Endocrine, *vol. 20, no. 1/2, 75–82, February 2003* 0969–711X/03/20:75–82/$20.00

Hyperprolactinemia in Men

Clinical and Biochemical Features and Response to Treatment

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Hyperprolactinemia induces hypogonadism by inhibiting gonadotropin-releasing hormone pulsatile secretion and, consequently, follicle-stimulating hormone, luteinizing hormone, and testosterone pulsatility. This leads to spermatogenic arrest, impaired motility, and sperm quality and results in morphologic alterations of the testes similar to those observed in prepubertal testes. Men with hyperprolactinemia present more frequently with a macroadenoma than a microadenoma. Symptoms directly related to hypogonadism are prevalent. In men hypogonadism leads to impaired libido, erectile dysfunction, diminished ejaculate volume, and oligospermia. It is present in 16% of patients with erectile dysfunction and in approx 11% of men with oligospermia. Treatment with bromocriptine or cabergoline (CAB) is effective in men with prolactinomas, with a response that is in general comparable to treatment in women. Seminal fluid abnormalities rapidly improve with CAB treatment, while other dopaminergic compounds require longer periods of treatment. Moreover, to improve gonadal function in men, the integrity of the hypothalamic-pituitary-gonadal axis is necessary. New promising data indicate that a substantial proportion of patients with either micro- or macroprolactinoma do not present hyperprolactinemia after long-term withdrawal from CAB. Whether this corresponds to a definitive cure is still unknown, but treat-ment withdrawal should be attempted in patients achieving normalization of prolactin levels and disappearance of tumor mass to investigate this issue.

Key Words: Pituitary; gender; prolactin; prolactinomas; hyperprolactinemia; cabergoline.

Received December 20, 2002; Accepted December 20, 2002.

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Introduction

Hyperprolactinemia is a clinical condition characterized by hypogonadism and infertility in both sexes *(1,2)*. In men it leads to impairmed of libido, erectile dysfunction, diminished ejaculate volume, and oligospermia *(1–3)*. If hyperprolactinemia occurs during puberty, delayed pubertal development with diminished facial and body hair may be its consequence *(4–7)*. Symptoms of secondary hypogonadism, frequently unrecognized by patients, cause the most important negative effects of hyperprolactinemia in men. Rarely is gynecomastia present, whereas galactorrhea occurs in approx 20% of patients. Hyperprolactinemia is present in 16% of patients with erectile dysfunction *(8)* and in approx 11% of men with oligospermia *(9)*. At diagnosis of hyperprolactinemia, a gender difference in tumor dimensions is suggested *(10)*: microadenomas are more commonly found in women and macroadenomas in men. It is still unknown whether this reflects a delay in diagnosis or a gender-specific difference in tumor pathogenesis. Recent data suggest that a subset of men may have rapidly growing prolactinomas with increased markers of cell proliferation *(10,11)*. The efficacy of pharmacotherapy has been reported predominantly in women *(1,12)*, while data in men are still limited.

In this report, some aspects of the pathophysiology of hyperprolactinemia, particularly concerning its negative effects on gonadal as well as seminal function in men, and treatment with dopamine agonists are reviewed.

Prolactin and Reproductive Function in Men

Steroid secretion is strictly correlated to testicular spermatogenesis. Testosterone synthesis is necessary for sperm production and for development of secondary sexual characters and normal sexual behavior *(13)*. The anterior pituitary controls these functions by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion secondary to hypothalamic gonadotropin-releasing hormone (GnRH) release. FSH is necessary to begin spermatogenesis and a high intragonadal testosterone concentration activates such a process *(14,15)*. LH, stimulating Leydig cells, induces high levels of intratesticular testosterone levels, which directly and/or by its metabolite, dihydrotestosterone (DHT), acts on spermatogonia and primary spermatocytes promoting

meiotic division. During spermatogenesis, FSH acting on Sertoli cells facilitates the transformation of spermatids to spermatozoa and can also accelerate the starting stages of spermatogonial maturation *(16)*. Afterward, testosterone alone can maintain this process; in hypophysectomized male rhesus monkeys prolonged testosterone administration at high doses was capable of preserving spermatogenesis *(17)*. These effects are probably owing to a direct action on peritubular myoid cells and on Sertoli cells in addition to an indirect action on the germinal epithelium; in fact androgen receptors are present only on Sertoli cells and on peritubular cells but not on germinal cells *(18)*.

