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MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Pituitary Dysfunction Among Men Presenting with Hypogonadism

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Abstract

Purpose of Review Hypogonadism is a common endocrine dysfunction. This review focuses on the most up-to-date guideline for evaluation of pituitary function among men presenting with signs and symptoms of hypogonadism.

Recent Findings The clinician must differentiate between primary (testicular) and secondary (pituitary-hypothalamic or central) hypogonadisms and be aware of adult-onset hypogonadism. If gonadotropins are low or inappropriately normal, the clinician must consider potential reversible causes in the hypothalamus-pituitary axis. Also, it is critical to understand the pitfalls of testosterone testing. When clinically indicated, evaluation of other pituitary hormone functions as well as pituitary magnetic resonance imaging may be necessary. Furthermore, it is essential to recognize that pituitary incidentalomas are common. Patients with microprolactinoma are more likely to present with symptoms of sexual dysfunction while those with macroprolactinoma are more likely to present with symptoms of mass effect. Some functional pituitary tumors respond to drug therapy while other nonfunctional tumors require surgical intervention.

Summary It is important for the clinician to understand the proper work-up of the hypogonadal patient with pituitary dysfunction and when necessary to refer to an endocrinologist or a neurosurgeon.

Keywords Pituitary microadenoma · Pituitary macroadenoma · Male hypogonadism · Testosterone deficiency

Introduction

Hypogonadism is a common endocrine dysfunction. Several guidelines have been developed including those from the Endocrine and Urology societies for evaluation and treatment of hypogonadism in men [1••, 2•]. This review focuses on the evaluation of pituitary function among men presenting with signs and symptoms of hypogonadism.

The Endocrine Society defines hypogonadism in men with symptoms and signs of testosterone deficiency associated with unequivocal, consistent low serum total testosterone or free testosterone concentrations [1••]. In contrast, the American Urological Association's 2018 definition of hypogonadism uses a serum total testosterone level below 300 ng/dL combined with symptoms or signs of hypogonadism [2•]. Both societies acknowledge that because of diurnal variation in serum testosterone concentration, the low testosterone level should be confirmed with 2 total testosterone measurements performed on separate occasions in the early morning.

Although men with hypogonadism can present with a variety of complaints, a low serum testosterone level is not always associated with symptoms. The most common symptoms are erectile dysfunction, low libido, fatigue, decreased muscle strength, depressed mood, and hot flashes (Table 1). In younger men with hypogonadism, infertility often brings the patient to seek medical attention. Based on a multi-clinic primary care study, the prevalence of hypogonadism among men aged 45 years or older was estimated to be about 9% [3].

Evaluation of Men with Hypogonadism

Urologists see a significant number of patients with erectile dysfunction. The cause of erectile dysfunction can be vascular, pharmacologic, hormonal, neurologic, or psychiatric. To differentiate among various etiologies for hypogonadism, a

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Table 1 Signs and symptoms suggestive of testosterone deficiency in men

Specific symptoms and signs	Suggestive symptoms and signs	Nonspecific symptoms and signs
Incomplete or delayed sexual development	Reduced libido	Decreased energy and motivation
Loss of body hair	Decreased spontaneous erections	Feeling sad or blue
Small testes < 6 mL	Gynecomastia	Poor concentration or memory
	Eunuchoidal body proportion	Sleep disturbance
	Inability to father children	Mild unexplained anemia
	Height loss, low trauma fracture	Reduced muscle bulk and strength
	Hot flashes	Increased body fat

Modified from Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103:1715–44

detailed history and physical examination is vital. The clinician must differentiate between primary (testicular) and secondary (pituitary-hypothalamic or central) hypogonadisms by measuring serum luteinizing hormone and follicle-stimulating hormone concentrations. If primary hypogonadism is confirmed, treatment with testosterone may be initiated in symptomatic patients.

