



# Knosp and Hardy Grading Systems are Useful in Predicting Persistence of Male Hypogonadism in Prolactinomas Following Prolactin Normalization

Knosp ve Hardy Sınıflamaları, Prolaktinoması Olan Erkek Hastalarda Prolaktin Normalizasyonunu Takiben Hipogonadizminin Kalıcılığını Öngörmeye Yararlıdır

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## Abstract

**Objective:** Despite serum prolactin normalization and tumor shrinkage being obtained using dopamine agonist treatment, hypogonadism may persist in several men with prolactinomas. In this study, we evaluated the effects of tumor magnetic resonance imaging features on the persistence of hypogonadism among normoprolactinemic men with prolactinomas objectively using Knosp and Hardy grading systems. **Material and Methods:** The patients with prolactinomas who achieved serum prolactin normalization using cabergoline therapy were evaluated, respectively. The extent of tumor growth was evaluated on the basis of Knosp and Hardy grading systems both at diagnosis and six months of medical therapy with serum prolactin normalization. **Results:** A total of 28 cases (18 macro- and 10 microprolactinomas) were included. After six months of treatment with cabergoline, all microprolactinoma patients with hypogonadism at baseline showed recovery (3, 100%). Moreover, nine of 14 macroprolactinoma patients with hypogonadism at inclusion recovered at the end (group 1), and five did not (group 2). Baseline Knosp grades and Hardy numbers did not differ between groups. However, higher Knosp grades and Hardy numbers were observed in patients who consistently had low serum testosterone in the sixth month (group 2) ( $p=0.01$ ,  $p=0.02$ , respectively). All patients in group 2 had invasive tumors (Hardy number III-IV) both at inclusion and the sixth month according to this classification. **Conclusion:** We demonstrated that macroprolactinomas with persistent hypogonadism despite serum prolactin normalization more commonly showed cavernous sinus invasion and sellar destruction. We proposed that Knosp and Hardy grading systems are useful in predicting the persistence of male hypogonadism in prolactinomas following prolactin normalization.

**Keywords:** Prolactinoma; male; hypogonadism; magnetic resonance imaging

## Özet

**Amaç:** Prolaktinoması olan erkek hastalarda, dopamin agonistleri ile tedavi sonrası serum prolaktin normalizasyonu ve tümör küçülmesi sağlanmasına rağmen hipogonadizm devam edebilir. Bu çalışmada, normoprolaktinematik erkek prolaktinoma hastalarında, Knosp ve Hardy sınıflamalarını kullanarak tümörün manyetik rezonans görüntüleme özelliklerinin, kalıcı hipogonadizm gelişimi üzerine etkisini objektif olarak değerlendirdik. **Gereç ve Yöntemler:** Kabergolin tedavisi ile serum prolaktin normalizasyonu sağlanan prolaktinoma hastaları retrospektif olarak değerlendirildi. Hem tanı anında hem de medikal tedavi ile serum prolaktin normalizasyonunun sağlandığı altıncı ayda tümör büyümesinin derecesi Knosp ve Hardy sınıflamaları kullanılarak değerlendirildi. **Bulgular:** Yirmi sekiz olgu (18 makro ve 10 mikroprolaktinoma) dâhil edildi. Altı aylık kabergolin tedavisi ile başlangıçta hipogonadizmi olan bütün mikroprolaktinoma olgularında (3, %100) hipogonadizm düzeldi. Başlangıçta hipogonadizmi olan 14 makroprolaktinoma olgusunun 9'unda hipogonadizm düzeldi (Grup 1), 5 tanesinde hipogonadizm devam etti (Grup 2). Tanı anındaki Knosp ve Hardy skorları gruplar arasında farklılık göstermedi. Bununla birlikte, altıncı ayda düşük serum testosteronu olanlarda Knosp ve Hardy skorları daha yüksek olarak bulundu (Grup 2) (sırasıyla  $p=0,01$ ,  $p=0,02$ ). Bu sınıflamaya göre Grup 2'deki tüm hastaların hem tanı anında hem de altıncı ayda invaziv tümörleri (Hardy III-IV) vardı. **Sonuç:** Serum prolaktin normalizasyonuna rağmen hipogonadizmi düzelmeden makroprolaktinoma olgularında, kavernöz sinüs invazyonu ve sellar destrüksiyonun daha sık olduğunu gösterdik. Prolaktinoması olan hastalarda, prolaktin normalizasyonunu takiben erkek hipogonadizminin kalıcılığını öngörmeye Knosp ve Hardy sınıflamalarının yardımcı olabileceğini düşünmekteyiz.

