



Recovery from hypogonadism in men with prolactinoma treated with dopamine agonists

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Abstract

Purpose In men with prolactinoma treated with dopamine agonists (DA), the extent, timeline, and predictive factors of gonadotropic axis recovery are still unclear.

Methods We analyzed data of 97 men with a prolactinoma treated with DA (77/97 macroprolactinomas). We excluded patients with primary hypogonadism, surgery < 12 months after DA initiation, and patients with tumors < 5 mm or prolactin < 45 µg/l at diagnosis.

Results Among the 97 patients, 12 had normal total testosterone (NT group) and 85 had low testosterone at diagnosis (LT group). In the NT group, testosterone rose from a mean of 13.5 nmol/l to 17.1 nmol/l at 6 months ($n=11$; $p<0.05$) then remained stable at 12 months ($n=8$). In the LT group, testosterone rose from a mean of 5.2 nmol/l to 9.6 nmol/l at 6 months ($n=66$; $p<0.001$) and further to 13.1 nmol/l at 12 months ($n=40$; $p<0.001$) then remained stable. Recovery from hypogonadism occurred in 43%, 50%, and 54% of patients at 6, 12 and 24 months, respectively (61%, 69 and 69% if prolactin was normal). Factors independently associated with persistent hypogonadism at 12 months were at baseline the presence of visual field deficit and lower testosterone levels, while the most significant independent predictor of persistent hypogonadism at one year was a testosterone level < 7.4 nmol/l at 6 months, with 91% sensitivity and 94% specificity.

Conclusion Testosterone levels recover in a small majority of men with prolactinoma mostly during the first year of DA treatment. However, testosterone replacement could be considered earlier in patients with large and compressive tumors, and in whom testosterone remains below 7.4 nmol/l after 6 months of DA treatment.

Keywords Prolactinoma · Hypogonadism recovery · Testosterone recovery · Dopamine agonists

Introduction

Men with prolactinoma frequently suffer from hypogonadotropic hypogonadism, manifesting as decreased libido, erectile dysfunction, gynecomastia, weight gain, anemia and bone loss [1]. The symptoms may occur long before the diagnosis of prolactinoma is recognized [2]. Hypogonadism in prolactinoma may be the result of a mechanical compression of the normal pituitary gland or stalk by a macroadenoma and/or the inhibitory effect of excess prolactin on kisspeptin neurons in the hypothalamus [3]. Recovery from

hypogonadism is an important objective of any treatment of prolactinoma. The 2023 guidelines from the Pituitary Society recommend reassessing testosterone levels 6 months after treatment initiation and starting exogenous testosterone therapy if frank hypogonadism persists at that time [4]. Because of the lack of enough evidence-based data, both recommendations are however graded as « weak » [4] and do not define at which level of testosterone the start of hormonal substitution is warranted.

The extent and timeline of gonadotropic axis recovery have been studied mostly in small series of less than 50 medically-treated men and showed variable rates of recovery ranging from 27 to 53% [5–9]. In 2022, two reports described hypogonadism recovery in slightly larger cohorts of men with macroprolactinoma treated with dopamine agonists (DA) [10, 11]. In 63 patients with a median tumor size of 2.9 cm, Al Dahmani et al. reported a recovery rate of hypogonadism of 65% mostly within the first 24 months of

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cabergoline therapy [11]. They observed that patients who recovered had smaller adenoma size, lower prolactin level and higher testosterone at diagnosis, less secondary hypothyroidism and they achieved earlier prolactin normalization. The series reported by Rudman et al [10] was restricted to 58 male patients who had achieved normal prolactin levels on medical therapy. In this setting, predictors of hypogonadism persistence were initial visual field defects, the presence of TSH and ACTH deficiency, and low baseline testosterone (mean: 2.4 nmol/l compared to 5.5 nmol/l in patients with eugonadism recovery). In both series, patients who had surgery were excluded (even if surgery might have occurred after more than 12 months of medical treatment), as well as those with normal testosterone or microadenoma at baseline, thus resulting in the exclusion of a significant subset of patients encountered in real life practice. Two other studies reported the evolution of testosterone levels in prolactinoma patients with normal initial testosterone, which interestingly showed a significant hormone increase of more than 50% with DA therapy [12, 13].

The purpose of our study was to assess the evolution of central hypogonadism during the first two years of treatment with dopamine agonists in a larger and more representative cohort of 97 men, with either micro- or macroprolactinoma, independently of baseline testosterone levels and normalization of prolactin concentrations.

Patients and methods

Population

We retrospectively analyzed patients' files of men with a diagnosis of prolactinoma made between 1986 and 2022 at the Cliniques Universitaires Saint-Luc, in Brussels, Belgium ($n=163$). The diagnosis of prolactinoma was based on (a) the confirmation of hyperprolactinemia on at least two separate blood samples (≥ 45 $\mu\text{g/l}$ or 3x the upper limit of normal (ULN) for the assay used); (b) the presence of a pituitary adenoma with size ≥ 5 mm on magnetic resonance imaging (MRI), and (c) exclusion of other causes of prolactin elevation such as renal failure, significant macroprolactin interference or chronic use of antidopaminergic drugs. These stringent inclusion criteria were used in order to avoid including patients with non functioning adenomas. In particular, the 3xULN prolactin cut-off was based on the report published by Burke et al [14] showing that this value was as a good predictor of the final diagnosis of prolactinoma for operated pituitary tumors with a volume <0.5 cm^3 (corresponding to microadenomas less than 8 mm in all dimensions). We also excluded patients with primary hypogonadism ($n=3$), those with initial prolactin concentrations

less than three times the upper limit of normal or tumor diameter less than 5 mm ($n=17$), and those with unavailable testosterone levels at diagnosis or at least at one time point between diagnosis and 2 years after DA initiation ($n=29$). We also excluded patients who had surgery less than one year after DA initiation ($n=17$), but analyzed the presurgical data of those who were initially treated medically and had surgery after more than one year of dopamine agonist treatment. If patients underwent surgery after 12 months, their data were also withdrawn from the analyses made at 24 months. We included patients who received exogenous supplementation with testosterone. In these patients, underlying persistent gonadotropic deficiency was assumed if treatment was ongoing, and the testosterone levels of these patients were discarded from the point of exogenous supplementation onwards.

