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ORIGINAL ARTICLE

The factors associated with the persistence of hypogonadism in male patients with prolactinoma

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Abstract

PURPOSE: It was aimed to compare the testosterone level during the treatment and the factors associated with the persistence of hypogonadism in prolactinoma.
MATERIAL AND METHODS: Thirty-five patients with hypogonadism who were diagnosed with prolactinoma were recruited to this retrospective study. Age, hemoglobin, hematocrit, glucose, lipid parameters, prolactin, follicle-stimulating hormone, luteinizing hormone, total testosterone, and the adenoma size were compared at the baseline and 6th month of the treatment. The parameters were also compared between the patients with hypogonadism (n=8) and the patients without hypogonadism at the 6th month of the treatment (n=27). Correlation analysis was also performed in terms of parameters that may be associated with the testosterone levels at the 6th month of the treatment.
RESULTS: The mean current age of the whole study group was 45.6±13.0 years, and the mean adenoma size was 23.9±11.4 mm. Thirty patients had macroadenoma, and five patients had microadenoma. Eight patients (23%) had low testosterone levels and hypogonadism symptoms at the 6th month of the prolactinoma treatment. The adenoma size was larger in patients with persistent hypogonadism than the patients without hypogonadism at the 6th month of the treatment, while the prolactin levels were similar between the groups, and macroadenoma was detected in all patients with persistent hypogonadism. A negative correlation was found between the testosterone levels at the 6th month of the prolactinoma treatment with the adenoma size.
CONCLUSION: Adenoma size is the prominent factor than prolactin levels for predicting persistent hypogonadism in patients with male prolactinoma.

Abbreviations:
LH - luteinizing hormone
FSH - follicle-stimulating hormone
LDL - low-density lipoprotein
HDL - high-density lipoprotein

INTRODUCTION

Prolactin hormone is only synthesized and secreted from pituitary lactotroph cells (Melmed 2003; Bole-Feysot *et al.* 1998; Melmed *et al.* 2011). Estrogen, thyrotropin-releasing hormone, epidermal growth factor, and dopamine are the factors that affect prolactin synthesis and secretion. The main effect

of the prolactin hormone is to stimulate and maintain lactation (Melmed 2003; Bole-Feysot *et al.* 1998; Melmed *et al.* 2011). Hyperprolactinemia is almost entirely caused by diseases that cause excessive prolactin secretion by lactotroph cells, and some of these causes are physiological (Melmed 2003; Bole-Feysot *et al.* 1998). Apart from physiological reasons, an increased level of prolactin is also observed due to pharmacological and pituitary reasons (Melmed 2003; Bole-Feysot *et al.* 1998; Melmed *et al.* 2011). Lactotroph adenomas are the most common functional pituitary tumors and are seen four times more frequently in women than men (Fernandez *et al.* 2010). The prolactin level secreted by the lactotroph adenoma is related to the size of the adenoma. Therefore, prolactin levels higher than 250 ng/mL are usually observed in macroadenoma with a size larger than 1 cm (Melmed *et al.* 2011).

Increased prolactin levels inhibit hypothalamic gonadotropin-releasing hormone, and as a result, LH (luteinizing hormone), and FSH (follicle-stimulating hormone), levels decrease (Saitoh *et al.* 1990). Therefore regardless of the etiology, hyperprolactinemia causes hypogonadism in men and women by inhibiting gonadotropins (Klibanski 2010; Saitoh *et al.* 1990). Deterioration in menstrual functions (amenorrhea, oligo amenorrhea) is commonly observed in women. Impotence, loss of libido, infertility, weakness, decrease in muscle strength, decrease in facial body hair, and osteopenia/osteoporosis occur due to hypogonadism in men (Bhasin *et al.* 2018; Matsumoto 2016). Male patients with hypogonadism also had a higher risk of deterioration in metabolic parameters, including lipid profile and glucose metabolism, due to low testosterone levels (Bhasin *et al.* 2018).