**Anahtar kelimeler:** Prolaktinoma; erkek; hipogonadizm; manyetik rezonans görüntüleme

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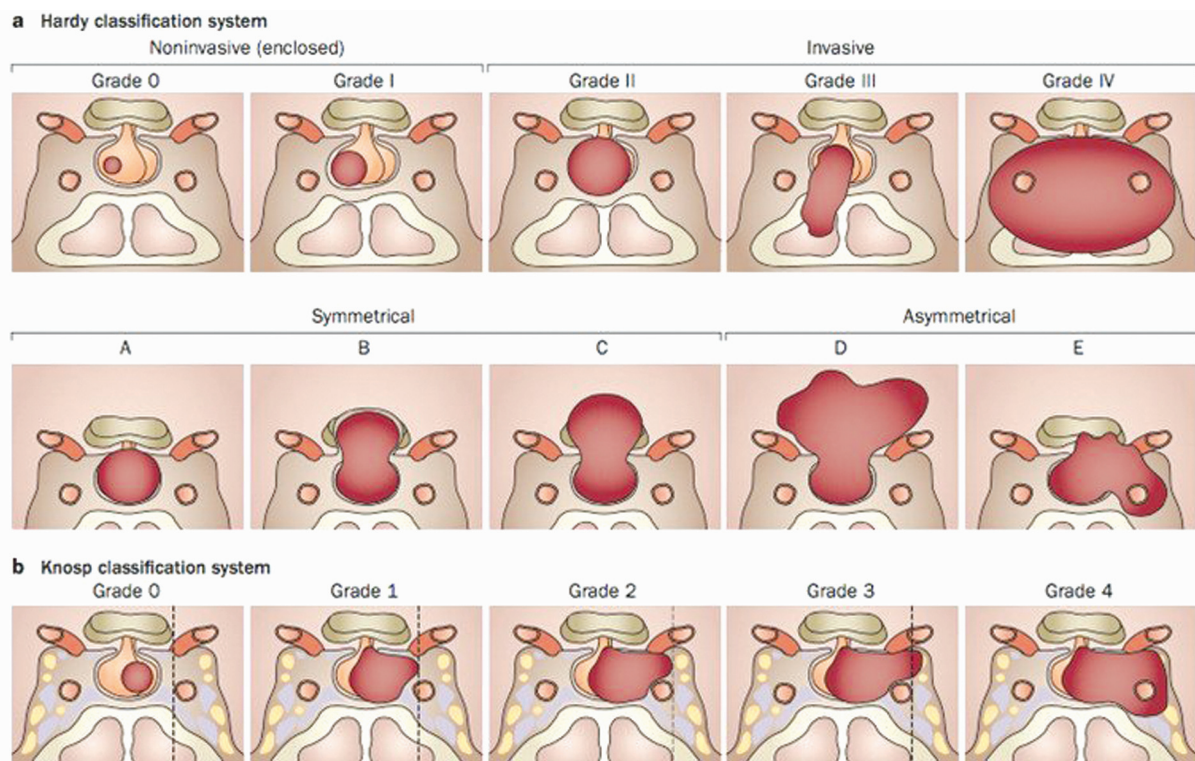
## Introduction

Prolactinomas are the most common functional pituitary adenomas, with an annual incidence of 30 per 100,000 people (1). Several of them are microadenomas, and the female to male ratio is 20:1; however, no difference is observed with regard to gender for macroadenomas (2).

Elevated prolactin level causes sexual dysfunction by inhibiting gonadotropin-releasing hormone pulse frequency and amplitude. Moreover, it causes decreased libido, impotence, oligospermia, or azospermia in male patients. Men typically harbor larger and more invasive prolactinomas and present with more severe signs (3-6). Hypopituitarism resulting from a big tumor size and invasiveness may worsen the symptoms of hyperprolactinemia in macroprolactinomas. Prolactin levels are associated with tumor size and, as expected are typically higher in male patients (2,3).

