Chapter 4
Hyperprolactinemia in Men with Testosterone Deficiency

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4.1 Introduction

The appropriate diagnosis and management of male testosterone (T) deficiency requires a thorough understanding of several physiologic processes and may require the integration of subspecialty services. The lack of understanding or appreciation of the complex nuances of low T may lead to missed diagnoses, inappropriate therapy, and potentially significant ramifications to a patient's overall health and well-being. One of these nuances includes the role and relevance of prolactin (PRL) and, more specifically, hyperprolactinemia as an important clinical condition. However, despite its importance, relatively few clinicians who treat low T have significant experience in managing PRL abnormalities. Given this observation, the objective of this chapter is to provide the practicing clinician a practical guide to evaluating and managing hyperprolactinemia. To accomplish this objective, the chapter is outlined to review the anatomy and physiology of PRL, associated findings and symptoms, its causative role in low T, the appropriate evaluation of hyperprolactinemia, and available management strategies. Although many clinicians may simply choose to refer men with hyperprolactinemia to an endocrinologist, a deeper understanding of these principles remains relevant, given that the initial diagnosis of hyperprolactinemia is most often dependent upon the sexual medicine clinician.

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4.2 Prolactin and Hypothalamic-Pituitary-Gonadal Axis

Prolactin is a hormone produced in the anterior pituitary gland that serves predominantly to facilitate milk production in women. Several different actions lead to PRL secretion, including nursing, estrogen therapy/hormones, sexual activity, eating, and ovulation. As with other pituitary hormones, PRL is secreted in a pulsatile fashion and often occurs between stimulating events. It has additionally been suggested to have roles in immunomodulation and cell growth and differentiation and is particularly involved in hematopoiesis and angiogenesis.

Prolactin is most active during periods of pregnancy, where it leads to breast growth and mammary gland milk production. The regulation of PRL secretion is largely controlled via the inhibitory effects of dopamine, although thyrotropin-releasing hormone (TRH) also contributes and is able to directly stimulate release. Central serotonin also shows a stimulatory effect on PRL secretion. Prolactin exhibits mild gonadotropic effects and sensitizes luteinizing hormone (LH) receptors in Leydig cells, thereby increasing T production. Both T and PRL are subsequently able to suppress gonadotropin releasing hormone (GnRH), thereby helping to maintain appropriate PRL homeostatic levels.

The specific mechanism by which hyperprolactinemia causes low T has not been definitively described, although it likely includes both direct and indirect contributions. The presence of a pituitary adenoma (secreting or non-secreting) may result in suppression of GnRH/LH or destruction of GnRH/LH producing cells with subsequent declines in T production. Additionally, as a mild gonadotroph, PRL may feed back directly to the pituitary, resulting in the suppression of LH and T. Of note, from a purely diagnostic standpoint, true hyperprolactinemia occurs in the absence of macroprolactinemia, which may otherwise result in elevated prolactin levels without associated symptoms. The differentiation between these two conditions and diagnostic testing are beyond the scope of this chapter.

4.3 Clinical Symptoms and Prevalence of Hyperprolactinemia in Men

Symptoms related to hyperprolactinemia may be due to the effect of PRL itself, suppression of other hormones (e.g., T), or a mass effect from a PRL-secreting mass. See Table 4.1 for a summary of common presenting symptoms in men with hyperprolactinemia. In a recent study evaluating the presenting symptoms of 28 elderly males (>65 year old) who were diagnosed with hyperprolactinemia, 61% complained of sexual dysfunction (e.g., low libido and erectile dysfunction [ED]), while 36% had no symptoms and were incidentally diagnosed [1]. Interestingly, only 7% complained of headaches or visual disturbances due to the mass effect from an underlying pituitary tumor. In contrast, in men who have large prolactinomas (defined as ≥40 mm diameter or ≥ 20 mm of suprasellar extension), visual

Table 4.1 Common presenting symptoms in men with hyperprolactinemia

Symptoms*	Frequencies
Sexual dysfunction (e.g., low libido and erectile dysfunction)	61%
Incidental finding (asymptomatic)	39%
Headache	7%
Visual disturbances	7%
Gynecomastia	Unknown (likely <5%)
Galactorrhea	Unknown (likely <5%)

*Symptoms as identified in men aged >65 [1]

disturbances are reported in up to 65% of cases [2]. This important finding highlights that earlier detection at the sexual dysfunction stage may prevent progression to a more advanced condition. Other symptoms such as gynecomastia or galactorrhea seldom occur with hyperprolactinemia in men, although the exact frequency with which they occur is unknown and is likely low.