In animals physiologic prolactin (PRL) secretion is required to support testosterone biosynthesis *(19)*, and PRL is well known to act as a modulator of the hypothalamic-pituitary-gonadal axis function. In particular, in seasonal breeding animals, it acts as a signal to start or to interrupt reproductive activity *(20–23)*. These effects are caused mostly through changes in gonadotropin secretion, although in some species PRL can exert modulatory effects on the number of LH receptors on Leydig cells *(24–26)*. In fact, PRL increases the number of these receptors, thus increasing Leydig cell sensitivity to LH. PRL also influences tissue sensitivity to androgens, increasing their binding to reproductive tissues *(27)*.

On the other hand, high PRL concentrations have inhibitory effects in both humans and animals. In particular, hyperprolactinemia decreases the pulsatile secretion of LH and, to a lesser extent, of FSH *(28)* and of LH–releasing hormone secretion *(29)*. In fact, PRL significantly suppresses mean LH values by notably increasing the interpeak interval without affecting the pulse amplitude in orchiectomized adult male rats *(30)*.

Independent of its action at the central level on the pituitary gland or at the peripheral level on the Leydig cell, the negative effect of hyperprolactinemia on spermatogenesis is owing to the induction of hypotestosteronemia *(31)*. On the other hand, hyperprolactinemia, induced by drugs or a pituitary microadenoma, induces minimal damage to spermatogenesis *(32)*, probably because in these conditions PRL levels might be only slightly elevated. Hyperprolactinemia interferes with 17-β-estradiol synthesis from Leydig cells and reduces testosterone levels with an increased response to human chorionic gonadotropin (hCG) while hypoprolactinemia similarly induces hypotestosteronemia without modifying the response to the hCG *(33)*.

On the other hand, PRL knockout mice have a significant reduction in median eminence dopamine (DA) content, reducing pituitary LH release and affecting growth of the seminal vesicle and ventral prostate *(34)*. PRL is required for the maintenance of a normal concentration of testicular LH/hCG and PRL receptors as demonstrated in mature hamsters by injection of bromocriptine (BRC), a dopamine agonist, or BRC plus PRL: BRC decreases LH and PRL receptor (PRLR) concentration whereas BRC plus PRL increases both LH and PRLR concentration *(35)*. PRL is also linked to human prostate disease *(36)*; it synergizes with androgens in the stimulation of prostate growth and metabolism through increasing access of the steroid to the cellular machinery of the gland *(37)*. Moreover, in the Wistar rat with sulpiride-induced hyperprolactinemia, enlargement and inflammation of the lateral lobe of the prostate is observed *(38)*. PRL also reduces 5-α-reductase concentration in androgen-dependent tissues, decreasing more profoundly DHT than testosterone levels *(39)*.

PRLRs are present in the testes of many species of animals and, perhaps, also in human males *(40)*. An antagonistic effect of PRL in the testes, though not functionally relevant, has been hypothesized. In fact, testosterone response to hCG administration seems to be normal in drug-induced as well as in organic hyperprolactinemia *(41)*. However, a change in Leydig cell sensitivity to hCG stimulation in chronic hyperprolactinemia has been suggested since anterior pituitary–grafted rats show a higher testosterone response than controls after hCG *(42)*.

To summarize, hyperprolactinemia induces hypogonadism by inhibiting GnRH pulsatile secretion and, consequently, inhibits FSH, LH, and testosterone secretion; this induces arrest of spermatogenesis, impairs motility and sperm quality, and produces morphologic alterations similar to those observed in prepubertal testes *(43,44)*.