Magnetic resonance imaging (MRI) is the gold standard method for evaluating pitu-

itary adenomas. Pituitary tumor volume can be measured using different methods, such as perimeter or ellipsoid methods. In addition, Knosp and Hardy grading systems are objective tools that provide crucial information about pituitary space-occupying lesions. The Knosp grading system indicates tumor encroachment or invasion into the cavernous sinuses (CVS). It grades the parasellar extension of the tumor towards the cavernous sinus in relation to the intracavernous carotid artery. According to this classification, grades 3 and 4 tumors are invasive pituitary tumors. The Hardy grading system considers both the sella base-met disruption denoted by numbers 0-IV and mostly suprasellar extension denoted by letters A-E. In the Hardy grading system, invasive adenomas can be either grade III or grade IV tumors, and suprasellar extension is not considered a radiological marker of invasiveness, as shown in Figure 1 (7-10). Dopamine agonist (DA) therapy is recommended for lowering prolactin levels, de-



**Figure 1.** Classification systems characterizing pituitary adenomas. a) Hardy classification system, Sella turcica tumors can be invasive (grade III; localized sellar destruction, grade IV; diffuse destruction). b) Knosp classification system used to quantify invasion of the cavernous sinus (grade 3; the tumor extends laterally to the internal carotid artery within the cavernous sinus, grade 4; total encasement of the intracavernous carotid artery).<sup>10</sup>

creasing tumor size, and restoring gonadal functions for patients with both micro- and macroadenomas. Optimal treatment outcomes for prolactinoma include serum prolactin normalization and tumor shrinkage with the reversal of tumor mass effects (11-13).

Although serum prolactin normalization and tumor shrinkage can be obtained using DA treatment, serum testosterone levels remain under normal levels in several men (14-16). Furthermore, severe hypogonadism may even persist. Radiological determinants of the persistence of hypogonadism in men with prolactinoma treated with DA are not clear. In the literature, several studies have reported the effects of tumor size on the persistence of male hypogonadism, although no accurate data exist about tumor invasiveness (17-21).

This study aimed to evaluate the effects of tumor MRI features on the persistence of hypogonadism among men with prolactinomas, whose serum prolactin levels were normalized with DA therapy by using the objective Knosp and Hardy grading systems.

## Material and Methods

This retrospective study was performed at the Outpatient Endocrinology Clinic of Baskent University Faculty of Medicine, Adana hospital between 2013 and 2017. Male patients with prolactinoma who achieved serum prolactin normalization and whose serum testosterone measurements and pituitary MRIs were performed at the sixth month of medical therapy were recruited in the study, and their medical records were collected. A total of 28 out of 175 male prolactinoma patients were found to be eligible for inclusion. All patients were treated with cabergoline using a dose titration regimen.

Pituitary MRI findings of these 28 patients were evaluated by the same neuroradiologist both at diagnosis and the sixth month of cabergoline treatment with prolactin normalization. The MRIs using a 1.5-T scanner were performed using MR System Magnetom Avanto (Siemens, Erlangen, Germany). Adenoma volumes were calculated manually on sagittal and coronal T1A views using three dimensions. They were categorized as microadenoma (diameter, <1 cm; volume,

<0.52 cm<sup>3</sup>) and macroadenoma (diameter, ≥1 cm; volume, ≥0.52 cm<sup>3</sup>) depending on the size. The extent of tumor growth was evaluated on the basis of Knosp and Hardy grading systems both at diagnosis and the sixth month of medical therapy with serum prolactin normalization.

All information about laboratory tests (follicle-stimulating hormone [FSH], luteinizing hormone [LH], total testosterone, and prolactin levels) was recorded. Gonadotropin deficiency was diagnosed depending on low or "inappropriately normal" serum FSH and LH levels combined with serum testosterone below the reference values: FSH normal range: 1.42-15.4 mIU/mL, LH normal range: 1.24-7.8 mIU/mL, and total testosterone normal range: 2.41-8.27 ng/mL (2). None of the patients received testosterone replacement therapy during the study period.

