Annales d'Endocrinologie 83 (2022) 9–15

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Optimal testosterone level to improve symptoms of hypogonadism without causing dopa-testotoxicosis in male macroprolactinoma

Quel taux de testostérone pour améliorer les symptômes de l'hypogonadisme sans induire une dopa-testotoxicose en cas de macroprolactinome masculin?

Ozge Telci Caklili[a,b,*], Ayse Merve Ok[a,b], Zulal Istemihan[a], Ozlem Selcukbiricik[a,b], Sema Yarman[a,b]

[a] *Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey*
[b] *Division of Endocrinology and Metabolic Disease, Istanbul, Turkey*

ARTICLE INFO

Keywords:
Male
Macroprolactinoma
Fertility
Dopamine agonist
Dopa-testotoxicosis

ABSTRACT

Background. – Male prolactinoma treatment by dopamine agonists (DA) restores sexual function. However, excessive DA dose can lead to impulse control disorder.
Objectives. – The aim of this retrospective study was to determine the level of testosterone that eliminates symptoms and provides fertility in male macroprolactinoma, without causing these adverse effects.
Materials and methods. – Twenty-seven male patients with macroprolactinoma were included. There were 16 macro (≥ 1–2.8 cm), 7 large macro (≥ 2.9–3.9 cm) and 4 giant (≥ 4 cm) adenomas. Prolactin (PRL) and testosterone (T) levels were evaluated. A timeline was created to analyze improvement in symptoms of hypogonadism and infertility. Testosterone levels were compared with age-matched controls.
Results. – Mean PRL, basal tumor diameter and shrinkage were 2846 ± 3415 ng/mL, 27.2 ± 10.2 mm and 63.4%, respectively. Basal T levels were 1.6 ± 1.0 ng/mL for patients and 4.4 ± 1.5 ng/mL for controls ($P < 0.001$). Mean T level in the asymptomatic period was significantly lower than in controls (3.2 ± 0.4 ng/mL vs. 4.4 ± 1.5 ng/mL, respectively; $P = 0.002$), while mean PRL was 27.2 ng/mL. Fertility was achieved in 6 of the patients seeking fertility, and there was no difference in T level between these patients and controls (3.7 ± 0.8 ng/mL and 4.4 ± 1.5 ng/mL, respectively; $P = 0.14$); when fertility was achieved, mean PRL was 26.9 ± 23 ng/mL.
Conclusion. – Patients should be carefully questioned regarding complaints at each consultation, and DA dose should not be increased unnecessarily, to avoid possible serious adverse effects.
© 2021 Published by Elsevier Masson SAS.

Mots clés :
Masculin
Macroprolactinome
Fertilité
Agoniste dopaminergique
Dopa-testotoxicose

RÉSUMÉ

Contexte. – Les agonistes dopaminergiques (AD) permettent une récupération des fonctions sexuelles en cas de prolactinome masculin, mais le surdosage risque d'induire des troubles du contrôle des impulsions.
Objectifs. – L'objectif de cette étude rétrospective était de déterminer le taux de testostérone qui supprimerait les symptômes et assurerait la fertilité en cas de macroprolactinome masculin, sans induire ces effets secondaires néfastes.
Matériels et méthodes. – Vingt-sept hommes présentant des macroprolactinomes étaient inclus dans l'étude, avec 16 macro-adénomes (≥ 1–2,8 cm), 7 grands macro-adénomes (≥ 2,9–3,9 cm) et 4 adénomes géants (≥ 4 cm). Les taux de prolactine (PRL) et de testostérone (T) ont été mesurés. Une chronologie a été établie pour analyser l'amélioration des symptômes de l'hypogonadisme et de l'infertilité. Les taux de testostérone ont été comparés à ceux de sujets témoins appariés pour l'âge.

* Corresponding author.
E-mail address: wattersonx@gmail.com (O. Telci Caklili).

https://doi.org/10.1016/j.ando.2021.11.005
0003-4266/© 2021 Published by Elsevier Masson SAS.

Résultats. – Les valeurs moyennes de la PRL, du diamètre initial de la diminution du volume tumoral étaient de 2846 ± 3415 ng/mL, de 27,2 ± 10,2 mm et de 63,4 %, respectivement. Le taux moyen initial de testostérone était de 1,6 ± 1,0 ng/mL pour les patients et de 4,4 ± 1,5 ng/mL pour les témoins ($p < 0,001$). Le taux moyen de testostérone des patients en phase asymptomatique était statistiquement inférieur à celui des sujets témoins (3,2 ± 0,4 ng/mL vs 4,4 ± 1,5 ng/mL, respectivement; $p = 0,002$), alors que le taux moyen en PRL était de 27,2 ng/mL. La fertilité a été restaurée pour 6 patients parmi ceux qui faisaient état de cette demande, sans différence significative entre ces patients et les sujets témoins en termes de concentration en testostérone (3,7 ± 0,8 ng/mL et 4,4 ± 1,5 ng/mL, respectivement; $p = 0,14$), et avec un taux moyen de PRL de 26,9 ± 23 ng/mL.
Conclusion. – Lors de chaque visite, un interrogatoire détaillé doit recenser les symptômes, et il faut éviter d'augmenter inutilement le dosage en AD, pour éviter tout effet secondaire potentiellement grave.
© 2021 Publié par Elsevier Masson SAS.