Prevalence of Hyperprolactinemia and Clinical Findings in Men

Data on hyperprolactinemia in men are still limited compared with in women and have usually been analyzed in small retrospective studies *(11,45–53)*. In a recent study *(54)*, we reevaluated all consecutive *de novo* cases with hyperprolactinemia coming to our department from 1996 to 2000, to analyze gender differences in clinical, biochemical, and radiologic presentation and response to long-term cabergoline (CAB) treatment in hyperprolactinemia. We enrolled 212 patients (139 women and 73 men) with an age range of 15–72 yr; of these patients, 105 had a diagnosis of macroprolactinoma (46 women and 59 men), 92 of a microprolactinoma (78 women and 14 men) and only 15 women of nontumoral hyperprolactinemia. In the entire series macro- and microprolactinomas were equally frequent (49.5 vs 43.4%), but nontumoral hyperprolactinemia (7%) was significantly less frequent than the tumoral forms ($p < 0.0001$). The prevalence of hyperprolactinemia was higher in women ($p < 0.001$), but within each single diagnostic category, microprolactinomas (85 vs 15%; $p < 0.001$) and nontumoral hyperprolactinemia (100 vs 0%; $p < 0.0001$) were higher in women than in men, while the prevalence of macroprolactinomas was similar between genders (44 vs 56.2%; $p = 0.09$). In other studies, macroprolactinomas were reported to be equally distributed between genders *(55–57)*, more prevalent in men *(58,59)* or in women *(60–62)*, while microprolactinomas were almost invariably more prevalent in women.

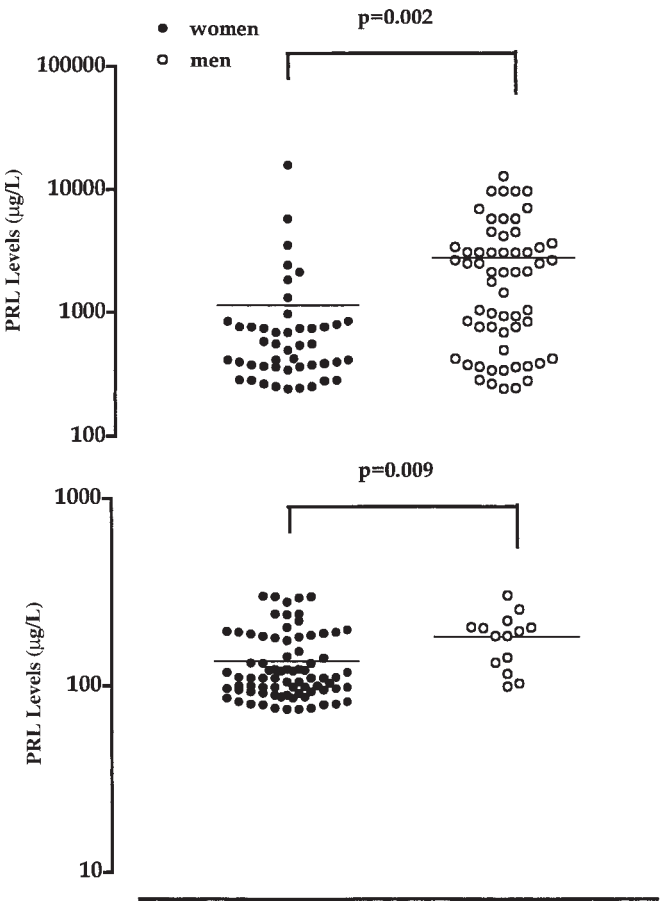

Fig. 1. PRL levels in two groups of men and women affected by macroprolactinoma (**top**) or microprolactinoma (**bottom**). (Data modified from ref. *54*.)