The Ethics Committee of Faculty of Medicine, Baskent University approved the study (Project No. KA 18/205, approval date: 10/07/2018) performed in accordance with the declaration of Helsinki principles.

## Statistical analysis

Statistical analysis was performed using SPSS software (Version 16.0, SPSS Inc., Chicago, IL, USA). All numerical data were expressed as median values (minimum-maximum). For each continuous variable, normality was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests and histograms. Groups were compared using the Mann-Whitney U test for the data not normally distributed. The pre- and post-measurement data were analyzed using the Wilcoxon test. The categorical variables between the groups were analyzed using the Chi-squared test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

## Results

A total of 28 cases (18 macro- and 10 microprolactinomas) were included. Table 1 shows the general characteristics of the patients with macro- and microadenomas at presentation. More number of patients with macroprolactinoma had hypogonadism at inclusion: 14 (77.8%) vs. 3 (30.0%) (p=0.019). More than one deficient hor-

Table 1. General baseline characteristics of the patients with macro and microprolactinomas.

n=28	Macroprolactinomas (n=18)	Microprolactinomas (n=10)	p
Mean age (years, mean±SD)	44.77±13.44	44.4±13.9	>0.05
Main complaint (n, %)			
Visual defect	6 (33.3)	0 (0.0)	<b>0.04</b>
Headaches	10 (55.6)	1 (10.0)	<b>0.02</b>
Sexual dysfunction	9 (50.0)	9 (90.0)	<b>0.04</b>
Incidental	1 (6.6)	0 (0.0)	0.64
Hypogonadism (n, %)	14 (77.8)	3 (30.0)	<b>0.01</b>
PRL (ng/ml)	4912.0±10655.3	104.9±43.1	<b>0.00</b>
Tumor volumes (cm <sup>3</sup> )	8.83	0.16	<b>0.02</b>
Knosp grade (n, %)			
0	1 (5.6)	7 (70.0)	<b>0.01</b>
1	5 (27.8)	2 (20.0)	
2	6 (33.3)	1 (10.0)	
3	4 (22.2)	0 (0.0)	
4	2 (11.1)	0 (0.0)	
Hardy number (n, %)			
0	0 (0.0)	6 (60.0)	<b>0.00</b>
I	1 (5.6)	2 (20.0)	
II	4 (22.2)	1 (10.0)	
III	12 (66.7)	1 (10.0)	
IV	1 (5.6)	0 (0.0)	
Hardy letter (n, %)			
A	3 (16.7)	9 (90.0)	<b>0.04</b>
B	2 (11.1)	1 (10.0)	
C	1 (5.6)	0 (0.0)	
D	4 (22.2)	0 (0.0)	
E	8 (44.4)	0 (0.0)	

PRL (normal range: 2.1-17.7 ng/ml).

Statistically significant p values are written as bold.

none was found in four (22.2%) of macro- and two (20.0%) of microprolactinoma patients at diagnosis.

Under six months on cabergoline treatment, all microprolactinoma cases with hypogonadism at baseline (3, 100%) exhibited recovery. Four of 18 macroprolactinomas had normal serum testosterone at inclusion. Two of them developed hypogonadism at the end of the study period (n=2/18, 11.1%), whereas the other two remained eugonadal (n=2/18, 11.1%). The remaining of macroprolactinoma patients (n=14) were separated into two groups:

**Group 1:** Patients who had hypogonadism at inclusion and recovered with serum prolactin normalization (9/14, 64.2%).

**Group 2:** Patients who had hypogonadism both at inclusion and the sixth month despite prolactin normalization (5/14, 35.7%). Details of gonadotrophin-gonadal axis and tumor volume on admission and after six months of cabergoline treatment with serum prolactin normalization are shown in Table 2. Mean serum prolactin levels at the sixth month of therapy in macro- and microprolactinoma patients were 10.5±5.7 ng/mL versus 8.1±6.1 ng/mL (p>0.05).

Knosp grades, Hardy numbers, and Hardy letters measured during the presentation were not statistically different regarding hypogonadism status in all macroprolactinoma patients (n=18; p=0.43, p=0.46, p=0.89, respectively).

Table 2. Details of gonadotrophin-gonadal axis and tumor volume on admission and at the sixth month of CAB treatment with serum PRL normalization.

