Predicting hypogonadotropic hypogonadism persistence in male macroprolactinoma

Yaron Rudman
Rabin Medical Center
Hadar Duskin-Bitan
Rabin Medical Center
Hiba Masri-Iraqi
Rabin Medical Center
Amit Akirov
Rabin Medical Center
Ilan Shimon (ilanshi@clalit.org.il)
Rabin Medical Center

Research Article

Keywords: Men, Prolactinoma, Prolactin, Testosterone, Hypogonadism

Posted Date: May 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1642554/v1

Abstract

Purpose:

To study the baseline characteristics predicting hypogonadotropic hypogonadism (HH) persistence in men with macroprolactinoma that achieved prolactin normalization.

Design:

Retrospective cohort study.

Methods:

Male patients diagnosed with macroprolactinoma and HH that received cabergoline treatment with subsequent prolactin normalization were included: men that achieved eugonadism, and men that remained hypogonadal. Patient's demographic, clinical and biochemical parameters, sellar imaging and visual fields tests were obtained.

Univariate and multivariate models were used to identify predictors of HH persistence.

Results:

Fifty-eight male patients (age, 49.2±12.6 years) with a median baseline prolactin of 1154 ng/mL (IQR, 478-2763 ng/mL) and adenoma (maximal) diameter of 25.9±14.8 mm were followed for a median of 5.6 years (IQR, 3.0-10.7). Twelve men (21%) suffered from HH persistence at the end of follow-up and 46 men achieved eugonadism. Forty-two out of 46 men (91%) accomplished eugonadism within the first year following prolactin normalization.

In a multivariate logistic regression model, hypopituitarism (OR=10.1; 95% CI 1.10 – 101.94), visual field defect (OR=9.9; 95% CI 1.07 – 92.33), and low baseline testosterone levels (OR=0.5; 95% CI 0.29 – 0.93) were independent predictors of HH persistence.

Conclusion:

In our cohort of men with macroprolactinoma that reached prolactin normalization with cabergoline treatment, 21% had HH persistence. Pituitary hormone deficiency, visual field defects, and low baseline testosterone levels were independently associated with HH persistence. 91% of men achieved eugonadism within the first year following prolactin normalization. These findings may support informed clinical decision-making regarding the initiation of testosterone replacement in men with macroprolactinomas.

Introduction

Prolactinomas (i.e., prolactin-secreting adenomas) are the most common functional pituitary tumors, accounting for 40 to 60 percent of all pituitary tumors [1, 2]. Prolactinomas larger than 10 mm in diameter (i.e., macroprolactinomas) exhibit male predominance and a tendency to a more aggressive course, compared with smaller prolactinomas [3, 4].

Symptoms secondary to mass effect are encountered in 29–54% of men [5–7]. These symptoms develop as the tumor presses against critical sellar and parasellar structures, leading to visual field defects (VFD), headaches and rarely ophthalmoplegia. Patients may suffer from central hypothyroidism (present in 18–41% of affected men) and central adrenal insufficiency (12–67% of men) [5, 8, 9].

Men with macroprolactinomas frequently present with symptoms secondary to hyperprolactinemia. Hypogonadotropic hypogonadism (HH) occurs in approximately 76–100% of men at the time of diagnosis [10, 11], clinically reflected by erectile dysfunction, decreased libido, and decreased sperm counts. Low serum testosterone levels may cause secondary anemia in up to 83% of men [12].

Previous studies suggest that HH in patients with macroprolactinoma derives from the inhibitory effect exerted by prolactin upon the hypothalamus [13], with incidental cases of HH that result from direct structural pituitary damage caused by large tumors [14].

Medical treatment with cabergoline is recommended as first-line therapy for patients with symptomatic prolactinomas [15]. The main goals of treatment in male macroprolactinoma include prolactin normalization, tumor mass reduction and gonadal axis recovery [16].

With cabergoline treatment, HH persistence is seen in 11–73% of men with macroprolactinoma [7–11, 17, 18]. Because of the small sample size in the different studies, the variable tumor size, the changing duration of treatment and follow-up, and the diverse ethnicity of the populations studied, there is a considerable between-studies variability in the proportion of men with HH persistence. Moreover, some studies included patients with dopamine agonist resistance or with normal baseline testosterone levels, while others included patients that underwent surgery and radiation (treatments that may result in HH persistence), which may have caused incorrect patient classification.

De rosa et al. (2006, Italy) [10] prospectively evaluated 38 medically treated male patients with macroprolactinoma and identified high baseline serum prolactin, low baseline testosterone and large tumor size as predictors of short-term HH persistence (up to 6 months after prolactin normalization). In 2020, Sehemby et al. [11] investigated a cohort of 30 men from Mumbai, India, that achieved normoprolactinemia with cabergoline therapy and found that baseline serum prolactin and tumor size predicted HH persistence after a median follow-up of two years (from prolactin normalization to the end of follow-up).

The aim of this study was to identify the baseline characteristics predicting long-term HH persistence in a large cohort of male macroprolactinoma, that achieved normoprolactinemia following medical treatment

with cabergoline. This study also reports the long-term response to medical treatment in this population, with and without HH persistence.

Study Design And Methods

This is a single-center retrospective study of male macroprolactinoma, treated at the pituitary clinic in the Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center (RMC), Israel. The study was approved by the institutional ethics review board.

Patients

Patients were identified by reviewing our pituitary clinic prolactinoma registry. All patients were diagnosed or referred directly after prolactinoma detection to the pituitary clinic at the RMC. Male patients with pituitary macroadenoma, over 10 mm in maximal diameter on magnetic resonance imaging (MRI), and serum prolactin above 100 ng/ml were included.