The first treatment option in prolactinoma is a medical treatment with dopamine agonists in patients with microadenoma and also macroadenoma (Colao *et al.* 2002; Cooper & Greenman 2018). Prolactin level begins to decrease within days, but it may take a few months to return to normal, and tumoral shrinkage occurs within weeks with medical treatment (Melmed *et al.* 2011; Klibanski 2010). Surgical treatment may be considered in case of resistance and intolerance to cabergoline, visual impairments, and apoplexy in macroadenoma (Klibanski 2010; Melmed *et al.* 2011). Treatment with dopamine agonists and/or surgery is effective the restoring gonadal function and could improve the symptoms of hypogonadism. The persistence of the hypogonadism was reported in different series despite the treatment of prolactinoma (Andereggen *et al.* 2017; Colao *et al.* 2004; Shimon 2019; Tirosh *et al.* 2015).

In the present study, it was aimed to compare the testosterone level during the treatment and the factors associated with the persistence of hypogonadism in prolactinoma patients presented with hypogonadism.

MATERIAL AND METHOD

The present study was a cross-sectional and retrospective study. The medical files of 55 male prolactinoma patients with laboratory and/or clinical findings

Tab. 1. Characteristics of patients in terms of clinical and laboratory findings at the beginning

N=35	Mean±SD or N	Min-Max
Age (years)	45.6±13.0	19-72
Pituitary adenoma size (mm)	23.9±11.4	4-48
Macroadenoma (n) / microadenoma (n)	30/5	
Patients with giant adenoma (n)	4	
Patients with pituitary surgery (n) / without pituitary surgery (n)	3/32	
Hemoglobin (g/dL)	13.5±0.8	12-15
Hematocrit (%)	40.4±3.7	36-51
Glucose (mg/dL)	120.2±43.7	84-269
Total cholesterol (mg/dl)	225.0±55.4	169-347
Triglyceride (mg/dl)	253.5±172.2	63-534
LDL cholesterol (mg/dl)	138.1±39.6	105-231
HDL cholesterol (mg/dl)	39.0±6.7	26-45
Prolactin (pg/mL)	1838.9±2714.4	120-16100
FSH (mIU/mL)	4.0±2.6	0.6-13.9
LH (mIU/mL)	2.4±1.3	0.4-5.6
Total testosterone (ng/mL)	1.7±0.8	0.1-3.8
Patients with hypopituitarism (n) / without hypopituitarism (n)	4/31	

Mean±SD, mean±standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Tab. 2. Comparison of the patients at the beginning and 6th month of the treatment in terms of clinical and laboratory findings

N=35	Patients at the beginning	Patients at 6th month of the treatment	*p*
Pituitary adenoma size (mm)	23.9±11.4	12.5±8.0	***< 0.001***
Hemoglobin (g/dL)	13.5±0.8	13.8±1.2	*NS*
Hematocrit (%)	40.4±3.7	41.1±3.1	***0.02***
Glucose (mg/dL)	120.2±43.7	102.8±22.2	***0.006***
Total cholesterol (mg/dl)	225.1±55.4	206.6±29.8	*NS*
Triglyceride (mg/dl)	253.4±172.2	175.1±84.7	***0.03***
LDL cholesterol (mg/dl)	138.1±39.6	124.8±26.2	*NS*
HDL cholesterol (mg/dl)	39.0±6.7	41.8±7.0	*NS*
Prolactin (pg/mL)	1839.2±2714.3	18.4±20.3	***< 0.001***
FSH (mIU/mL)	4.0±2.6	5.8±4.9	***< 0.001***
LH (mIU/mL)	2.4±1.3	3.7±1.8	***< 0.001***
Total testosterone (ng/mL)	1.7±0.8	3.2±1.6	***< 0.001***

Data were given as mean±standard deviation.
$P < 0.05$ statistically significant. Significant p-values are shown in bold.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

of hypogonadism between the years 2015 and 2021 were reviewed. Patients with additional chronic disease and receiving testosterone replacement therapy were excluded from the study. Thirty-five male patients with the symptoms (impotence, infertility, and decreased libido) and laboratory findings of hypogonadism who were diagnosed with prolactinoma and had documented long-term follow-up data (> 1 year) were recruited to the study.

The diagnosis of prolactinoma was defined as the presence of sustained hyperprolactinemia and the radiographic evidence of pituitary adenoma (without evidence of pituitary stalk compression). Hypopituitarism was also defined as impaired secretion of one or more pituitary hormones (Higham *et al.* 2016).

