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# Anemia in a cohort of men with macroprolactinomas: increase in hemoglobin levels follows prolactin suppression

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**Abstract** Men with hypogonadism tend to have low hemoglobin (HGB) levels. We have investigated a cohort of 36 consecutive male patients with macroprolactinomas to evaluate HGB during presentation and following treatment with cabergoline to suppress prolactin (PRL). Patients' mean age at diagnosis was 48 years, the mean adenoma size measured 31 mm. The median PRL at baseline was 1,969 ng/ml; the mean testosterone level was low, 1.5 ng/ml. PRL had been successfully normalized in all but six men by using cabergoline. Mean baseline HGB at diagnosis was 13.1 gr%. Sixteen patients had HGB $\leq$ 13 gr%, including 4 men with HGB $\leq$ 11.5 gr%. In the subgroup of 15 men with very low testosterone ($\leq$1 ng/ml), baseline HGB was 12.6 gr% compared with 13.5 gr% in patients with higher testosterone ($P < 0.005$). In 30 men in whom follow-up CBC data were available, mean baseline HGB increased from 13.2 to 13.9 gr% following PRL suppression by cabergoline. Baseline HGB levels inversely correlated with tumor size, reaching levels of 13.7 gr% in 10 men with macroprolactinomas of 10–20 mm in size, 13.0 gr% in 18 subjects with macroadenomas of 21–40 mm, and 12.4 gr% in 7 patients with giant prolactinomas (>40 mm). In 22 men with normal follow-up testosterone, current HGB levels measured 14.5 gr%, but only 12.8 gr% in 9 men with current low testosterone ($P < 0.0005$). In men with macroprolactinomas, anemia is common. It is associated with hypogonadism and tumor size, and improves following treatment that normalizes PRL and increases testosterone.

**Keywords** Anemia · Cabergoline · Hemoglobin · Hypogonadism · Prolactinoma · Testosterone

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## Introduction

Prolactinomas, the most common hormone-secreting pituitary tumors, are usually defined as a microprolactinoma ($\leq$10 mm diameter) or a macroprolactinoma (>10 mm diameter), based on tumor size. Microprolactinomas, the most common form, are frequent in women; macroprolactinomas, which are less frequent, are reported to be more common in men [1, 2].

Symptoms of prolactinoma are caused by hyperprolactinemia or by tumor-mass effect on surrounding tissues, and are usually gender-related: in women, high levels of prolactin (PRL) often cause changes in menstruation and infertility, as well as galactorrhea; in men, the most common symptom is usually hypogonadism, with decreased libido, erectile dysfunction and abnormal semen analysis, followed by headaches or visual field defects, which are related to the enlarged pituitary mass pressing against the optic chiasma [3, 4]. Traditionally, the insidious nature of prolactinomas-associated symptoms and signs in men induce a delay in the diagnosis of these tumors; however, rapidly growing prolactinomas, with increased markers of cellular proliferation, have been recently reported to occur in male population [5, 6].

In both men and women diagnosed with prolactinomas, serum PRL levels were found to correlate with tumor size

[4, 7]; increased PRL levels are usually accompanied by lower serum testosterone levels in the macroprolactinoma subgroup of male patients. Noteworthy, although serum testosterone levels have been reported to be lower in men with macroprolactinomas, the complaints of hypogonadism and sexual dysfunction seem to be similar in both micro- and macro-prolactinomas patients [7].

The main goals in the treatment of patients with prolactinomas are to suppress PRL secretion to normal and reduce tumor size, to correct any visual abnormalities, and to restore normal pituitary function [8]. Medical therapy with dopamine agonists (bromocriptine and cabergoline) is considered to be the first-line treatment for these patients [8, 9] To date, data published on dopamine agonists' treatment of macroprolactinomas in men have documented their efficacy in the normalization of PRL levels, as well as in inducing tumor shrinkage and preserving residual pituitary function [9–11].

Successful lowering of PRL results in serum testosterone normalization in approximately half of the patients with macroprolactinomas, with normalization in the sperm volume and count in patients who normalized testosterone levels [10]; however, sexual dysfunction may persist in some patients despite dopamine agonist therapy, indicating the importance of follow-up in all male patients with prolactinomas [1, 7, 12].

Interestingly, men older than 50 years of age with clinically nonfunctioning pituitary tumors and with low serum levels of testosterone were noted to be anemic, due to a physiologically related decrease in hematocrit [13]; However, these findings were not assessed in men harboring other pituitary tumors, including prolactinomas.