Men with hyperprolactinemia secondary to antipsychotic medication use or “pituitary stalk effect” were not included in the registry.

Patients were treated with cabergoline monotherapy.

We excluded men that did not reach normoprolactinemia (i.e., dopamine agonist resistant patients), men with eugonadism at presentation, and men that underwent surgery or radiotherapy. Patients with less than 12 months of follow-up were also excluded.

Data collection

Patient’s demographic, clinical and biochemical parameters, sellar MRI and visual fields tests (interpreted by a neuro-ophthalmologist) were obtained. Laboratory tests at presentation and during follow-up, included prolactin, total testosterone, LH, FSH, morning cortisol, TSH and FT_4 measurements. Data regarding cabergoline treatment, testosterone replacement, surgical therapy, and radiotherapy were collected.

HH was defined as low serum total testosterone (< 2.8 ng/mL) with low or inappropriately normal LH levels. HH persistence was defined as HH at the end of follow-up, after at least 12 months of cabergoline treatment, and a minimum of 6 months interval between prolactin normalization and end of follow-up testosterone measurement. Central adrenal insufficiency was defined as 9:00 a.m. cortisol value below 100 nmol/L or below 450 nmol/L following ACTH stimulation. Central hypothyroidism was defined as low or inappropriately normal TSH levels in the presence of low FT_4 levels.

Treatment and follow-up protocol

Cabergoline treatment was initiated at a weekly dose of 0.5 mg, or at a higher weekly dose of 1 mg in cases of baseline prolactin levels ≥ 1000 ng/ml. Doses were up-titrated every 2–3 months according to

prolactin levels, as needed, until they reached either normalization or plateau.

Patients that suffered from HH persistence for ≥ 6 months following prolactin normalization and remained symptomatic were offered testosterone therapy.

The RMC pituitary clinic's treatment and follow-up protocol for this cohort of male macroprolactinoma is available in a previously published article [7].

Biochemical evaluation

Serum prolactin levels were measured by immunometric assay (Immulite 2000; Siemens), which has a sensitivity of 0.15 ng/ml. The intra-assay coefficients of variation (CVs) for prolactin concentrations of 22 and 164 ng/ml were 2.3% and 3.8%, respectively; the corresponding inter-assay CV was 6%. Reference levels for men in our laboratory are 2–20 ng/ml. Levels ≥ 200 ng/ml were calculated after appropriate serum dilutions.

Reference total testosterone levels for men in our laboratory are 2.8–9.6 ng/ml.

Reference levels for other laboratory tests were determined according to each kit manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY).

Continuous variables were presented by Mean (SD) or Median (IQR) as appropriate. Dichotomous variables were presented by N (%).

In order to compare the baseline characteristics of included and excluded patients, analysis of variance (ANOVA) was used for normally distributed continuous variables. Kruskal–Wallis test was used for non-normal continuous variables and Chi-square test for categorical variables.

All men with macroprolactinoma were screened and divided into 3 groups: patients with eugonadism at presentation (group A, Fig. 1), patients with HH at presentation and dopamine agonist resistance or a tumor that required surgery and/or radiotherapy (group B, Fig. 1), and patients with HH at presentation and a good response to medical therapy with cabergoline (group C, Fig. 1). In order to better characterize the group under investigation (group C), we compared the above groups and identified differences between baseline variables of the excluded (groups A and B) and included (group C) patients.

The study cohort included only group C patients, who were divided into 2 subgroups: men that achieved eugonadism at the end of follow-up, and men that remained hypogonadal. In the event of testosterone replacement, the last testosterone, LH and FSH measurements recorded just before replacement treatment were documented as end of follow-up measurements, in a "last observation carried forward" manner.

Univariate analyses exploring associations between baseline characteristics and HH persistence were performed. Independent-samples T test was used to compare the values of normally distributed continuous variables among the two groups. Mann–Whitney test was used for non-normal continuous variables and Chi-Square test for categorical variables.

Relative risk (RR) was calculated for dichotomous variables to describe the strength of the relationship between the categorical risk factors and HH persistence.

Correlations between normally distributed continuous variables were performed using Pearson's R. Spearman's Rho was used for correlations between non-normal continuous variables.

Multivariate logistic regression model for HH persistence was developed to explore the relative contributions of the predicting factors, including age at diagnosis, baseline prolactin, testosterone, LH, FSH, adenoma maximal diameter, cavernous sinus invasion, suprasellar invasion, visual field defect, central hypothyroidism, central adrenal insufficiency, and sexual function status. Continuous variables were included in the model if the P-value was less than 0.05. Dichotomous variables were included in the model if the RR was 2.5 or greater and the P-value was less than 0.05.

Complete data were collected for all study variables, except LH, FSH and sexual function status. No imputation for missing data was done, as missing at random cannot be assumed.

Two-sided P-values less than 0.05 were considered statistically significant.

Results

From February 1993 to December 2020, we identified 103 registered men with macroprolactinoma, that were divided into 3 groups (Fig. 1, Table 1): male patients that were excluded due to eugonadism at presentation (group A, excluded, n = 14), patients that were excluded because they did not reach normoprolactinemia, had surgery and/or radiotherapy or had less than 12 months of follow-up (group B, excluded, n = 31), and

Table 1
Baseline characteristics of male patients with macroprolactinoma that were (A) excluded because of eugonadism at presentation, (B) excluded because they did not reach normoprolactinemia, had surgery and/or radiotherapy, suffered from prolactin-secreting carcinoma, or had less than 12 months of follow-up, and (C) included patients, with hypogonadotropic hypogonadism at presentation and normoprolactinemia achievement with treatment.

