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5

Hypopituitarism in patients with prolactinomas: a narrative review

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Pituitary adenomas are the most frequent cause of hypopituitarism in adults, due to the mass effect of the lesion on the pituitary gland, and/or their treatments (particularly surgery and/or radiotherapy). Prolactinomas represent the most frequent histotype of hormone-secreting pituitary adenomas. As is well known, high prolactin levels induce a suppression of the gonadotropic axis and subsequent hypogonadotropic hypogonadism. Overall, the reported prevalence of hypopituitarism is highly heterogeneous in the different studies, depending on the definition used and the cohort examined. Treatment of prolactinomas, whether medical or surgical, can lead to improvement or recovery of pituitary function in a substantial proportion of patients, particularly of the gonadal axis. Conversely, new pituitary deficits can also develop after surgical treatment or, more frequently, radiotherapy. In this review, we aim to summarize the currently available literature data on hypopituitarism in patients with prolactinoma, in order to better characterize patients requiring replacement therapy.

Introduction

Hypopituitarism is a systemic condition caused by a partial or complete deficit of hormone secretion by the anterior or posterior pituitary gland [1]. The presentation can be heterogeneous, depending on the involved hormonal axes, leading to systemic complications (e.g., cardiovascular, musculoskeletal, metabolic diseases), reduced quality of life, and increased mortality compared to the general population [1]. A meta-analysis reported a standardized mortality rate (SMR) of 1.55 (95 % CI 1.14–2.11), and the increased mortality rate persisted despite substitutive treatment [2]. The most frequent cause of hypopituitarism in adults is the presence of a pituitary adenoma and/or its treatment (particularly transsphenoidal surgery [TSS] and/or radiotherapy) [1]. Prolactinomas represent the most common type of hormone-secreting pituitary adenoma, with an estimated prevalence between 25 and 63 cases per 100,000 people [3]. Prolactinomas have a clear sex dimorphism, being more frequent in young women, typically presenting as

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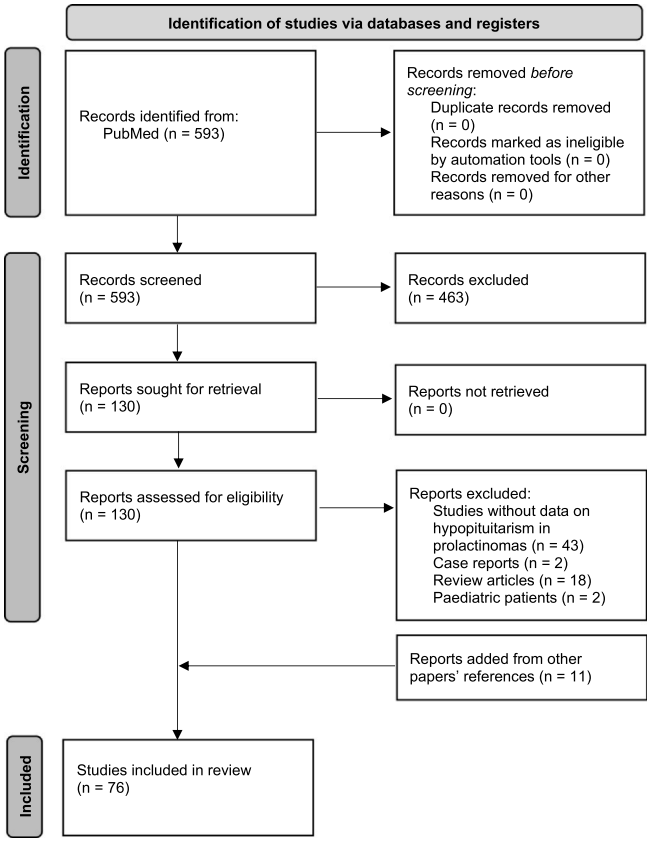

Fig. 1. Preferred reporting items for systematic review (PRISMA) 2020 flow diagram selection of the literature search from PubMed. The papers were sorted on the basis of the inclusion and exclusion criteria detailed in the manuscript.

microadenomas (i.e., maximum diameter of the adenoma < 10 mm) [3]. After menopause, the incidence is similar between women and men; however in the latter, prolactinomas are more frequently macroprolactinomas at diagnosis (i.e., maximum diameter ≥ 10 mm) and often show a more aggressive clinical behaviour [3]. In particular, the ratio of microprolactinoma to macroprolactinoma is 8:1 in women, whereas it is 1:4 in men [3].

To date, dopamine agonists (DAs), particularly the ergot-derivative cabergoline, represent the first-line treatment in the vast majority of cases, achieving prolactin (PRL) normalization in about 90 % of microadenomas and 83 % of macroadenomas, while a significant tumour shrinkage in observed in more than 70 % of cases [4]. However, TSS has been recently reconsidered in microadenomas as a first-line treatment due to the high expected cure rate associated to a low incidence of complications [3]. Moreover, TSS is indicated in patients resistant or intolerant to medical therapy; radiotherapy is the third line of treatment in case of TSS failure [3].