We thus conducted a retrospective study in a group of 36 consecutive male patients with macroprolactinomas and hypogonadism, in order to define anemia characteristics and prognostic factors of severity and cure.

## Patients and methods

We have investigated 36 men with macroprolactinomas treated medically with cabergoline between 2001 and 2009. This retrospective study included consecutive subjects who were diagnosed, treated and followed in our Endocrine outpatient clinic at Beilinson Hospital, Petah-Tiqva, Israel. Information on clinical presentation, laboratory tests (including hormonal profile as well as complete blood counts (CBC)), pituitary imaging and visual field assessment, at presentation and during follow-up period were collected. Response to treatment and clinical improvement were also revised. The study was approved and conducted according to the local ethical institutional review board.

### Cabergoline treatment protocol

The starting oral dose of cabergoline was 0.5 mg, administered twice weekly from the first week. Doses were increased progressively every 2 months, as necessary, according to the degree of PRL suppression, until levels normalized and a decrease in dose could be safely considered. Serum total testosterone level was measured in parallel with PRL. Complete blood counts were performed before and every 4–6 months during cabergoline treatment, and at least 6 months after PRL and testosterone normalization. Sellar MRI was performed before treatment, 6 months after onset of treatment, and then once a year. Goldmann perimetry and clinical visual acuity examination were performed before treatment, 1–2 months after treatment onset, and then every 6 months until findings normalized.

### Biochemical evaluation

Serum PRL 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 PRL 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 5–17 ng/ml. Levels higher than 200 ng/ml were calculated after appropriate serum dilutions. Total testosterone was determined by radioimmunoassay (Coat-A-Count) which has a sensitivity of 0.1 ng/ml; the intra- and inter-assay CVs were 4 and 10%, respectively. Reference levels for total testosterone ranged from 3 to 10 ng/ml in men aged 20–50 years, to 1.8–8 ng/ml in men aged >50 years.

CBCs were measured using an automatic ABX Micros CRP 200 analyzer (Clinical Laboratory International, Brussels, Belgium).

### Radiological assessment

The results of magnetic-resonance imaging (MRI) were summarised, in order to assess the extension of patients' adenomas.

### Statistical analysis

Results were expressed as median or mean ± SD, as specified. Differences in variables were analyzed by the chi-square test and paired and unpaired Student's *t*-test (as appropriate). Hemoglobin (HGB) level was the only variable with normal distribution; therefore a non-parametric test (Spearman's) was used to check correlation between the different variables (HGB, PRL, testosterone, tumor size). Statistical analysis was performed using the

SigmaStat 2.03 computerized program (Systat Software Inc., Point Richmond, CA). A $P$ value of <0.05 was considered significant.

## Results

### Patients' characteristics at presentation

The study cohort included 36 men with a mean age of 47.9 ± 13.5 years (range, 22–76 years). Mean adenoma size was 30.8 ± 14.3 mm (range, 11–82 mm). Ten subjects harbored adenomas sized 11–20 mm, 19 measured 21–40 mm, and 7 men had giant macroadenomas (41 mm or larger). Sixteen out of the 36 men (44%) had significant visual fields damage at presentation. Mean baseline PRL level was 11,940 ng/ml, and median PRL was 1,969 ng/ml (range, 77–270,000 ng/ml, normal <17 ng/ml). Mean testosterone level at presentation was 1.5 ± 1.2 ng/ml (normal, 3–10 ng/ml). Tumor size was correlated with PRL levels ($r = 0.62$, $P < 0.001$) and inversely correlated with testosterone ($r = -0.41$, $P = 0.016$) and HGB level ($r = -0.44$, $P = 0.01$).

Nine men in the cohort presented with central hypothyroidism, and 4 had also low cortisol serum levels, requiring glucocorticoid replacement. The clinical characteristics of the patients included in the study are shown in Table 1.

### Prolactinoma treatment

The mean weekly cabergoline dose was 1.7 mg (range, 0.5–7 mg/week). Cabergoline normalized PRL in all but six men (in 83% of the cohort). In those few men that did not achieve hormonal normalization, PRL decreased however to a mean value of 45 ng/ml. The mean time interval to PRL normalization since cabergoline initiation (in those men that achieved PRL remission), was 8.5 months. All but three subjects (92%) had low testosterone levels (<3 ng/ml) before dopamine agonist treatment, whereas 15 subjects (41%) had very low testosterone (≤1 ng/ml). Twenty-three men treated with cabergoline increased testosterone to normal range (out of 34 with available testosterone levels; 68%), whereas eleven out of the 34 men studied (32%) remained hypogonadal when PRL was suppressed and normalized medically. Four men with low testosterone levels that failed to normalize are replaced with testosterone preparations.