Variable	A (excluded, n = 14)	B (excluded, n = 31)	C (included, n = 58)	p-value
Age at diagnosis, years - mean (SD)	44.0 (19.6)	41.8 (12.7)	49.2 (12.6)	0.06
Hypogonadotropic hypogonadism – n (%)	0 (0%)	31 (100%)	58 (100%)	-
Prolactin, ng/ml - median (IQR)	759 (258–1920)	2987 (977–5054)	1154 (478–2763)	< 0.01
Adenoma maximal diameter, mm - mean (SD)	18.1 (4.3)	35.4 (15.6)	25.9 (14.8)	< 0.01
Testosterone, ng/ml - mean (SD)	4.4 (0.9)	1.3 (0.8)	1.5 (0.8)	< 0.01
Luteinizing hormone, mIU/ml - mean (SD)[a]	3.1 (1.9)	1.2 (0.9)	1.5 (1.4)	< 0.01
Follicle-stimulating hormone, mIU/ml - mean (SD)[a]	3.2 (1.7)	1.9 (1.5)	3.0 (2.8)	0.15
Cavernous sinus invasion - n (%)	9 (64%)	27 (87%)	44 (76%)	0.21
Suprasellar invasion - n (%)	6 (43%)	24 (77%)	25 (43%)	< 0.01
Visual field defect - n (%)	4 (29%)	18 (58%)	9 (16%)	< 0.01
Hypopituitarism - n (%)[b]	1 (7%)	10 (32%)	8 (14%)	0.05
Central hypothyroidism - n (%)	1 (7%)	8 (26%)	7 (12%)	0.15
Central adrenal insufficiency - n (%)	0 (0%)	5 (16%)	4 (7%)	0.16
Sexual dysfunction - n (%), n = 101	6 (43%)	22 (71%)	48 (86%)	< 0.01
a – only 10/14, 28/31 and 51/58 measurements were collected (n = 89).				
b – central adrenal insufficiency and/or central hypothyroidism.				

male patients with HH at presentation, that received cabergoline treatment with subsequent prolactin normalization (group C, included, n = 58).

Baseline characteristics of included and excluded patients

Median baseline prolactin levels were 759, 2987 and 1154 ng/ml ($p < 0.01$) in groups A, B and C, respectively (Table 1). Mean prolactinoma (maximal) diameter at presentation was 18.1, 35.4 and 25.9 mm ($p < 0.01$) in groups A, B and C, respectively (Table 1).

Mean baseline testosterone levels were 4.4, 1.3 and 1.5 ng/ml ($p < 0.01$), and mean baseline LH levels were 3.1, 1.2 and 1.5 mIU/ml ($p < 0.01$) in groups A, B and C, respectively (Table 1).

At diagnosis, VFDs were documented in 4 (29%), 18 (58%) and 9 (16%) patients in groups A, B and C, respectively ($p < 0.01$). Hypopituitarism (i.e., central adrenal insufficiency and/or central hypothyroidism) was diagnosed in 1 (7%), 10 (32%) and 8 (14%) of men, respectively ($p = 0.05$, Table 1).

Men with baseline HH that achieved normal prolactin levels with cabergoline

The cohort included 58 male patients with HH at presentation, that received cabergoline treatment with subsequent prolactin normalization (i.e., group C, Fig. 1).

All patients received cabergoline as first-line treatment.

Twelve men (21%) suffered from HH persistence at the end of follow-up, and 46 men (79%) achieved eugonadism.

Baseline characteristics of men with and without HH persistence

The age at diagnosis did not differ between the 2 groups (Table 2).

Table 2
Baseline characteristics of male patients with macroprolactinoma that achieved normal prolactin levels with cabergoline treatment, with and without hypogonadotropic hypogonadism persistence at the end of follow-up.

Variable	Without HH persistence (n = 46)	HH persistence (n = 12)	RR	95% confidence interval	p-value
Age at diagnosis, years - mean (SD)	49.5 (13.6)	48.3 (8.6)	-	-	0.76
Prolactin, ng/ml - median (IQR)	1014 (478–2416)	2003 (474–6593)	-	-	0.17
Adenoma maximal diameter, mm - mean (SD)	23.7 (12.8)	34.6 (18.9)	-	-	0.02
Testosterone, ng/ml - mean (SD)	1.6 (0.7)	0.7 (0.6)	-	-	< 0.01
Luteinizing hormone, mIU/ml - mean (SD)[a]	1.8 (1.5)	0.4 (0.3)	-	-	< 0.01
Follicle-stimulating hormone, mIU/ml - mean (SD)[a]	3.4 (2.9)	0.9 (0.7)	-	-	< 0.01
Cavernous sinus invasion - n (%)	34 (74%)	10 (83%)	1.6	0.4–6.4	0.07
Suprasellar invasion - n (%)	15 (33%)	10 (83%)	6.6	1.6–27.8	< 0.01
Visual field defect - n (%)	4 (9%)	5 (42%)	3.8	1.5–9.3	0.01
Hypopituitarism - n (%)[b]	2 (4%)	6 (50%)	6.3	2.6–14.8	< 0.01
Central hypothyroidism - n (%)	2 (4%)	5 (42%)	-	-	< 0.01
Central adrenal insufficiency - n (%)	1 (2%)	3 (25%)	-	-	0.03
Sexual dysfunction - n (%), n = 56	36 (82%)	12 (100%)	NA	NA	0.18
NA means not applicable.					
a – only 42/46 and 9/12 measurements were collected (n = 51).					
b – central adrenal insufficiency and/or central hypothyroidism, in addition to HH.					