In a series of men presenting to a sexual medicine clinic with varied sexual medicine complaints, a prevalence of mild elevations in prolactin (20–35 ng/mL) was found in 3.3%, while that of higher elevations (>35 ng/mL) was observed in 1.5% [3]. After controlling for low testosterone, TSH levels, and psychotropic drugs, higher prolactin levels remained significantly associated with low libido (HR 8.6). Similarly, following appropriate treatment of the elevated prolactin, libido improved at 6-month follow-up.

The prevalence of hyperprolactinemia in men with low T has not been well established. In contrast, majority of men with hyperprolactinemia are found to have low T. In a study of men >65 years old, 75% were found to have low T, while a second study of men aged 22–78 identified similarly high rates of low T (86%) [1, 4]. As noted earlier, this high rate of concomitant sexual dysfunction as well as sexual symptoms being the most common initial complaint of men with hyperprolactinemia suggests an essential role for the sexual medicine physician in appropriately identifying this condition through selective testing.

4.4 Etiologies for Hyperprolactinemia

Several different conditions and substances have been associated with hyperprolactinemia, including tumors, comorbid conditions, and medications, among others. See Table 4.2 for a more complete list of potential etiologies. Although pituitary tumors are relatively uncommon in men with low T, among those who are found to have hyperprolactinemia, they represent the most common single etiology and account for 41% of cases [5]. Other common causes included seizures (17%), medications (15%), acute illness (14%), chronic kidney disease (11%), transient (10%), and idiopathic (3%).

Table 4.2 Causes of hyperprolactinemia

Categories	Factors
Physiological	Sexual activity, exercise, sleep, stress
Hypothalamic-pituitary issues	Hypothalamic-pituitary stalk damage, acromegaly, lymphocytic hypophysitis, parasellar mass, prolactinoma, adenoma, surgery, trauma, radiation
Comorbid conditions	Chronic renal failure, cirrhosis, seizures
Medications	Antipsychotics (less with aripiprazole), bowel promotility agents (metoclopramide), tramadol, anesthetics, anticonvulsants, antidepressants (tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, nefazodone, venlafaxine), antihistamines (H2), antihypertensives (verapamil)

In the majority of cases, management of the underlying cause for hyperprolactinemia typically leads to normalization of PRL levels. For example, among men with prolactin-secreting tumors, medical treatment with dopamine agonists resulted in normal PRL levels in 86% of individuals [1]. Similarly, men with chronic kidney disease and hyperprolactinemia who undergo renal transplantation experience subsequent declines in PRL levels [6].

In contrast to the above examples, medication-associated hyperprolactinemia is less well defined, and relatively limited data are available. The most common medication class implicated in hyperprolactinemia is anti-dopaminergic agents, including antipsychotics, with first-generation drugs being most commonly associated. More recent, second-generation agents have lesser impacts on PRL levels, which is thought to be secondary to combined dopamine agonist and antagonist properties (e.g., aripiprazole) [7]. However, this traditional concept of antipsychotic medication use being the sole cause of hyperprolactinemia has recently been called into questions. In a study of men with schizophrenia, 56% were found to have concomitant hyperprolactinemia at baseline, prior to antipsychotic use [8]. More recent data further supports this concept and suggests that the underlying psychotic disorder may actually contribute more to hyperprolactinemia than the antipsychotic medications themselves [9]. Furthermore, PRL levels may positively correlate with the severity of underlying psychosis. It is also unclear if drug substitution that results in lower PRL levels is due to the effects of the drug themselves, lesser effects of newer generation antipsychotics, or is indicative of improved underlying disease control [10]. Interestingly, in the above-mentioned study, among those who complained of concomitant sexual dysfunction, 92% were found to have elevated PRL levels compared to only 18% among those without sexual symptoms. The findings again highlight the interconnected nature and important predictive value of sexual symptoms in diagnosing hyperprolactinemia.

Other medications that have been associated with hyperprolactinemia include tramadol, verapamil, anti-dopaminergic bowel promotility agents (including metoclopramide), and select antidepressants (tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, nefazodone, and venlafaxine) [11–13]

Primary hypothyroidism is also associated with hyperprolactinemia, likely due to reflexively elevated TRH levels. Although PRL typically improves with normalization of thyroid hormone, hyperprolactinemia has been reported even in the absence of overt thyroid hormone alterations (i.e., subclinical hypothyroidism) [14]. Hypothyroidism can be readily tested by obtaining a thyroid stimulating hormone (TSH) level. If this is elevated, it is suggestive of hypothyroidism and warrants referral to an endocrinologist for further management.