If secondary hypogonadism is confirmed with either low or inappropriately normal serum levels of luteinizing hormone and follicle-stimulating hormone, further evaluation is required. A number of conditions and therapies can cause secondary hypogonadism including hypothalamic or pituitary tumors, iron overload, infiltrative or destructive diseases of the pituitary or hypothalamus, hyperprolactinemia, or use of opioids, narcotics, or glucocorticoids. Other etiologies include systemic illness, nutritional deficiency, excessive exercise, severe obesity, sleep disorders, organ failure, and idiopathic hypogonadism [1••]. Thus, if gonadotropins are low or inappropriately normal, one must consider potential reversible causes in the hypothalamus-pituitary axis. Under such circumstances, both serum prolactin and iron levels should be measured (see Fig. 1). When clinically indicated, appropriate other pituitary hormone evaluations as well as pituitary magnetic resonance imaging (MRI) may be necessary. If significant pituitary hormone abnormalities such as elevated serum prolactin or MRI suggest a pituitary adenoma, we recommend a referral to an expert endocrinologist (Fig. 1).

Laboratory Assessment of Low Testosterone Levels

When evaluating a patient for hypogonadism, clinicians should measure total testosterone concentrations on 2 separate mornings when the patient is fasting. This process is necessary to account for the diurnal and daily variations in testosterone concentrations.

Total testosterone is bound to sex hormone–binding globulin (SHBG). Several conditions are associated with decreased or increased SHBG and can cause falsely elevated or low serum total testosterone without necessarily altering serum free or bioavailable testosterone levels. Obesity, diabetes, glucocorticoid therapy or endogenous excess cortisol secretion, nephrotic syndrome, hypothyroidism, and acromegaly are associated with decreased SHBG. Other conditions cause increased SHBG, as seen in aging, human immunodeficiency virus, cirrhosis and hepatitis, hyperthyroidism, some anticonvulsants, and estrogens. Thus, in a man with a condition known to alter SHBG, a free testosterone concentration should be obtained by either equilibrium dialysis assays or calculations that use total testosterone, SHBG, and albumin concentrations [1••].

Management of Male Hypogonadism

Goal of therapy is to maintain serum testosterone concentrations in the mid-normal range for healthy young men and to improve symptom and signs of hypogonadism. If hematocrit is > 54%, therapy should be discontinued until the hematocrit decreases to < 50%. Testosterone therapy should be reinitiated with a reduced dose to prevent future elevations in hematocrit level. The AUA does not recommend routine PSA testing in men 40–54 years of age unless they are at higher risk, such as having a positive family history or African American race. In those men, PSA testing should be individualized. However, in men 55–69 years of age, the AUA recommends PSA testing every other year. On the other hand, the Endocrine Society guidelines state that for men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer who choose prostate monitoring, a digital rectal examination should be performed along with PSA prior to treatment