	Macroprolactinomas (n=18)			Microprolactinomas		
	Before	After	p	Before	After	p
FSH (mIU/mL)	2.5±1.4	4.1±1.7	0.001	2.4±0.9	5.0±2.1	0.008
LH (mIU/mL)	2.0±1.2	3.6±2.1	0.005	2.4±1.1	4.3±1.7	0.030
Total testosterone (ng/ml)	1.4±0.8	2.7±1.6	0.009	2.6±1.4	4.5±2.0	0.007
Tumor volumes (cm <sup>3</sup> )	8.83	3.16	0.031	0.16	0.13	0.55

Sixth month serum PRL: 10.7±5.7 ng/ml in macro and 8.1±6.1 ng/ml in microprolactinoma cases.

CAS: Cabergoline; PRL (normal range: 2.1-17.7 ng/ml).

Statistically significant p values are written as bold.

Baseline Knosp grades, Hardy numbers, and Hardy letters of patients (9/5) in groups 1 and 2 were statistically indifferent. However, at the sixth month, Knosp grades and Hardy numbers were higher in group 2 (p=0.01, p=0.02, respectively) and Hardy letters were similar (p=0.11) (Table 3).

Baseline and final Knosp, Hardy numbers, and Hardy letters of the two macropro-

lactinoma patients who were eugonadal at the baseline but became hypogonadal at the sixth month were as follows: Case 1: 4, II, E versus 4, II, E and Case 2: 1, III, E versus 1, III, E, respectively. No change was observed between them.

Patients were divided into two groups according to the Knosp and Hardy grading systems: invasive adenomas (n=15, 53.6%,

Table 3. Magnetic resonance imaging findings of macroprolactinomas evaluated via using Knosp, Hardy number and Hardy letter grading systems with regard to hypogonadism status at baseline and at sixth month of CAB therapy.

	Baseline (n, %)		p	At sixth month (n, %)		p
	Group 1 (n=9)	Group 2 (n=5)		Group 1 (n=9)	Group 2 (n=5)	
Tumor volumes (cm <sup>3</sup> )	2.89	20.55	<b>0.001</b>	1.30	5.68	<b>0.02</b>
Knosp grade						
0	1 (11.1)	0 (0.0)	0.10	3 (33.3)	0 (0.0)	<b>0.01</b>
1	2 (22.2)	1 (20.0)		3 (33.3)	1 (20.0)	
2	5 (55.6)	1 (20.0)		3 (33.3)	0 (0.0)	
3	1 (11.1)	2 (40.0)		0 (0.0)	2 (40.0)	
4	0 (0.0)	1 (20.0)		0 (0.0)	2 (40.0)	
Hardy number						
0	0 (0.0)	0 (0.0)	0.98	0 (0.0)	0 (0.0)	<b>0.02</b>
I	1 (11.1)	0 (0.0)		2 (22.2)	0 (0.0)	
II	2 (22.2)	0 (0.0)		3 (33.3)	0 (0.0)	
III	6 (66.7)	4 (80.0)		4 (44.4)	3 (60.0)	
IV	0 (0.0)	1 (20.0)		0 (0.0)	2 (40.0)	
Hardy letter						
A	2 (22.2)	0 (0.0)	0.19	4 (44.4)	0 (0.0)	0.11
B	2 (22.2)	0 (0.0)		0 (0.0)	0 (0.0)	
C	1 (11.1)	0 (0.0)		1 (11.1)	0 (0.0)	
D	1 (11.1)	2 (40.0)		1 (11.1)	1 (20.0)	
E	3 (33.3)	3 (60.0)		3 (33.3)	4 (80.0)	

Group 1: Patients that exhibited hypogonadism at inclusion and recovered with serum PRL normalization, Group 2: Patients who had hypogonadism both at inclusion and at sixth month, despite of PRL normalization, CAB: Cabergoline.

Statistically significant p values are written as bold.



Table 4. Hormonal evaluation and magnetic resonance imaging findings of invasive and non-invasive tumors.