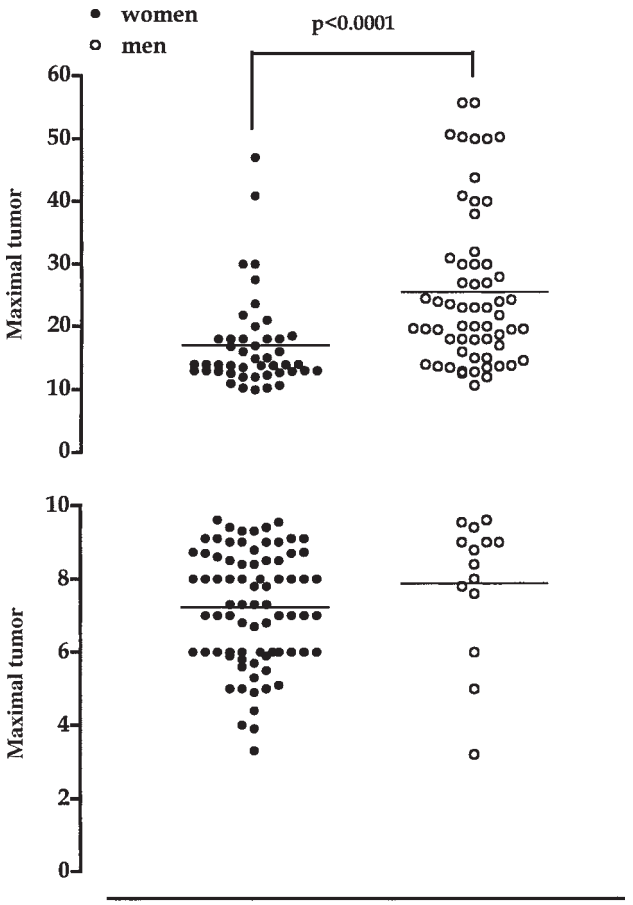

Fig. 2. Tumor size in men and women affected by macroprolactinoma (**top**) or microprolactinoma (**bottom**). (Data modified from ref. *54*.)

Age and sexual dysfunction were similar between men and women but PRL levels were higher in men than in women in both macro- and microadenomas (Fig.1), and tumor size was larger in men than in women only with macroprolactinoma (Fig. 2). Tumor size was reported not to be correlated with the duration of symptoms in previous studies *(11,51)*. Markers of cellular proliferation, such as Ki-67 and proliferating cell nuclear antigen, were shown to be expressed more in prolactinomas from men than women *(10, 11)*, and this could explain the greater macroprolactinoma size in men, suggesting true gender-related factors modifying the rate of tumor growth in men.

We also found that clinical symptoms at presentation differ according to gender, and galactorrhea, headache, and weight gain were more frequent in women than in men; infertility was the primary cause for consultation more frequently in women than in men *(54)*. It should also be considered, however, that the increased tumor size in some men might be owing to the inability to detect early sexual dysfunction, leading to a delay in diagnosis. In fact, men with hyperprolactinemia are diagnosed at a rather old age. Berezin et al. *(46)*, Walsh and Pullan *(47)*, and Pinzone et al. *(45)* reported a mean age of 40 yr or older for their study patients. In our series, median age of diagnosis was 33 yr, thus a little younger than in previous studies, suggesting that in our patients the diagnosis was made earlier.

In agreement with the literature *(45,63)*, we found that higher serum PRL levels were accompanied by lower serum total testosterone levels *(54)*, but, although serum testosterone levels were lower in men with macroprolactinomas, since they were correlated with higher PRL levels (Fig. 3), complaints of sexual dysfunction were similar to those in men with microprolactinomas.

As already stated, hyperprolactinemia induces hypogonadism mostly by indirect mechanisms. Giant lesions generally compress gonadotroph cells; in these conditions FSH, LH, testosterone levels are markedly reduced from a diminished number of gonadotropin-secreting cells, and recovery of gonadal function in patients bearing large tumors is unusual after treatment. This condition occurs more frequently in men *(10)*, and we also found larger tumors in men than in women *(64)* (Fig. 2). Since tumor volume is correlated with PRL levels (Fig. 3), this also explains the higher PRL levels in men than in women.