Figure 1 illustrates the flow chart of patient inclusion and exclusion for the present study.

For patients treated with bromocriptine ($n=9$) and quinagolide ($n=1$) we converted their dose to an equivalent cabergoline dose as follows: 1 mg cabergoline per week was defined as equivalent to 10 mg bromocriptine per day or 0.15 mg quinagolide per day [15, 16]. Dopamine agonist dose was up-titrated in each patient to the maximal tolerated dose in order to achieve normal prolactin.

Methods

Patients were separated in two groups: the normal testosterone group (NT) if they had normal initial testosterone, and the low testosterone group (LT) if they had low initial testosterone.

We defined male hypogonatropic hypogonadism as a low morning total testosterone, less than 10.0 nmol/l, on two separate consecutive samples, along with low or normal LH concentration. Recovery from hypogonadism was defined as a morning total testosterone level that increased to more than 10.0 nmol/l during follow-up on a single morning sample. Testosterone was measured by radioimmunoassay before 2003 (normal range 10–35 nmol/l), using Roche Elecsys® Testosterone I from 2003 to 2008 (normal range 12–35 nmol/l, DXL-Beckman Coulter® from 2008 to 2014 (normal range 10–35 nmol/l) and finally Roche Elecsys® Testosterone II since 2014 (normal range 10.0–28.3 nmol/l). Despite these variations in the assays used over time, normal age-related ranges have remained similar especially at the lower end of normal values. The results of hormonal evaluation were recorded at different time points after DA treatment: around 6 months (accepted range 3–9), 12 months (range 10–18) and 24 months (range 19–32).

We looked for factors influencing gonadal axis recovery after 12 months of treatment. If patients had recovered

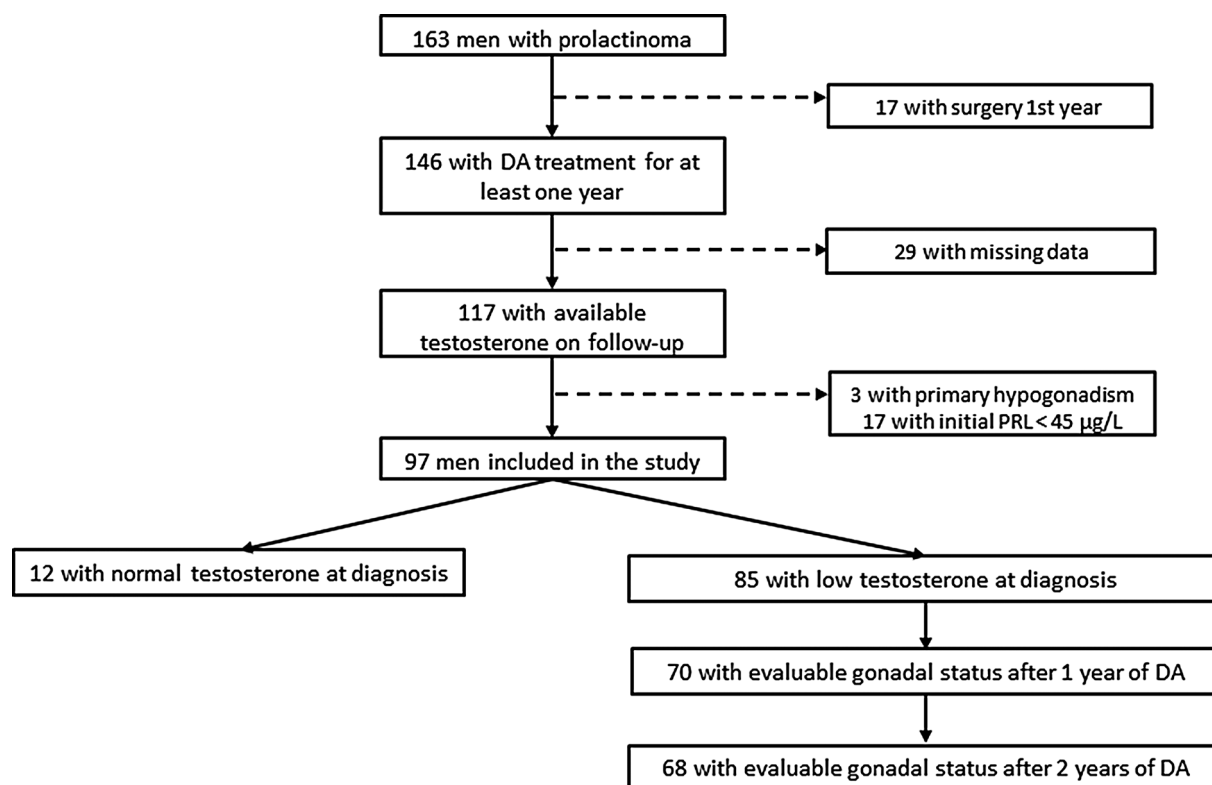


Fig. 1 Flow chart of patient inclusion and exclusion in the study. Dotted lines indicate excluded patient groups. DA: dopamine agonists, PRL: prolactin

normal testosterone after 6 months and 24 months of treatment, but did not have any available testosterone levels at 12 months of treatment, they were considered to have recovered from hypogonadism at one year.

If patients had persistently low testosterone after 6 months and 24 months of treatment, but did not have any available testosterone level at 12 months of treatment, they were considered to have persistent hypogonadism at one year.