Age, hemoglobin, hematocrit, glucose, total cholesterol, triglyceride, LDL (low-density lipoprotein) cholesterol, HDL (high-density lipoprotein) cholesterol, prolactin, FSH, LH, total testosterone, size of the pituitary adenoma were recorded at the baseline and 6th month of the treatment. The normal values of parameters in our center are as follows: hemoglobin, 12.9–15.9 g/dL; hematocrit, 39–49 %; glucose, 74-106 mg/dL; total cholesterol, 90-200 mg/dL; triglyceride, <150 mg/dL; LDL cholesterol, <100 mg/dL; HDL cholesterol, 40-60 mg/dL; prolactin, 2.64-13.13 ng/mL; FSH, 1.27-19.26 mIU/mL; LH, 1.24-8.62 IU/L; total testosterone, 2.7–10 ng/ml (for men aged 20–50 years), and 2.4-8 ng/mL (aged > 50 years).

Total testosterone level was measured by the chemiluminescence method using a Beckman Coulter Analyzer. Androgen deficiency was defined in patients with hypogonadism, and two consecutively fasting total testosterone concentrations measurements were used for the diagnosis.

The cabergoline treatment was started at 0.25 mg/weekly in the first week, and then dose adjustment was based on prolactin levels and clinical follow-up of the patients. The cabergoline doses used by the patients for six months were recorded, and the cumulative cabergoline dose in 6th month of the treatment was calculated in all patients.

A conventional 1.5-T pituitary MRI was conducted at diagnosis and at follow-up. Tumor diameter of between 1-10 mm was defined as microadenoma, > 10 mm as macroadenoma, and > 40 mm as giant macroadenoma. Surgery was recommended in patients with local complications of the adenoma (apoplexy, visual impairments, cystic tumors, etc.) and in case of resistance and intolerance to medical treatment.

The patients were compared in terms of age, hemoglobin, hematocrit, glucose, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, prolactin, FSH, LH, total testosterone, size of the pituitary adenoma at the baseline and at the 6th month of treatment.

The patients with low testosterone levels and hypogonadism symptoms at the 6th month were defined, and the patients with and without hypogonadism at the 6th month were compared in terms of the baseline pituitary adenoma size and the baseline prolactin levels.

The correlations analysis was performed between the total testosterone levels at 6th month with the clinical and laboratory parameters both at the baseline and at 6th month of the treatment in the whole study group.

Statistical analyses were performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation (SD). The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. The

Tab. 3. Comparison of the patients according to the gonadal status at the 6th month of the treatment

N=35	Patients with hypogonadism n=8	Patients without hypogonadism n=27	*p*
Age (years)	50.6±11.9	44.1±13.1	*NS*
Macroadenoma (n) / microadenoma (n)	8/0	22/5	
Patients with giant adenoma (n)	2	2	
Patients with pituitary surgery (n)	1	2	
Pituitary adenoma size (mm) (at the beginning)	31.8±10.3	21.6±10.7	***0.024***
Pituitary adenoma size (mm) (at the 6th month of the treatment)	14.7±7.5	11.8±8.3	*NS*
Normalization of prolactin levels (n) (at the 6th month of the treatment)	6	23	*NS*
Prolactin (pg/mL) (at the beginning)	2015.5±1384.7	1786.6±3017.7	*NS*
Prolactin (pg/mL) (at the 6th month of the treatment)	16.4±18.0	19.0±21.2	*NS*
Total testosterone (ng/mL) (at the beginning)	0.6±04	2.0±0.6	***< 0.001***
Total testosterone (ng/mL) (at the 6th month of the treatment)	1.9±0.5	3.8±1.1	***< 0.001***
LH (mIU/mL) (at the beginning)	1.4±1.1	2.8±1.2	***0.001***
LH (mIU/mL) (at the 6th month of the treatment)	1.9±0.5	4.2±1.6	***< 0.001***
The cumulative cabergolin dose (mg/six months)	17.0±4.4	17.9±4.3	*NS*

Data were given as mean ±standard deviation.
$P < 0.05$ statistically significant. Significant p-values are shown in bold.
LH, luteinizing hormone.

student's t-test was performed for normally distributed numeric variables, and the Mann-Whitney U test was performed for non-normally distributed data for independent group comparison. Wilcoxon signed-rank test was used to evaluate paired differences of the levels before and after the treatment. Correlations were expressed by Pearson's correlation analysis or Spearman's correlation analysis when indicated. The logistic regression analysis was used to realize the variables were the predictors of hypogonadism persistence at the 6th month. Enter method selection was used with variables with a p-value. Statistically significant results were defined with a *p*-value of < 0.05.

