difficulties (10%). In China, 12% elderly men reported ED.¹⁴ Another study showed that the incidences of ED were 10.93% in the infertile men and 8.28% in the fertile men.¹⁵ ED is affecting both the physical and psychological health of male patients, as well as the quality of life in both partners.¹⁶

The present study aimed to investigate whether tumor size, pathological type of tumor, degree of invasiveness, hormone level, and resection rate can influence sexual function in male patients with pituitary adenomas, and thus optimize treatment options for such patients.

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PATIENTS AND METHODS

This was a retrospective cohort study involving 254 consecutive male patients diagnosed with pituitary adenomas and undergoing surgery between March 1, 2014, and December 31, 2015. Patients were selected from the Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Studies were eligible for inclusion in this review if they fulfilled the following criteria:

1. Male patients aged between 18 and 60 years with surgery as the primary treatment
2. Sexual function of patients was fully evaluated before surgery, after surgery, and 1 year after surgery as follow-up
3. Complete medical records were available, including full medical history, accurate laboratory test results, and pre- and post-surgical magnetic resonance imaging (MRI) of the head
4. All the patients were histologically diagnosed as pituitary adenoma
5. All the patients got serum testosterone tests at follow-up
6. During the follow-up, patients did not receive any other treatments.

Patients were excluded from the study if:

1. Patients had received any previous medical intervention, including radiotherapy or medical treatment
2. Medical data of patients were incomplete
3. Patients died for other reasons during the follow-up
4. SD was caused by other systemic diseases.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 2013 Helsinki Declaration. Informed written consents were obtained from all patients prior to their enrollments in this study.

Brain imaging

Brain MRI was performed prior to surgery and 1 week after surgery to confirm tumor size and the degree of resection. Tumor size was evaluated by measuring the longest width, length, and height. In accordance with the literature, pituitary adenomas were classified as either microadenomas (<1 cm in diameter), macroadenomas (1–3 cm in diameter), or giant adenomas (>3 cm in diameter).^{17–19} A combination of preoperative MRI and intraoperative visual findings was used to identify pituitary adenomas according to Hardy's classification; only grade tumors graded as either Stage III or IV were considered as being invasive of the suprasellar extension. However, according to Knosp's classification, tumors of Grade III or above are considered invasive into the cavernous sinus.^{17–21}

Evaluation of sexual function

The International Index of Erectile Function (IIEF-5) is used, a multidimensional self-reporting instrument, to evaluate male sexual function.²² The diagnosis of ED was generally based on an IIEF-5 score of 21 or less, while the severity of ED was designated according to established IIEF-5 guidelines (no ED, 22–25; mild, 17–21; mild to moderate, 12–16; moderate, 8–11; and severe, 1–7). It is considered that the degree of ED had improved following surgery if the original score had increased by three points, and that the patient's sexual function had returned to normal if the postsurgery score was 22 or more. The questionnaires used for evaluating sexual desire and ejaculation in the study were from

previous studies.^{23–25} The severity of sexual desire and ejaculation were classified into several degrees. The Index of Sexual Desire was classified as normal (4), mild (3), moderate (2), or severe (1). It is considered that the sexual desire had improved if the score had increased by one point following surgery and considered that the patient had returned to normal if the score had reached four after surgery. The Index of Ejaculation Function was graded as either normal (3), mild (2), or severe (1). It is considered that the patient had improved if the score had increased by one or more points following surgery and that the patient had returned to normal if the score had reached three points. A patient suffering any of the symptoms described above was diagnosed as having SD. Sexual function was evaluated prior to surgery and 1 year after surgery.

Patient follow-up

All patients were followed up by clinical examination, evaluation of sexual function at 3 months, 6 months, and 12 months after surgery separately. All patients were followed up by MRI studies 3 months after surgery to identify the resection rate.