1. Introduction

Prolactinomas are the most common secretory pituitary tumors. Microprolactinomas are more prevalent in women whereas macroprolactinomas are more common in males accounting for 82.6% and 14.1% of these cases were giant adenomas [1]. Therefore, the clinical findings of prolactinoma vary with gender. Most male patients complain of decreased gonadal function can present itself in the form of impotence, oligospermia, erectile dysfunction and infertility [2–4]. The course of prolactinoma is longer in males and the tumors tend to be larger. Thus, tumor mass effects can cause visual field defects, decreased vision, headaches and can even be life threatening due to pituitary apoplexy [5–7]. However, it is well known that the majority of prolactinomas respond to dopamine agonists (DA) with a rapid lowering of prolactin (PRL) levels, and this treatment can restore fertility. In addition to this effect, bromocriptine (BRC) and cabergoline (CAB) are capable of inducing significant tumor shrinkage within the first three months of therapy in 80–90% of the patients [5,8–10]. In the past BRC was effective in most male patients with macroprolactinoma to normalize PRL levels and to reduce tumor size, but nowadays CAB is often first choice [11]. Even in patients with macroadenomas it is expected to respond satisfactorily to lower doses of DA within 6 months of treatment [12]. On the other hand, in the literature showing that the use of high doses of DA in the treatment of Parkinson's disease leads to impulsive control disorders (ICDs; hypersexuality, pathological gambling, compulsive shopping and eating) as an undesirable side effect [13]. Recently, ICDs have begun to be observed in prolactinomas with much lower doses [14,15]. Hypersexuality, which is a serious component of the ICD, has been called "dopa-testoxicosis", which occurs as a result of rapid correction of hypogonadism with DA, even if the T value is within the normal range [14]. Considering this serious side effect, patients with prolactinomas should be questioned carefully about their sexual functions during DA treatment. When gonadal function returns to normal, patients often stop complaining of their hypogonadotropic symptoms. At this point, the measured PRL level may not have fallen below the expected upper normal limit. When such a slightly elevated PRL level is encountered, it should be kept in mind that macroprolactin may be included in the measurement of PRL [16,17]. Therefore, in patients who are asymptomatic under treatment, DA dose should not be increased for mild PRL elevations, taking into account the possible serious side effects of the drug. To our knowledge, there are no studies to describe the T threshold levels at which hypogonadism improve under DA treatment. Therefore, our aim was to determine the optimal T level in male macroprolactinomas when hypogonadism symptoms disappear and fertility was achieved, regardless of the PRL level, also to avoid possible serious side effects of DA by preventing unnecessary dose increase.

2. Material and methods

2.1. Ethics

Ethics Board approval was obtained from Istanbul University Ethics Committee (rule number: 21680). Rules of Helsinki Declaration were followed and because the study's retrospective nature patient consent was not needed.

2.2. Subjects

This is a single-center retrospective study of male patients with macroprolactinoma who were followed up from pituitary outpatient clinic of Istanbul University Hospital between 2000–2020. All patients suffered from reduced libido and decreased potency, and some of them infertility.

2.3. Inclusion/exclusion criteria

Only patients with macroprolactinoma under 65 years of age and with a follow-up period of at least 12 months after DA withdrawal were included to the study. Patients with T replacement therapy and treatment other than DA (such as radiotherapy, surgery) were excluded. Patients who have children prior to diagnosis were excluded from fertility statistical analysis. Control group consisted of age matched subjects who applied to our general internal medicine out-patient clinic with complaints other than hypogonadism and infertility and without disease and/or medication which may interfere with gonad function and/or fertility.

2.4. Diagnosis and follow-up

Prolactinoma diagnosis was made in compliance with prolactinoma guidelines [5]. Diagnosis of macroadenoma was made with serum PRL level > 200 ng/mL, and with the presence of pituitary adenoma on magnetic resonance imaging (MRI) with the largest dimension > 1 cm. Large macroadenoma was defined an adenoma with a dimension > 2.9 cm [10]. The definition of giant adenomas in the literature has not always been homogeneous, but in the most published series, the definition used was that pituitary adenomas with maximum diameter measured 40 mm or more [18–20]. A diagnosis of hypogonadotropic hypogonadism was based on at least two measurements of low T (non-fasting) with inappropriately low levels of gonadotropins and symptoms of T deficiency. This approach agrees with the current guidelines and reflects that there is no consensus on strict criteria to make a diagnosis of hypogonadotropic hypogonadism [21]. In a recent guideline, central hypogonadism in males was based on manifests with low serum T levels and features of T deficiency, and/or impaired spermatogenesis [22].