We recorded the body mass index (BMI) at baseline, and at 6 and 12 months after treatment initiation. TSH deficiency was defined as a low free T4 concentration along with low/normal TSH. Corticotrope insufficiency was defined as a low morning cortisol < 138 nmol/l (that has been described as a cut-off for corticotrope deficiency [17]) or an abnormal cortisol response < 400 nmol/l after ACTH stimulation. Cystic component dimensions were measured on T2 weighted sections. Visual field defects were assessed by a neuro-ophthalmologist.

Statistical analysis

We used SPSS® (IBM®) version 28.0 for statistical analyses. Results are shown either as mean ± standard deviation or median and percentiles [5–95]. Comparisons of categorical

unpaired variables between subgroups were performed using Pearson's χ^2 tests or Fisher's exact tests depending on expected count size. Student's *t*-test was used for comparing means of continuous unpaired variables, exception being made for prolactin levels where Mann Whitney's test was used for comparing distributions because of asymmetric distributions. For comparing the evolution of testosterone levels during treatment, we used Wilcoxon's test (if $n < 30$) or paired *t*-test (if $n > 30$). Binary stepwise logistic regression was performed first for one variable at a time and then for several variables at the same time (limited to one variable for every 10 events). We performed ROC (receiver operating characteristics) curve analysis to look for variable cut-offs best predicting the persistence of hypogonadism. We also performed Kaplan-Meier survival analysis to analyze the probability of gonadal axis recovery and performed a log-rank test to compare survival curves between different patient subgroups. Statistical significance was set as a *p*-value < 0.05 (bilateral). We used GraphPad® Prism version 10.0 for figure design.

Ethics

The Ethics Committee of Saint Luc University Hospital approved this study (IRB reference 2022/13JUL/280) and

patient's informed consent was waived due to the retrospective design of the study. We handled study data according to national laws and European general data protection regulation.

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Results

The study included 97 men at diagnosis of prolactinoma, with a mean age of 44.2 ± 15.4 years and a median follow-up of 81.5 months. We divided the cohort in two groups: patients with normal initial testosterone (NT group) and low initial testosterone (LT group). Table 1 describes the characteristics of the entire cohort and compares these two groups.

Twelve patients (12.4%) had a normal initial total morning testosterone. They were diagnosed at a mean age of 48.8 ± 14.5 years, with a median PRL of 1068 $\mu\text{g/l}$ [47–6255] and a mean tumor size of 19.7 ± 11.8 mm (Table 1). During the first year of medical treatment (cabergoline in 10/12), mean testosterone in the NT group rose significantly (Supplementary Fig. 1) from 13.5 nmol/l at diagnosis to 17.1 nmol/l at 6 months ($n=11$; $p<0.05$), then remained stable at 12 months ($n=8$) and 24 months ($n=6$).

The other 85 patients had low total testosterone concentrations at diagnosis. They were diagnosed at a mean age of 43.5 ± 15.2 years, with a median PRL of 620 $\mu\text{g/l}$ [67–11022] and a mean tumor size of 20.8 ± 13.1 mm (Table 1).

On treatment with DA (cabergoline in 78/85), mean initial testosterone in the LT group rose significantly (Fig. 2) from 5.2 nmol/l at diagnosis to 9.6 nmol/l at 6 months ($n=66$, $p<0.001$), and further to 13.1 nmol/l at 12 months ($n=40$, $p<0.001$), then remained relatively stable at 14.9 nmol/l at 24 months ($n=38$, $p=0.087$ vs. 12 months). When comparing the characteristics of the NT group to the LT group, no significant difference could be found in tumor size, cystic component prevalence, median prolactin levels, BMI, rates of hypopituitarism or invasiveness (Table 1). Furthermore, even when comparing the NT group ($n=12$) to the 57 patients the LT group with very low testosterone (<6.9 nmol/l), no statistically significant difference was found in tumor size ($p=0.385$) or prolactin levels ($p=0.532$) (data not shown).

Exogenous testosterone supplementation was initiated in 23/85 patients in the LT group, after a median of 6 months (range 1–20 months).

Of these 23 patients with exogenous testosterone, 10 patients had testosterone initiated early, before 6 months of treatment, and none of these 10 recovered eugonadism at 24 months. These 10 patients all had initial testosterone levels <6.5 nmol/l and a mean tumor diameter of 28.1 mm and 5 of them suffered from another pituitary hormone deficit (TSH/ACTH).

Among patients whose gonadal status could be ascertained, recovery from hypogonadism was achieved in 33/77 patients (43%) at 6 months, 35/70 patients (50%) at 12 months, 37/68 patients (54%) at 24 months. In patients who had achieved normal prolactin (52% and 61% of the patients at 12 and 24 months, respectively), the proportion of hypogonadism recovery rose to 61% at 6 months and 69% at 12 and 24 months.

Table 1 Baseline characteristics of the 97 male patients with a prolactinoma and of these same patients divided according to the presence of a normal (NT group; $n=12$) or low testosterone (<10.0 nmol/L) at diagnosis (LT group, $n=85$)