Median baseline prolactin levels were 2003 ng/ml (IQR, 474–6593 ng/ml) in the group of men with HH persistence and 1014 ng/ml (478–2416 ng/ml) in the group of men that achieved eugonadism (p = 0.17).

Mean prolactinoma (maximal) diameter was larger in men with HH persistence (34.6 ± 18.9 vs 23.7 ± 12.8 mm, p = 0.02, Table 2).

Mean baseline testosterone was 0.7 ± 0.6 and 1.6 ± 0.7 ng/mL (p < 0.01), LH was 0.4 ± 0.2 and 1.8 ± 1.5 mIU/mL (p < 0.01), and FSH 0.9 ± 0.7 and 3.4 ± 2.9 mIU/mL (p < 0.01) in men with and without HH persistence, respectively (Table 2).

Cavernous sinus invasion was evident in 10 (83%) and 34 (74%) men with and without HH persistence, respectively (RR 1.6; 95% CI 0.4–6.4, Table 2). Suprasellar tumor invasion was evident in 10 (83%) patients with HH persistence vs 15 (33%) men without HH persistence (RR 6.6; 95% CI 1.6–27.8, Table 2).

VFD was diagnosed in 5 (42%) and 4 (9%) patients with and without HH persistence, respectively (RR 3.8; 95% CI 1.5–9.3, Table 2).

Hypopituitarism (i.e., central adrenal insufficiency and/or central hypothyroidism, apart from HH) was more common in patients with HH persistence: 6 (50%) vs 2 (4%) men (RR 6.3, 95% CI 2.6–14.8, Table 2).

Independent predictors of HH persistence

Baseline testosterone levels had a significant correlation with both LH levels (R = 0.45, p = 0.01) and FSH levels (R = 0.33, p = 0.01). VFD correlated well with suprasellar invasion (R = 0.49, p = 0.01).

The multivariate logistic regression model (Table 3) demonstrated that the presence of hypopituitarism (OR = 10.1; 95% CI 1.10–101.94), VFD (OR = 9.9; 95% CI 1.07–92.33), and low baseline testosterone levels (OR = 0.5; 95% CI 0.29–0.93) were independent predictors of HH persistence in men with macroprolactinoma that reached prolactin normalization with cabergoline treatment. Adenoma (maximal) diameter (OR 1.0; 95% CI 0.96–1.07) did not predict HH persistence in the multivariate model. Area under curve (AUC) of the receiver operating curve (ROC) was 0.906.

Table 3
Multivariate logistic regression model for hypogonadotropic hypogonadism persistence in male patients with macroprolactinoma that achieved normal prolactin levels with cabergoline treatment.

Variable	OR	95% confidence interval	p-value
Hypopituitarism[a]	10.1	1.10–101.94	0.04
Visual field defect	9.9	1.07–92.33	0.04
Baseline testosterone, ng/ml	0.5	0.29–0.93	0.02
Adenoma (maximal) diameter, mm	1.0	0.96–1.07	0.56
Area under curve (AUC) of the receiver operating curve (ROC): 0.906			
a - central adrenal insufficiency and/or central hypothyroidism, apart from HH.			

Baseline testosterone levels below 1.5 ng/ml together with either VFD or hypopituitarism, demonstrated a sensitivity of 75% and specificity of 93.5% to predict HH persistence.

Long term response to cabergoline treatment in men with and without HH persistence

Our cohort of 58 men was followed for a median of 5.6 years (IQR, 3.0-10.7 years). The mean weekly maximal cabergoline dose was 2.0 ± 1.1 and 1.6 ± 1.7 mg in patients with and without HH persistence, respectively ($p = 0.05$, Table 4). The median time elapsed from medical treatment initiation to prolactin normalization was 5.0 (IQR, 3.2–10.5) and 5.0 (IQR, 2.7–11.3) months in patients with and without HH persistence, respectively ($p = 0.86$, Table 4).

Table 4
Long term response to cabergoline treatment.

Variable	Without HH persistence (n = 46)	HH persistence (n = 12)	p-value
Cabergoline dose, mg/week - mean (SD)	1.6 (1.7)	2.0 (1.1)	0.05
Time to prolactin normalization, months - median (IQR)	5.0 (2.7–11.3)	5.0 (3.2–10.5)	0.86
Prolactin, ng/ml - median (IQR)	7.9 (4.1–13.3)	5.8 (3.7–8.8)	0.17
Testosterone levels, ng/ml - mean (SD)[a]	4.6 (1.1)	1.0 (0.6)	< 0.01
Luteinizing hormone, mIU/ml - mean (SD)[a,b]	4.1 (2.7)	1.0 (1.0)	< 0.01
Follicle-stimulating hormone, mIU/ml - mean (SD)[a,b]	6.2 (4.3)	2.3 (2.3)	0.02
Adenoma maximal diameter, mm - mean (SD)	12.1 (7.4)	12.8 (11.7)	0.78
Reduction in adenoma maximal diameter - % (SD)	46.7 (26.1)	63.0 (32.0)	0.07
Residual visual field defect - n (%)	1/4 (25%)	2/5 (40%)	NS
Residual pituitary hormone deficiency - n (%)	2/2 (100%)	5/6 (83%)	NS
Central hypothyroidism - n (%)	2/2 (100%)	5/5 (100%)	NS
Central adrenal insufficiency - n (%)	1/1 (100%)	1/3 (33%)	NS
No sexual dysfunction improvement - n (%)[c]	3/34 (9%)	10/10 (100%)	< 0.01
NS means no statistical significance (i.e., insufficient sample size).			
a – in men treated with testosterone replacement: the last Testosterone, LH and FSH measurements recorded just before replacement treatment were documented as their end of follow-up measurements, in a “last observation carried forward” manner.			
b - only 31/46 and 7/12 measurements were collected (n = 38).			
c – data was available for 34/46 and 10/12 subjects (n = 44).			

