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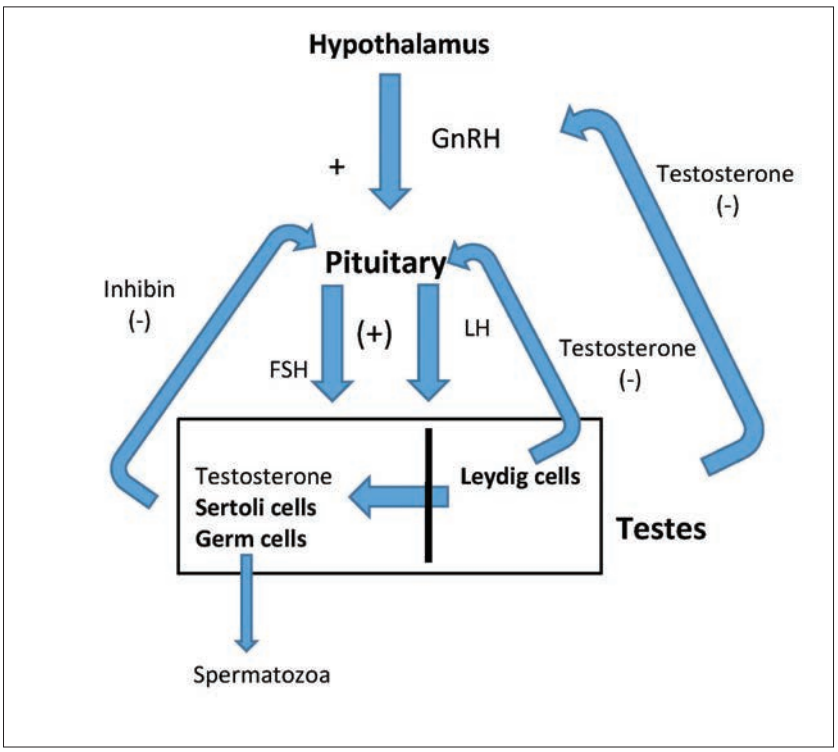


FIGURE 1
Hypothalamic-pituitary-gonadal axis adapted from the European Association of Urology guidelines on male hypogonadism[5]

How do men with androgen deficiency present?

What investigations should be carried out?

Which patients should be referred?

ANDROGENS PLAY A CRUCIAL ROLE IN NORMAL BONE, MUSCLE AND FAT METABOLISM, erythropoiesis and cognitive health. Consequently untreated male hypogonadism can have a significant impact on multiple organ functions and severely affect quality of life.[1,2] In men aged between 40 and 79 the incidence of biochemical androgen deficiency and clinical symptomatic hypogonadism is 2.1-5.7%.[3]

CAUSES

The causes of male hypogonadism can be classified by the anatomical location of the abnormality resulting in androgen deficiency:

- Testes (primary hypogonadism)
- Hypothalamus and pituitary (secondary hypogonadism)
- Hypothalamus/pituitary and gonads (commonly adult-onset hypogonadism)
- Androgen target organs (androgen insensitivity)

Androgen insensitivity syndrome (AIS) is a rare cause of hypogonadism and can be complete, partial or mild. AIS describes a person who has a male genetic make-up (XY karyotype) but appears to have female characteristics or to be phenotypically female. AIS occurs because the androgen receptor is unresponsive to normal levels of circulating androgens.[4]

Patients may present:

- In the neonatal period with bilateral inguinal hernias in a female
- In adolescence, when a female has failed to start menstruation
- Simply as male infertility in mild AIS

TESTOSTERONE PHYSIOLOGY

Testosterone, a steroid hormone produced by the testis and adrenal glands, plays a pivotal role in the formation of the male secondary sexual organs and testicular descent in addition to maintenance of male secondary sexual characteristics.[5] Intratesticular testosterone maintains spermatogenesis. The hypothalamic-pituitary-gonadal axis, illustrated in figure 1, above, regulates intratesticular testosterone production.[6] Decreased intratesticular testosterone levels may lead to azoospermia or oligospermia resulting in male infertility.[7] Bone health is maintained by the metabolism of testosterone to oestradiol by aromatase and is essential for bone mineralisation.[8]

PRESENTATION

Male hypogonadism can be multi-factorial and difficult to recognise and diagnose. Symptoms and signs may become evident at any age from birth to adulthood depending on when androgen deficiency occurs. Possible presentations are described in table 1, p20.

The clinical history may be the only factor leading to androgen deficiency being included in a differential diagnosis.

Among the most common reasons that men may ask for help is concern regarding sexual symptoms: decreased libido or reduced frequency and quality of erections. Fatigue, irritability, infertility or a diminished feeling of wellbeing may also be presenting complaints. As male »

hypogonadism is increasingly featured in men's health forums some men may present with a direct concern that their testosterone levels may be low.