RESULTS

Thirty-five male prolactinoma patients with hypogonadism were included in the study. Characteristics of patients at the baseline were summarized in table 1. All patients with hypopituitarism had macroadenoma, and one of these patients had pituitary surgery. The cabergoline drug was given in weekly doses to all patients for six months without interruption, and total cabergoline doses were calculated. The cumulative cabergoline dose in the whole study group at 6th month of the treatment was 17.5 ± 4.3 mg/6 months. The group comparison of the patients between at the beginning and at the 6th month of the treatment was presented in table 2.

All patients had low testosterone levels at the baseline in our study group. Despite the fact that normalization of prolactin levels in 83% of all patients, eight patients (23%) had low testosterone levels and hypogonadism symptoms at the 6th month of the treatment. Normalization of prolactin levels was observed in six of eight patients (75%) in patients with persistent hypogonadism at the 6th month of the treatment. The mean adenoma size at baseline was 31.8 ± 10.3 mm in patients with persistent hypogonadism at the 6th month, and the adenoma size was larger than 20 mm in all of these patients. When the patients with adenoma size larger than 40 mm at baseline (n = 4) were separately evaluated, hypogonadism persisted in 50% of them in the 6th month despite the treatment of prolactinoma. In-group comparisons with and without hypogonadism at the 6th month of the treatment were presented in table 3. The testosterone levels at the 6th month were significantly higher than the testosterone levels at the baseline in patients with hypogonadism at the 6th month

Tab. 4. Correlation between the total testosterone levels at 6th month of the treatment with clinical and laboratory parameters in the whole study group

Total testosterone levels at 6th month of the treatment (ng/mL) (n = 35)					
Levels at the beginning	**r**	***p***	**Levels at 6th month of the treatment**	**r**	***p***
Age (Years)	-0.252	0.144	Age (Years)	-0.252	0.144
Hemoglobin (mg/dL)	**0.618**	**0.011**	Hemoglobin (mg/dL)	0.350	0.168
Hematocrit (%)	-0.009	0.975	Hematocrit (%)	0.398	0.114
Glucose (mmol/l)	**-0.591**	**0.006**	Glucose (mmol/l)	**-0.450**	**0.046**
Total cholesterol (mg/dl)	-0.043	0.907	Total cholesterol (mg/dl)	-0.027	0.926
Triglyceride (mg/dl)	0.003	0.992	Triglyceride (mg/dl)	-0.095	0.746
LDL cholesterol (mg/dl)	-0.167	0.693	LDL cholesterol (mg/dl)	-0.039	0.900
HDL cholesterol (mg/dl)	-0.027	0.946	HDL cholesterol (mg/dl)	0.158	0.643
Prolactin (mg/dL)	-0.199	0.251	Prolactin (mg/dL)	-0.141	0.414
FSH (mIU/mL)	0.220	0.218	FSH (mIU/mL)	0.213	0.277
LH (mIU/mL)	0.267	0.127	LH (mIU/mL)	**0.410**	**0.022**
Pituitary adenoma size (mm)	**-0.535**	**0.001**	Pituitary adenoma size (mm)	**-0.435**	**0.009**
			The cumulative cabergoline dose (mg/six months)	-0.157	0.465

$P < 0.05$ statistically significant. Significant p-values are shown in bold.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

of the treatment (n = 8), and the testosterone levels at the 6th month were also significantly higher than the testosterone levels at baseline in patients without hypogonadism at the 6th month of the treatment (n = 27) ($p = 0.01$ and $p < 0.001$, respectively).

The correlation analyses between the total testosterone levels at 6th month with the clinical and laboratory parameters both at the baseline and at 6th month of the treatment in the whole study group were presented in table 4 and figure 1.

The logistic regression analysis was performed on the indicators related to hypogonadism persistence (Table 5), and it was concluded that pituitary adenoma size at baseline is an independent risk factor for hypogonadism persistence ($p = 0.034$; OR = 1.130, 95% CI: 1.009–1.265).