Each patient was followed up every 3–6 months after starting DA therapy, as necessary, and at longer intervals thereafter. A timeline was created to analyze the progress regarding symptoms of hypogonadism and infertility. Answers of the patients to the inquiries regarding their hypogonadism symptoms and fertility at each visit were assessed. PRL levels and DA doses were recorded when fertility was achieved and when hypogonadism symptoms improved. T levels of the patients when fertility and eugonadism were achieved were compared to age matched controls. After diagnosis, first sellar MRI was performed at 3 months after onset of DA treatment, and then as required according to the patient's clinical response. Remission was considered when normoprolactinemia was achieved and if it maintained for > 1 year without therapy or radiological evidence of pituitary tumor [23].

2.5. Biochemical evaluation

From patient medical records PRL, LH, FSH, T and other relevant laboratory data were investigated. Serum PRL, follicle stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), free thyroxine (fT4), thyroid stimulated hormone (TSH) and basal cortisol levels were measured between 08:00 and 09:00 in the morning following a night fast. Serum PRL levels were measured by using an electrochemiluminescence immunoassay (Elecsys Prolactin II, Roche Diagnostics, Indianapolis, IN, USA), and reference levels for men was 4.04–15.2 ng/mL. Total testosterone was determined by electrochemiluminescence immunoassay (Elecsys Testosterone II, Roche Diagnostics, Indianapolis, IN, USA), and reference levels ranged from 2.8–8.0 ng/mL in men. FSH was measured with (Elecsys FSH, Roche Diagnostics, Indianapolis, IN, USA), and normal range was 1.5–12.4 mIU/mL. LH was assessed with (Elecsys LH, Roche Diagnostics, Indianapolis, IN, USA), and normal range was 1.7–8.6 mIU/mL. Serum free T4 level below the laboratory reference range in conjunction with a low, normal, or mildly elevated TSH usually confirms central hypothyroidism. Reference for free T4 and TSH in our laboratory were 12–22 pmol/L and 0.27–4.2 mIU/L, respectively. Baseline morning cortisol level under 3 μg/dL is indicative of secondary adrenal insufficiency.

2.6. Statistical analysis

Statistical analysis was performed using the SPSS software version 16. Normality of the variables were tested using visual (histogram) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether they are normally distributed. Student *t*-test and Mann–Whitney *U* test were conducted to compare parameters among groups. Chi^2 was used to compare categorical variables. An overall 5% type-I error level was used to infer statistical significance. A ROC curve was performed to establish cut-off values.

3. Results

Twenty-seven male patients with macroprolactinoma and 33 controls were included in this study, and mean age of the patients was 38.8 ± 11.8 and 41.6 ± 10.2 for controls ($P = 0.34$). All patients suffered from sexual dysfunction. The mean age at which patients' hypogonadotropic symptoms began was reported to be 34.8 ± 10.2 years. Therefore, an average of 4.3 years in delay of diagnosis for etiology of hypogonadism was observed. At presentation, mean PRL level and tumor diameter were 2846 ± 3415 ng/mL and 27.2 ± 10.2 mm, respectively. Baseline T levels of the patients were significantly lower than control group [(1.6 ± 1.0 ng/mL and 4.4 ± 1.5 ng/mL, respectively) ($P < 0.001$)]. There were 3 patients with macroprolactinomas and one giant adenoma with borderline and normal pre-treatment T levels (between 2.9 to 3.75 ng/mL). Mean initial dose of BRC and CAB treatments were 3.7 ± 1.8 mg daily and 0.6 ± 0.2 mg weekly, respectively. We classified adenomas as 16 macroadenomas (≥ 1–2.8 cm), 7 large macroadenomas (≥ 2.9–3.9 cm) and 4 giant adenomas (≥ 4 cm). According to adenoma classification, demographic, biochemical and radiological findings of the patients are summarized in Table 1. The mean T level of the patients under treatment when they are asymptomatic is significantly lower than the control group (3.2 ± 0.4 ng/mL and 4.4 ± 1.5 ng/mL, respectively, $P = 0.002$), while the PRL value at this time was slightly above the upper limit of normal as 27.2 ng/mL.

Among the patients, fertility was achieved in six patients who desired fertility, and characteristics of these patient were summarized on Table 2. Mean T level of the patients at the time of fertility was statistically not different from the controls (3.7 ± 0.8 ng/mL vs. 4.4 ± 1.5 ng/mL, respectively, $P = 0.14$). When fertility was achieved mean PRL level was 26.9 ± 23 ng/mL. Additionally, the highest mean T levels of the patients under DA therapy was not significantly different from controls (4.9 ± 1.6 ng/mL vs. 4.4 ± 1.5 ng/mL, respectively, $P = 0.14$), and mean PRL level accompanying these T levels was 12.1 ± 15.2 ng/mL. The mean maximum BRC and CAB doses were 11.1 ± 5.1 mg/day and 1.7 ± 0.6 mg/week, respectively. PRL levels in patients whose symptoms disappeared, who became fertile under treatment and the maximal T levels achieved by the treatment are shown on Fig. 1 with corresponding PRL levels.