Statistical analysis

Data were processed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to test the parameter distribution. Correlations were assessed using Pearson's or Spearman's method for normally or nonnormally distributed data. Unpaired two-sided Student's *t*-tests were used for comparison of means of normally distributed parameters. Mann–Whitney U-test was used for comparisons between nonnormally distributed parameters. Paired *t*-test was used to compare normal parameters while Wilcoxon signed-rank test was used for nonparametric factors. Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 254 male patients were included in our analysis. Patients' age varied from 18 to 60 years, with a mean age of 44.16 ± 10.14 years. Of the 254 patients, 2.8% (7/254) were diagnosed with microadenomas, of which 71.4% (5/7) had SD; 54.7% (139/254) were diagnosed with macroadenomas, of which 59.7% (83/139) had SD; and 42.5% (108/254) were diagnosed with giant adenomas, of which 65.7% (71/108) had SD. Of all patients recruited, 59.5% (22/37) had SD from 14.6% (37/254) patients with growth hormone (GH)-secreting adenomas; 82.8% (24/29) had SD from 11.4% (29/254) patients with prolactinomas; 55.6% (5/9) had SD from 3.5% (9/254) patients with thyroid-stimulating hormone (TSH)-secreting adenomas; 76.0% (38/50) had SD from 19.7% (50/254) patients with gonadotroph adenomas; and 62.5% (10/16) suffered from SD from 6.3% (16/254) patients with adrenocorticotrophic hormone (ACTH)-secreting adenomas. To sum up, 70.2% (99/141) patients had SD from 55.5% (141/254) with functioning pituitary adenomas (FPAs). Besides, 53.1% (60/113) patients suffered from SD from 44.5% (113/254) patients with nonfunctioning pituitary adenomas (NFPAs). In addition, 44.9% (114/254) patients came to hospital with a complaint about hyposexuality; 36.6% (93/254) patients came to hospital with a complaint about having difficulty with ejaculation.

Table 1 shows the baseline demographics and clinical characteristics of our patient population as categorized by preoperative pituitary adenoma size. These demographics and clinical characteristics were significantly different compared between different sizes of pituitary adenoma when considered in terms of vertical size, suprasellar extension, infrasellar extension, parasellar extension, ED, the extent

of tumor resection, and testosterone level ($P < 0.05$). The incidence of SD in male patients with pituitary adenomas was much higher than that in the Chinese population ($P < 0.05$).

Patients with larger tumors exhibited lower mean IIEF-5 scores (microadenomas: 21.00 ± 1.00 ; macroadenomas: 19.18 ± 3.32 ; and giant adenomas: 18.12 ± 3.56 ; $P = 0.019$). These data showed that patients with larger tumors exhibited a higher incidence of ED. As tumor size increased, mean serum testosterone level decreased (microadenomas: 2.54 ± 0.88 ng ml⁻¹; macroadenomas: 1.91 ± 1.42 ng ml⁻¹; and giant adenomas: 1.54 ± 1.48 ng ml⁻¹; $P = 0.025$).

Tumor size and sexual function

Of the 254 patients selected, 62.6% (159/254) suffered from SD prior to surgery. Since prolactinomas secrete prolactin, which may disturb the effect of tumor volume upon SD, patients with prolactinomas were from the study investigating the specific relationship between tumor size and sexual function. Thus, 225 patients were included in the final analysis, of which 60.0% (135/225) suffered from SD prior to surgery. **Table 2** shows sexual function data categorized by tumor size prior to surgery. Tumor size was significantly different when analyzed according to index of ED ($P = 0.004$), sexual desire ($P = 0.021$), and ejaculation function ($P = 0.001$). When follow-up data regarding improvement in sexual function in patients with SD prior to surgery were analyzed according to tumor size, we observed that the extent of improvement in sexual function differed significantly with tumor size ($P < 0.05$) (**Figure 1a**).

Of the patients without prolactinomas who had SD prior to surgery, 99.3% (134/135) suffered from ED, 68.1% (92/135) patients suffered from hyposexuality, and 54.1% (73/135) suffered ejaculation dysfunction. **Figure 1b** shows the relationship between preoperative and follow-up IIEF-5 as categorized by preoperative pituitary adenoma size. The improvement of ED at follow-up was significantly different when compared between pre- and post-surgery in patients with microadenomas, macroadenomas, and giant adenomas ($P < 0.05$). There was no significant difference between preoperative and follow-up sexual desire or ejaculation function when categorized by preoperative tumor size ($P > 0.05$).

Resection rate and sexual function

In total, there are 159 patients with SD before surgeries. 64.3% (45/70) patients with total resection got complete recovery from SD; 7.9% (7/89) patients with partial resection got complete recovery from SD. There was a significant difference between resection rate and the improvement of sexual function at follow-up. Moreover, patients with total resection achieved better levels of improvement ($P < 0.01$).