	Baseline		p	At sixth month		p
	Invasive tumors (n=15, 53.6%)	Non-invasive tumors (n=13, 46.4%)		Invasive tumors (n=15, 53.6%)	Non-invasive tumors (n=13, 46.4%)	
FSH (mIU/mL)	2.5±1.3	2.5±1.2	0.93	4.6±1.9	4.3±2.0	0.71
LH (mIU/mL)	1.7±0.8	2.6±1.4	<b>0.05</b>	3.7±2.2	4.1±1.6	0.55
Total testosterone (ng/ml)	1.4±0.8	2.3±1.4	<b>0.03</b>	2.7±1.7	4.1±2.0	0.07
Hypogonadism (n, %)	11 (73.3)	6 (46.1)	<b>0.00</b>	7 (46.6)	0 (0.0)	<b>0.00</b>
PRL (ng/ml)	5775.1±11533.3	218.4±341.9	<b>0.00</b>	11.4±5.1	7.6±6.1	0.08
Tumor volumes (cm <sup>3</sup> )	10.29	0.47	<b>0.02</b>	3.7	0.2	<b>0.01</b>
Knosp grade (n, %)						
0	0 (0.0)	8 (61.5)	<b>0.00</b>	2 (13.3)	8 (61.5)	<b>0.00</b>
1	2 (13.3)	5 (38.4)		3 (20.0)	5 (38.4)	
2	7 (46.6)	0 (0.0)		4 (26.6)	0 (0.0)	
3	4 (26.6)	0 (0.0)		3 (20.0)	0 (0.0)	
1	2 (13.3)	0 (0.0)		3 (20.0)	0 (0.0)	
Hardy number (n, %)						
0	0 (0.0)	6 (46.1)	<b>0.00</b>	0 (0.0)	7 (53.8)	<b>0.00</b>
I	0 (0.0)	3 (23.0)		1 (6.6)	2 (15.3)	
II	1 (6.6)	4 (30.7)		2 (13.3)	4 (30.7)	
III	13 (86.6)	0 (0.0)		10 (66.6)	0 (0.0)	
IV	1 (6.6)	0 (0.0)		2 (13.3)	0 (0.0)	

Statistically significant p values are written as bold.

Knosp grades 3-4, Hardy number III-IV) and noninvasive adenomas (n=13, 46.4%, Knosp grades 1-2, Hardy number 1-II) (Table 4). All patients in group 2 had invasive tumors (Hardy number III-IV) both at inclusion and the sixth month according to this classification (Table 3).

## Discussion

Prolactinoma is a well-identified cause of hypogonadism in men. Hyperprolactinemia has a direct suppressive effect on the hypothalamic-pituitary-gonadal axis (22-24). Increased intrasellar pressure causing pituitary cell damage may be another reasonable explanation for gonadal and other pituitary hormonal deficiencies in macroprolactinomas (18,23,25). Medical DA treatment effectively controls serum prolactin levels and tumor size, often resulting in significant tumor shrinkage. Cabergoline is the preferred DA of choice worldwide. Despite prolactin normalization with cabergoline, several men still suffer from hypogonadism.

This study was conducted because the objective radiological determinants of the persistence of hypogonadism in men with prolactinoma treated with DA are unclear in the literature.

The MRI findings at the baseline and sixth month among 28 men with prolactinomas-18 with macroadenomas and 10 with microadenomas-who achieved serum prolactin normalization with cabergoline therapy were evaluated using Knosp, Hardy number, and Hardy letter grading systems. More men in the macroprolactinoma group had hypogonadism at the baseline, as expected. All the microadenoma patients with baseline hypogonadism had a full recovery. Two of four macroprolactinoma patients with a normal serum testosterone level at inclusion developed hypogonadism at the end of the study period, and the other two remained eugonadal. Nine of 14 macroprolactinoma patients with hypogonadism at inclusion recovered at the end, and five did not. The recovery rate was 64.2% in patients with

macroprolactinomas. Knosp, Hardy number and Hardy letter grades at the baseline did not differ among the 14 hypogonadal macroprolactinoma patients with regard to the final status. However, higher Knosp grades and Hardy numbers, but not Hardy letters, were observed in patients who consistently had a low serum testosterone level in the sixth month (Group 2). All patients in group 2 had invasive tumors both at inclusion and during the sixth month according to this classification.