Seven patients in the cohort had trans-sphenoidal pituitary tumor resection because of pituitary apoplexy (2 patients), CSF leak (1 patient), failure to normalize PRL medically (1 patient) or large adenomas compressing the optic chiasma at presentation (3 subjects). Another patient underwent trans-cranial surgery for a giant tumor that involved the temporal lobe.

**Table 1** Baseline clinical characteristics of men included in the study

| Characteristics | $N = 36$ (%) |
|---|---|
| Age (yrs); (mean ± SD) | 47.9 ± 13.5 (range, 22–76) |
| Adenoma size (mm); (mean ± SD) | 30.8 ± 14.3 (range, 11–82) |
| 10–20 mm | $N = 10$ |
| 20–40 mm | $N = 19$ |
| >40 mm | $N = 7$ |
| Erectile dysfunction and low libido | $N = 21$ (46%) |
| Visual field defects | $N = 16$ (35%) |
| Weakness and dizziness | $N = 7$ (15%) |
| PRL level (ng/ml, normal, <17); median | 1,969 (range, 77–270,000) |
| Testosterone level (ng/ml, normal, >3); (mean ± SD) | 1.5 ± 1.2 |
| HGB level (gr%, normal, >14); (mean ± SD) | 13.1 ± 1.2 |

### Hemoglobin (HGB) levels

Mean baseline HGB in our cohort of men was 13.1 ± 1.2 gr% (normal range for males, 14–18 gr%). Thirty men had HGB level below 14 gr%, and sixteen patients had HGB ≤ 13 gr%, including 4 men with HGB ≤ 11.5 gr%. Baseline HGB was 12.6 gr% in the 15 men who presented with very low testosterone (≤1 ng/ml), compared with 13.5 gr% in the other 20 patients presented with higher baseline testosterone (>1 ng/ml; $P < 0.05$). Importantly, all subjects had normal white blood cell and platelet counts. Also, the CBCs in all patients showed normal RBCs cell characteristics with mean MCV of 87 ± 5.9 (normal, 80–94).

Baseline HGB was inversely correlated with tumor size ($r = -0.44$, $P = 0.01$), and reached 13.7 gr% in the 10 men with prolactinomas of 10–20 mm in size; 13.0 gr% in the 18 subjects with macroadenomas of 21–40 mm; and 12.4 gr% in the 7 patients with giant prolactinomas (>40 mm). There was a weak inverse correlation between HGB and PRL levels that was not significant statistically ($r = -0.23$, $P = 0.19$).

Mean baseline HGB in the 30 men with follow-up CBC data was 13.2 gr% and increased to 13.9 gr% ($P < 0.02$) following PRL suppression by cabergoline. In 20/30 patients HGB increased (≥0.5 gr%), in 7/30 was unchanged, and in 3 decreased (≥0.5 gr%). Figure 1 shows the baseline (pre-treatment; mean, 12.7) and current (on-treatment following PRL suppression; mean, 13.6) HGB levels in the 24 men who had baseline HGB < 14 gr%.

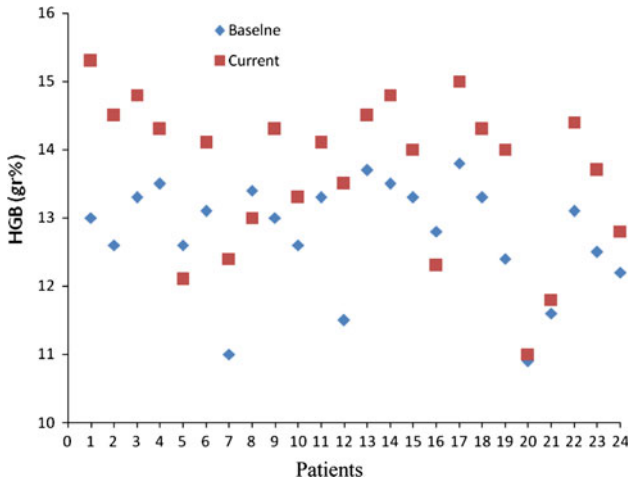


**Fig. 1** Baseline and current (following PRL suppression with Cabergoline) HGB levels in 24 men with macroprolactinomas

Among the 24 men that increased testosterone significantly (not always to normal) during cabergoline treatment and had follow-up CBC values, only 11 increased the baseline HGB level ≥1 gr%. However, 6 of the other 13 had normal baseline HGB (>14.0 gr%) and 5 others increased the HGB value by 0.5–0.9% following PRL normalization.