Histological type of pituitary adenomas and sexual function

Of all patients recruited, 70.2% (99/141) patients from 141 patients with FPAs suffered from SD; 53.1% (60/113) patients from 113 patients with NFPAs suffered from SD. The incidence of SD in patients with FPAs was much higher than that in patients with NFPAs ($P = 0.014$). **Figure 2** shows the incidence of SD among

Table 1: Baseline demographics and characteristics categorized by preoperative pituitary adenoma size

Variable	Total (n=254)	Microadenomas (n=7)	Macroadenomas (n=139)	Giant adenomas (n=108)	P
Characteristics					
Age (year, mean±s.d.)	44.16±10.14	45.57±7.25	43.96±10.41	44.33±10.00	0.789 ^a
Tumor vertical size (mm, mean±s.d.)	29.06±11.15	8.00±1.73	22.71±5.38	38.60±9.12	<0.001 ^a
Tumor extension					
Suprasellar extension, n (%)	165 (65.0)	0	71 (51.1)	94 (87.0)	<0.001 ^b
Infrasellar extension, n (%)	122 (48.0)	0	49 (35.3)	73 (67.6)	<0.001 ^b
Parasellar extension, n (%)	153 (60.2)	0	68 (48.9)	85 (78.7)	<0.001 ^b
Sexual function					
Sexual dysfunction, n (%)	159 (62.6)	5 (71.4)	83 (59.7)	71 (65.7)	0.618 ^b
IIEF-5, mean±s.d.	18.78±3.44	21.00±1.00	19.18±3.32	18.12±3.56	0.019 ^a
Hyposexuality, n (%)	114 (44.9)	3 (42.9)	51 (36.7)	60 (55.5)	0.191 ^b
Ejaculation dysfunction, n (%)	93 (36.6)	0	41 (29.5)	52 (48.2)	0.17 ^b
Total resection, n (%)	137 (53.9)	7 (100.0)	81 (58.3)	49 (45.4)	0.028 ^b
Hormone					
PRL (ng ml ⁻¹ , median [25%, 75%])	13.30 (7.94, 23.31)	7.12 (6.33, 14.00)	14.38 (8.38, 28.80)	12.00 (7.87, 20.00)	0.81 ^a
T (ng ml ⁻¹ , mean±s.d.)	1.75±1.48	2.54±0.88	1.91±1.42	1.54±1.48	0.025 ^a
LH (mIU ml ⁻¹ , median [25%, 75%])	2.56 (1.45, 4.07)	2.94 (1.72, 4.17)	2.62 (1.42, 4.06)	2.26 (1.45, 4.13)	0.452 ^a
FSH (mIU ml ⁻¹ , median [25%, 75%])	5.31 (3.34, 8.58)	7.88 (5.55, 8.82)	5.43 (3.64, 8.44)	5.05 (3.15, 8.77)	0.146 ^a

Data described as mean±s.d. when normally distributed, median when nonnormally distributed for continuous variables and n (%) for categorical variables. ^aMeans are analyzed using a Type III sum of squares ANOVA: PROC GLM model=Treatment sequence; ^bFrequencies are analyzed using Pearson's Chi-square test. IIEF-5: international Index of Erectile Function; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin; s.d.: standard deviation; T: testosterone

Table 2: Sexual function as categorized by tumor size prior to surgery

Variable	Total (n=225)	Microadenomas (n=7)	Macroadenomas (n=121)	Giant adenomas (n=97)	P
Sexual dysfunction, n (%)	135 (60.0)	5 (71.4)	67 (55.4)	63 (64.9)	0.294 ^a
Sexual function					
IIEF-5, mean±s.d.	19.05±3.42	21.00±1.00	19.56±3.26	18.22±3.51	0.004 ^b
Hyposexuality, n (%)	95 (41.3)	3 (42.9)	37 (30.6)	53 (54.7)	0.021 ^a
Ejaculation dysfunction, n (%)	76 (33.0)	0 (0)	27 (22.3)	47 (48.5)	0.001 ^a

^aFrequencies are analyzed using Pearson's Chi-square test; ^bMeans are analyzed using a Type III sum of squares ANOVA: PROC GLM model=Treatment sequence. IIEF-5: International Index of Erectile Function; s.d.: standard deviation