DISCUSSION

In the present study, the patients with prolactinoma who had hypogonadism at baseline and increased testosterone levels were followed up with the treatment. Persistent hypogonadism was observed in 23 % of our patients at the 6th month of the treatment, and macroadenoma was detected at baseline in all of these patients. Consistent with this result, a negative correlation was found between the testosterone levels at the 6th month of the treatment with the pituitary adenoma size both at the baseline and the 6th month.

Prolactinoma could be diagnosed earlier since the symptoms of hypogonadism were recognized earlier in females (Duskin-Bitan & Shimon 2020). Previous studies suggested that the diagnosis of prolactinoma was delayed in most male patients due to ignorance of the symptoms (Shimon 2019; Colao *et al.* 2003; De Rosa *et al.* 2003; Duskin-Bitan & Shimon 2020). Another plausible explanation for the high frequency of macroadenoma in male patients was the impact of gender on the biological activity of prolactinomas (Duskin-Bitan & Shimon 2020). Therefore, macroadenomas and complications related to mass effects such as hypogonadism were probably more common in male patients (Colao *et al.* 2003; De Rosa *et al.* 2003; Duskin-Bitan & Shimon 2020). Additionally, higher hypogonadism prevalence in macroadenoma may be related to the hormonal suppressive effect of hyperprolactinemia and/or the damage to pituitary cells by tumor mass effect (Iglesias *et al.* 2012). Colao *et al.* showed a higher prevalence of hypogonadism among patients with larger prolactinomas at presentation (Colao *et al.* 2004). Tirosh *et al.* also found that hypogonadism was detected more frequently in patients with adenoma size > 20 mm than the smaller adenomas (Tirosh *et al.* 2015). All patients had hypogonadism at the baseline in our study group, and macroadenoma was detected in % 86 of our patients at the beginning, similar to these studies.

Persistent hypogonadism in prolactinoma was previously reported ranging from 10 to 63% (Andereggen *et al.* 2017; Shimon 2019; Naliato *et al.* 2005; Shimon *et al.* 2016. Persistent hypogonadism was observed in 23 % of our patients at the 6th month and all of these patients

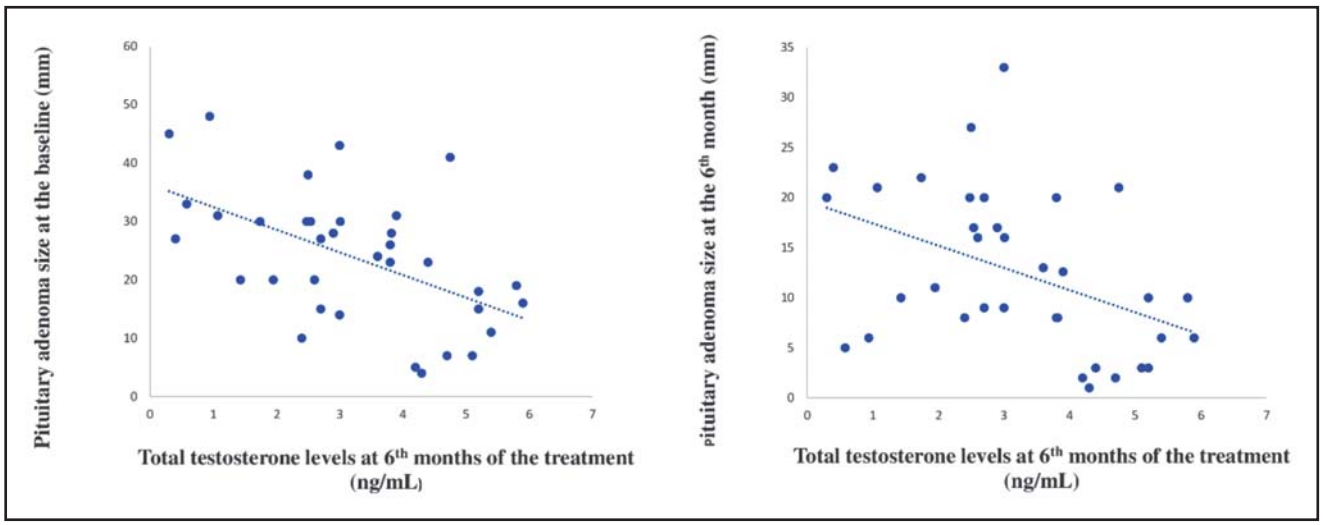

Fig. 1. Correlation between the total testosterone levels at the 6th months of the treatment with pituitary adenoma size