	Total cohort ($N=97$)	LT group ($n=85$)	NT group ($n=12$)	<i>P</i> value
Age (years)	44.2 ± 15.1	43.5 ± 15.2	48.8 ± 14.5	0.265
BMI (kg/m^2)	29.4 ± 5.7	29.5 ± 5.7	28.4 ± 5.8	0.611
Tumor maximal diameter (mm)	20.7 ± 12.9	20.8 ± 13.1	19.7 ± 11.8	0.792
Macroadenoma (%)	77/97 (79%)	67/85 (79%)	10/12 (83%)	0.531
Cystic component (%)	26/65 (40%)	22/57 (39%)	4/8 (50%)	0.402
PRL ($\mu\text{g/l}$)	673 [61–10866]	620 [67–11022]	1068 [47–6255]	0.952
LH (U/l)	2.3 ± 1.5	2.1 ± 1.3	3.8 ± 1.5	<0.001
Testosterone (nmol/l)	6.2 ± 3.9	5.2 ± 2.7	13.5 ± 2.4	<0.001
TSH deficiency (%)	24/96 (25%)	21/84 (25%)	3/12 (25%)	0.622
ACTH deficiency (%)	10/96 (10%)	10/84 (12%)	0/12 (0%)	0.245
Visual field deficit (%)	18/94 (19%)	15/82 (18%)	3/12 (25%)	0.413
Cavernous sinus invasion (%)	49/95 (52%)	41/83 (49%)	8/12 (67%)	0.263

Values are shown as mean \pm standard deviation, median [P5–P95] or proportions (%). *P* values refer to comparisons between the NT and the LT groups

BMI: body mass index. PRL: prolactin LH: luteinizing hormone. FSH: follicle-stimulating hormone. TSH: thyroid stimulating hormone
ACTH: adrenocorticotrophic hormone

Fig. 2 Testosterone levels during the first 24 months of dopamine agonist treatment in men with prolactinoma and low initial testosterone concentrations. Green dots represent testosterone levels in patients with normal prolactin after one year of treatment and red dots show testosterone levels in patients with elevated prolactin after one year of treatment. Full lines represent mean testosterone levels. Dotted line represents the inferior limit of normal for testosterone in men (10 nmol/l). ns: non-significant. *** $p < 0.001$. Statistical analysis of the mean testosterone levels for the entire cohort, not restricted to those patients with elevated prolactin at one year (red dots) or not (green dots)

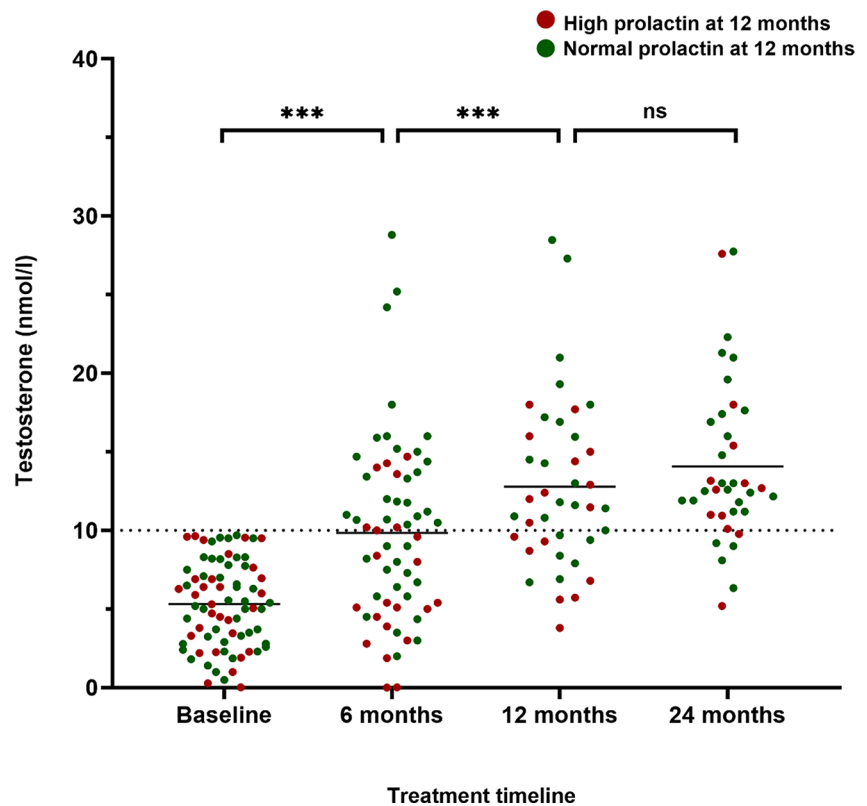
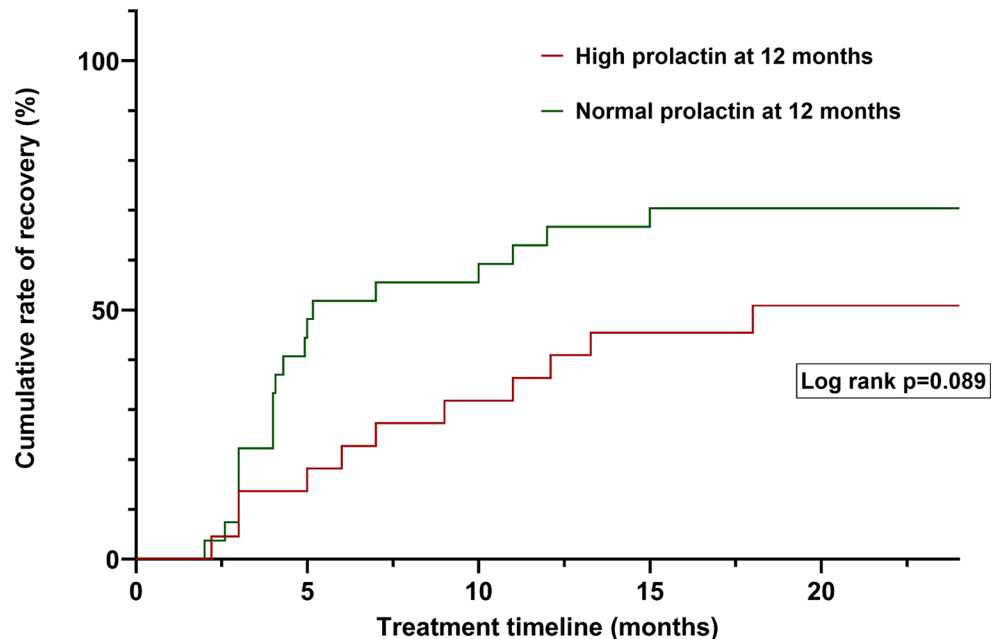