End of follow-up prolactin levels and adenoma (maximal) diameter were not significantly different between patients in the two groups (Table 4).

In accordance with the pre-determined allocation, total testosterone levels at the end of follow-up were lower in the group of men with HH persistence: 1.0 ± 0.6 compared to 4.6 ± 1.1 ng/ml (P < 0.01, Table 4).

LH was 1.0 ± 1.0 vs 4.1 ± 2.7 mIU/mL ($p < 0.01$), and FSH was 2.3 ± 2.3 vs 6.2 ± 4.3 mIU/mL ($p = 0.02$) in men with and without HH persistence, respectively, at the end of follow-up (Table 4). We found a linear correlation between baseline testosterone levels and end of follow-up testosterone levels (Fig. 2).

In the group of men that achieved eugonadism with cabergoline, the median time elapsed from prolactin normalization to eugonadism restoration was 2.9 months (IQR, 0.1-6.0 months). In this group of 46 men, after normoprolactinemia was achieved 36 (78%) men normalized their testosterone levels within the first 6 months, and 42 (91%) men normalized testosterone within the first 12 months.

In the group of men that suffered HH persistence, the median time elapsed from prolactin normalization to testosterone replacement initiation was 16.4 months (IQR, 10.0-19.9 months).

At the end of follow-up, residual VFDs were evident in 2/5 (40%) and 1/4 (25%) men with and without HH persistence, respectively (Table 4).

Residual pituitary hormone deficiency was demonstrated in 5/6 (83%) and 2/2 (100%) men with and without HH persistence, respectively (Table 4). Only two men in the cohort (both suffered HH persistence) accomplished full recovery of hypothalamic–pituitary–adrenal axis.

No sexual dysfunction improvement was noted in those with HH persistence, while 91% of men who achieved eugonadism experienced sexual improvement ($p < 0.01$, Table 4).

Discussion

In our cohort of men with macroprolactinoma and hypogonadism at presentation that reached normoprolactinemia with cabergoline treatment, 21% showed HH persistence. This is the first study to report hypopituitarism and VFD (reflecting significant tumor mass effect) as independent predictors of HH persistence in men with macroprolactinoma. We found substantial correlations between baseline LH and FSH levels with testosterone levels (reflecting central functional modification) and identified low baseline testosterone as an independent predictor of HH persistence.

In order to correctly select this study's population, 103 men with macroprolactinoma (with overall baseline HH in 86% of men, Table 1) were screened and divided into 3 groups (Fig. 1). Compared with the patients included in the cohort (group C), patients in group B had a more aggressive disease: they had larger tumors at presentation, with higher serum prolactin levels, lower LH and testosterone levels, and they suffered higher rates of VFDs and hypopituitarism. Eugonadism at presentation, as in group A, was associated with more benign baseline characteristics, compared with groups B and C. Group A had lower rates of sexual dysfunction, and yet, 43% of men in group A suffered sexual dysfunction at presentation, that may be explained by the relatively low mean serum testosterone of 4.4 ng/ml (within the lowest quartile of the normal range, Table 1), which usually increases upon prolactin normalization [19].

Noteworthy, in this study design, there is an inherent selection bias because patients with a more benign presentation must be excluded (group A, with no HH), as well as patients with more aggressive tumors

(group B, normoprolactinemia not achieved with cabergoline monotherapy). Additionally, this rigorous selection requires a relatively large sample size, as in our cohort.

Previous studies, with a similar study design, investigated the prevalence of HH persistence, while some performed univariate analysis to reveal clinical factors associated with HH persistence in male macroprolactinoma. In 2000, Pinzone et al. [6] retrospectively evaluated 27 men with macroprolactinoma and found that 93% of men had hypogonadism at presentation, with 48% suffering HH persistence after 4.4 years. They reported no age difference between men with and without HH persistence. Sibal et al. [8] demonstrated gonadal axis dysfunction in 27 out of 35 men (77%) and recovery of function in 16 out of 26 (62%) men under medical treatment with dopamine agonists. In 2006, De rosa et al. [10] prospectively evaluated 50 men with macroprolactinomas (76% had baseline HH) and found that 18 out of 38 (47%) patients that achieved normoprolactinemia had HH persistence after 6 months of cabergoline treatment. The investigators demonstrated that higher basal prolactin levels, larger tumors, and lower testosterone levels were associated with HH persistence after 6 months. Karavitaki et al. (2013) [17] investigated 10 men (9 had gonadal axis dysfunction) treated with cabergoline for 2 years, with HH persistence seen in 5 out 9 men (56%). Men who achieved eugonadism with cabergoline, did so within the first year of treatment.