However, a significant proportion of men with androgen deficiency will be identified when they present for unrelated concerns. Many men may not complain of their symptoms or attribute symptoms to their perception of the normal ageing process.

Table 1

Presenting complaints in men with androgen deficiency

- Hot flushes
- Mood changes
- Depression
- Fatigue
- Poor concentration and reduced cognition
- Gynaecomastia
- Visceral obesity
- Metabolic syndrome
- Reduction in lean body mass
- Type 2 diabetes
- Anaemia
- Decrease in bone density
- Erectile dysfunction
- Reduced sexual desire
- Reduced early morning erections
- Male infertility
- Lack of secondary sexual characteristics
- Reduced testicular volume

Men presenting with erectile dysfunction may also enquire about testosterone supplementation. The limited randomised controlled trial data available indicate that there is no evidence that testosterone replacement therapy in men with androgen deficiency improves erectile dysfunction.[9] An earlier meta-analysis of the effects of testosterone on sexual function in men suggested that testosterone supplementation may benefit vasculogenic erectile dysfunction in selected subjects with low or low-normal testosterone levels. However, the caveats that the effect tends to decline over time and is progressively smaller with increasing baseline testosterone levels in addition to the fact that long-term safety data were not available were stated.[10] The authors therefore suggest that the primary treatment for men presenting with erectile dysfunction after baseline investigations, which may include a testosterone level, and correction of lifestyle factors should be a phosphodiesterase-5 inhibitor.

ASSESSMENT

Important factors to elicit from the history in addition to the presenting complaint include: a history of obesity, type 2 diabetes, systemic diseases or metabolic syndrome which all impact on testosterone physiology.[11]

Obesity significantly impacts on the hypothalamic-pituitary-gonadal axis and in turn leads to androgen deficiency. In the obese state, the increased number of adipocytes leads to the aromatisation of testosterone to oestrogen. This exerts a negative feedback on the hypothalamus and pituitary, resulting in low testosterone levels. Type 2 diabetes and metabolic syndrome are conditions intricately linked with obesity. Adipose tissue releases the hormone leptin and exerts a negative feedback on the hypothalamus, inhibiting LH release and leading to reduced testosterone production by the Leydig cells.[12] Low levels of androgens cause a further increase in adipose tissue deposition and a reduction in lean muscle mass, therefore exacerbating the problem.

'A digital rectal examination and BP measurements should be carried out if considering treatment for androgen insufficiency'

A comprehensive medication review will identify agents which can cause low testosterone levels such as statins, steroids, opioids, dopamine antagonists and 5-alpha reductase inhibitors. Alcohol, anabolic steroids and illicit substance use such as marihuana can impact on testosterone levels and non-prescribed drug use should be routinely discussed.[13]

'If primary or secondary male hypogonadism is suspected measurement of LH and FSH levels may facilitate diagnosis'

Physical examination should include assessing secondary sexual characteristics (body hair pattern, presence of gynaecomastia), genitalia (testicular volume), muscle development and obesity (body mass index, hip to waist ratio). Many men, however, may

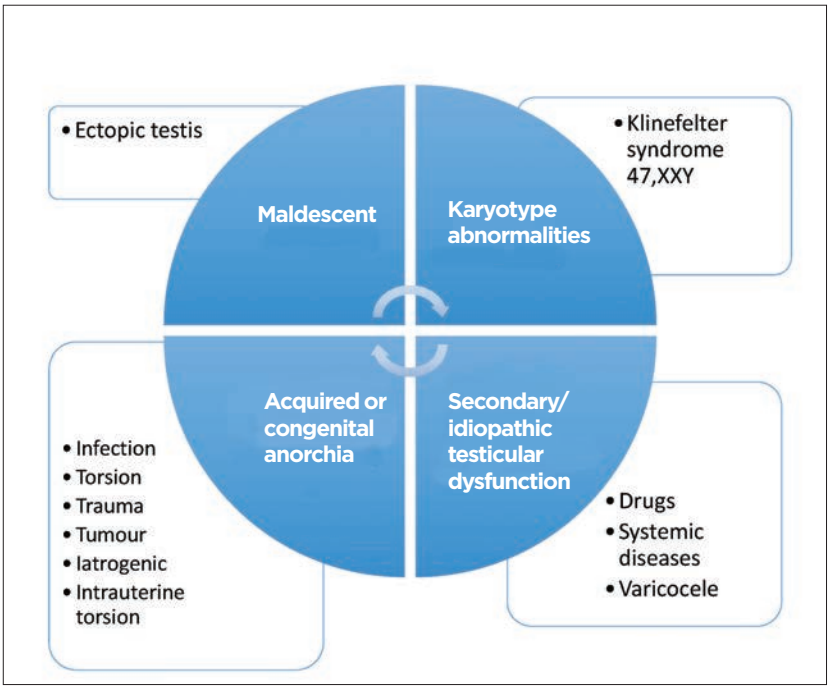


FIGURE 2
Most common causes of primary hypogonadism

have no physical manifestations of androgen deficiency.