A limited number of studies exist about male prolactinoma and hypogonadism in the current medical literature. The normalization of serum testosterone levels ranged between 50% and 60% in males with the successful treatment of hyperprolactinemia (3). Karavitaki et al. treated 12 macroprolactinoma patients with cabergoline, 44% of whom had recovered from hypogonadism (22). Tirosh et al. treated 71 men who had pituitary macroadenomas with cabergoline. Hypogonadism has been observed in 57 of 63 patients (90.5%) at presentation, whereas only 22 of 65 (33.8%) have had low testosterone levels following treatment and prolactin suppression (26). Shimon et al. studied 12 males with giant prolactinomas who were treated with cabergoline. Testosterone levels, initially low in all patients, were normalized in eight patients (67%) (27). Colao et al. studied 41 males with macroprolactinoma who were treated with cabergoline. Testosterone deficiency was observed in 73% of them at presentation; after six months of cabergoline treatment, 60.9% of patients recovered (20). Tirosh et al. reported that patients with an adenoma diameter of greater than 20 mm more frequently presented with hypogonadism than smaller adenomas. The prevalence of hypogonadism has been found to be 87.6% (64/73) at presentation and 33.3% (23/69) following treatment among macroprolactinoma patients (17). Keeping in accordance with the literature, 64.2% of our macroprolactinoma patients with hypogonadism at the baseline gained normal gonadal functions with prolactin normalization.

In daily clinical practice, the medical treatment of microprolactinomas almost always results in the recovery of gonadal status in men. However, some macroprolactinoma

patients recover, but others do not, and it is clear that the currently used termination, macroprolactinoma, is not sufficient to identify individuals who would have persistent hypogonadism. This study was the first in the medical literature to use the validated grading systems, Knosp and Hardy, in defining tumor MRI properties in prolactinomas beyond the traditional micro-macro termination.

Higher Knosp grades and Hardy numbers at the sixth month in MRIs of the macroprolactinoma patients with persistent hypogonadism underline the negative effects of CVS invasion and sella destruction but not the suprasellar extension. The high grades of the two macroprolactinoma patients who became hypogonadal following prolactin normalization also pointed to the importance of CVS invasion and sella basement disruption in the persistence of hypogonadism. We proposed that increased intrasellar pressure may be a reasonable explanation for our results. Gonadotroph hormone-secreting cells are known to be located widely throughout the pituitary gland. The intrasellar pressure of macroprolactinomas that exhibit parasellar extension toward the CVS may be higher than the ones that grow upward to the suprasellar system because of the barrier function of CVS bone walls. This may result in gonadotroph cell damage and thus the persistence of hypogonadism.

This study had a few limitations. The retrospective design and the low number of patients included may be criticized. However, considering the patient numbers in similar studies in the literature, we believed it might be appreciated.

## Conclusion

In this study, we clearly demonstrated that macroprolactinomas with persistent hypogonadism despite serum prolactin normalization more commonly showed CVS invasion and sella destruction using Knosp and Hardy grading systems. This may be attributed to their possibly higher intrasellar pressures than that of the tumors with suprasellar extension lacking bony barriers.

We concluded that the Knosp and Hardy grading systems are useful in predicting the persistence of male hypogonadism in prolactinomas following prolactin normalization.

## Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

## Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authors Contributions

Idea/Concept: Melek Eda Ertörer, Gülay Şimşek Bağır; Design: Melek Eda Ertörer, Gülay Şimşek Bağır; Control/Supervision: Melek Eda Ertörer, Gülay Şimşek Bağır, Okan Sefa Bakiner; Data Collection and/or Processing: Gülay Şimşek Bağır, Filiz Ekşi Haydardedeoğlu, Okan Sefa Bakiner; Analysis and/or Interpretation: Melek Eda Ertörer, Gülay Şimşek Bağır, Özlem Alkan, Aylin Güneşli; Literature Review: Melek Eda Ertörer, Gülay Şimşek Bağır, Özlem Alkan, Aylin Güneşli; Writing the Article: Gülay Şimşek Bağır, Melek Eda Ertörer; Critical Reviewing: Melek Eda Ertörer; References and Funding: Gülay Şimşek Bağır, Melek Eda Ertörer; Materials: Gülay Şimşek Bağır, Melek Eda Ertörer.

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