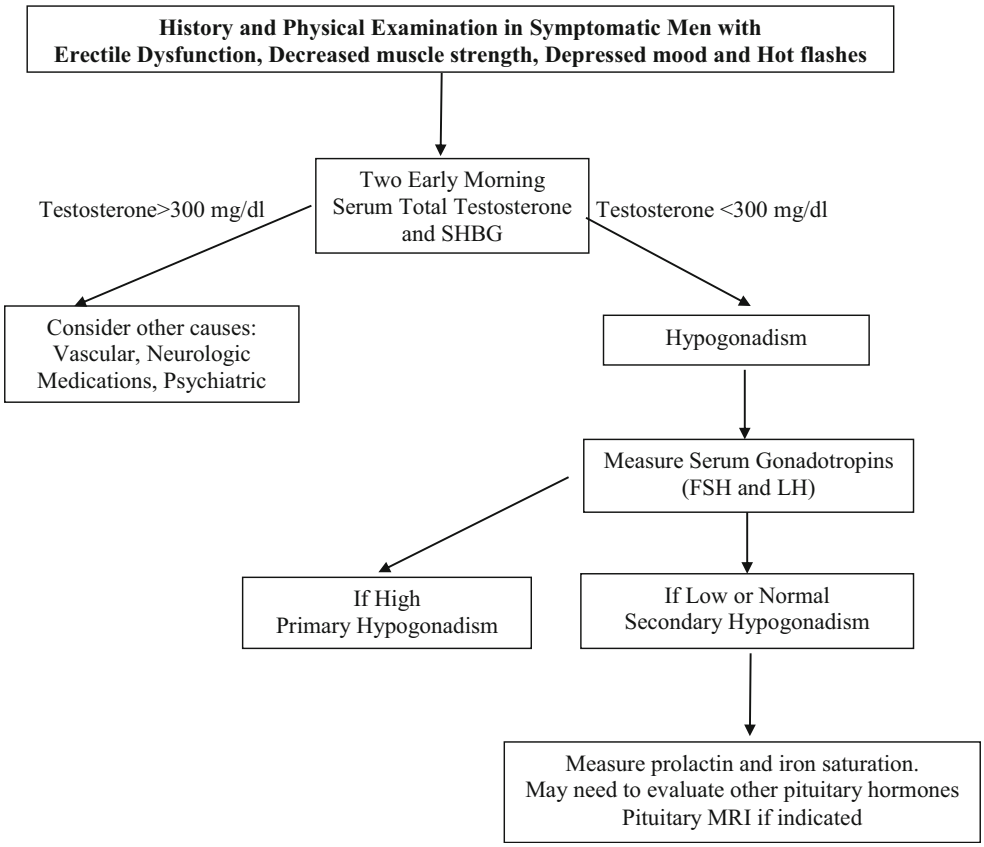

Fig. 1 Suggested diagnostic evaluation of hypogonadism in men

initiation. Furthermore, they advise that PSA and digital rectal exam is done 3–12 months after initiation of therapy.

If PSA concentration increases more than 1.4 ng/mL above baseline or if the absolute value is more than 4 ng/mL on replacement therapy, or if a prostatic abnormality is detected on digital rectal exam, urology evaluation is recommended [1••, 4].

Patients should be evaluated every 3–12 months after treatment initiation to determine symptom response and any adverse effects, such as gynecomastia, weight gain, or worsening sleep apnea. Serum testosterone and hematocrit should be obtained 3–6 months from initiation of therapy and then annually.

Prevalence of Secondary Hypogonadism

In the European Male Ageing Study of 3369 community-dwelling men aged 40–79 years from 8 European countries, the prevalence of hypogonadism was 13.8%. Of the 465 men with hypogonadism, 85% were classified as having secondary hypogonadism [5]. In a study of 4220 men presenting to a sexual dysfunction clinic, only 11% diagnosed with secondary hypogonadism had an underlying medical cause. However, of these 11% (465 men), only 1.1% had prolactin-secreting adenomas, 0.1% had empty-sella syndrome, and the remainder had other medical conditions such as genetic disorders, previous head or brain surgery, radiotherapy to the brain, head trauma, and use of drugs known to cause hypogonadism. Thus, a vast majority of men with confirmed diagnosis of secondary hypogonadism in this study did not have an etiology [6••]. The authors speculated that within this group, a large proportion would be in the category of adult-onset hypogonadism (AOH). The term AOH was applied to define middle-aged and older men with low total testosterone accompanied by low or normal gonadotropin levels and associated signs and symptoms of hypogonadism. These men likely have a component of both primary and secondary hypogonadisms. An expert panel convened in Washington, DC, in 2015 coined the term AOH to differentiate it from primary and secondary hypogonadisms. The prevalence of AOH is unknown. Nevertheless, it is important to recognize this group of patients because they may be misdiagnosed as secondary hypogonadism, and further evaluation of such men may generate unnecessary health care costs and anxiety for the patients.