In 2020, Sehemby et al. [11] studied a cohort of 30 men, and found high rate of baseline central hypogonadism of 100%. All men included achieved normoprolactinemia with cabergoline therapy, and yet 73% of men had HH persistence at the end of the study period (median follow-up of 2 years). In this study of well selected population, higher baseline prolactin levels and larger tumor size were found to be predictors of HH persistence, both factors reflect tumor aggressiveness. The authors provided cutoffs for tumor size smaller than 32 mm (sensitivity and specificity of 75% and 63.6%) and basal prolactin levels below 2098 ng/ml (87.5% and 77.3%) for HH reversal prediction. It should be noted that these cutoffs will probably yield lower specificity in populations of other ethnical origin, with less aggressive prolactinomas and with lower rates of HH persistence: in our cohort, tumor size < 32 mm had 82.6% sensitivity and 50% specificity, and prolactin < 2098 ng/ml had 71.7% sensitivity and 50% specificity for HH reversal prediction.

In their study, Sehemby et al. [11] demonstrated selective suppression of the LH-testosterone axis (without suppression of the FSH-inhibin B axis) and thus they suggest that “chronic functional modification” of the hypothalamus, and not gonadotroph cell damage, is the biological mechanism of persistent HH.

In our cohort, lower baseline testosterone, LH and FSH levels were associated with HH persistence (Table 2). Prolactin levels were lower in men without HH persistence (Table 2). On one hand, these observations suggest that the impairment of the gonadal axis is primarily functional and is derived from the known effect of high prolactin levels over the hypothalamus. On the other hand, we found hypopituitarism and VFD to be strong predictors of HH persistence. These predicting factors reflect tumor mass effect, which may be associated with an irreversible pituitary damage.

Previous studies already demonstrated the relationship between tumor size and permanent gonadal axis suppression. Tirosh et al. [9] illustrated HH persistence in 9 out of 20 men (45%) with giant prolactinoma (i.e., adenoma diameter ≥ 40 mm) and hypogonadism, compared with 14 out of 46 men (32%) with non-giant tumors and HH persistence.

Iglesias et al. [20] found higher HH persistence rates in men with giant prolactinomas, treated with dopamine agonists, compared to men with non-giant prolactinomas (86% vs 20%, respectively) with a similar prolactin normalization rate of approximately 70%.

After normoprolactinemia was achieved (in 46 men), we found that 36 (78%) men in our cohort normalized their testosterone levels within the first 6 months, and 42 (91%) men accomplished eugonadism within the first year. One patient demonstrated recovery of the gonadal axis after as long as 4.5 years. Accordingly, it is possible that a limited number of patients may benefit from gonadal axis function reassessment, even after a long period of axis suppression. In order to aid in the decision of testosterone replacement initiation, our data suggest that men who present with testosterone levels below 1.5 ng/ml along with either VFD or hypopituitarism are more likely to remain hypogonadal despite prolactin normalization (75% sensitivity, 93.5% specificity) and can benefit from testosterone treatment.

Although baseline HH is associated with a more aggressive disease, our data suggest that the long-term outcomes in men with and without HH persistence are comparable, including normal prolactin levels achieved and tumor shrinkage (Table 4). Accordingly, the mean time elapsed from medical treatment initiation to prolactin normalization was identical (5 months) in the two groups. As anticipated, in accordance with the low LH and the pre-specified testosterone levels, men with HH persistence did not demonstrate sexual function improvement (Table 4).

The present study has many strengths including the meticulous data collection of a large cohort at a single tertiary center with a uniform treatment protocol, long-term follow-up, and the ability to ascertain several predictors of HH persistence, two of them (VFD and hypogonadism) have not been previously reported.

This study has a number of limitations. Because of its retrospective nature, outcomes reported by patients were subject to reporting bias. Many patients were not included in the main analysis, due to the severity of their disease (Group B, Table 1). This may be the result of referral bias: as a tertiary referral center, our patients usually present with larger and more aggressive adenomas and require a more aggressive treatment approach. Another limitation is the lack of data regarding free testosterone or sex hormone-binding globulin levels. In addition, our protocol does not specify time intervals for serum testosterone measurements after the patients reached normal prolactin levels. This may have caused overestimation of time elapsed from prolactin normalization to eugonadism restoration.

In conclusion, in this cohort of men with macroprolactinoma that reached prolactin normalization with cabergoline treatment, 21% had HH persistence. We identified low baseline testosterone levels, visual field defect and pituitary hormone deficiency as independent predictors of HH persistence. We found that 91%

of men accomplished eugonadism within the first year following prolactin normalization. These findings may support informed clinical decision-making regarding the initiation of testosterone replacement in men with macroprolactinomas.

Declarations

Author contributions

All authors contributed to study conception and design. YR, IS performed a literature search. YR, HDB, HMI, IS contributed to data collection. YR, IS contributed to data analysis and synthesis. YR, IS drafted the first version of the manuscript. All authors contributed to writing and critically reviewing the manuscript. All authors read and approved the final manuscript.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

References

1. Fernandez A, Karavitaki N, Wass JA (2010) Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 72:377–382. doi: 10.1111/j.1365-2265.2009.03667.x
2. Mindermann T, Wilson CB (1994) Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 41:359–364. doi: 10.1111/j.1365-2265.1994.tb02557.x
3. Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J (1997) Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab 82:2102–2107. doi: 10.1210/jcem.82.7.4088
4. Calle-Rodrigue RD, Giannini C, Scheithauer BW et al (1998) Prolactinomas in male and female patients: a comparative clinicopathologic study. Mayo Clin. Proc. 73, 1046–1052 doi: 10.4065/73.11.1046
5. Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, Zarrilli S, Lombardi G (2004) 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 89:1704–1711. doi: 10.1210/jc.2003-030979
6. 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 85:3053–3057. doi:

10.1210/jcem.85.9.6798

7. Rudman Y, Duskin-Bitan H, Manisterski Y, Pertzov B, Akirov A, Masri-Iraqi H, Shimon I (2021) Long-term response to cabergoline and multi-modal treatment in men with macroprolactinoma: Does size really matter? Clin. Endocrinol (Oxf) 95:606–617. doi: 10.1111/cen.14541
8. Sibal L, Ugwu P, Kendall-Taylor P, Ball SG, James RA, Pearce SH, Hall K, Quinton R (2002) Medical therapy of macroprolactinomas in males: I. Prevalence of hypopituitarism at diagnosis. II. Proportion of cases exhibiting recovery of pituitary function. Pituitary 5:243–246. doi: 10.1023/a:1025377816769
9. Tirosh A, Benbassat C, Lifshitz A, Shimon I (2015) Hypopituitarism patterns and prevalence among men with macroprolactinomas. Pituitary 18:108–115. doi: 10.1007/s11102-014-0563-z
10. De Rosa M, Ciccarelli A, Zarrilli S, Guerra E, Gaccione M, Di Sarno A, Lombardi G, Colao A (2006) The treatment with cabergoline for 24 month normalizes the quality of seminal fluid in hyperprolactinaemic males. Clin Endocrinol (Oxf) 64:307–313. doi: 10.1111/j.1365-2265.2006.02461.x
11. Sehemby M, Lila AR, Sarathi V, Shah R, Sankhe S, Jaiswal SK, Ramteke-Jadhav S, Patil V, Shah N, Bandgar T (2020) Predictors of Chronic LH-Testosterone Axis Suppression in Male Macroprolactinomas With Normoprolactinemia on Cabergoline. J Clin Endocrinol Metab 105:dgaa650. doi: 10.1210/clinem/dgaa650
12. Shimon I, Benbassat C, Tzvetov G, Grozinsky-Glasberg S (2011) Anemia in a cohort of men with macroprolactinomas: increase in hemoglobin levels follows prolactin suppression. Pituitary 14:11–15. doi: 10.1007/s11102-010-0251-6
13. Moult PJ, Rees LH, Besser GM (1982) Pulsatile gonadotrophin secretion in hyperprolactinaemic amenorrhoea an the response to bromocriptine therapy. Clin Endocrinol (Oxf) 16:153–162. doi: 10.1111/j.1365-2265.1982.tb03159.x
14. Espinosa E, Sosa E, Mendoza V, Ramírez C, Melgar V, Mercado M (2016) Giant prolactinomas: are they really different from ordinary macroprolactinomas? Endocrine 52:652–659. doi: 10.1007/s12020-015-0791-7
15. Melmed S, Casanueva FF, Hoffman AR et al (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. ;96, 273–288 (2011). doi: 10.1210/jc.2010-1692
16. Colao A, Savastano S (2011) Medical treatment of prolactinomas. Nat Rev Endocrinol 7:267–278. doi: 10.1038/nrendo.2011.37
17. Karavitaki N, Dobrescu R, Byrne JV, Grossman AB, Wass JA (2013) Does hypopituitarism recover when macroprolactinomas are treated with cabergoline? Clin. Endocrinol (Oxf) 79:217–223. doi: 10.1111/cen.12124
18. Walia R, Bhansali A, Dutta P, Khandelwal N, Sialy R, Bhadada S (2011) Recovery pattern of hypothalamo-pituitary-testicular axis in patients with macroprolactinomas after treatment with cabergoline. Indian J Med Res 134:314–319

19. Shimon I, Benbassat C (2014) Male prolactinomas presenting with normal testosterone levels. Pituitary 17:246–250. doi: 10.1007/s11102-013-0497-x
20. Iglesias P, Arcano K, Berrocal VR, Bernal C, Villabona C, Díez JJ (2018) Giant Prolactinoma in Men: Clinical Features and Therapeutic Outcomes. Horm Metab Res 50:791–796. doi: 10.1055/a-0752-0741