In this narrative review, we aim to summarize the currently available literature data on the prevalence of hypopituitarism in prolactinomas, identifying patients at a higher risk of developing this complication. Moreover, we also summarize the recovery rate of different pituitary axes, with a particular focus on the gonadotroph axis.

Methods

We conducted a comprehensive literature search using PubMed database with the following research string: ("prolactinoma" OR "prolactin-secreting pituitary adenoma" OR "prolactin-secreting PitNET") AND ("hypogonadism" OR “hypothyroidism" OR "hypopituitarism" OR “hypocortisolism” OR “central adrenal insufficiency” OR “GH deficiency” OR “GHD” OR "diabetes insipidus" OR "AVP deficiency" OR "AVP-D"). The last search was performed on the 6th of January 2026. We included only original articles and meta-analysis, and we excluded studies not in English, involving paediatric patients, and case reports. In Fig. 1 the flowchart describing the study selection according to PRISMA is reported [5].

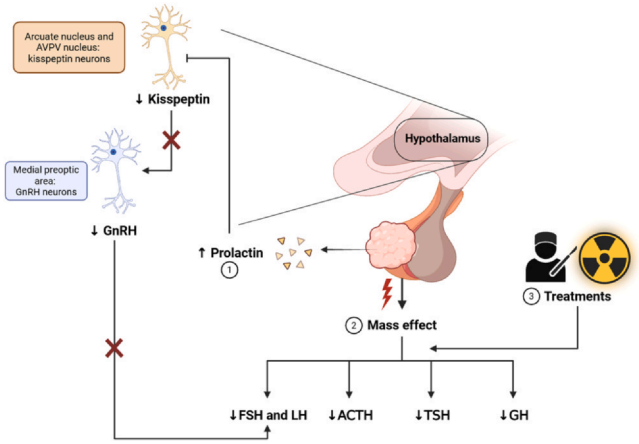

Fig. 2. Pathophysiology of hypopituitarism development in prolactinomas. 1) Prolactin-induced inhibition of the kisspeptin pathway and resulting functional suppression of gonadotrophic axis. 2) Local compression by the macroprolactinoma results in pituitary cell dysfunction. 3) New pituitary deficits due to prolactinoma treatment (surgery and radiotherapy). Legend: AVPV, anteroventral-paraventricular nucleus; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; GH, growth hormone.
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Overview of anterior hypopituitarism in prolactinomas

Hypopituitarism in patients with prolactinomas can be attributed to the direct mass effect of the tumour on the rest of the pituitary gland and/or to its treatment, as depicted in Fig. 2. Moreover, as mentioned below, high prolactin levels can induce a functional suppression of the gonadotrophic axis (Fig. 2). The prevalence of hypopituitarism in patients with prolactinomas at diagnosis varies significantly among studies, ranging from 6 % to 98 % of patients [6–21]. This high variability can be due to the inclusion or exclusion of hypogonadotropic hypogonadism (HH) in the definition of hypopituitarism, the heterogeneous definition of hormonal deficits, and the different populations included in the study. In a multicentre study including only male patients, Iglesias and colleagues reported a higher frequency of intact pituitary function or a deficit in only one axis in microadenomas (46.7 % and 46.7 %, respectively) compared to macroadenomas (21.9 % and 41.1 %, respectively). Accordingly, macroadenomas have more frequently a deficit of two, three, or four axes (15.1 %, 4.1 %, and 17.4 %, respectively) compared to microadenomas (6.6 %, 0 %, and 0 %, respectively) [21]. Similarly, a recent study including only macroadenomas reported no pituitary deficits in 24 % of patients, the impairment of one pituitary axis in 30 % of two axes in 28 %, and of three axes in 18 % of patients. Of note, the presence of growth hormone deficiency (GHD) was not assessed in this study [22]. Although it has been demonstrated that microadenomas have a lower risk of developing hypopituitarism [1,23], a direct correlation between the prolactinoma size and the presence of pituitary deficits has not been demonstrated [11,14]. However, studies focused on giant prolactinomas (maximum adenoma diameter $\geq$ 40 mm) generally reported a higher prevalence of hypopituitarism (72–98 %) compared to the findings observed in smaller tumours [8,9,11,12], and a recent study identified tumour size as the only statistically significant risk factor for developing hypopituitarism at multivariate analysis [6].

The prevalence of the impairment of each pituitary axis and the recovery rate after treatment will be discussed in the dedicated sub-chapters below.

In general, an improvement of pituitary function has been reported both with medical and surgical treatment, particularly as concerns the gonadotroph axis. A recent study evaluated the outcomes of medical vs surgical treatment in giant prolactinomas; no statistically significant difference in the recovery rate of hypopituitarism was observed between the two treatment groups (11.9 % vs 4.2 %, p = 0.066) [9]. Interestingly, a meta-analysis showed that the incidence of new pituitary deficits after TSS is similar between prolactinomas, non-functioning pituitary adenomas (NFPA), and patients with acromegaly [24].