Current HGB levels reached 14.5 gr% in the 22 men with on-treatment normal testosterone levels, but only 12.8 gr% in the 9 men with current low testosterone (<3 ng/ml) ($P < 0.0005$). However, we couldn't demonstrate any correlation between HGB and testosterone levels, probably due to the small size of our study group.

## Discussion

Androgens and especially testosterone stimulate erythropoiesis in men. Hemoglobin levels are similar in boys and girls before puberty, and increase by 15–20% in boys at puberty, in parallel with testosterone elevation. Testosterone contributes to the 1–2 gr% difference in the HGB concentration between adult men and women. Men with hypogonadism frequently have anemia, and older persons with low testosterone levels tend to have lower than normal HGB concentrations [14], whereas testosterone replacement therapy and diseases associated with elevated testosterone levels generate HGB rise that sometimes reach the level of polycythemia [15, 16]. Moreover, patients with aplastic anemia or myelofibrosis treated in the past with androgens showed hematologic improvement in red blood cell counts [17, 18].

In this cohort of 36 men with macroprolactinomas and hypogonadism we studied the prevalence and characteristics of anemia, the association of HGB levels with low testosterone, and the likelihood of HGB rise following cabergoline treatment, PRL suppression and testosterone level increase. Hemoglobin levels have been found to be well below the normal range at diagnosis in almost all subjects (83%), this finding being associated with larger size of the pituitary adenoma. Moreover, anemia improved following dopamine agonist treatment, especially in those male patients that normalized testosterone following treatment.

In hypogonadal men, testosterone replacement is usually accompanied by improvement in muscle mass, bone density, mood and anemia [19]. Interestingly, similar to old men, older women with low testosterone levels are also more likely to have anemia [14]. In an in vitro study in which human erythroblasts derived from cord blood of male and female newborns were expanded in the presence of dihydrotestosterone, this enhanced cell proliferation of female erythroblasts only, with no effect on male-originating cells [20].

The mechanism through which testosterone stimulates erythropoiesis is still unclear. Testosterone induced the proliferation of erythroid burst-forming units and colony-forming units by stimulating specific nuclear receptors. Testosterone partially exerts its erythropoietic effects by stimulating erythropoietin [21]. However, androgens have also erythropoietic activity that is erythropoietin independent, like seen in men with end-stage renal failure [22]. Interestingly, in mice recombinant human PRL can promote hematopoiesis in vivo and reverse anemia and myelosuppression induced by myeloablative therapies, by increasing erythroid and myeloid progenitor numbers [23]. Thus, PRL may have direct promoting effects on hematopoiesis [24] but opposite inhibitory effects on erythropoiesis through testosterone suppression.

To our knowledge this is the first large study investigating the impact of hypogonadism in men with prolactinomas on HGB levels, and the effect of suppressing high PRL levels to normal on the improvement of anemia following treatment (Fig. 1), in parallel with testosterone elevation. Importantly, the gradual development of anemia in parallel with testosterone decline, may advise when a prolactinoma has become clinically significant, as the size of the tumor is inversely associated with HGB levels. Moreover, as anemia is so common in men with macroprolactinomas, one can assume that patients presenting with normal HGB levels have probably developed only a mild or a short-duration hypogonadal state so far. Although the association between low testosterone and low HGB levels is clear, we couldn't demonstrate any significant correlation between HGB and testosterone levels, probably due to the small size of our study group. Moreover, some participants with hypogonadism in our cohort were not anemic, and others that normalized testosterone following treatment did not improve HGB levels. This can partially

be explained by other undiagnosed contributing factors for anemia in our patients, including iron, B12, and folate deficiencies or other anemia-associated etiologies.

In summary, macroprolactinomas and the associated hypogonadism should be considered in the differential diagnosis as a potential etiology for normocytic normochromic anemia in male patients, being associated with larger tumor size, and improving significantly following dopamine agonist treatment, in parallel with decrease in PRL and increase in testosterone levels.

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