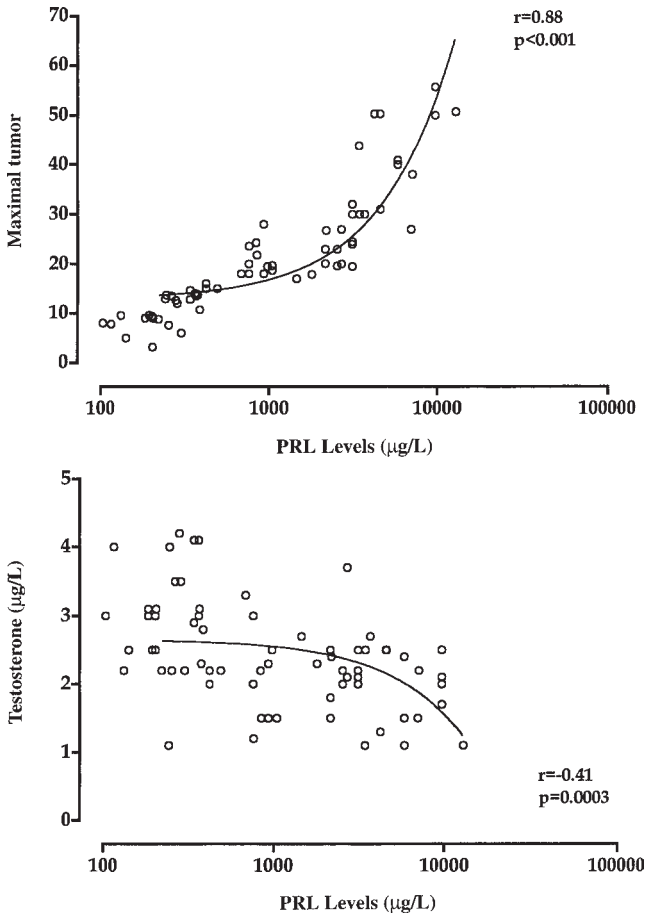

Fig. 3. Correlation study calculating Pearson coefficient between PRL levels at diagnosis and testosterone levels (**bottom**) and maximal tumor size (**top**) in men with either micro- or macroprolactinoma.

As stated earlier, in men hyperprolactinemia induces erectile dysfunction and abnormal spermatogenesis *(9,19,64–66)*, and restoring normal androgen levels alone is not sufficient to correct sexual and seminal dysfunction, since achievement of normoprolactinemia is necessary. In fact, erectile dysfunction and abnormal spermatogenesis do not respond to testosterone administration until PRL levels are completely normalized *(9,67)*. Data on semen analysis in men with hyperprolactinemia demonstrate low sperm counts with oligoasthenospermia, reduced motility, and rapid progression with an abnormal morphology and decreased viability *(9,68–71)*. Severe erectile dysfunction is likely an early marker of hyperprolactinemia *(72)*, which is owing to a central effect, not mediated by hypogonadism *(73)*. Low numbers of erections have also been recently documented by measurement of nocturnal penile tumescence *(69)*.

Treatment of Hyperprolactinemia in Men

The objectives of the treatment of hyperprolactinemia are to suppress excessive hormone secretion and its clinical consequences (in particular infertility, sexual dysfunction, and osteoporosis); to remove tumor mass to relieve disturbances in vision and cranial nerve function' to preserve residual pituitary function; and, if possible, to prevent disease recurrence or progression *(1,2)*. Prior to the advent of medical therapy for hyperprolactinemia, therapy usually consisted of surgical resection and/or pituitary irradiation, which are currently restricted to a few cases resistant to pharmacotherapy. Levodopa was first used to treat hyperprolactinemia *(74)*, but because of its short duration of action it was found to be of little clinical value. Some ergot alkaloids display long-acting DA agonist properties but were shown to be toxic and not clinically useful. Other nontoxic ergot derivatives were developed, such as BRC a semisynthetic tripetide containing ergoderivative, which lowers circulating PRL levels for about 8–2 h after acute doses. Its side effects can be prevented by administering the drug in the middle of meals in slowly rising doses to a usual maintenance dose of 2.5 mg two or three times daily. Another nonpeptydyl ergoline, lergotrile, has been described with similar length of action, but it has received little clinical evaluation *(75)*. Other more potent ergot derivatives were used: lisuride, which is shorter acting *(76)*, and pergolide *(77)* and mesulergine *(78)*; which are longer acting than BRC. Pergolide and mesulergine treatments enable a once daily administration. Occasionally, a patient intolerant of one drug might be more tolerant of another so that a choice of agents is useful *(78)*.