As concerns radiotherapy, few studies have investigated its impact on pituitary function in patients affected exclusively by prolactinomas. New pituitary deficits have been observed in 8–25 % of patients treated with stereotactic radiosurgery (SRS) [25–29]. Consistently, a recent meta-analysis reported the development of new pituitary deficits in 8 % (95 % CI 6–9 %) of patients with pituitary adenomas treated with gamma knife (including both functioning and clinically non-functioning adenomas; 34 % were prolactinomas) [30]. Noteworthy, as the Authors underlined, the evaluation of GHD is frequently missing and, therefore, the prevalence of pituitary deficits could be underestimated [30]. Iglesias and colleagues evaluated the pituitary function in patients with prolactinomas treated with multimodal therapies and all patients treated with DA, TSS, and/or conventional radiotherapy developed hypopituitarism [21]. Due to the high prevalence of endocrine complications, and the long time before the onset of new deficits (reported around 98 months for SRS [25]), a long-term follow-up is recommended.

Hypothalamic-pituitary-gonadic axis

Hypogonadotropic hypogonadism (HH) is the most frequent pituitary deficit observed in patients with prolactinoma. High PRL levels inhibit kisspeptin secretion, a key regulator of gonadotropin-releasing hormone (GnRH) secretion, by neurons located in the arcuate and anteroventral-periventricular nuclei of the hypothalamus. In rodents with induced hyperprolactinemia, the inhibition of kisspeptin secretion has been shown to reduce GnRH secretion. This leads to a decreased secretion of LH and FSH by the anterior pituitary [31] (Fig. 2). Moreover, HH in patients with macroprolactinomas can also be caused by the direct compression of the tumour mass on normal gonadotroph pituitary cells [1].

In women, HH manifests as shortened luteal phase, oligo-amenorrhea, infertility, and decreased libido, whereas in men it is mainly associated with erectile dysfunction, decreased libido, and impaired spermatogenesis. The prevalence of HH in patients with prolactinomas is highly variable depending on the study design and the definition of hypogonadism, varying between 17 % and 100 % of cases [6–12,14,15,18,19,29,32–49]. A recent study evaluated pituitary function in patients with a diagnosis of prolactinoma in young ($\leq$ 18 years) and old age ($\geq$ 65 years); the presence of hypogonadism was reported in 70 % of young patients and in 90 % of older patients [7]. Of note, the prevalence of macroadenomas was higher in elderly patients [7].

As concerns women, two recent studies reported a huge difference in the prevalence of HH, varying from 17.4 % as reported by Prinzi and colleagues (that defined HH in pre-menopausal women as low or inappropriately normal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) associated to oestradiol below 200 pmol/L with menstrual disturbances [6]) up to 63 % as reported by Detomas and colleagues (who defined low oestradiol as $<$ 110 pmol/L [33]). Moreover, an even higher rate of hypogonadism was reported in different studies (range 92 %-100 %) in which a clear definition of HH was not provided [32,40].

The prevalence of HH has been related to tumour size. A recent study reported a lower prevalence of HH in microadenomas compared to macroadenomas, although the difference was not statistically significant (60 % vs 76 %, respectively); of note, patients with macroprolactinoma had significantly higher PRL levels [33]. Similarly, a previous study reported an increased prevalence of menstrual cycle alterations in patients with prolactinomas with higher PRL levels [50]. A meta-analysis conducted on giant prolactinomas reported HH in 87 % of female patients [8], suggesting a correlation of HH with both PRL levels and tumour size, at least in women.

Multiple studies have investigated HH in men; however, also in this population, the definition of HH is quite heterogeneous among studies and it is based on total testosterone cut-offs varying between 8 nmol/L and 10.4 nmol/L. Moreover, multiple studies did not provide a specific testosterone cut-off, limiting the comparability of the different findings. With these limitations, the prevalence of HH at diagnosis in men is reported between 50 % and 72.3 % in microadenomas [19,21,33,35,51–53] and between 53 % and 93.5 % in macroadenomas and giant prolactinomas [8,11,15,19,21,33,35,45,52,53]. One of the major determinants identified to date is tumour size [6,19,21,33,35,45]. In particular, Peng and colleagues described a negative correlation between testosterone levels and tumour size, as well as between testosterone levels and PRL levels at diagnosis [14]. PRL levels are indeed another possible factor influencing the prevalence of HH at diagnosis and are strictly linked to tumour size [3,35]. However, a recent study did not find a significant difference in tumour size, PRL levels, BMI, rate of other pituitary deficits, or invasiveness between patients presenting with normal or low testosterone levels ($<$ 10 nmol/L) [36].