However, in three of these patients, ICD occurred when T levels approached the upper limit of the normal range (as 7 ng/mL, 7.8 ng/mL, and 8.0 ng/mL) with optimal CAB doses (1.5, 1.5 and 2.5 mg/week, respectively). This drug side effect appeared as hypersexuality in two patients, and hypersexuality and compulsive shopping in one. These patients were included in the multicenter DA-derived ICD study which is recently published [15].

The mean follow-up period of the patients was 8.3 ± 4.8 years. In this time, five patients (18.5%) had central hypothyroidism and one (3.7%) both central hypothyroidism and partial hypocortisolism.

There were seven patients (25.9%) in remission; one patient with macroadenoma (14%), four patients with large macroadenoma (57%), and two patients with giant adenoma (29%). Characteristics of patients in remission are presented in Table 3. Age was not statistically different between groups in remission and non-remission. Mean duration of DA therapy before drug withdrawal was 7.9 ± 5.2 years, and mean duration of remission was 3.2 ± 4.3 years. At the last control, tumors have shrunk by a mean of 63.4%. Patients in remission had higher baseline PRL levels and longer duration of DA than non-remission patients (1865 vs. 864, $P = 0.046$, and 9 years vs. 8 years, $P = 0.041$, retrospectively). Patients in remission had more tumor shrinkage and had large macroadenoma at admission than who were not in remission (79.8% vs. 57.6%, $P = 0.047$, and 32.4 ± 4.7 vs. 25.4 ± 11.1, $P = 0.032$, retrospectively). A ROC curve showed that 70.5% of tumor shrinkage predicted remission with 85% sensitivity and 65% specificity ($P = 0.043$), (AUC: 0.76 [95% CI: 0.58–0.93], Fig. 2).

4. Discussion

The characteristics of male prolactinomas are elevated PRL and a suppressed serum T accompanied with symptoms of hypogonadism [2,3]. In our study, all patients complained from symptoms of hypogonadism at presentation. Despite the definition of hypogonadism in the guidelines, the lower limit of the normal T value (300 ng/dL) was given as the threshold for diagnosis of low T levels, but the applicability of this threshold to every human being has not been clearly established [21,22]. Although T threshold value attributable to the diagnosis of hypogonadism was reported as 250 to 300 ng/dL by the American Urological Association as a result of

Table 1
The characteristics of the patients at presentation and at the last visit according to the size of the adenomas.

	Macroadenoma $n=16$	Large adenoma $n=7$	Giant adenoma $n=4$
Age (years)	36.1 ± 9.2	44.0 ± 14.4	40.5 ± 16.2
Baseline maximum tumor diameter (mm)	20.7 ± 6.2	32.2 ± 3.0	44.2 ± 5.8
Baseline PRL level (ng/mL)	1589.6 ± 2533.3	2849.2 ± 2567.0	7872.0 ± 3702.0
Baseline T level (ng/mL)	1.9 ± 0.8	0.8 ± 0.8	1.5 ± 1.5
Baseline LH level (mIU/mL)	2.7 ± 1.7	2.0 ± 1.5	1.3 ± 0.7
Baseline FSH level (mIU/mL)	3.3 ± 2.2	2.0 ± 1.1	2.1 ± 1.5
Initial DA dose (mean ± StD)			
CAB (mg/wk)	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3
BRC (mg/daily	3.1 ± 1.2	2.5 ± 0.0	6.2 ± 1.7
At last control			
Case number (%)	2 (12%)	1 (14%)	3[a] (75%)
Other pituitary dysfunction	Central hypothyroidism	Central hypothyroidism	Central hypothyroidism

PRL: prolactin; T: total testosterone; LH: luteinizing hormone; FSH: follicle stimulating hormone; DA: dopamine agonist; BRC: bromocriptine; CAB: cabergoline.
[a] Additional partial hypocortisolism was observed in one patient.

Table 2
Characteristics of fertile patients.

Case No.	Age (years)	Baseline PRL level (ng/mL)	Baseline Tumor size (mm)	Tumor reduction percentage (%)	Fertile PRL level (ng/mL)	Fertile T level (ng/mL)	Other pituitary dysfunctions at last control and ICD*
1	37.0	259	40.0	75.0	72.0	3.0	No
2	27.0	286	11.0	65.0	31.0	3.0	No
3	22.0	934	31.0	70.0	25.0	3.2	Hypersexuality and compulsive shopping[a]
4	24.0	4700	40.0	30.0	18.0	4.1	Central hypothyroidism and partial hypocortisolism
5	43.0	7629	38.0	73.0	8.0	3.7	Hypersexuality[a]
6	27.0	470	20.0	60.0	7.7	5.3	Central hypothyroidism

PRL: prolactin; T: total testosterone; ICD: impulse control disorders.
[a] These patients are reported with more detail [15].