Fig. 3 Cumulative rate of recovery from hypogonadism in men with prolactinoma treated with dopamine agonists who had achieved normal prolactin or not after 12 months of dopamine agonist therapy



The cumulative rate of hypogonadism recovery according to normalization or not of prolactin is best illustrated with Kaplan Meier curves represented in Fig. 3. The log rank test revealed a trend towards faster and greater recovery of a normal gonadal axis in patients who achieved normal prolactin at 12 months compared to those who did not (median time to reach 50% recovery: 5.2 months vs. 18

months respectively, % cumulative probability of recovery at 24 months 70% vs. 50%; $p = 0.089$). The individual evolution of every patient's prolactin and testosterone levels are also illustrated in Supplementary Figs. 2 and 3.

Table 2 shows a comparison of the characteristics between patients with eugonadism or persistent hypogonadism after 12 months. Compared to those who had recovered

normal gonadotropic function after one year of medical treatment, patients with persistent hypogonadism had much bigger tumors at diagnosis, with more frequent cystic component and cavernous sinus invasion. The cystic component of the tumor occupied a mean of 24% of the coronal surface in patients with persistent hypogonadism at one year. Mean tumor diameter at diagnosis was 28.8 mm for cystic tumors ($n=21$) versus 16.1 mm in non-cystic tumors ($n=34$, $p<0.001$). Patients with persistent hypogonadism also had lower initial testosterone and LH concentrations and also more frequently suffered from visual field deficits (29% vs. 3% $p=0.003$) and from ACTH insufficiency (24% vs. 3%, $p=0.013$). Age and BMI at diagnosis did not differ between the two groups, nor did FSH levels or the proportion of patients suffering from TSH deficit. During treatment with DA (Table 2), the two subgroups differed in prolactin concentrations and the rate of prolactin normalization at 6 and 12 months ($p=0.003$ and 0.007 respectively), and in testosterone levels achieved after 6 months (13.3 ± 5.2 vs. 4.8 ± 2.5 nmol/l, $p<0.001$). The BMI at 6 months and the DA dose at 12 months were significantly higher in patients

with persistent hypogonadism. Coronal surface reduction was not associated with recovery of eugonadism.

In order to understand which factors had impeded gonadotrope recovery even though prolactin was normalized, we compared patients with normal prolactin and persistent hypogonadism ($n=10$) to those with normal prolactin and eugonadism recovery at 12 months ($n=22$). Patients with persistent hypogonadism had significantly larger initial tumors (mean diameter 26.9 mm vs. 14.9 mm, $p=0.011$) and lower initial testosterone (mean of 3.3 nmol/l vs. 6.8 nmol/l) than those who had recovered a normal gonadal status after prolactin normalization, while age and BMI did not differ significantly between these two groups ($p=0.958$ and 0.404 respectively; data not shown).

Unadjusted logistic regression analysis for factors associated with the persistence of hypogonadism after 12 months of treatment revealed a significant association with tumor diameter, ACTH deficit, visual field deficit, and LH and testosterone levels at diagnosis and during treatment (Table 3). In univariate logistic regression, there was no significant association with recovery of normal gonadal status

Table 2 Comparison between patients with recovery of eugonadism or persistent hypogonadism after one year of dopamine agonist (DA) treatment

	Patients with recovery of eugonadism after one year of DA treatment ($n=35$)	Patients with persistent hypogonadism after one year of DA treatment ($n=35$)	<i>P</i> value
Parameters at diagnosis			
Age (years)	41.6 ± 14.3	42.7 ± 15.0	0.763
BMI (kg/m ²)	27.9 ± 4.9	30.7 ± 5.7	0.110
Tumor maximal diameter (mm)	15.8 ± 12.1	26.9 ± 12.4	<0.001
Cystic component	5/26 (19%)	11/19 (58%)	0.007
Macroadenoma	22/35 (63%)	33/35 (94%)	0.001
PRL (μg/l)	165 [54-11229]	1155 [99-10603]	<0.001
LH (U/l)	2.6 ± 1.3	1.6 ± 1.0	0.003
Testosterone (nmol/l)	6.8 ± 2.4	3.7 ± 2.2	<0.001
TSH deficiency (%)	8/35 (23%)	11/34 (32%)	0.377
ACTH deficiency (%)	1/35 (3%)	8/34 (24%)	0.013
Visual field deficit (%)	1/34 (3%)	10/34 (29%)	0.003
Cavernous sinus invasion (%)	13/35 (37%)	20/33 (61%)	0.053
Parameters at 6 months			
Prolactin (μg/l)	5.6 [0.4-266.5]	44.0 [1.7-2188.5]	<0.001
Normal prolactin (%)	22/33 (67%)	10/33 (30%)	0.003
DA dose (cab-eq mg/week)	0.9 ± 0.4	1.1 ± 0.6	0.111
LH (U/l) *	3.7 ± 1.9	1.9 ± 1.1	0.040
Testosterone (nmol/l) *	13.3 ± 5.2	4.8 ± 2.5	<0.001
BMI (kg/m ²)	27.1 ± 4.4	31.1 ± 5.3	0.04
Parameters at 12 months			
Prolactin (μg/l)	10.3 [0.4-122.7]	22.7 [1.6-393.5]	0.023
Normal prolactin (%)	22/32 (69%)	10/29 (35%)	0.007
DA dose (mg/week)	0.9 ± 0.7	1.7 ± 1.1	0.005
LH (U/l) **	4.6 ± 2.1	3.4 ± 2.1	0.203
Testosterone (nmol/l) **	15.1 ± 4.7	7.4 ± 1.8	<0.001
BMI (kg/m ²)	27.5 ± 5.3	29.9 ± 5.1	0.217
%reduction in coronal surface	36.5 ± 26.4	55.5 ± 35.3	0.147