A digital rectal examination and blood pressure measurements should be carried out if considering commencing treatment for androgen insufficiency.

INVESTIGATIONS

While the clinical history is key to identifying signs and symptoms of androgen deficiency, it is important to elicit the patient's perception of their symptoms to help guide investigation and management strategies to address the cause and patient expectations.

Baseline investigations for men presenting with symptoms of hypogonadism are: FBC, U&Es, LFTs, HbA_{1c}, and early morning testosterone level. If the testosterone level is low then early morning testosterone should be repeated and at this point sex hormone binding globulin (SHBG), LH/FSH and prolactin would be appropriate.

The first investigation which should be performed if androgen deficiency is suspected is a total serum testosterone level. Testosterone levels vary over a 24-hour period and guidelines recommend measuring testosterone between 07.00 and 11.00 hours as this is when testosterone levels are at their highest. If a low value (< 12.1 nmol/L) is obtained the measurement should be repeated for confirmation.

Circulating serum testosterone is either free or bound to albumin or SHBG. Blood tests to identify free testosterone levels can be useful in men who have symptoms of androgen deficiency but have a normal total testosterone level. This is because free testosterone is bioavailable and may be low(< 243 pmol/L) thereby accounting for symptoms of androgen deficiency. In this situation a higher proportion of bound testosterone may be accounting for the normal total testosterone level. SHBG levels increase with age and may also be measured to confirm this.[14]

If primary or secondary hypogonadism is suspected measurement of LH and FSH levels may facilitate diagnosis. Persisting low levels of LH and FSH should prompt MRI imaging of the pituitary gland to exclude a tumour. LH levels may be normal in men with age-related low testosterone.

Prolactinoma is a rare (< 2%) but curable cause of testosterone deficiency. Serum prolactin should be measured if this is suspected.[15]

If infertility is the primary presenting complaint a semen sample should be requested according to local protocols.

REFERRAL

Men with primary or secondary hypogonadism, delayed puberty, hypopituitarism or infertility associated with androgen deficiency should be referred to secondary care for review.

Hypogonadal men with suspected prostate cancer or with a confirmed prostate cancer diagnosis for which they have undergone treatment or started on active surveillance should be discussed with, or reviewed by, their specialist on an individual case by case basis to ascertain whether commencing testosterone supplementation is appropriate.

PRIMARY HYPOGONADISM

Primary hypogonadism is also known as primary testicular failure because the testes are not functioning normally. The most common clinical presentations of primary hypogonadism are Klinefelter syndrome and testicular tumours.

Klinefelter syndrome affects 0.2% of males and is associated with the 47,XXY karyotype.[16] The primary presentation of Klinefelter syndrome may be sterility but males affected may be unusually tall with uncharacteristically weak musculature in addition to underdeveloped secondary sexual characteristics.

Testicular tumours can present as primary hypogonadism and up to 25% of patients are androgen deficient after treatment.[17,18]

Mumps can also cause primary hypogonadism.

Investigations will demonstrate low testosterone levels despite elevated LH and FSH levels. Impaired spermatogenesis may be identified in a semen specimen.

SECONDARY HYPOGONADISM

In secondary hypogonadism the functional failure originates outside the testes in the hypothalamus or pituitary gland. There are multiple causes of secondary hypogonadism which include: a prolactinoma (pituitary adenoma), congenital hypogonadotrophic hypogonadism and Kallmann's syndrome (hypogonadotrophic hypogonadism with anosmia). Secondary hypogonadism is the most common cause of delayed puberty.

Investigations will demonstrate low LH, FSH and GnRH as well as low testosterone levels.

TREATMENT

Adult-onset hypogonadism may result from a combination of primary and secondary testicular failure leading to low testosterone levels. It is paramount that in the first instance any reversible lifestyle and iatrogenic factors which could contribute to androgen deficiency are addressed. In obese patients weight loss can restore normal testosterone levels.[19]

The mainstay of treatment in persisting androgen deficiency is to restore normal physiological levels of testosterone by using exogenous testosterone in patients that are symptomatic of androgen deficiency.