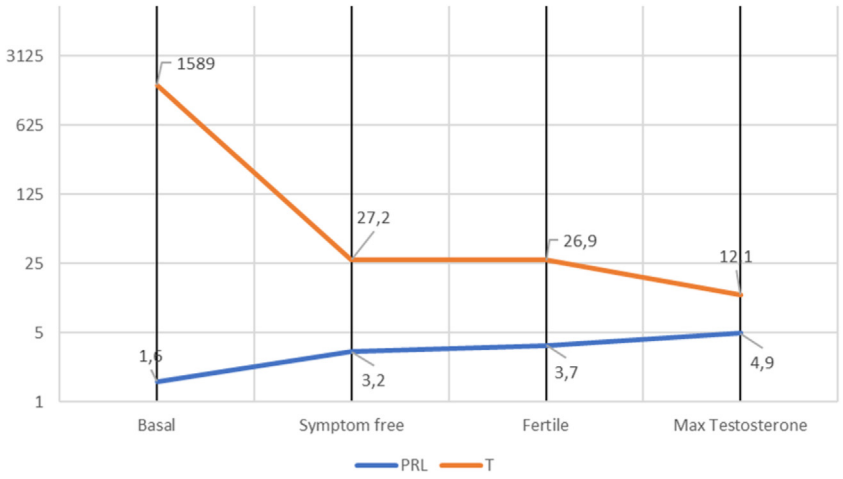


Fig. 1. Demonstration of patients' simultaneous T and PRL levels at admission and when the patients were asymptomatic and fertile; and with maximum T levels. PRL: prolactin; T: total testosterone.

a large-scale population study regardless of age, there is no consensus on the biochemical T threshold for the definitive diagnosis of hypogonadism [21]. In this study, the mean T level at presentation (1.6 ng/mL; 160 ng/dL) was below the T threshold defined as hypogonadism. On the other hand, clinical hypogonadism with normal baseline T was also reported to be more common in patients with small and non-invasive prolactinomas [24]. Our study demonstrated that about 15% of men (three macroprolactinomas and one giant prolactinoma) presented with borderline and normal pre-treatment T levels (between 2.9 to 3.75 ng/mL). This finding has been previously reported in some studies, and it was explained by lack of damage in the gonadotroph cell population. Also, it was suggested that patients harboring prolactinomas may retain an intact pituitary-gonadal hormonal axis, stimulating more T production, both before treatment initiation and while on DA [23,24]. Interestingly, we also observed that pre-treatment normal T levels of these patients increased further within the normal range with clinical improvement under treatment. Therefore, it is difficult to say precisely which low T level triggers hypogonadism symptoms due to the delays in diagnosis, but we can say that improvement in hypogonadism symptoms and infertility when mean T levels rise to 320 ng/mL and 370 ng/mL, respectively.

Table 3
Characteristics of patients in remission.

Case No.	Age at diagnosis (years)	Baseline PRL level (ng/mL)	Baseline maximal tumor diameter (mm)	Tumor shrinkage percentage (%)	Total DA treatment duration (years)	Max DA dose	Remission duration (years)	Last PRL level (ng/mL)	Last T level (ng/mL)	Other pituitary hormone deficiency at last control
1	47.0	1198	35.0	75.0	3.5	7.50*	3.0	1.1	4.90	No
2	59.0	1478	30.0	85.0	4.5	0.75**	1.0	3.1	3.60	No
3	60.0	1865	30.0	73.0	5.0	15.00*	13.0	4.8	3.34	No
4	28.0	1577	30.0	95.0	7.0	1.00*	1.0	28.0	5.50	No
5	49.0	5264	32.0	65.0	8.0	2.00**	2.0	15.0	3.10	Central hypo-thyroidism
6	26.0	10000	28.0	71.0	8.5	1.50**	1.5	44.0	5.00	No
7	38.0	10385	42.0	95.0	19.0	15.00*	1.0	14.4	3.75	Central hypo-thyroidism

PRL: prolactin; T: total testosterone; DA: dopamin agonist; *: bromocriptine (mg/daily); **: cabergoline (mg/wk).