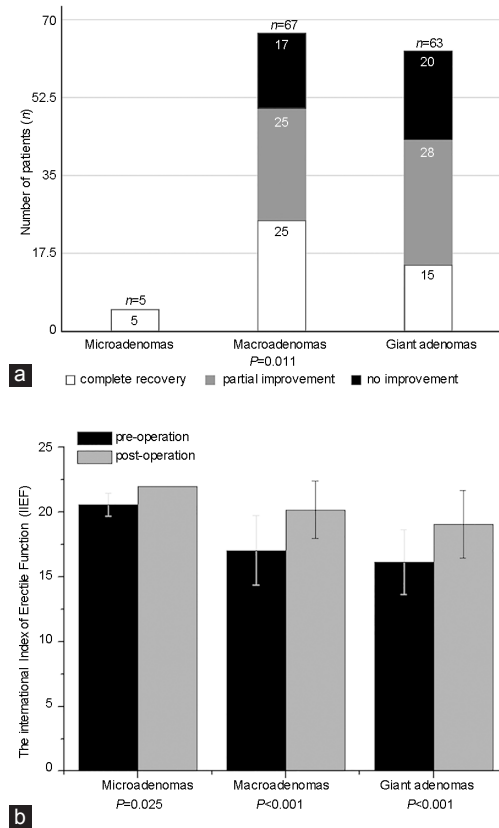


Figure 1: (a) Follow-up of sexual function as categorized by tumor size. (b) Relationship between preoperative and follow-up IIEF-5 as categorized by preoperative pituitary adenoma size. *P* value is analyzed using Pearson's Chi-square test in (a) and paired Student's *t*-test in (b). IIEF-5: International Index of Erectile Function.

FPA and NFPAs before surgery associated with the size of tumor. In the patients with macroadenomas, the incidence of SD with FPA was much higher than that in patients with NFPAs ($P = 0.038$). Besides, there were no significant differences in giant adenoma patients ($P > 0.05$).

According to the pathological types of pituitary adenomas, 14.6% (37/254) patients were diagnosed with GH-secreting adenomas, of which 59.5% (22/37) suffered from SD; 11.4% (29/254) were diagnosed with prolactinomas, of which 82.8% (24/29) suffered from SD; 3.5% (9/254) were diagnosed with TSH-secreting adenomas, of which 55.6% (5/9) suffered from SD; 19.7% (50/254) were diagnosed with gonadotroph adenomas with clinically relevant luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, of which 76.0% (38/50) suffered from SD; 6.3% (16/254) were diagnosed with ACTH-secreting adenoma, of which 62.5% (10/16) suffered from SD; and 44.5% (113/254) were diagnosed with NFPAs, of which 53.1% (60/113) suffered from SD (Figure 3a). Of all types of pituitary adenomas, the prevalence of SD was highest in the patients with prolactinomas, closely followed by patients with gonadotroph adenomas; this level of incidence was much higher than that observed for patients with NFPAs ($P < 0.01$).

The incidence of SD among different pathological types of pituitary adenomas when considered pre- and post-surgery is shown in Figure 3b. There was a significant difference in the incidence of SD before and after surgery in patients with GH-secreting adenomas ($P < 0.01$), prolactinoma patients ($P < 0.01$), gonadotroph

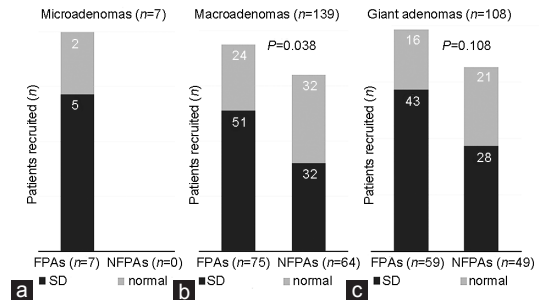


Figure 2: Incidence of sexual dysfunction (SD) among FPA and NFPAs before surgery according to the size of tumor, including (a) microadenomas, (b) macroadenomas, and (c) giant adenomas. FPA: functioning pituitary adenomas; NFPAs: nonfunctioning pituitary adenomas. *P* value is analyzed using Pearson's Chi-square test.

adenomas ($P < 0.01$), ACTH-secreting adenomas ($P < 0.05$), and NFPAs ($P < 0.01$).