Currently, the management of prolactinomas in both women and men and with either macro- or microprolactinoma is based on the chronic use of a D_2 selective DA agonist, CAB, which has become the first therapeutic option in prolactinomas *(59,62,79)*. This derives from the experience accumulated for over 20 yr with BRC, which not only inhibits PRL synthesis but in >80% of patients induces tumor shrinkage at doses of 2.5–5 mg/d *(80)*. However, while pharmacotherapy is undoubtedly the first choice therapy for macroprolactinomas, in microprolactinomas both surgery and pharmacotherapy can be considered successful first therapeutic choices owing to their high rehabilitation rate. In men, as in women, treatment with DA agonists is effective in normalizing PRL levels and reducing tumor mass *(45, 46,53,56-59)*. However, series including only men are still limited *(45,46,53)*.

In two previous studies from our group, three different dopamine agonists, BRC, quinagolide, and CAB, were equally effective in normalizing not only PRL levels but also gonadal and sexual function, with improvement in libido and a decrease in abnormal sperm forms *(70,81,82)*. However, CAB-treated patients already had significant improvement in libido, potency, and seminal parameters after 3 mo of treatment, whereas for after BRC and quinagolide treatments longer periods of therapy were required *(70,81,82)*. In fact, during the first months of BRC and quinagolide treatment only an insignificant increase in sperm count was observed in spite of PRL normalization, suggesting that in

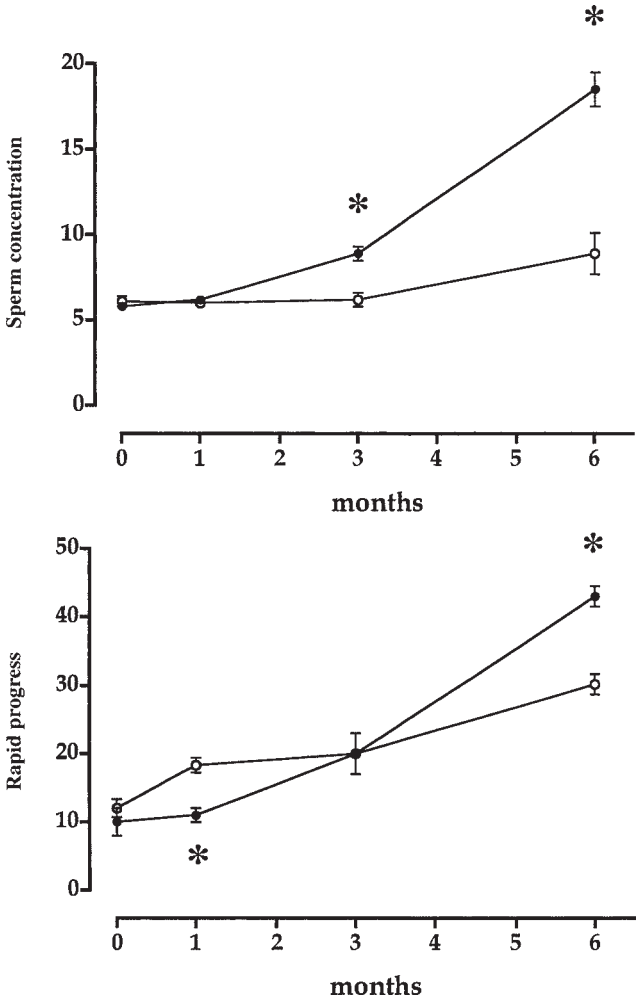

Fig. 4. Results of long-term CAB (●) and BRC (○) treatments on sperm number and rapid forward progression (%) in 22 male patients. *$p < 0.05$ vs BRC treatment.

the clinical evaluation of hyperprolactinemic hypogonadal patients a long time is necessary to achieve significant improvement in seminal patterns and testosterone levels, besides PRL level normalization. Note that CAB treatment improved seminal quality after 2 mo while BRC and quinagolide treatment achieved the same result after 6 mo of therapy *(70,81, 82)*. In particular, in CAB-treated patients an increase in sperm number, forward progression (Fig. 4), and penetration to cervical mucus together with reduced percentage of immature germ cells was observed after the first 3 mo of treatment *(69)*. The improvement in morphologic and functional parameters of ejaculates by CAB was not different but earlier in comparison with BRC and quinagolide treatment *(69)*. The beneficial effects on seminal parameters and sexual function persisted over 2 yr of continuous therapy *(71)*.