It is noteworthy that a significant proportion of men (around 10–15 %) maintain normal testosterone levels despite high PRL levels [21,46,54,55]. A study analysing 56 men with prolactinomas reported normal testosterone levels ($\geq$9 nmol/L) in 20 % of patients, 19 % with a mild impairment of the gonadal axis, while 61 % had an overt reduction of testosterone levels ($\leq$6.9 nmol/L). Interestingly, comparing patients with low, marginally low, and normal testosterone levels, no significant difference in PRL levels or tumour size was observed. Furthermore, symptoms of hypogonadism (erectile dysfunction, decreased libido, and/or gynecomastia) were present in 55 % of patients with normal testosterone levels and in up to 64 % of patients with marginally low testosterone levels [46]. After treatment with cabergoline, testosterone levels increased significantly in all three groups, with a similar pre- to post-treatment change in patients with normal or low baseline testosterone levels paralleled by improvement in hypogonadal symptoms. Of note, a recent study comparing eugonadal male patients (normal testosterone levels $\geq$10.4 nmol/L) harbouring a prolactinoma to eugonadal patients with a clinically non-functioning pituitary adenoma (NFPAs) in whose PRL levels at diagnosis were normal, described a significant increase in testosterone levels after DA treatment and prolactin normalization only in the prolactinoma group, with an improvement of hypogonadal symptoms in this population. In patients with NFPA, who did not undergo surgery or radiotherapy, after a similar follow-up duration (23.5 $\pm$ 14.7 months vs 26.5 $\pm$ 32.9 months in patients with prolactinomas), no significant increase of testosterone level nor improvement of hypogonadal symptoms was observed. Of note, at least one hypogonadal symptom was present at diagnosis in 72 % of patients with prolactinoma despite normal testosterone levels, whereas only 39 % of men with NFPAs reported hypogonadal symptoms [56]. Therefore, the Authors hypothesize that prolactinoma patients with normal testosterone levels at diagnosis may present with a clinical hypogonadism, and, beyond testosterone levels, signs and symptoms of hypogonadism should be carefully taken into consideration, since they can improve upon PRL normalization [46,56]. Interestingly, the presence of anaemia, a nonspecific sign of HH, has been reported in 25 % of patients with prolactinomas, and while it is rare in female patients (up to 5 % of cases), it is quite frequent in male patients (between 31.1 % and 83 %) [15,33,45,48,51,57]. In particular, Tirosh and colleagues observed an increased incidence of anaemia associated with a larger tumour size; as expected, patients with larger tumours also showed higher PRL levels and lower testosterone levels [45]. Testosterone has a well-known stimulatory effect on erythropoiesis, but other hormones can have an impact on it as well. As an example, in a previous study the presence of anaemia was associated with central hypothyroidism and central adrenal insufficiency (CAI) [15]. Therefore, the presence of anaemia has been suggested as a potential marker of hypopituitarism [15,33]. In this context, a recent study has investigated the possible role of anaemia as an early marker of hyperprolactinemia in men. The median time spent with low haemoglobin levels before diagnosis

Table 1
Recovery rate of hypogonadotropic hypogonadism in men with prolactinoma.

Author	Patients (n.)	Tumour size	Treatment modalities	HH diagnosis	HH recovery	Predictors of persistent HH	Caveats of the study
Sibal et al. [54]	35	M	DA	77 %	62 %	NA	NA
De Rosa et al. [52]	65	M (82 %) and m (18 %)	DA	76 % (M); 53.3 % (m)	64 % (M); 73 % (m)	NA	NA
Sehemby et al. [63]	30	M	DA monotherapy	100 %	27 %	Baseline PRL > 2098 ng/mL, baseline tumour size > 3.2 cm	HH at diagnosis in patients achieving PRL normalization
Rudman et al. [64]	58	M	DA monotherapy	100 %	79 %	Hypopituitarism, visual field defect at diagnosis, baseline testosterone < 5.2 nmol/L	HH at diagnosis in patients achieving PRL normalization
Al Dahmani et al. [39]	79	M	DA	80 %	65 %	Tumour size > 4 cm, baseline PRL > 1803 ng/mL**	NA
Guitelman et al. [53]	311	M (89 %) and m (11 %)	DA and/or surgery	90 %	63 % (M); 80 % (m)	NA	NA
Constantinescu et al. [36]	97	M (79 %) and m (21 %)	DA	88 %	61 % at 6 months and 69 % at 12 months*	Baseline testosterone levels < 5.35 nmol/L, or testosterone at 6 months < 7.4 nmol/L	NA
Rudman et al. [51]	47	m	DA	72 %	100 %*	NA	NA
Milioto et al. [65]	29	Isolated hyperprolactinemia (62 % M and 17 % m)	DA monotherapy	100 %	69 %	Baseline testosterone levels < 5.2 nmol/L	HH at diagnosis in patients achieving PRL normalization

Legend: n., number; HH, hypogonadotropic hypogonadism; NA, not available; M, macroprolactinoma; m, microprolactinoma;
* percentage calculated on patients achieving normal PRL after DA treatment;
** Although PRL levels were reported as IU/L in the original table, values are converted from mIU/L, according to the stated conversion method of the manuscript.

was 6.1 years and it was significantly longer compared to the time reported for sexual dysfunction (mean difference 4.1 years). No correlation was observed between the time spent with low haemoglobin values and PRL levels or tumour size at diagnosis [58].