There are many different testosterone preparations which vary in their route of administration and pharmacokinetics. A shared decision making process with the patient to select an appropriate preparation will ultimately lead to the best compliance with taking testosterone supplementation. Testosterone can be delivered orally or via intramuscular injections, transdermal gels and subdermal implants.

During the consultation men should be made aware of the contraindications and potential side effects of testosterone (see table 2, below).

»

Table 2

Testosterone replacement therapy: contraindications and side effects

Contraindications

- Breast cancer
- Severe chronic heart failure
- Raised haematocrit
- Locally advanced or metastatic prostate cancer receiving active treatment
- Planning to father children

Potential side effects

- Skin irritation - a common problem with patch transdermal preparations[21,22]
- Raised haematocrit and erythrocytosis - common when using injectable preparations of testosterone but less so with transdermal preparations[23]
- Fluid retention
- Hepatotoxicity with oral agents[24,25]
- Gynaecomastia
- Testicular atrophy and infertility as a result of reduced intratesticular testosterone levels[7]
- Adverse cardiovascular events – supported by anecdotal evidence; recent research indicates that testosterone may in fact be cardioprotective[25,26]
- Benign prostatic hyperplasia
- Prostate cancer - this is a theoretical risk supported by little evidence[27]
- Alteration in mood such as anger and aggression
- Skin changes such as acne and oily skin

key points

SELECTED BY

Dr Chris Barclay
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Androgens play a crucial role in bone, muscle and fat metabolism, erythropoiesis and cognitive health.

In men aged 40-79 years the incidence of biochemical deficiency and symptomatic hypogonadism is 2.1-5.7%. Decreased libido or reduced frequency and quality of erections, fatigue, irritability, infertility or a diminished feeling of wellbeing may be presenting complaints. However, a significant proportion of men with androgen deficiency will be identified when they present for unrelated concerns.

Important factors to elicit from the history in addition to the presenting complaint include: a history of obesity, type 2 diabetes, systemic diseases or metabolic syndrome which all impact on testosterone physiology. A comprehensive medical review will identify agents which can cause low testosterone levels such as statins, steroids, opioids, dopamine antagonists and 5-alpha reductase inhibitors. Alcohol, anabolic steroids and illicit substance use such as marihuana can impact on testosterone levels and non-prescribed drug use should be routinely discussed.

Causes of primary hypogonadism (primary testicular failure) include Klinefelter syndrome (47,XXY karyotype, affecting 0.2% of males) and mumps. In secondary hypogonadism the functional failure originates in the hypothalamus or pituitary gland. Causes include prolactinoma (pituitary adenoma), congenital hypogonadotrophic hypogonadism, and Kallmann's syndrome. Secondary hypogonadism is the most common cause of delayed puberty. Men with primary or secondary hypogonadism, delayed puberty, hypopituitarism or infertility associated with androgen deficiency should be referred to secondary care for review.

The mainstay of treatment in persisting androgen deficiency is to restore normal physiological levels of testosterone by using exogenous testosterone. It may take at least three to six weeks to notice any clinical improvement in symptoms. Men receiving testosterone supplementation should be followed closely and have their testosterone, haematocrit and PSA levels checked at three, six and twelve months after initiation of testosterone replacement therapy. Men should then be reviewed at least annually thereafter.

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The aim of supplementation is to achieve testosterone levels within the normal expected range. Men should be counselled that it may take at least three to six weeks to notice any clinical improvement in their symptoms.[20]

FOLLOW-UP

Men receiving testosterone supplementation should be followed closely initially to ensure that their symptoms improve on treatment and to monitor compliance with testosterone supplementation. Men should have their testosterone, haematocrit and PSA levels checked at three, six and twelve months after initiation of testosterone replacement therapy. Men should then be reviewed at least annually thereafter.

Testosterone levels should be within the normal range, if they are higher than normal reference values supplementation should be reduced. If high testosterone levels persist treatment should be stopped.

High haematocrit levels indicate an increased risk of thrombosis. Should the haematocrit level be above 0.55 the dosage of testosterone may need to be reduced or the route changed from parenteral or topical.[28] If haematocrit levels remain elevated on subsequent checks the testosterone dosage will need to be reduced further or stopped and advice sought from secondary care.

If the PSA rises from baseline on two consecutive values or rises to above recommended age specific limits the man should be referred for a review by a urologist.

CONCLUSION

Androgen deficiency is an important clinical condition which can affect quality of life. It is important that clinicians consider male hypogonadism in their differential diagnosis when appropriate. Through a shared decision making process a management plan to improve symptoms can be established, and patients should always be counselled with regard to the potential side effects of androgen supplementation before starting therapy.

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Useful information

European Association of Urology guidelines on male hypogonadism
https://uroweb.org/guideline/male-hypogonadism/