On this basis, morphofunctional changes in the gonadal and sexual axis are likely to be reversible in hyperprolactinemic males during DA agonist treatment, unless the integrity of the hypothalamic-pituitary-gonadal axis is compromised, as in giant or invasive macroadenomas *(83)*.

In a recent study, Pinzone et al. *(45)* reported in their retrospective series including 46 men a similar percentage of patients with microprolactinomas and macroprolactinomas achieving normalization of serum PRL. They also reported that macroprolactinoma patients were receiving higher doses of BRC (median dose: 3.75 vs 10 mg/d) and CAB (median dose: 1.5 vs 2.25 mg/wk). These data support the concept that for most male patients, DA agonist therapy can achieve PRL normalization, regardless of tumor size. Berezin et al. *(46)* in their series including 53 hyperprolactinemic men reported normalization of PRL level in 49% following DA agonist treatment. Published series in patients with prolactinomas suggest that CAB is more effective than BRC in normalizing serum PRL levels *(84)*, and we reported that prolactinomas resistant to BRC may respond to CAB *(57)*. In the reevaluation of 79 men followed in our department, we found that 46 (58.2%) patients, 35 macro- and 11 microprolactinomas, achieved normal PRL levels after 6 mo of CAB therapy. The remaining 33 men only had partial improvement of hyperprolactinemia. In patients partially responsive to CAB, basal PRL levels (3758 ± 647 vs 1452 ± 308 μg/L; $p = 0.0006$) and basal tumor size (30.5 ± 2.8 vs 17.3 ± 1.4 mm; $p < 0.0001$) were significantly higher than in those fully responsive (Fig. 5). In other words, basal PRL was significantly correlated with nadir PRL levels after CAB treatment ($r = 0.4$, $p = 0.006$), and basal tumor size correlated with tumor size after CAB treatment ($r = 0.8$, $p < 0.001$). Whether this depends on treatment duration cannot be ruled out at present, but long-term follow-up is required to analyze the role of basal PRL levels and tumor size on treatment outcome. A normal serum testosterone level was achieved in 35 fully responsive patients (80%) and in two partially responsive ones (7.5%); sexual dysfunction remained, however, a relevant complaint despite successful therapy in 25 patients.

These findings illustrate the need for surveillance of sexual dysfunction symptoms in all male patients with prolactinomas. In most patients with macroprolactinoma, there is an improvement in symptoms directly related to tumor expansion, in a percentage similar to that of women (see Table 1).

Conclusion

On the basis of the literature and in our own experience, men with hyperprolactinemia more frequently have a macroadenoma than a microadenoma. Symptoms directly related to hypogonadism are prevalent complaints, but others related to tumor mass expansion are also frequent and should be carefully investigated. Pharmacotherapy with old compounds, such as BRC, or new ones, such as CAB, is highly effective in men with prolactinoma, with an efficacy that is in general comparable with that in women. However, the outcome on PRL normalization and reduction in tumor size