4.5 When to Obtain Prolactin Testing

The appropriate management of men with low T includes obtaining PRL levels in select clinical scenarios. The American Urological Association (AUA) and Endocrine Society guidelines on T deficiency both recommend obtaining PRL in men with low T and low/low-normal LH [15, 16]. From a physiologic standpoint, if LH is in the normal range, then this suggests the ability of the pituitary to release LH to stimulate the testicles and indicates that PRL testing is not required. In contrast, if LH is low or low/normal in the setting of low T, then this represents an inappropriate response and indicates a need to evaluate for potential causes of the hypogonadotropic hypogonadism. In a related manner, men with total T levels <150 ng/dl and low/low-normal LH should undergo a pituitary MRI regardless of PRL levels, given the possibility for non-PRL-secreting adenomas and higher yield at T levels <150 ng/dl [17].

In a 2016 publication summarizing recommendations from the Fourth International Consultation for Sexual Medicine (ICSM), Corona and colleagues suggested that clinicians should evaluate prolactin levels in all men complaining of decreased sexual desire (Recommendation #4) [18]. These recommendations were based on two studies which identified low libido in approximately 84% of individuals with prolactin levels >35 ng/dl, with two-thirds of these individuals exhibiting secondary pathology related to the elevated prolactin [3, 19]. However, <1 to 1% of individuals complaining of low libido were subsequently found to have notably elevated prolactin, suggesting that universal testing among all men with low libido may be of relatively low yield. Additionally, the number of men who had elevated prolactin in the absence of low testosterone or other associated symptoms was not reported, which likely represents an even smaller cohort. The authors did report that prolactin >35 ng/dl was associated with low libido, independent of hypogonadism; however, given the low overall yield, the role of universal prolactin testing in all men with low libido is debatable at the present time.

The interpretation of PRL and what is considered normal are not well established, and significant debate remains on optimal investigational and treatment thresholds. From a practicality standpoint, PRL levels <50 ng/ml are rarely associated with significant pathology, while higher levels (>250 ng/ml) are positively correlated with increasing likelihood for identifiable intracranial pathology, and levels >500 ng/ml are diagnostic of macroprolactinoma [2, 5, 20]. However, in the absence

of better data, levels above normal thresholds, but lower than <50, should not prevent an investigation as to underlying causes or preclude treatment in the setting of hypogonadotropic hypogonadism.

Although transient elevations in PRL are not uncommon, the Endocrine Society does not recommend repeat or confirmatory testing in most cases of hyperprolactinemia [21].

4.6 Management of Hyperprolactinemia

As the target audience of this chapter is a non-endocrinologist practicing clinician, a complete and thorough description on the management of hyperprolactinemia is beyond the intended scope. In most cases, practicing clinicians will likely refer patients with elevated PRL to an endocrinology provider, which is consistent with AUA guideline recommendations [15]. However, a brief summary of general treatment strategies will be reviewed to provide a greater level of understanding, given that the initial diagnosis of hyperprolactinemia still relies on the sexual medicine provider. Each of the strategies noted below is based on the Endocrine Society Guideline on hyperprolactinemia [21]. See Fig. 4.1 for a proposed summary algorithm of the evaluation and treatment of hyperprolactinemia.

One of the first steps in managing hyperprolactinemia is to determine who does and does not merit treatment. Men with medication-induced hyperprolactinemia may be considered for medication substitution/trial of discontinuation if clinically viable. If this is not feasible, men with medication-induced hyperprolactinemia and low T (with associated symptoms/findings) are not recommended to undergo dopamine agonist therapies (e.g., cabergoline), but rather be treated with T directly. In cases of symptomatic hyperprolactinemia secondary to medications where the medication cannot be stopped, cautious consideration of a dopamine agonist may be elected.

Similarly, men with asymptomatic microprolactinomas are generally not recommended to be treated with dopamine agonists. In contrast, men with symptomatic microprolactinomas or macroprolactinomas (with or without symptoms) are appropriate for treatment.

Once the decision for therapy has been made, dopaminergic agents such as cabergoline are recommended as first-line agents. Initiation of cabergoline leads to normalization of PRL levels in 71–86% and tumor shrinkage in approximately 80% of men [1, 22]. Those with smaller microadenomas may experience even higher success rates (95%) [23]. In men who are resistant to cabergoline (approximately 10%), bromocriptine may be substituted.

Once successful treatment has been achieved for at least 2 years (normalized PRL levels and no visible tumor), therapy may be tapered off with subsequent biochemical follow-up. In men who do not respond, maximally tolerated dosing of dopamine agonists is recommended prior to consideration of surgery.