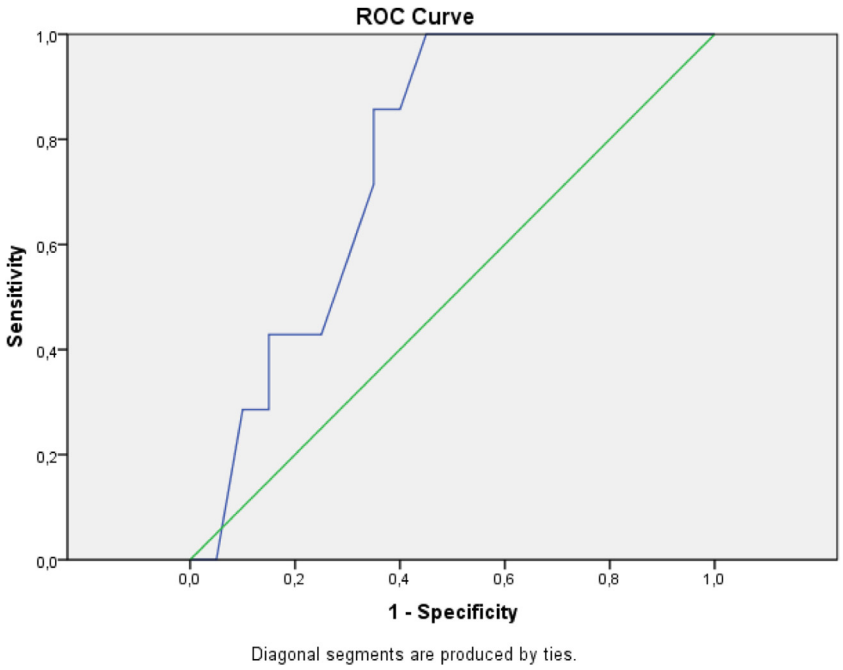


Fig. 2. ROC curve for tumor shrinkage that predicts remission. ROC curve showed that 70.5% of tumor shrinkage predicted remission with 85% sensitivity and 65% specificity (P = 0.043), (AUC: 0.76 (95% CI: 0.58–0.93).

In most of the male patients with prolactinoma, treatment with DA is effective to decrease PRL levels to normal and to reduce tumor size [11,23,25,26]. In a recent review of 12 published studies involving 309 patients with macroprolactinomas, PRL returned to normal in 80% of cases, and tumor decreased significantly in 87% with CAB treatment in 191 male prolactinomas [27]. In our country, BRC is the first DA approved for use in prolactinoma, therefore previously it has been prescribed more frequently than CAB. In this study, normalization of PRL was 84.6% and the mean tumor shrinkage was 63% after treatment with DA for an average of 8 years. In another recent study showed that in only 62% of the patients with macroprolactinomas achieved a $\geq$ 50% reduction in maximum tumor diameter after 1 and 2 years of DA treatment [12]. However, in our study, tumor shrinkage of 50% or more was detected in 70% of the patients at the last control.

It has been reported that PRL and T levels under treatment in men with giant prolactinomas return to normal by 60–68% and 40–67%, respectively [28,29]. While PRL level normalization was 75% in our four patients with giant prolactinomas, T levels returned to normal in all (100%). Colao et al. [26] reported that T levels normalized in 25 (60.9%) patients with macroprolactinoma and sperm volume and sperm count was normalized in all patients who had normal T levels. In this study, while the mean T levels of fertile patients was 370 ng/dL, PRL levels in three of these patients were slightly above normal. Unfortunately, we did not have the opportunity to perform semen analysis. Macroprolactin measurements were also not available in this retrospective study. As stated in the guideline, in some patients when gonadal function is normalized, PRL levels may remain above the upper limit of normal [30]. Providing fertilization before the PRL level returns to normal under treatment in our patients may depend on the coexistence of pituitary adenoma and macroprolactinemia or the production of macroprolactin by the pituitary tumor, as stated in the literature [16,17]. On the other hand, it is well known that increasing DA doses to normalize PRL levels is not as innocent as once suggested. Treatment with DA has been associated with neuropsychiatric side effects such as impulse control disorders (e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating). These serious side effects have been mainly reported in patients with Parkinson's disease, who are being treated with higher doses of DA [31]. However, recently, a multi-center study conducted in our country, we found an increased ICD risk in

prolactinoma patients as a serious side effect of DA treatment, and hypersexuality (6.5%) was the most common component of ICD in male prolactinomas [15]. In our study when gonadal function improved and fertilization was achieved under treatment, there was no increase in DA doses to decrease mild PRL elevation. Surprisingly, ICD occurred in our three patients who were included to the aforementioned multi-center study. In one patient T level increased from 1.0 ng/mL to 7.0 ng/mL with CAB 1.5 mg per week, in another from 1.6 ng/mL to 8.0 ng/mL with CAB 2.5 mg per week and in the last one with CAB 1.5 mg per week, T level increased from 1.0 ng/mL to 7.8 ng/mL. It seems that patients developed hypersexuality when T values were closer to the upper limit of normal even with the optimal doses of CAB. This side effect, a distinct drug toxicity has been described as "Dopa-testotoxicosis" in the literature [14,32]. Previously, Carter et al. [33] have reported that male prolactinoma patients with T levels less than 4 ng/mL may be clinically asymptomatic. Similar to above study, our macroprolactinoma patients whose mean T level was 3.7 ng/mL with treatment became asymptomatic and fertile. Additionally, the Massachusetts Male Aging Study has shown that in healthy men, serum T reaches the highest levels at around the age of 30 years with a gradual decline thereafter at a rate of 1–2% annually [34].

On the other hand, it has been reported that the large adenomas (10–82 mm) showed a strong correlation with central hypothyroidism following treatment, but persistent hypogonadism did not develop in these patients [35]. Similarly, in the present study, central hypothyroidism developed in six patients during follow-up, and one of them also had partial hypocortisolemia, but none of them developed persistent hypogonadism following DA treatment. Our result highlights the potential reversibility of gonadal function even in patients with giant prolactinomas, as reported by Tirosh et al. Conversely, a recent study reported that higher baseline tumor size and serum PRL levels predicted persistent hypogonadotrophic hypogonadism (73%) in men with macroprolactinoma who achieved normal PRL levels with CAB monotherapy. They noted that in patients with larger tumors with presumably longstanding disease, the delay between normalization of PRL and hypothalamic-pituitary-gonadal (HPG) axis recovery may be more extended (> 2 years), which may explain poor HPG axis recovery [36]. On the contrary, in our study, HPG axis improved in all patients with macroadenoma, despite a 4-year delay in diagnosis.