Pituitary Incidentalomas

Pituitary incidentalomas are tumors discovered serendipitously on computed tomography or MRI performed to evaluate unrelated disorders [7]. Headache is one of the most common reasons for imaging studies that lead to the discovery of pituitary incidentalomas [8]. Microincidentalomas are defined as

less than 1 cm, and macroincidentalomas are at least 1 cm in size [9]. In most cases, the pituitary incidentaloma is < 10 mm [10]. Based on autopsy data, the average frequency of pituitary adenoma was 10.6%, and nearly all were microadenomas [7]. In a review of 281 men with a diagnosis of hypogonadotropic hypogonadism in whom pituitary MRI was performed, 83.6% had a normal MRI, 8.5% had microadenoma, 1.8% had macroadenoma, and 0.4% had craniopharyngioma [11].

When evaluating patients with pituitary incidentalomas, start with a complete history and physical examination. The patient should also undergo an evaluation for pituitary hormone hypersecretion and hypopituitarism. Hypogonadism can be the result of hypopituitarism from tumor compression, leading to low gonadotropins, or a hormone-secreting tumor such as prolactinoma or growth hormone–secreting tumor. Hypogonadism has been reported in 35% of patients with nonfunctioning pituitary macroadenomas [12].

Prolactinoma is the most common type of functional adenoma. Decreased libido or impotence was found in 78–100% of patients with either macro- or microprolactinoma. Those patients with microprolactinoma were more likely to present with complaints of symptoms of sexual dysfunction. Macroprolactinoma patients were more likely to present with symptoms of mass effect [13•].

Growth hormone–secreting tumors often cause hypogonadism, but hypogonadism as the only presenting manifestation of acromegaly is extremely rare. When suspected, measurement of serum IGF-1 is recommended, and if elevated patient should be referred to an endocrinologist for further evaluation. Based on a registry database of pituitary tumors, 49% of men had hypogonadism, of whom 45% also had hyperprolactinemia. Their hyperprolactinemia may have been the cause of the hypogonadism, rather than from growth hormone excess. Of the men with microadenomas, 39% had testosterone deficiency but the majority of these subjects had normal serum prolactin levels. Thus, these data suggest that factors other than hyperprolactinemia may contribute to the pathogenesis of hypogonadism in men with acromegaly [14].

Management of Pituitary Incidentalomas and Tumors

Treatment of pituitary incidentalomas depends on their size, location, and hormone-secreting status. Based on the Endocrine Society guidelines, patients with visual field deficit, ophthalmoplegia, or neurological compromise due to compression by a pituitary lesion, a lesion abutting or compressing the optic nerves or chiasm on MRI, and pituitary apoplexy with visual disturbance should be referred for surgery. Dopamine agonist drugs, such as cabergoline and bromocriptine, are considered first-line therapy for macroprolactinomas. Drug therapy is effective and will decrease the tumor in most patients with prolactinomas. Surgical approach is reserved for tumors leading to neurological compressive symptoms and in patients resistant or intolerant to dopamine agonists [15].

Surgery is warranted for functional tumors that do not shrink or with visual field deficits that fail to improve with medical therapy, and for pituitary apoplexy and cystic macroadenomas, which generally do not regress with dopamine agonists [16]. At tertiary academic centers, transsphenoidal hypophysectomy has a success rate of 75% in microadenomas, with even higher cure rates in patients with prolactin levels < 200 μg/L, smaller tumors, and infertility of short duration [17]. However, curative rates for macroadenomas are not as high because of the tumor invasion into the cavernous sinus and other adjacent structures. In general, the operative success rates depend on the neurosurgical expertise and availability of a neurointensive care unit with ability to manage panhypopituitarism in the postoperative course.

Management of Prolactinoma

Dopamine agonist therapy is used to lower prolactin levels, decrease tumor size, and restore gonadal function in patients with micro- and macroprolactinomas. In a retrospective review of 46 male patients, 80% of men harboring macro- or microadenomas experienced prolactin normalization after treatment with bromocriptine, cabergoline, or other dopamine agonists [13•].

Published data documents that bromocriptine decreases pituitary tumor size by approximately 50% in two-thirds of patients [18] while cabergoline-treated patients exhibited a 92% significant decrease in tumor size [19]. Thus, cabergoline is preferred instead of other dopamine agonists because it has a higher efficacy in normalizing prolactin levels, as well as a higher frequency of decreasing pituitary tumor size. In terms of symptoms of sexual function, studies have shown 75% improvement with medication treatment [15, 20].