As previously described, DAs still represent the first-line treatment in most cases due to the high efficacy in PRL normalization and tumour shrinkage, with improvement or restoration of the gonadal function in a significant subset of patients. However, TSS has been recently re-evaluated as a first-line treatment in selected patients. A recent study investigating the recovery rate of hypopituitarism in macroprolactinoma treated with medical treatment or TSS reported restoration of the gonadal axis in 42 % of patients receiving DA and 43 % of patients treated with TSS. Whereas sex and type of treatment did not affect the recovery rate, tumour size and PRL normalization were significant determinants of eugonadism restoration. In detail, larger tumour size and lack of prolactin normalization increased the risk of HH persistence [22]. Of note, new gonadal dysfunctions after TSS have been reported in 3–6 % of patients in a recent meta-analysis [59].

As previously mentioned, microprolactinomas are more frequent in women, and restoration of eumenorrhea and ovulatory cycles is achieved in 78 % (ranging from 40 % to 100 %) of patients treated with DAs [60]. Among 85 patients with prolactinomas and infertility treated with DAs, 80 patients achieved at least one successful pregnancy (age range 35–40 years); of note, patients who failed to conceive were older (age range 38–41 years) [61]. Similarly, a more recent study reported the recovery of gonadal axis in 85 % of women evaluated six months after TSS. The recovery rate increased up to 100 % in the subset of patients with microadenomas [62]. In the evaluated cohort, the majority of women desiring pregnancy had successfully given birth (80 %) [62].

As previously reported, men have a higher incidence of macroadenomas, and therefore, the aetiology of HH can be both functional and structural. Multiple studies have investigated the gonadal axis restoration after treatment, particularly with DAs, with a recovery rate varying between 27 % and 100 %, as reported in Table 1 [14,19,36,39,51–54,63,64]. Of note, as it has been previously mentioned for HH prevalence, we have to take into account that different studies used different testosterone cut-offs to define HH, possibly impacting the observed recovery rate. Sehemby and colleagues reported the lowest recovery rate (27 %), despite the exclusion of patients resistant to DA treatment, defining low testosterone as a value below 10.4 nmol/L. The Authors hypothesized that the relative short follow-up (2 years), the inclusion of only macroadenomas (mean tumour size 40.8 mm), as well as a different susceptibility of the gonadal axis in patients of Asian ethnicity could be all possible explanations for their findings [63]. On the other hand, Rudman and colleagues reported a 100 % recovery rate in patients achieving normal PRL levels; the normalization of testosterone levels was also described in two patients despite mildly elevated PRL levels. This study included men with microprolactinomas with a relatively low PRL at diagnosis (median 70 ng/mL), and the cut-off used to define low testosterone was 9.7 nmol/L [51]. Other studies more consistently reported a recovery rate ranging from 63 % to 80 % [36,39,52–54,64]. Multiple factors were identified to help clinicians to stratify patients at risk of persistent HH, in which a prompt start of replacement therapy is needed. The most consistent factors identified were baseline testosterone levels, baseline PRL levels, and tumour size. Two studies found baseline PRL levels as a significant predictor of HH recovery, identifying consistent PRL level cut-offs. In detail, Sehembly and colleagues identified a PRL cut-off of 2098 ng/mL with a sensitivity of 85.7 % and a specificity of 77.3 %, whereas Al Dahmani and colleagues identified a PRL cut-off of 1803 ng/mL (sensitivity 71,7 %, specificity 50 %) [39,63]. In these studies, tumour size resulted as a significant predictor of HH; the identified cut-offs were a maximum tumour diameter of 32 mm (sensitivity 75 %, specificity 63.6 %) in the former study [63], and 40 mm (sensitivity 81.6 %, specificity 57.1 %) in the latter [39].

Baseline testosterone was another parameter reported as predictor of HH persistence in multiple studies [36,64]. In detail, Rudman and colleagues identified baseline testosterone levels < 5.2 nmol/L, the presence of hypopituitarism (defined as central adrenal insufficiency and/or central hypothyroidism) or visual field defects as significant predictors of HH persistence. This model reached a sensitivity of 75 % and a specificity of 93.5 % [64]. A similar baseline testosterone cut-off was identified by Constantinescu and colleagues (5.35 nmol/L, sensitivity 73 % and a specificity 71 %). In this study the evaluation of testosterone levels after 6 month treatment with DAs had a high predictive value in identifying patients with persistent HH after one year of ongoing medical therapy (testosterone cut-off at 6 months 7.4 nmol/L, sensitivity 91 %, specificity 94 %) [36]. Of note, a recent study by our group identified a remarkably similar baseline testosterone cut-off (5.2 nmol/L, sensitivity 80 %, specificity 78 %) despite the different study design. This study included male patients with isolated hyperprolactinemia of different aetiology, of which 79 % had a diagnosis of prolactinoma, treated with DAs [65].