In the literature, the remission rate has been reported between 16–46.9% in macroprolactinomas [30,37,38]. In this study, the remission rate after discontinuation of DA between 12–156 months was 25.9%, while this rate was found as 36% after a drug-free period of 5–50 months in our previous study [39]. The difference between our remission rates may be related to the fact that the average duration of DA treatment in this study was longer than in our previous study (42–228 and 39–192 months, respectively). However, our new remission rate is also compatible with the literature.

Due to the retrospective nature of our study, there are some limitations such as the small sample size and the inability to analyze semen and macroprolactin. On the other hand, there is the advantage that the data of male patients with macroprolactinoma are recorded from a single center and by a single endocrinologist experienced in this field. In addition, the long follow-up period significantly contributes to the recording of possible side effects of exposure to DA and determining the prognosis in these patients.

5. Conclusions

It was concluded that the improvement of gonadal dysfunction in the treatment of hyperprolactinemia is an important endpoint and male patients who will use DA to reach a healthy T level should be informed about their sexual status before starting treatment. It should also be considered that although gonadal function returns to normal in some patients under this treatment, PRL levels may remain slightly higher than normal. Therefore, when such a PRL level is encountered, it is thought that it is more important to evaluate the clinical response before increasing the DA dose. One should also remember that because serum T levels decrease with age, dopa-testoxicosis may develop even with the optimal DA dose. As a result, to improve of hypogonadism findings and to avoid the possible serious side effect of the drug, it is considered appropriate to keep the serum T level in the lower half of the laboratory normal reference range, with careful observation of clinical improvement during treatment.

Availability of data and material (data transparency)

Data is available upon request.

Code availability

Not applicable.

Ethics approval

Ethics Board approval was obtained from Istanbul University Ethics Committee (rule number: 21680).

Consent to participate

Rules of Helsinki Declaration were followed and because the study's retrospective nature patient consent was not needed.

Consent for publication

Each author confirms that this manuscript is prepared and sent with his/her approval having been taken. Authors acknowledge that the copyright of this paper is transferred to the property of your journal.

Authors' contributions

Sema Yarman desgined the Project, Ozge Telci Caklili, Ayse Merve Ok and Zulal Istemihan recruited the patients, Ozge Telci Caklili performed the analysis and wrote the manuscript, Ozlem Selçukbiricik and Sema Yarman edited the manuscript.

Funding

Not applicable.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Song YJ, Chen MT, Lian W, Xing B, Yao Y, Feng M, et al. Surgical treatment for male prolactinoma: a retrospective study of 184 cases. Medicine 2017;96:e5833.
[2] Colao A, Di Sarno A, Cappabianca P, Briganti F, Pivonello R, Di Somma C, et al. Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J Endocrinol 2003;148:325–31, http://dx.doi.org/10.1530/eje.0.1480325.
[3] Schlechte JA. Prolactinoma. N Engl J Med 2003;349:2035–41, http://dx.doi.org/10.1056/NEJMcp025334.
[4] Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol 2006;65:265–73.