Twenty-two (91.2%) patients with prolactinomas got improvement from SD. Thirty-five (92.1%) patients with gonadotroph adenomas got improvement from SD. Forty (66.7%) patients with NFPAs got improvement from SD. There was a significant difference in the improvement rate of SD following surgery when compared between patients with prolactinomas and NFPAs ($P = 0.037$) and between patients with gonadotroph adenomas and NFPAs ($P = 0.008$).

Serum testosterone level and sexual function

The mean concentration of serum testosterone of our patients prior to surgery was 1.75 ± 1.48 ng ml⁻¹, which was lower than normal levels (2.80–8.00 ng ml⁻¹) ($P < 0.05$). The mean concentration of serum testosterone prior to surgery in patients without SD was 2.29 ± 1.38 ng ml⁻¹, which was higher than that of patients with SD (1.42 ± 1.45 ng ml⁻¹; $P < 0.001$). One hundred and fifty-nine patients suffered from SD prior to surgery. Figure 4a shows the mean concentration of serum testosterone of the patients with SD before surgery and 3 months, 6 months, and 12 months after surgery (preoperation: 1.42 ± 1.45 ng ml⁻¹; 3 months after surgery: 0.96 ± 1.24 ng ml⁻¹; 6 months after surgery: 3.58 ± 1.52 ng ml⁻¹; and 12 months after surgery: 3.62 ± 1.46 ng ml⁻¹). The patients' serum testosterone levels got increased 6 months after surgery than that before surgery ($P < 0.001$) (Figure 4b). However, they did not get improved after 6 months for that there is no significant difference between 6 months after surgery and 12 months after surgery in serum testosterone level ($P > 0.05$).

In our study, 159 patients suffered from SD prior to surgeries. The relationship between testosterone level and improvement in sexual function was evaluated 6 months after surgery. Thirty-nine (75.0%) patients with normal testosterone level got complete recover from SD; 13 (12.1%) patients with abnormal testosterone level got complete recover from SD. There was a significant difference in patients whose testosterone returned to normal levels within 6 months of surgery ($P < 0.001$).

DISCUSSION

The anterior lobe of the pituitary gland is linked to the hypothalamus by the hypothalamic-hypophyseal portal system. Thus, blood from the hypothalamus that contains high concentrations of hypothalamic hormones is delivered directly to the adenohypophysis. Hypothalamic hormones then stimulate or inhibit the release of anterior pituitary hormones. The hormones mediate many

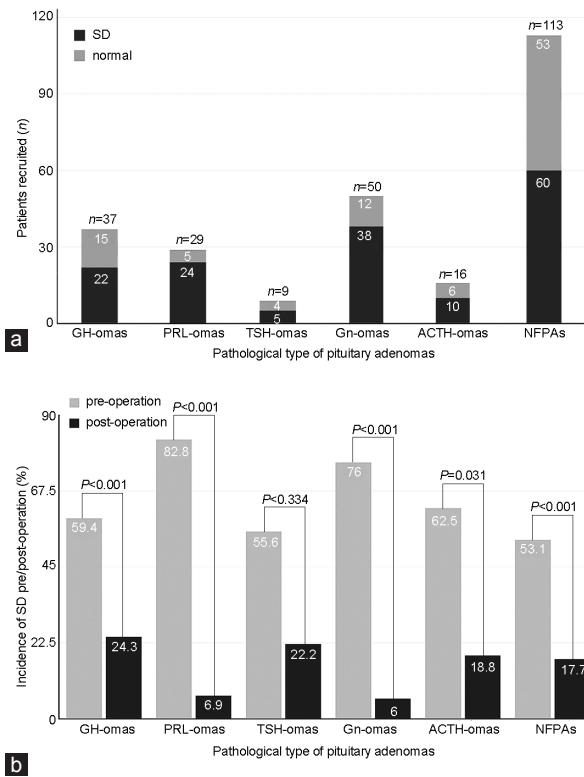


Figure 3: (a) Incidence of sexual dysfunction (SD) among different pathological types of pituitary adenomas. (b) Incidence of SD among different pathological types of pituitary adenomas when considered pre- and post-surgery. *P* value is analyzed using Pearson's Chi-square test. ACTH-omas: adrenocorticotrophic hormone-secreting adenomas; Gn-omas: gonadotroph adenomas; GH-omas: GH-secreting adenomas; NFPAs: nonfunctioning pituitary adenomas; PRL-omas: prolactinomas; TSH-omas: TSH-secreting adenomas.