Of note, it has been occasionally reported that the increase of testosterone levels, in patients with previous longstanding hypogonadism treated with DA, may lead to hypersexuality, a condition named dopa-testotoxicosis [55,66]. Of note, hypersexuality, as well as other impulse control disorders (e.g., compulsive shopping, punding, and compulsive eating) are reported as potential side effects of DA. Whereas hypersexuality is more common in men than women, a correlation with testosterone levels is debated [67,68].

The timing of testosterone recovery after PRL normalization is often reported from 3 to 12 months; however, both the synchronous normalization of PRL and testosterone levels, as well as a longer delay between PRL normalization and the restoration of eugonadism have been reported [36,39,52,64,65,69]. Of note, a direct positive correlation between baseline PRL levels and the time to gonadal axis recovery has been reported [65].

Current guidelines suggest starting testosterone replacement in case of persistent HH for more than 6 months following DA treatment and re-evaluation over time in patients who achieve normal PRL levels [3]. Few studies investigated the improvement of semen quality to evaluate the complete reversibility of HH. In particular, early studies observed an improvement in seminal fluid quality after 6 and 12 months of treatment with DA, although it remained significantly impaired compared to healthy controls despite testosterone normalization [19,52]. After 24 months of treatment, the seminal fluid characteristics showed a further improvement; however, few parameters remained impaired compared to healthy controls [19,52]. More studies are needed to confirm these data and better define fertility restoration, also taking into account the advancement in the evaluation of the semen analysis [70].

Hypothalamic–pituitary–thyroid axis

The reported prevalence of central hypothyroidism, defined as low free thyroxine (fT4) and low or normal TSH levels, varies considerably among patients with prolactinomas, depending on the inclusion criteria of the different studies. In patients with microprolactinomas, central hypothyroidism is virtually absent [19,21,33,35], although it has been occasionally reported [6]. However, in patients with macroprolactinomas or giant prolactinomas, it is more frequently reported, ranging from 5.4 % to 79 % [6,8,11,12,14,21,22,33–35,37–39,41,42,45,47,48,54,63,64]. In a study comparing females and males, no significant differences were observed between sexes, despite a higher prevalence of macroprolactinomas in men [40]; however, other studies reported a higher prevalence in men, possibly due to the higher prevalence of macroadenomas in this population [6,18]. Of note, tumour size has been shown to be a factor in central hypothyroidism development in multiple studies [11,12,34,45]. Moreover, in a recent study, it has been suggested that tumour size can also have an impact on thyrotrophic cells' recovery after treatment, whereas age, sex, and treatment modalities (TSS vs DAs) did not have a significant impact [22]. Conversely, a previous study identified a more frequent new onset of hypothalamus-pituitary-thyroid axis alteration in patients treated with TSS (25 % of patients experienced new central hypothyroidism) compared to patients treated with DAs (2.4 % of patients) [9]. Of note, there is no consensus on the rate of recovery of the thyrotrophic axis, being reported in none (0 %) of the patients with giant prolactinomas, in 0–44 % of patients with macroprolactinomas [47,54,63], whereas a more recent study, including both micro- and macroprolactinomas, reported a recovery rate of 66 % [6]. Of note, due to the relatively low incidence of central hypothyroidism in patients with prolactinomas, small cohorts of patients have been investigated to assess the recovery of this specific axis; therefore, more studies, with a bigger sample size, are needed to properly answer this question.

Furthermore, it has to be taken into account that macroprolactinomas and giant prolactinomas frequently need to be treated with multimodal therapy, thus increasing the risk of developing new pituitary deficits. In a large study of patients with giant prolactinomas, a significantly higher prevalence of central hypothyroidism was observed in patients treated with multimodal treatment (77 %) compared to patients treated only with DAs (33 %) [38].

Hypothalamic–pituitary–adrenal axis

Central adrenal insufficiency (CAI) represents a potentially life-threatening complication associated with pituitary adenomas. It is defined as low plasma cortisol and ACTH levels and/or an inadequate cortisol response to the cosyntropin stimulation test. Hystorically, the hypothalamic–pituitary–adrenal axis is the last to be impaired in the setting of pituitary damage. The reported baseline prevalence of CAI in patients with prolactinomas ranges from 4.16 % to 59.25 % [6–10,14,16,18–20,22,25,29,33,38,40–43,45,47,49,54,63,71–75].

This huge variability is largely attributable to tumour size, as most studies have reported a higher prevalence of CAI in patients with larger pituitary adenomas, with increasing prevalence corresponding to greater maximal tumour diameter [6,34,41,45,72]. Consequently, studies focusing exclusively on macroprolactinomas or giant prolactinomas have identified higher rates of CAI at diagnosis compared to studies including also microprolactinomas. In two studies, CAI was observed exclusively in patients with macroprolactinomas [19,33]. However, few studies including only macroprolactinomas and/or giant prolactinomas failed to demonstrate a significant direct correlation between adenoma size and CAI prevalence [10,12,14].