Once dopamine agonist therapy is initiated, repeat prolactin levels within 1 month and adjust dopamine agonist therapy with a goal of prolactin normalization and reversal of hypogonadism. MRI can be repeated in 1 year or earlier (3 months) if the patient has a macroprolactinoma, new visual disturbance, headache, or a continued rise in prolactin level despite drug therapy.

According to the Endocrine Society guidelines, tapering of dopamine agonist can be considered after 2 years of therapy if the patient has a normal prolactin level and no visual defect. The risk of recurrence after discontinuation of medication is > 60% and up to 28% may develop hypogonadism [21].

Neurosurgical Management of Nonfunctioning Pituitary Tumors

Neurosurgical management of nonfunctioning pituitary tumors has been largely driven by the Congress of Neurological Surgeons guidelines on the management of pituitary adenomas. Adequate preoperative assessment includes high-resolution MRI with sella protocol. Sequences with gradient echo at certain institutions may reveal tumoral vascularity and hemorrhage.

Preoperative work-up of pituitary adenomas should also involve a formal ophthalmological evaluation. Even in asymptomatic patients without visual field deficits on a standard physical exam, advanced techniques by ophthalmologists may uncover quantitate functional deficits (quantitation of afferent pupillary defect and visual evoked potentials), psychophysical deficits (acuity and visual fields), and anatomical deficits (disc appearance and ocular coherence tomography). Optic disc atrophy, in particular, as well as age has been strongly correlated with postoperative vision recovery [22]. Symptomatic patients with visual field deficits > 4 months should be counseled on the reduced likelihood of visual improvement: 58% among ages 18 to 44, 44% among ages 45 to 64, and 41% among ages ≥ 65 years old [23].

Surgical treatment of symptomatic pituitary adenomas has been undoubtedly supported in the literature [24, 25]. Resection leads to immediate tumor volume reduction with a residual tumor rate of 10–36% depending on surgeon experience and tumor invasion [24, 26–28]. With more refined surgical techniques, complication rates have diminished to approximately 7%, most commonly cerebrospinal fluid leak (4.7%), meningitis (2.0%), and visual deterioration (2.0%) [25]. These risks cannot completely justify neurosurgical intervention of asymptomatic, nonfunctioning pituitary adenomas. Insufficient evidence exists to recommend surgery for the asymptomatic cases.

Conclusion

For male hypogonadism, the clinician must differentiate between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadisms and be aware of AOH. When appropriate, men should be treated with exogenous testosterone therapy. While on therapy, proper monitoring of testosterone concentration, hematocrit, and PSA is recommended.

The differential diagnosis of secondary hypogonadism includes pituitary dysfunction due to multiple etiologies including pituitary tumor. Most pituitary incidentalomas are < 1 cm and can be accompanied by symptoms of sexual dysfunction. Macroincidentalomas are more likely to cause mass effect. Men with pituitary dysfunction leading to hypogonadism should undergo appropriate laboratory and imaging work-up. It is important for the clinician to be able to interpret the results to provide appropriate treatment and avoid unnecessary work-up and cost to the patients. Treatment of pituitary incidentalomas depends on their size, location, and hormone-secreting status. Pituitary tumors that hormonally secrete prolactin can be treated with drug therapy such as dopamine agonist. Patients with visual field deficit, ophthalmoplegia, or neurological compromise due to compression by a pituitary lesion, a lesion abutting or compressing the optic nerves or chiasm on MRI, and pituitary apoplexy with visual disturbance should be referred for surgery. The hypogonadal male with pituitary dysfunction should have appropriate monitoring with hormone evaluation and pituitary imaging when appropriate.

Compliance with Ethical Standards

Conflict of Interest Shiri Levy, Mingxue Arguello, Mohamed Macki, and Sudhaker D. Rao each declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with unethical treatment of human or animal subjects.

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