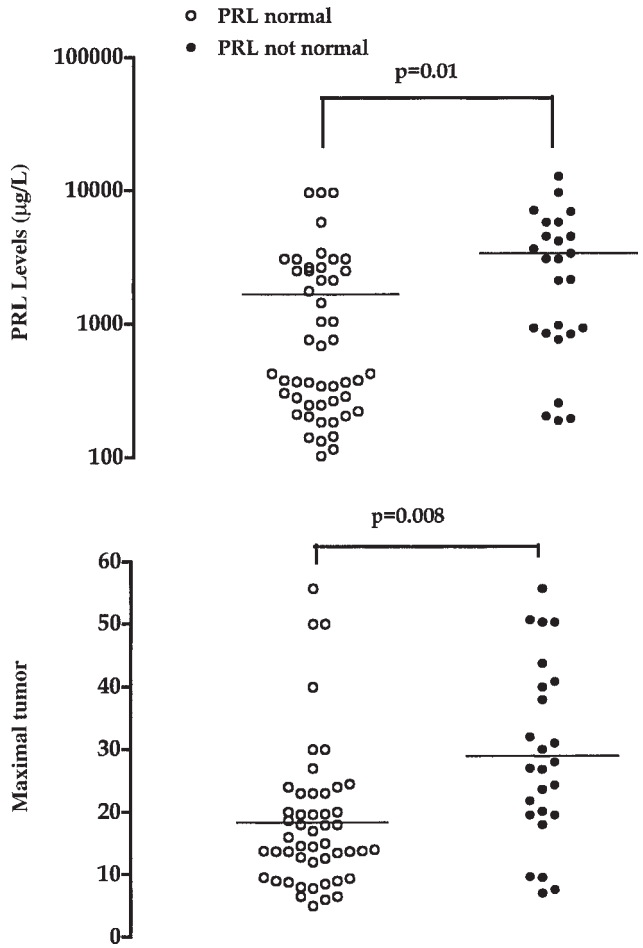

Fig. 5. Serum PRL levels and maximal tumor diameter before CAB treatment in patients fully responsive ($n = 46$) compared with those only achieving partial response to the drug ($n = 27$).

Table 1
Efficacy of 6-mo Treatment with CAB on Clinical Symptoms According to Gender[a]

	Responsive					Resistant				
	Women		Men			Women		Men		
	n	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Macroprolactinomas	31		35			15		24		
Hypopituitarism	12/13	92.3	23/25	92	0.9	9/9	0	9/9	0	1
Visual field defects	4/12	33.3	4/22	18.2	0.6	3/5	60	4/6	66.7	0.7
Headache	5/20	25	2/14	14.3	0.7	7/11	63.6	2/8	25	0.2
Galactorrhea[b]	3/30	10	0/13	100	0.6	3/6	50	0/0	0	NA
Infertility[c]	6/8	75	7/7	0	0.5	2/2	100	4/4	0	1
Menses/libido disturbances	0/26	100	5/31	16.1	0.09	9/10	90	15/17	88.2	0.6
Weight loss	27/30	10	16/20	80	0.6	4/14	28.6	9/11	81.8	0.02
Microprolactinomas	66		11			11		3		
Headache	0/20	100	0	0	NA	1/5	20	0	0	NA
Galactorrhea	0/25	100	0	0	NA	3/7	42.9	0	0	NA
Infertility[c]	20/35	57.1	2/2	0	0.6	6/6	0	0	0	NA
Menses/libido disturbances	2/48	4.2	3/9	33.3	0.03	6/11	54.5	3/3	0	0.4
Weight loss	30/36	83.3	1/2	50	0.8	2/9	22.2	1/1	0	0.6

[a]Data are expressed as number of patients with persistence of symptom compared to diagnosis. NA, not applicable. (Data from ref. *54*.)
[b]Either spontaneous or expressible.
[c]As presenting complaint.

is directly related to baseline findings, and since men have higher basal PRL levels and tumor size than women, a higher treatment efficacy can be observed in women, at least in short-term follow-ups. It is important to note that seminal fluid abnormalities can be rapidly improved by CAB treatment. Both BRC and quinagolide, and presumably other dopaminergic compounds, might display similar beneficial effects although requiring a longer period of treatment. There is a possibility that some sexual impairment persists despite optimal treatment, and, thus, careful monitoring should be performed in these patients who may also require additional treatment for this disorder.

Finally, control of hyperprolactinemia in men as in women seems to be obtained only under treatment with DA agonists since withdrawal from these drugs often results in recurrent hyperprolactinemia *(85–89)*. Scan data on this issue are available and refer mainly to small cohorts of patients followed for short periods after BRC withdrawal. For example, remission rates of 9% in macroprolactinomas *(87)* and 22% in microprolactinomas *(88)* have been reported. Tumor regrowth was uncommon, but it might be delayed with the consequent risk of compromised vision *(85–89)*. Recently, in a large series of 131 patients achieving PRL normalization during BRC treatment, 27 (20.6%) had persistent normoprolactinemia after BRC withdrawal for a median time of 44 mo without any tumor reexpansion in patients with macroprolactinomas *(90)*. These latter data open a new possibility for a definitive cure of micro- and macroprolactinomas treated only by medical therapy; however, long-term observational studies after CAB withdrawal are required to achieve definitive statements on this relevant clinical issue.

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