As previously mentioned, macroprolactinomas are more frequent in men. This has been proposed as a potential explanation for the higher prevalence of CAI in male patients reported in several studies [6,18,33,40]. However, this finding has not been confirmed in patients with giant prolactinomas. In a recent meta-analysis of 196 patients with giant prolactinomas (153 men and 43 women), CAI was more prevalent among women than men (56 % vs 38 %), despite larger adenoma diameters being observed in male patients [8]. Similarly, in a Swedish registry study including 84 patients with giant prolactinomas, 17 % presented with CAI at baseline, with a slightly higher, though not statistically significant, prevalence in women [38]. A smaller cohort study on giant prolactinomas also reported a higher prevalence of CAI among women (33.33 %) compared to males (17.24 %) [42].

Two studies reported that CAI was more frequently diagnosed in older patients ($>$ 65 years and $\geq$60 years, respectively) compared with younger individuals [7,76]. This finding is particularly relevant given the high morbidity and mortality associated with undiagnosed AI, especially in elderly patients in whom symptoms may be subtle and easily misinterpreted.

Treatment modalities for prolactinomas, particularly TSS and radiotherapy, may variably affect pituitary function. The incidence of new-onset CAI following TSS ranges from 0.5 % to 2.47 % [10,14,18,22,29,45,75], highlighting that although CAI may represent a surgical complication, its occurrence is relatively uncommon when procedures are performed by experienced surgeons. Some studies have reported higher rates of postoperative CAI; this could be related to differences in follow-up duration and postoperative management protocols among centres. In a French observational study of 114 patients with microprolactinomas treated with TSS, low early morning cortisol levels ($<$ 275 nmol/L) were observed in 63 % of patients; however, cortisol levels normalized in all patients within three months after TSS [77]. The Authors hypothesized that this finding reflected a transient impairment of corticotropic function due to sellar bone drilling and/or routine postoperative hydrocortisone supplementation, which may suppress endogenous cortisol levels even when measured more than 12 hours after the last dose [77].

Kristof and colleagues retrospectively analysed 60 patients undergoing TSS for prolactinomas and observed an increase in CAI prevalence from 47.2 % preoperatively to 61.1 % in the early postoperative phase, followed by a progressive reduction to 37.5 % at three months and 26.9 % at last follow-up [20]. Comparable data have been shown by other authors, with a reported recovery rate of CAI exceeding 50 % of cases in some series [14,22,78], depending on treatment protocols, patient characteristics, and tumour size [14].

Medical therapy alone (i.e., DAs) rarely results in the deterioration of the hypothalamic–pituitary–adrenal axis and it has been shown to be associated with a lower risk of CAI compared with surgery, radiotherapy, or multimodal treatment approaches [8,10,11,16,38,43,45].

The recovery of adrenal function following medical therapy is variable, with some studies reporting no recovery [42,47,49], while others document recovery rates ranging from 43 % up to 85.7 % [6,19,33,45,54,63,72]. Kim and colleagues reported a higher prevalence of CAI in patients resistant to DA treatment, particularly in those developing cerebrospinal fluid rhinorrhoea, suggesting that hormone deficiencies may reflect advanced and prolonged tumour-related damage leading to irreversible pituitary dysfunction [74].

Reported rates of new-onset CAI after SRS are variable. Li and colleagues reported no new cases [25], whereas other studies documented higher rates of corticotropic cells dysfunction, ranging from 3.6 % to 18 % of cases [26,28,79]. These discrepancies may be explained by differences in treatment protocols, including radiation dose and tumour proximity to normal pituitary tissue.

Growth hormone axis

Only a limited number of studies have evaluated GHD in patients with hyperprolactinemia. This is partly due to several confounding factors, including the presence of mixed GH/PRL-secreting adenomas and inconsistent effects of cabergoline therapy on the GH/ insulin-like growth factor 1 (IGF-1) axis. While some studies have reported a paradoxical increase in IGF-1 levels during cabergoline treatment, others found no consistent directional changes [40,80,81]. In particular, a recent study observed a modest early increase in IGF-1 levels, likely due to mass effect relief, followed by slight declines with prolonged exposure and higher cumulative cabergoline doses, reflecting the dopamine type 2 receptor (D2R) -mediated effect on somatotroph cells. Importantly, IGF-1 levels remained within the age-adjusted reference ranges throughout the study [82].

When reported, GHD prevalence at diagnosis ranges between 0 % and 83 % [6,8–10,14,16,18–20,29,33,42,47,78]. Incomplete data collection, particularly in retrospective analyses, may explain why some studies surprisingly report GHD less frequently compared to other pituitary hormone deficits [8,12,33].

As mentioned in the previous paragraphs for central hypothyroidism and CAI, a correlation between GHD and tumour size has been reported [6], suggesting that the evaluation of specific populations (e.g., macroprolactiomas or giant prolactinomas) can significantly impact prevalence estimates [19,33,71]. However, several studies did not confirm a direct relationship between GHD prevalence and tumour diameter [10–12,14], underscoring the need for further research to achieve more consistent results.