physiological functions of the human including reproductive organs.^{26,27} Pituitary adenomas are usually considered as benign tumors derived from adenohypophysis and can present either as a result of the hypersecretion of pituitary hormones and/or a result of local space-occupying effects and the hyposecretion of some or all of the pituitary hormones.^{1,17–19,21,28} As a direct consequence, patients with pituitary adenomas not only suffer from headache, visual impairment, and acromegaly, but also suffer from lactation, sterility, irregular menstrual cycles and gynecomastia in females, and SD in males.

Of the total number of patients suffering from SD, estimated 1%–5% are diagnosed with pituitary adenomas. However, the pathological type of these adenomas represents a major risk factor for SD, which results in the prevalence of SD in patients with FPAs being much higher than that in patients with NFPAs.⁸ The incidence of SD in our patients was much higher than that in normal Chinese males. More than half of the male patients with pituitary adenomas in the study suffered from SD, which bothered them a lot. Therefore, it is very important to focus on this issue to let the male patients with pituitary adenomas have a better future life. The main types of pituitary adenoma include prolactinomas, clinically NFPAs, GH-secreting adenomas, ACTH-secreting adenomas, TSH-secreting adenomas, and gonadotroph adenomas with clinically relevant LH and FSH secretion. Of these, prolactinomas and gonadotroph adenomas are the main causes for clinical SD.^{18,19,21}

In the study population, more patients with FPAs suffered from SD before surgery, which was consistent with previous researches.

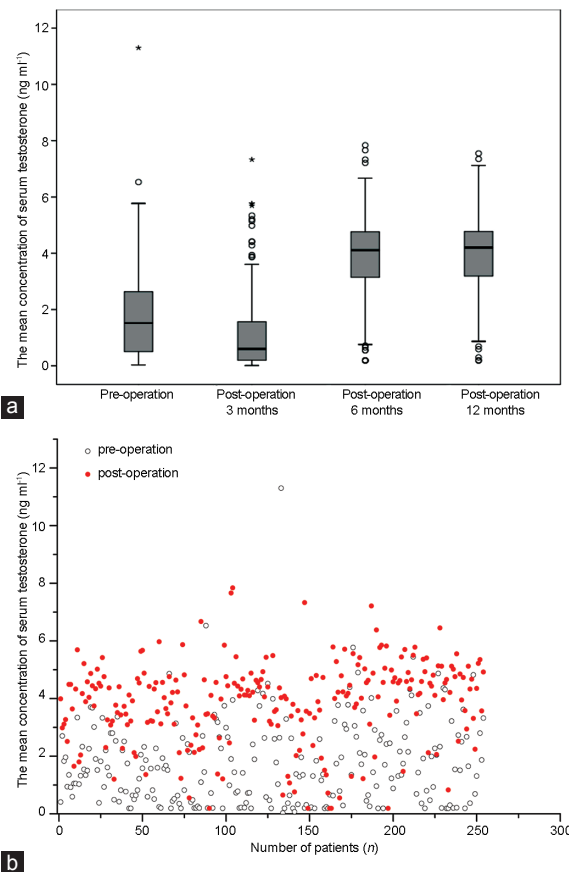


Figure 4: (a) The mean concentration of serum testosterone of the patient with sexual dysfunction (SD) before surgery and 3 months, 6 months, and 12 months after surgery. (b) Patients' serum testosterone level before surgery and 6 months after surgery. *P* value is from paired *t*-test.

Furthermore, in the patients with macroadenomas, more patients had SD. However, this did not happen in the patients with giant adenomas, both FPAs and NFPAs had high rates of SD. Besides, the incidence of SD was highest in patients with prolactinoma (82.8%), and the second highest incidence was in patients with gonadotroph adenoma (76%), much higher than in patients with NFPAs (53.1%). This is consistent with data reported previously.²¹ Except for patients with TSH-secreting adenoma, it could be found that the symptom of SD was improved in all patients following surgical therapy. In addition, of the patients suffering from SD prior to surgery, 91.7% were diagnosed with prolactinoma and 92.1% with gonadotroph adenoma and showed improvement in SD postsurgery; these rates of improvement were both higher than those in patients with NFPAs.