BMI: body mass index. LH: luteinizing hormone. FSH: follicle-stimulating hormone. TSH: thyroid stimulating hormone. ACTH: adrenocorticotrophic hormone. DA: dopamine agonist. BMI: body mass index

*: values from 10 patients treated with exogenous testosterone at 6 months were discarded

**: values from 19 patients treated with exogenous testosterone at 12 months were discarded

at one year with cavernous sinus invasion ($p=0.055$), PRL at diagnosis ($p=0.138$) and at 6 months ($p=0.0118$), and BMI at 6 months ($p=0.056$). We performed a correlation matrix analysis for baseline parameters (data not shown) and observed a significant correlation between tumor size and all the other baseline factors significantly associated with gonadotropic axis recovery on univariate analysis. We therefore included in our multivariate regression model only tumor size at diagnosis, visual field deficit and testosterone levels at 6 months. We included visual field deficit as an objective clinical sign of mass effect and testosterone levels at 6 months as it is recommended in the guidelines to wait at least 6 months before initiating exogenous testosterone. Multivariate logistic regression revealed only a significant association between low testosterone levels at 6 months and persistence of hypogonadism at 12 months, with an odds ratio at 2.036 ($p<0.001$, Table 3). We also tried including ACTH deficit instead of visual field deficit in this three variable model, or using only two variables (tumor size and testosterone at 6 months) and obtained the same results: only testosterone levels at 6 months remained significant (data not shown). We also performed another multivariate analysis with only baseline parameters that were the most significant in univariate analysis (initial tumor size, baseline total testosterone concentration and the presence of visual field deficits), revealing that low testosterone and visual field deficits were independent significant predictors of gonadal function recovery at one year (Table 3).

ROC analysis revealed that a testosterone level of less than 7.4 nmol/l at 6 months predicted hypogonadism persistence at 12 months with a sensitivity of 91% and a specificity of 94% (area under the curve of 0.96), while for the same outcome parameter, a baseline testosterone cut-off of 5.35 nM had a lower predictive value with a sensitivity of 73% and specificity of 71%.

Discussion

We report on a large cohort of men with prolactinoma treated medically with dopamine agonists and found a high prevalence (87%) of low testosterone at diagnosis and a reversibility of this hypogonadotropic hypogonadism in slightly more than 50% of men. Recovery from hypogonadism mainly occurred during the first year of treatment and was more frequent in patients with prolactin normalization and in those with smaller tumors and no mass effect.

Interestingly, men with normal initial testosterone (13% of the total cohort) did not have lower prolactin levels or smaller tumors at diagnosis, suggesting that the sensitivity of the gonadal axis to hyperprolactinemia is variable in male individuals. In light of the known regulatory mechanisms of prolactin signaling in the hypothalamus [18], we hypothesize that inter-individual variability should exist in the bioactivity of prolactin, the response of kisspeptin neurons to prolactin, the response of GnRH neurons to kisspeptin, and/or in the resistance of gonadotrope cells to mechanical stress, and this particularly in men [19].

However, DA treatment in this NT subgroup induced a significant increase in testosterone levels, especially in the first 6 months, highlighting the fact that these patients still suffered from partial central hypogonadism that may recover rapidly with medical treatment. Our study was not designed to determine whether this increase of testosterone within the normal range was associated with a change in sexual function parameters or other androgen related parameters (anemia, bone density).

In men with low initial testosterone, we show that sex hormone levels rise significantly in the majority of patients during the first year of DA treatment, reaching normal concentrations in 54% of them and remaining mostly stable afterwards. These observations are in line with two recent reports on the subject (Table 4). In the study reported by Al-Dahmani et al.¹⁰, the percentage of patients with initial

Table 3 Uni- and multivariate logistic regression analysis of factors predicting persistence of hypogonadism at one year

	Univariate analysis		Multivariate analysis 1*		Multivariate analysis 2**	
	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
Maximal diameter (mm)	0.001	1.075 (1.028-1.123)	0.129	1.037 (0.922-1.166)	0.412	1.024(0.968-1.082)
Cystic component	0.010	5.775 (1.521-21.932)				
ACTH deficit	0.032	10.462 (1.23-88.975)				
Visual field deficit	0.015	13.75 (1.647-114.761)	0.474	4.125(0.085-199.545)	0.014	32.202(2.014-514.783)
LH at diagnosis (U/l)	0.006	0.489 (0.293-0.816)				
Testosterone at diagnosis (nmol/l)	<0.001	0.583 (0.449-0.758)			<0.001	0.487 (0.335-0.707)
LH at 6 months (U/l)***	0.030	0.388 (0.208-0.722)				
Testosterone at 6 months (nmol/l)***	<0.001	0.488 (0.332-0.718)	<0.001	0.491 (0.320-0.754)		

ACTH: adrenocorticotrophic hormone. LH: luteinizing hormone. PRL: prolactin. ULN: upper limit of normal BMI body mass index

*: adjusted for tumor diameter, visual field deficit and testosterone at 6 months

**: adjusted for tumor diameter, testosterone at diagnosis and visual field deficit

*** LH and testosterone levels of patients already treated with exogenous testosterone at 6 months were discarded for this analysis

hypogonadism (80%) was similar to our result of 87%, while the percentage of hypogonadism recovery was slightly higher (65%), occurring mostly within the first two years. In the study of Rudman and colleagues [10], reversibility of hypogonadism was observed in a higher proportion of men (79%) but only those with normal prolactin concentrations were included. Variable lower rates of testosterone recovery, ranging from 27 to 53%, have been observed in older size-limited studies [5–9].