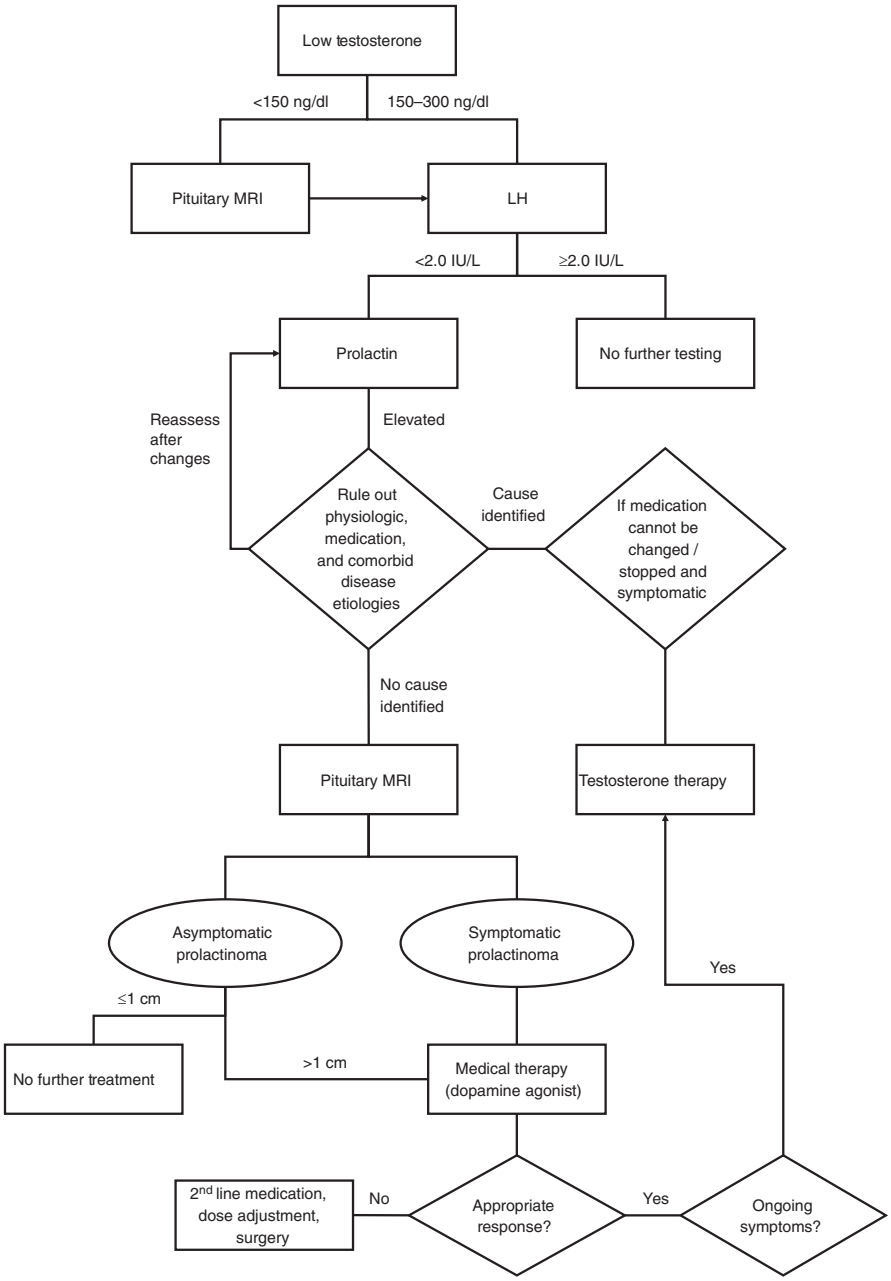

Fig. 4.1 Proposed algorithm for the evaluation and management of low testosterone as it relates to prolactin and hyperprolactinemia

Surgery is recommended in select cases, including symptomatic patients with prolactinomas who cannot tolerate high-dose cabergoline or are unresponsive to dopamine agonists. Those with aggressive or malignant prolactinomas are recommended for radiation therapy.

4.7 Summary

Hyperprolactinemia is a relatively infrequent, but important, condition that occurs in men with low T. The most common symptoms associated with hyperprolactinemia include sexual symptoms (e.g., low libido and ED), although these are relatively indistinguishable from low T and are likely directly related to T levels. In men with low T, a LH level should be obtained and, if found to be low, PRL levels should subsequently be performed. Current ICSM guidelines also recommend obtaining prolactin in all men presenting with low libido. Men with severely low T (<150 ng/dl) and those with elevated PRL levels without a clearly defined cause should undergo a pituitary MRI to evaluate for the presence of micro- or macroadenomas. Further evaluations are warranted to identify the cause of hyperprolactinemia, which may include medications, hypothyroidism, and chronic kidney disease, among others. The treatment of hyperprolactinemia is typically best managed by an endocrinologist and consists of medical therapy with cabergoline in the majority of cases. Surgery and radiation are infrequently utilized and are reserved for men who are refractory or intolerant to medications.

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