[5] Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273–88, http://dx.doi.org/10.1210/jc.2010-1692.
[6] Salazar-López-Ortiz CG, Hernández-Bueno JA, González-Bárcena D, López-Gamboa M, Ortiz-Plata A, Porias-Cuéllar HL, et al. Clinical practice guideline for the diagnosis and treatment of hyperprolactinemia. Ginecol Obstet Mex 2014;82:123–42.
[7] Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. J Clin Neurosci 2015;22:1562–7, http://dx.doi.org/10.1016/j.jocn.2015.03.058.
[8] Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. Endocr Rev 1992;13:220–40.
[9] Ferrari CI, Abs R, Bevan JS, Brabant G, Ciccarelli E, Motta T, et al. Treatment of macroprolactinoma with cabergoline: a study of 85 patients. Clin Endocrinol 1997;46:409–13.
[10] Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. Eur J Endocrinol 2015;172:R205–13, http://dx.doi.org/10.1530/EJE-14-0848.
[11] Yarman S, Kurtulmus N, Bilge A. Optimal effective doses of cabergoline and bromocriptine and valvular lesions in men with prolactinomas. Neuroendocrinol Lett 2012;33.
[12] Araújo C, Marques O, Almeida R, Santos MJ. Macroprolactinomas: longitudinal assessment of biochemical and imaging therapeutic responses. Endocrine 2018;62:470–6.
[13] Garcia-Ruiz PJ, Castrillo JCM, Alonso-Canovas A, Barcenas AH, Vela L, et al. Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. J Neurol Neurosurg Psychiatry 2014;85:840–4.
[14] De Sousa SM, Chapman IM, Falhammar H, Torpy DJ. Dopa-testotoxicosis: disruptive hypersexuality in hypogonadal men with prolactinomas treated with dopamine agonists. Endocrine 2017;55:618–24.
[15] Dogansen SC, Cikrikcili U, Oruk G, Kutbay NO, Tanrikulu S, Hekimsoy Z, et al. Dopamine agonist-induced impulse control disorders in patients with prolactinoma: a cross-sectional multicenter study. J Clin Endocrinol Metab 2019;104:2527–34.
[16] Mounier C, Trouillas J, Claustrat B, Duthel R, Estour B. Macroprolactinaemia associated with prolactin adenoma. Hum Reprod 2003;18:853–7.
[17] Elenkova A, Abadzhieva Z, Genov N, Vasilev V, Kirilov G, Zacharieva S. Macroprolactinemia in a patient with invasive macroprolactinoma: a case report and minireview. Case Rep Endocrinol 2013:5 [Article ID 634349].
[18] Goel A, Nadkarni T, Muzumdar D, Desai K, Phalke U, Sharma P. Giant pituitary tumors: a study based on surgical treatment of 118 cases. Surg Neurol 2004;61:436–45.
[19] Mortini P, Barzaghi R, Losa M, Boari N, Giovanelli M. Surgical treatment of giant pituitary adenomas: strategies and results in a series of 95 consecutive patients. Neurosurgery 2007;60:993–1004.
[20] Rahmanian M, Meybodi HA, Larijani B, Mohajeri-Tehrani MR. Giant prolactinoma: case report and review of literature. J Diabetes Metab Disord 2013;12:1–3.
[21] Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–59.
[22] Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, et al. Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018;200:423–32, http://dx.doi.org/10.1016/j.juro.2018.03.115.
[23] Iglesias P, Bernal C, Villabona C, Castro JC, Arrieta F, Díez JJ. Prolactinomas in men: a multicentre and retrospective analysis of treatment outcome. Clin Endocrinol 2012;77:281–7.
[24] Shimon I, Benbassat C. Male prolactinomas presenting with normal testosterone levels. Pituitary 2014;17:246–50.
[25] Bhansali A, Walia R, Dutta P, Khandelwal N, Sialy R, Bhadada S. Efficacy of cabergoline on rapid escalation of dose in men with macroprolactinomas. Indian J Med Res 2010;131:530–5.
[26] Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, et al. Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. J Clin Endocrinol Metab 2004;89:1704–11.
[27] Tirosh A, Shimon I. Management of macroprolactinomas. Clin Diabetes Endocrinol 2015;1:1–8, http://dx.doi.org/10.1186/s40842-015-0006-4.
[28] Moraes AB, Marques Dos Santos Silva C, Vieira Neto L, Gadelha MR. Giant prolactinomas: the therapeutic approach. Clin Endocrinol (Oxf) 2013;79:447–56.
[29] Espinosa E, Sosa E, Mendoza V, Ramírez C, Melgar V, Mercado M. Giant prolactinomas: are they really different from ordinary macroprolactinomas? Endocrine 2016;52:652–9.
[30] Teixeira M, Souteiro P, Carvalho D. Prolactinoma management: predictors of remission and recurrence after dopamine agonists withdrawal. Pituitary 2017;20:464–70.
[31] Athanasoulia-Kaspar AP, Popp KH, Stalla GK. Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist. Endocr Connect 2018;7:R88–94, http://dx.doi.org/10.1530/EC-18-0030.
[32] Bancos I, Nippoldt TB, Erickson D. Hypersexuality in men with prolactinomas treated with dopamine agonists; 2017, http://dx.doi.org/10.1007/s12020-017-1247-z.
[33] Carter JN, Tyson JE, Tous G, Van Vliet S, Faiman C, Friesen HG. Prolactin-secreting tumors and hypogonadism in 22 men. N Engl J Med 1978;299:847–52, http://dx.doi.org/10.1056/nejm197810192991602.
[34] Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, et al., European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008;93:2737–45.
[35] Tirosh A, Benbassat C, Lifshitz A, Shimon I. Hypopituitarism patterns and prevalence among men with macroprolactinomas. Pituitary 2015;18:108–15.
[36] Sehemby M, Lila AR, Sarathi V, Shah R, Sankhe S, Jaiswal SK, et al. Predictors of chronic LH-testosterone axis suppression in male macroprolactinomas with normoprolactinemia on cabergoline. J Clin Endocrinol Metab 2020;105:e4551–7, http://dx.doi.org/10.1210/clinem/dgaa650.
[37] Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:43–51.
[38] Colao A, Di Sarno A, Guerra E, Pivonello R, Cappabianca P, Caranci F, et al. Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. Clin Endocrinol 2007;67:426–33.
[39] Dogansen SC, Selcukbiricik OS, Tanrikulu S, Yarman S. Withdrawal of dopamine agonist therapy in prolactinomas: in which patients and when? Pituitary 2016;19:303–10.