Prolactin normalization, a smaller initial tumor size, the absence of cystic components and mass effect (as reflected by the absence of visual field or ACTH deficits) at diagnosis are closely related to the ability of the gonadal axis to recover. This highlights the importance of mechanical compression of the normal pituitary or stalk as the main mechanism of persistent hypogonadism. Again, these results confirm the report by Rudman et al [10] who also found visual field and ACTH deficits to be predictors of a poor prognosis in their cohort of 58 patients, that had achieved normal prolactin (thus avoiding the confounding factor of hyperprolactinemia that induces functional hypogonadism). The underlying hypothesis is that long-standing mechanical compression of the normal pituitary axis by a large tumor induces irreversible damage or atrophy of the gonadotroph cells. For the first time, we also show that a cystic tumoral component (occupying in our series a mean of 24% of the coronal surface) is also a risk factor for poor prognosis, probably because of the treatment resistance associated with heterogeneous tumors [20] and larger tumor size in cystic tumors than in solid tumors in our cohort.

Another interesting finding is that a total morning testosterone concentration of less than 7.4 nmol/l after 6 months

of dopamine agonist treatment may predict the persistence of hypogonadism with excellent sensitivity and specificity (> 90%). In our model, testosterone at 6 months was the best independent predictor of recovery from hypogonadism, perhaps because it takes into account not only the initial severity of the disease but also the early response to treatment with DAs, reflecting the recovery potential of each patient. When only baseline characteristics were considered, we did find that baseline testosterone was a significant parameter with a cut-off of < 5.35 nmol/l best predicting hypogonadism persistence at 12 month. This value is remarkably similar to the results reported by Rudman et al. (< 5.2 nmol/l) in their series of patients who had all normalized prolactin [10]. Nevertheless, this cut-off had less predictive power than testosterone at 6 months. Our results indicate that testosterone replacement therapy might be initiated at that time in those patients with large initial tumors and mass effects if their testosterone levels remain low. It seems indeed more relevant to wait for at least 6 months before considering hormone replacement therapy, as suggested by the recent guidelines of the Pituitary Society [4].

Evaluation of morning total testosterone levels as the main indicator of gonadal function in a cohort of overweight patients may have led to a falsely elevated proportion of hypogonadism, because of the known decrease in sex hormone binding globulin (SHBG) concentrations that are associated with obesity and insulin resistance in men [21]. Indeed, the measurement of free testosterone may be normal in men with low total testosterone, in as many as 66% of obese men (BMI > 30 kg/m²) and 44% of overweight men (BMI < 30 kg/m²) [21]. Because we and others did not measure free testosterone or SHBG, the true proportion

Table 4 Comparison of series describing hypogonadism recovery in men with prolactinoma during medical treatment

First author, year	N	N micro prolactinoma	Country	Median duration of DA treatment	Gonadal axis recovery	Normal PRL	Predictors of hypogonadism persistence
Pinzone et al. 2000 [5]	36	12/36	USA	53 months	56%	80%	/
Sibal et al. 2002 [6]	26	0	USA	31 months	38%	83%	/
De Rosa et al. 2006 [7]	65	15/65	Italy	6 months	66%	77%	/
Schemby et al. [9]	30	0	India	24 months	36%	100%	/
Rudman et al. 2022 [10]	58	0	Israel	67 months	79%	100%	Visual field deficit TSH/ACTH deficit
Al-Dahmani et al. 2022 [11]	63	0	UAE	72 months	65%	84%	TSH/GH deficit
This study	68*	15/68	Belgium	24 months	54%	61%	Visual field deficit ACTH deficit Cystic tumor

DA: dopamine agonists; PRL: prolactin. TSH: thyroid stimulating hormone. ACTH: adrenocorticotrophic hormone. T: testosterone GH: growth hormone

*: We report here the recovery rate for the 68 patients with available data after two years of medical treatment in our cohort

of hypogonadism at baseline and during treatment may be overestimated, and recovery rates underestimated, although the observed trend in hormone concentrations remains valid. Our proposed testosterone threshold must be interpreted with caution as it might be influenced by several factors including the BMI and age of the patient, as well as concomitant diseases and medications. Nevertheless, it may represent a simple indicator obtained in a real-life study performed in a typical Caucasian population with such pathology. Whether the lower BMI found at 6 months in patients who recovered is one of the causal factors or merely the consequence of gonadal recovery is not clear, but indicates that all patients should be encouraged to maintain a healthy diet and exercise regularly in order to improve their testosterone levels [22].

Early testosterone supplementation in some patients in our cohort may have masked the potential recovery from hypogonadism. However, testosterone was usually initiated in those patients with severe symptoms of hypogonadism, low baseline testosterone, and large tumors, so that the probability of rapid recovery was low. Nevertheless, it is advisable to attempt withholding testosterone treatment for 3 months to reassess gonadal status during treatment if there is an excellent radiological response and the patient has a normal prolactin on DA treatment.

The strengths of our study include the large and representative cohort of patients (the largest published to date on this subject), the inclusion of microprolactinoma (5–9 mm), the evaluation of cystic components and analysis of the tumor response in parallel to biological response. Limitations include the retrospective design of the study, with missing data for some patients during follow-up, the lack of objective data on sexual function parameters, the lack of free testosterone (index) measurements and the small number of patients who achieved normal prolactin ($n=32$) at one year, which however reflects real-life practice in our tertiary referral center for resistant or complex cases.