had macroadenoma at baseline. In a study that evaluated male patients with adenomas larger than 60 mm, the persistence of hypogonadism with the treatment of prolactinoma was observed in 63% of patients (Shimon *et al.* 2016). Espinosa *et al.* also showed that hypogonadism persisted in 45 % of the patients with adenoma size between 1–4 cm and in 68% of the patients with adenoma size larger than 4 cm (Espinosa *et al.* 2016). Although the number of patients with adenomas larger than 4 cm was low in our study, hypogonadism persisted in 50% of them. On the other hand, Colao *et al.* also showed that low testosterone levels were found in 39 % of the patients with macroadenoma and 40 % of the patients with microadenoma after the six-month of the treatment (Colao *et al.* 2004). However, the recovery of the hypogonadism was detected in all of our patients with microadenoma. Hypogonadism persisted in eight patients with macroadenoma despite the fact that the prolactin levels were normalized in 75% of them at the 6th month of treatment. This result was probably attributed to long-term irreversible damage to the pituitary gonadotroph cells due to the mass effect rather than prolactin levels.

It was previously shown that low baseline prolactin level and smaller adenoma size could predict recovery of hypogonadism (Voica *et al.* 2021; Andereggen *et al.* 2017; Naliato *et al.* 2005). We also evaluated the parameters that may be related to testosterone levels at the 6th month of the treatment. While a negative correlation was observed between the testosterone levels at the 6th month of the treatment with the pituitary adenoma size in the whole study group, a correlation did not found with prolactin levels. All these results suggest that pituitary adenoma size is more prominent than prolactin level at baseline and the 6th month of the treatment in the persistence of the hypogonadism.

Mild anemia was associated with hypogonadism and usually improved following the treatment of prolactinoma (Iglesias *et al.* 2011). A significant increase in hematocrit levels was observed in the 6th month of treatment in our study, and the testosterone levels at the 6th month of the treatment were positively correlated with the hemoglobin levels in our study. It is known that the testosterone hormone has an essential effect on the regulation of body composition and metabolic profile. Therefore, male patients with hypogonadism have a higher risk of developing metabolic syndrome, and testosterone replacement improves various metabolic parameters, including lipid profile and glucose metabolism (Auriemma *et al.* 2015). Several studies reported the recovery in lipid profile with the treatment of prolactinomas probably due to the normalization of prolactin and testosterone levels (Auriemma *et al.* 2015; Naliato *et al.* 2007; Ciresi *et al.* 2013). Consistent

Tab. 5. Logistic regression analysis identifying the variables of hypogonadism persistence at the 6th month

Variables	B	*P*	OR	95 % CI	
				Lower	Upper
Age	0.057	0.200	1.059	0.970	1.155
Pituitary adenoma size (at the baseline)	0.122	0.034	1.130	1.009	1.265
Pituitary adenoma size (at the 6th month)	-0.074	0.307	0.929	0.806	1.070

P < 0.05 statistically significant. Significant p-values are shown in bold.
B, regression coefficient; P, probability value; OR, Odds ratio; CI, Confidence interval.

with these results, the improvement in total, LDL, and HDL cholesterol, as well as in triglyceride, and glucose levels were also found in our study.

The limitations of our study were the retrospective design of the study and the single-center design.

In conclusion, hypogonadism was frequently found in male patients with prolactinoma, especially in those with larger adenomas. Our study showed that the adenoma size was related to persistent hypogonadism rather than prolactin levels in male patients with prolactinoma. In light of our findings, we suggest that the change in adenoma size rather than prolactin level could be considered for the recovery of hypogonadism in the follow-up of patients with prolactinoma. Further and larger studies are required to clarify the factors related to persistent hypogonadism in prolactinoma patients.

Contributors

HP and ST designed the study and collected the data. HP wrote the manuscript. HP and ST evaluated the results and supervised the study.

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None.

Competing interests

Hamide Piskinpasa and Seda Turgut declare that they have no conflict of interest in this study

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Patient consent for publication

Not required.

Data sharing statement

All data relevant to the study are included in the article.

The present study was approved by the Clinical Ethics Committee and was performed in accordance with the Helsinki Declaration.

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