Figures

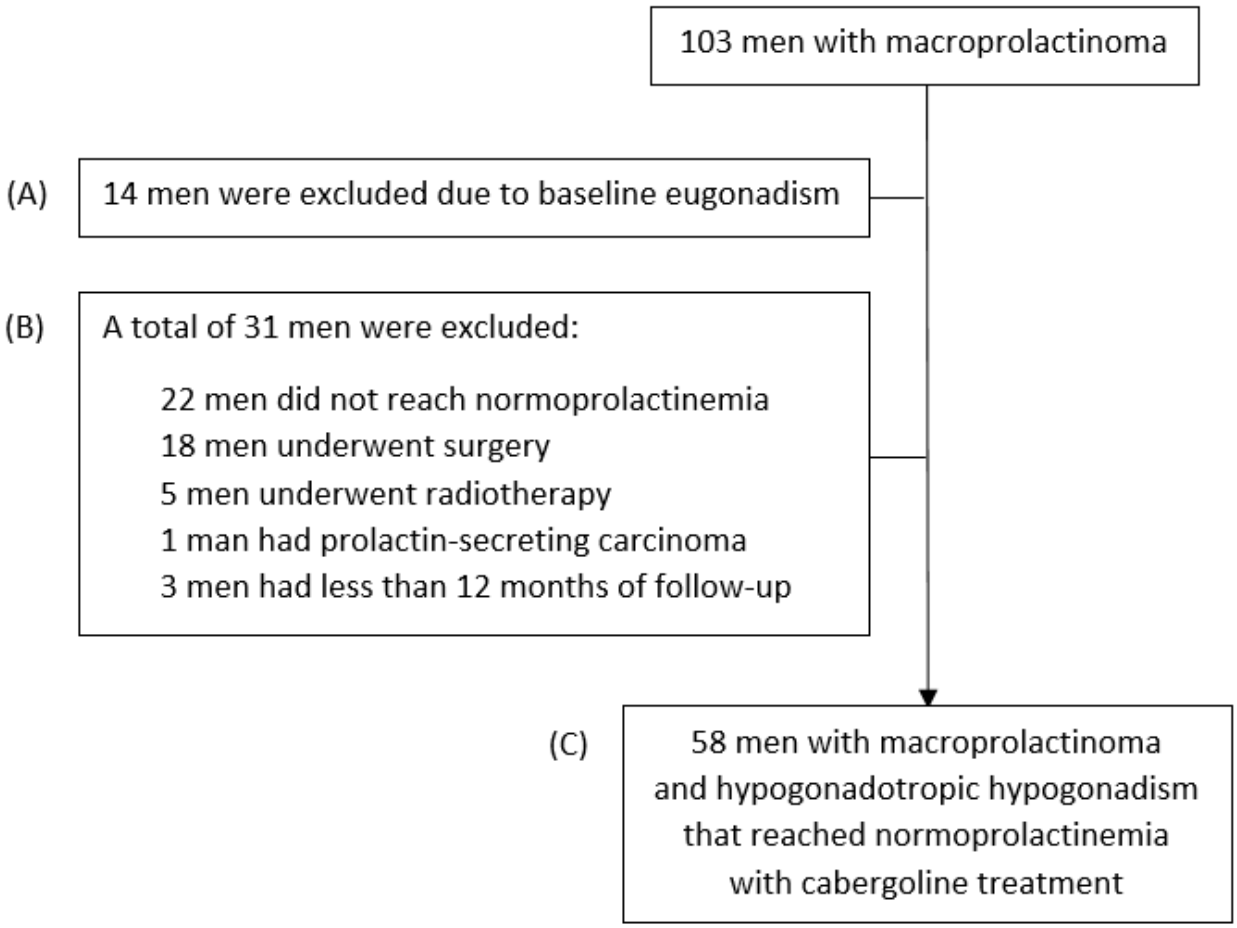

Figure 1

Patient selection flowchart.

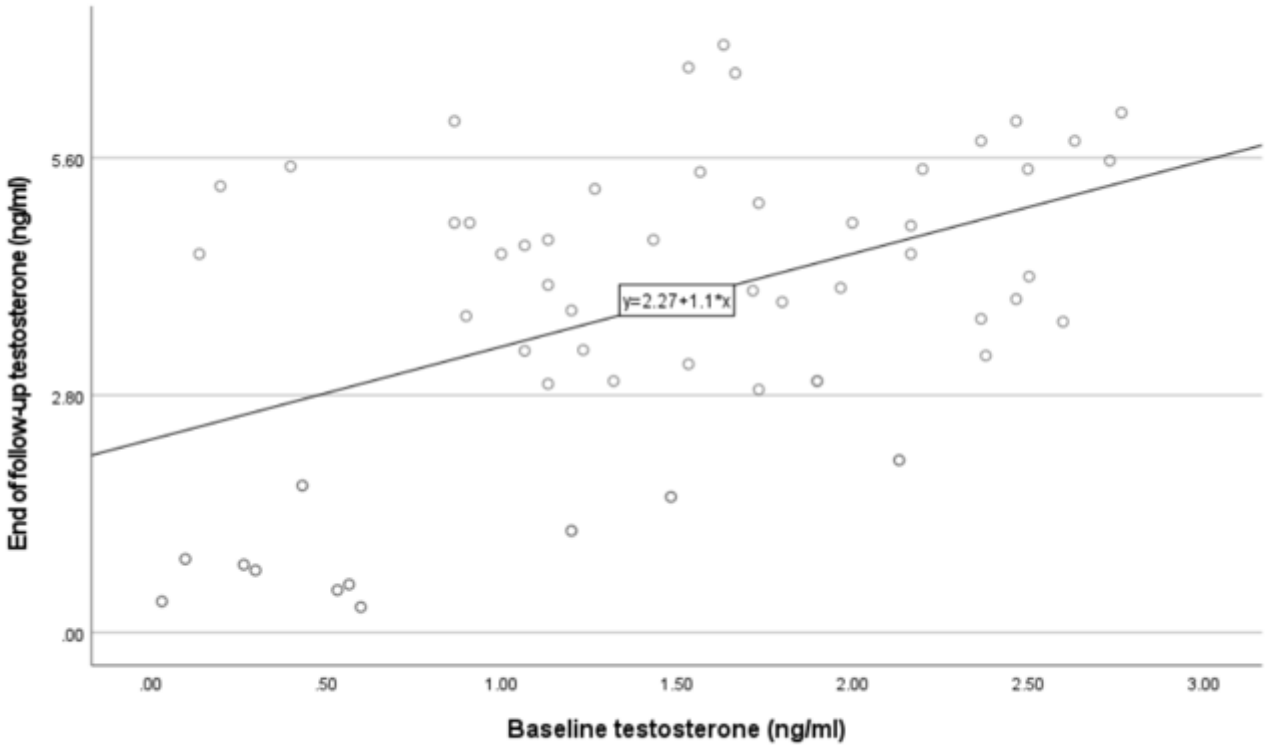

Figure 2

Correlation between testosterone levels at diagnosis and at the end of follow-up, with cabergoline monotherapy (n=58).