In conclusion, a large majority of men with prolactinoma suffer from hypogonadotropic hypogonadism at diagnosis. Dopamine agonist treatment will lead to a significant increase in testosterone levels, even among those with normal initial testosterone, revealing some degree of initial hypogonadism. Among patients with hypogonadism, recovery of gonadal function was finally observed in 54% of patients, raising to 69% in those who achieved normal prolactin, and this occurs mostly within the first year of medical treatment. We confirm that indicators of mass effect such as tumor size, the presence of a large cystic component, visual field deficit and/or ACTH deficit and low initial testosterone are predictors of persistent hypogonadism. We suggest to consider starting testosterone therapy after 6 months in such patients, especially if total morning testosterone at this time

point remains below the cut-off of 7.4 nmol/l. Future studies should strive to prospectively assess both SHBG and free testosterone to better refine our decision making process.

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Author contributions SMC wrote the main manuscript text, and prepared Figs. 2 and 3DM prepared Fig. 1 DM and OA were responsible for study design and oversightAll authors reviewed the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval The Ethics Committee of Saint Luc University Hospital (IRB reference 2022/13JUL/280) approved this study and patient's informed consent was waived due to the retrospective design of the study.

Competing interests The authors declare no competing interests.

References

1. Duskin-Bitan H, Shimon I (2020) Prolactinomas in males: any differences? *Pituitary* 23(1):52–57
2. Rudman Y, Duskin-Bitan H, Richter I, Tsvetov G, Masri-Iraqi H, Akirov A et al (2023) Hemoglobin decline as a signal for hyperprolactinemia onset prior to prolactinoma diagnosis in hypogonadal men. *Andrology* 11(7):1398–1407
3. Chanson P, Maiter D (2019) The epidemiology, diagnosis and treatment of Prolactinomas: the old and the new. *Best Pract Res Clin Endocrinol Metab* 33(2):101290
4. Petersenn S, Flseriu M, Casanueva FF, Giustina A, Biermasz N, Biller BMK et al (2023) Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. *Nat Rev Endocrinol* 19(12):722–740
5. Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A (2000) Primary medical therapy of micro- and macroprolactinomas in men. *J Clin Endocrinol Metab* 85(9):3053–3057
6. Sibal L, Ugwu P, Kendall-Taylor P, Ball SG, James RA, Pearce SH et al (2002) Medical therapy of macroprolactinomas in males: I. Prevalence of hypopituitarism at diagnosis. II. Proportion of cases exhibiting recovery of pituitary function. *Pituitary* 5(4):243–246
7. De Rosa M, Ciccarelli A, Zarrilli S, Guerra E, Gaccione M, Di Sarno A et al (2006) The treatment with cabergoline for 24 month normalizes the quality of seminal fluid in hyperprolactinaemic males. *Clin Endocrinol (Oxf)* 64(3):307–313

8. Karavitaki N, Dobrescu R, Byrne JV, Grossman AB, Wass JA (2013) Does hypopituitarism recover when macroprolactinomas are treated with cabergoline? *Clin Endocrinol (Oxf)* 79(2):217–223
9. Sehemby M, Lila AR, Sarathi V, Shah R, Sankhe S, Jaiswal SK et al (2020) Predictors of chronic LH-Testosterone Axis suppression in male Macroprolactinomas with Normoprolactinemia on Cabergoline. *J Clin Endocrinol Metab.* ;105(12)
10. Rudman Y, Duskin-Bitan H, Masri-Iraqi H, Akirov A, Shimon I (2022) Predicting hypogonadotropic hypogonadism persistence in male macroprolactinoma. *Pituitary* 25(6):882–890
11. Al Dahmani KM, Almalki MH, Ekhzaimy A, Aziz F, Bashier A, Mahzari MM et al (2022) Proportion and predictors of Hypogonadism Recovery in men with Macroprolactinomas treated with dopamine agonists. *Pituitary* 25(4):658–666
12. Shimon I, Benbassat C (2014) Male prolactinomas presenting with normal testosterone levels. *Pituitary* 17(3):246–250
13. Auriemma RS, Galdiero M, Vitale P, Granieri L, Lo Calzo F, Salzano C et al (2015) Effect of chronic cabergoline treatment and testosterone replacement on metabolism in male patients with prolactinomas. *Neuroendocrinology* 101(1):66–81
14. Burke WT, Penn DL, Castlen JP, Donoho DA, Repetti CS, Iuliano S et al (2019) Prolactinomas and nonfunctioning adenomas: pre-operative diagnosis of tumor type using serum prolactin and tumor size. *J Neurosurg* 133(2):321–328
15. Di Sarno A, Landi ML, Marzullo P, Di Somma C, Pivonello R, Cerbone G et al (2000) The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. *Clin Endocrinol (Oxf)* 53(1):53–60
16. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *N Engl J Med* 331(14):904–909
17. Kazlauskaitė R, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB et al (2008) Corticotropin tests for hypothalamic-pituitary- adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab* 93(11):4245–4253
18. Millar RP, Sonigo C, Anderson RA, George J, Maione L, Brailly-Tabard S et al (2017) Hypothalamic-pituitary-ovarian Axis Reactivation by Kisspeptin-10 in Hyperprolactinemic Women with Chronic Amenorrhea. *J Endocr Soc* 1(11):1362–1371
19. Maiter D (2019) Prolactinomas in men. In: Tritos NA, Klibanski A (eds) *Prolactin disorders: from Basic Science to Clinical Management*. Springer International Publishing, Cham, pp 189–204
20. Burlacu MC, Maiter D, Duprez T, Delgrange E (2019) T2-weighted magnetic resonance imaging characterization of prolactinomas and association with their response to dopamine agonists. *Endocrine* 63(2):323–331
21. Cooper LA, Page ST, Amory JK, Anawalt BD, Matsumoto AM (2015) The association of obesity with sex hormone-binding globulin is stronger than the association with ageing—implications for the interpretation of total testosterone measurements. *Clin Endocrinol (Oxf)* 83(6):828–833
22. Singh A, Dobs AS (2019) Is it Time to test the Effect of Weight loss on Testosterone? *Clin Chem* 65(1):48–50

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