In our opinion, both the compression effect and endocrine function of the tumor itself could influence the normal function of the hypothalamic-hypophyseal portal system, thus creating SD in male patients. NFPAs do not secrete hormones and thus influence sexual function in patients via local space-occupying effects. FPAs such as prolactinomas and gonadotroph adenomas not only exhibit local space-occupying effects but can also secrete endocrine hormones such as prolactin, LH, and FSH, thus causing SD. Consequently, SD in patients with prolactinoma and gonadotroph adenoma was more extensive than in NFPAs patients. When tumors were removed by surgery, the pituitary gland was no longer compressed, and without the endocrine function of tumors, hormone levels soon returned to normal.

Lotti *et al.*²⁹ found that patients with complicated acromegaly were at an increased risk of developing ED, especially those with cardiovascular morbidities. They also found that there was no correlation between ED and serum GH and testosterone levels. ED occurred in acromegalic patients mainly because of the psychological component. Except for the function of hormone on patients, body appearance changes and chronic diseases were also caused by GH abnormal secretion, such as acromegaly and cardiovascular morbidities, which made GH patients have no desire in sex. According to the size of tumor, only in the patients with macroadenomas, the incidence of SD with FPAs was much higher than that in the patients with NFPAs. But with the giant adenomas, majorities suffered from SD both in FPAs and NFPAs. It indicated in patients with microadenomas or macroadenomas, the causing of SD was mainly hormones secretion rather occupying effects, and the tumor was no big enough to compress the pituitary gland causing SD. Hence, most SD patients with microadenomas or macroadenomas were FPAs. In giant adenomas, the elevated rate of SD could be the consequence of pituitary stalk compression by tumor itself even in the NFPAs. Most patients with giant adenomas had SD regardless of the pathological type of tumors. It can be said that the effect of hormone was more obvious than that of volume whether the patients had SD in microadenomas or macroadenomas. In giant adenomas, the occupation effect is obvious enough to cause SD no matter which type of tumor was. We also obtained similar results when we studied the relationship between tumor volume and SD. The compression of the tumor can cause the disorder of pituitary secretion, which would cause many clinical symptoms including SD.

All of our patients suffering from SD achieved a certain degree of improvement following surgery. The reason why the rate of SD improvement in patients with prolactinoma and gonadotroph adenoma was higher than that of NFPAs patients is complex. It was believed that on the one hand, there were more macroadenomas in NFPAs than in prolactinomas and gonadotroph adenomas. This created a long-term occupying effect and made it difficult to achieve complete resection; collectively, this reduced the effects of surgery in patients with SD to a level lower than that seen in patients with NFPAs. On the other hand, without disturbing the secretion of hormones from a functional tumor, in the study, there were more patients with a normal hormonal level following surgeries for prolactinomas and gonadotroph adenomas than for NFPAs. The surgical effect of SD upon prolactinomas and gonadotroph adenomas was therefore more obvious.

In an earlier study, Wu *et al.*²⁴ surveyed a random population of 3369 men between 40 and 79 years of age at eight European centers. Their studies revealed that symptoms of poor morning erection, low sexual desire, ED, inability to perform vigorous activity, depression, and fatigue were significantly related to the levels of serum testosterone.²⁴ In the present study, it could be found that there was not only an inverse relationship between decreasing testosterone level and increasing incidence of SD before surgery but also an inverse relationship between decreasing testosterone level and increasing incidence of SD following surgery. At the same time, surgical therapy could increase patients' serum testosterone. With surgical procedure influencing the normal function of pituitary, the patients' serum testosterone did not get increased at the first 3 months after surgery. But at 6 months after surgery, the patients' serum testosterone got increased. Furthermore, there was no significant difference in serum testosterone between 6 months and 12 months after surgery. We could predict the patients' outcome about serum testosterone level 1 year after surgery from the result at 6 months after surgery. Whether the testosterone level returned to normal following surgery would determine the rate of recovery from

SD. More patients achieved improvement in SD when they had normal testosterone levels following surgeries. SD outcome should be routinely evaluated by testing testosterone level 6 months after surgery. To sum up, patients' serum testosterone level gets increased significantly after surgery and the level of testosterone 6 months after surgery can be used as a sensitive indicator to predict the postsurgical recovery rate of sexual function in patients with pituitary adenomas.