Overall, a higher prevalence of GHD has been reported in male patients [6,18], although one meta-analysis focused only on giant prolactinomas found a greater prevalence among women [8].

The recovery of somatotroph axis following treatment remains controversial, ranging from 0 % to 62 % in patients treated with DAs [6,19,33,47]. George and colleagues reported higher rates of GHD recovery following cabergoline therapy in patients with partial hypopituitarism compared to those with panhypopituitarism, suggesting a more extensive and persistent pituitary damage in the latter group [17].

New-onset GHD following TSS and/or radiotherapy is a recognized complication, with reported rates ranging from 2 % to 34 % [11,14,47]. Hamidi and colleagues reported a higher incidence of GHD in surgically treated patients compared with those managed non-surgically (24 % vs 5.6 %, p = 0.04) [10]. In a cohort of 37 patients, GHD was present in 77.1 % preoperatively, increased to 83.3 % in the early postoperative period, then declined to 80.6 % at three months and to 61.1 % at last follow-up [20]. These differences may reflect heterogeneity in GHD diagnostic criteria (basal IGF-1 values versus dynamic testing), as well as in follow-up duration among available studies.

Alterations of water metabolism

Surgical procedures involving the sellar region are frequently associated with disturbances in water and electrolyte homeostasis, including arginine vasopressin peptide deficiency (AVP-D), which may lead to severe hypernatremia, and syndrome of inappropriate antidiuresis (SIAD), which may lead to hyponatremia [1].

AVP-D is unlikely in patients with pituitary adenomas before surgery. However, our literature search identified a total of 3 cases reported with AVP-D at diagnosis, described in 2 retrospective studies of giant prolactinomas [10,42]. The findings have to be interpreted with caution as workup to demonstrate the diagnosis of AVP-D was not presented. More frequently, AVP-D is reported after treatment, particularly TSS. The majority of published studies reported predominantly transient AVP-D after TSS, ranging from 4.2 % to 21.4 % (1,2,6,8,18,28,33,34,42), whereas permanent AVP-D is rarely encountered (0–13 %) [9,18,29,38,43,71,75,77,83,84].

SIAD is caused by inappropriate AVP secretion, primarily due to direct surgical trauma, but also influenced by postoperative factors such as stress and pain. In the postoperative setting, it usually develops 6–12 days after TSS [85]. Hyponatremia due to SIAD in patients with prolactinomas has been reported in 1–8.9 % [18,20,40,62,71,75,78,84].

Summary

Prolactinomas represent the most common histotype of hormone-secreting pituitary adenomas. Partial or complete hypopituitarism is a frequent and often overlooked complication, attributable both to the tumour itself and/or to its therapeutic management, particularly surgery and radiotherapy. The actual prevalence of pituitary axis dysfunctions in patients with prolactinoma, beyond

hypogonadism, remains difficult to determine, possibly caused by the heterogeneity of diagnostic criteria of hypopituitarism among centres, the retrospective design of most studies, and the presence of highly selected cohorts (i.e., giant prolactinomas) in the literature available so far. Importantly, the relatively high rate of recovery of the normal pituitary function after prolactinoma treatment, as well as the possible pituitary impairment due to the treatment of the lesion, highlights the need for structured, long-term, and comprehensive follow-up strategies encompassing all pituitary axes, in order to accurately identify and manage complications related to both insufficient and excessive treatment.

Research Agenda

- The presence of highly selected cohorts, and the retrospective design of most studies available to date limit the generalization of the different findings. Multicentre, prospective studies are needed to better stratify patient risk of developing hypopituitarism.
- Use of standardized definitions, in particular for hypogonadotropic hypogonadism, would allow to better define the prevalence of pituitary deficit in patients with prolactinoma and to identify subjects at high risk of persistent hypogonadism, in which replacement therapy should be started.
- There is a clinical need for multicentre studies aimed to better investigate the recovery rate of the pituitary axes less frequently affected (e.g., thyrotropic axes, corticotropic axes), due to the small sample size of the studies available to date.

Practice Points

- Reported anterior hypopituitarism prevalence in prolactinomas is highly variable among different studies, but it is more common in macroprolactinomas.
- Hypogonadotropic hypogonadism is present at diagnosis in the majority of patients and its aetiology can be functional and/or due to mass effect.
- Predicting factors for recovery of hypogonadotropic hypogonadism after medical treatment in men are tumor size, baseline prolactin values and baseline testosterone values. In women, the persistence of hypogonadotropic hypogonadism is rare.
- Central hypothyroidism and central adrenal insufficiency are more frequent in patients with macroprolactinomas, and in patients treated with multimodal therapy. Growth hormone deficiency is probably overlooked.
- In patients treated with radiotherapy a long-term follow-up to monitor pituitary function is needed.

Declaration of Competing Interest

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