Rogers *et al.*³⁰ discovered that tumor size in patients with pituitary adenoma has a direct impact upon prognosis following surgery and that 50%–60% of patients with macroadenomas would show improvements in hyposecretion, much lower than the number of patients with microadenomas (60%–95%). In the study population, patients with macroadenomas or giant adenomas were associated with lower IIEF-5 scores and higher rates of hyposexuality or ejaculatory problems, which meant that these patients were associated with a higher probability of being compromised by SD. It could be considered that the size of microadenomas was relatively small and only caused minimal compression upon the pituitary gland, and that the relative impact upon normal endocrine function of the pituitary gland was therefore limited. However, macroadenomas and giant adenomas were able to compress the pituitary gland easily and could even cause severe compression to the pituitary stalk and hypothalamus as a result of the larger volume of tumor. In addition, almost half of our patients (44.5%) were diagnosed with NFPAs. These tumors did not have an endocrine function and did not affect the hypothalamic-hypophyseal portal system. Prolactinoma patients were excluded when analyzing the potential relationship between tumor size and sexual function. Tumor volume was one of the determinants underlying SD in patients with pituitary adenoma. Thus, patients with macroadenomas or giant adenomas had a higher probability of suffering from SD than patients diagnosed with microadenomas. Patients with macroadenomas achieved a significantly higher IIEF-5 score following surgery than other patients. Following removal of the tumor, the problems of local space-occupying effects were solved and SD patients readily achieved notable improvement in sexual behaviors. In patients with giant adenoma, the tumor had already caused irreversible damage to the pituitary, largely because of the larger tumor volume and the greater exposure to space-occupying effects. Indeed, SD problems in patients with giant adenoma could not be solved with surgery. Consequently, surgical therapy represents an effective treatment for patients to achieve a certain degree of relief for both ED and SD.

In the present study, patients with microadenomas would achieve significant improvement in SD following surgical therapy, but this was not evident in patients with macroadenomas or giant adenomas. Microadenomas exert little impact upon the pituitary gland and such tumors can be completely resected surgically. With tumor resected, hypothalamic-hypophyseal system could work back to normal without abnormal hormone affection, patient's hormone levels could return back to normal. As the concentration of serum testosterone increased, it became possible to relieve the symptoms of SD significantly. However, in the case of macroadenomas or giant adenomas, it would first take a long time to produce a tumor with such large volumes. Furthermore, the tumor would compress upon the pituitary gland, pituitary stalk, and hypothalamus for a long time, which could cause irreversible damage. Since it is difficult to completely resect macroadenomas and giant adenomas, such notable levels of compression could be continued. For some large FPAs, hormone levels can return to normal with only partial resection and the function of the hypothalamic-hypophyseal system would be continually compromised. Surgical therapy is far less likely to rectify SD problems in patients with macroadenomas or giant adenomas than in patients with microadenomas. Consequently, it is

possible to predict the course of postoperative improvement in the SD of patients with pituitary adenoma, and who suffered from SD prior to surgery, by considering both tumor size and the rate of resection.

The limitation of our study mostly is that our study is a single-center research and most of patients in our hospital are from North China, which cannot fully present the patients all around China. Another limitation is that most of our patients went back to their hometown for future hormone replace treatments, it was hard for us to collect their secondary treatment data. The last limitation is that we failed in getting the results of sex hormone-binding globulin (SHBG) and free testosterone, which were very important indexes of evaluating sexual function in patients.

CONCLUSIONS

Tumor volume, the histological type of pituitary adenoma, and the concentration of serum testosterone all represent predictable factors which can influence the sexual function of male patients with pituitary adenomas prior to surgery. Surgical therapy can therefore be optimized for improvements in SD. Testosterone level also represents as a sensitive indicator with which to predict the postoperative recovery rate of sexual function in patients with pituitary adenomas and the serum testosterone level will stay stable in 6 months after surgery.

AUTHOR CONTRIBUTIONS

WJLZ carried out the studies, participated in the data analysis, and drafted the manuscript. SCM, MZ, CL, XDG, ZSB, and GJJ carried out the data collection and performed the statistical analysis. WJ conceived of the study, participated in its design and coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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