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Pharmacotherapy of male hypogonadism

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Abstract

Hypogonadism is frequent with a prevalence of 2% in the general population. Hypogonadism may derive from any condition able to disrupt the hypothalamic-pituitary-testis (HPT) axis at one or more levels. Hypogonadism may be classified according to the age of onset, its potential reversibility and level of the HPT axis damage. The latter categorization is useful to decide on the treatment. Damages to the hypothalamus-pituitary may benefit from either GnRH, gonadotropin or T therapy with the former carrying the advantage of stimulating spermatogenesis. Conversely, when the testis is damaged, T therapy is the only option and restoration of spermatogenesis is not possible. Therefore, the choice of therapy is primarily based on the diagnosis and patients' needs and both should be carefully considered.

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Introduction

The function of the male gonad, the testis, is devoted to androgens and spermatozoa production and is tightly regulated by the action of two pituitary gonadotropins (Gn): follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In turn, the medial preoptic area (MPA) of the hypothalamus regulates Gn secretion through Gn releasing hormone (GnRH), which is controlled by a complex array of neurotransmitters, the most important represented by kisspeptin. Male hypogonadism is a pathological condition resulting from impairment in hypothalamus-pituitary-testis (HPT) axis activity due to a large variety of diseases, which leads to a defective production of testosterone and sperms [1–3].

Male hypogonadism (HG) is frequent, in particular in the aging male. In fact, male HG affects - in its symptomatic form - more than 2% of the European general population older than 40 years [4]. In middle-aged and elderly men, the most specific symptoms of T deficiency pertain to sexual dysfunction and include loss of sexual desire and reduced spontaneous or sex-related erections [4–7]. Other common signs and symptoms are infertility, osteoporosis, fatigue, altered body composition (i.e. increased fat and decreased lean mass), and psychological disturbances [8–12]. Pharmacotherapy of male hypogonadism is essentially dictated by several factors, including the etiology of hypogonadism, the age of onset of the deficiency, its possible reversibility and last, but not least, the patient's needs [1–3,13,14].

Classification of male Hg

According to site of origin

According to the site of origin of the disease, male HG can be classified as *hypogonadotropic (or secondary or central) hypogonadism*, when the defect resides in the hypothalamus (reduced GnRH) or in the pituitary (reduced or inappropriately normal LH and/or FSH). HG is classified as *hypergonadotropic (or primary) hypogonadism*, when the defect resides within the testis and gonadotropins are elevated to force testicular activity. Both hypo- and hypergonadotropic HG are characterized by reduced T and sperm production. Normal or even increased T concentrations could also be associated with symptoms and signs of T deficiency when the action of T on its receptor (androgen receptor, AR) is hampered because of genetic alterations or because of the use of antiandrogen medications, or, finally, because the bioavailability of androgens is reduced, due to an increased level of their major binding protein, sex hormone binding globulin (SHBG) [8].

According to age of onset

The age of onset of the disease is another milestone in defining HG [8]. When the altered secretion or action of androgens is present early on during fetal life, the final effects could even be dramatic, spanning from an intersex condition with a pseudo-female phenotype (e.g. Morris syndrome) to relevant problems in the appearance and activity of male genitalia (cryptorchidism, hypospadias, micropenis, e.g. Kallmann syndrome). This *very early onset hypogonadism* is a rare condition (1:10−100.000; *clinical features evident since birth*). When T deficiency is orchestrating its effect during the pubertal transition (*early onset hypogonadism*, e.g. Klinefelter syndrome, prevalence 1:1.000; *clinical features evident before 14 year old*) a eunuchoid phenotype is often present. In contrast, when the defect is apparent later on during adulthood (*late onset hypogonadism*, LOH *clinical features evident after 14 year old*) the phenotype is not (or only mildly) affected, with the aforementioned vague and unspecific symptoms and signs. However, as stated before, LOH is a very common condition [4].

According to reversibility

The most recent classification of male HG is based on the potential reversibility of the T deficiency, which is possible in functional forms (*functional hypogonadism*, FHG) but rare in organic forms, due to an either congenital or acquired organic perturbation of the HPT axis activity (*organic hypogonadism*) [8]. In particular, in the latter condition, T treatment can restore a normal hypothalamus pituitary testis axis in a minority (less than 10%) of subjects with isolated congenital hypogonadotropic hypogonadism [2]. Accordingly, it has been suggested that, in the latter subjects, increasing T levels may modulate hypothalamic-pituitary neural circuits leading to spontaneous resumption of pulsatile GnRH secretion [2]. FHG is definitively more prevalent than organic HG and it essentially overlaps with the previously defined LOH. In FHG and in LOH, secondary HG is the prevalent form and is often due to metabolic disturbances (such as obesity, type 2 diabetes mellitus and metabolic syndrome) or other illnesses which hamper GnRH secretion, most probably through metaflammation of the MPA of the hypothalamus [15−17]. In these subjects, lifestyle measures, such as dieting or physical activity, are definitively effective in restoring T levels [8,18] although difficult to obtain, also because the underlying metabolic conditions and the HG-induced physical limitations (reduced muscle and increased fat mass) limit patient willingness and ability to adhere to the dedicated lifestyle programs. In addition, possible associated erectile dysfunction (ED) and loss of libido often require a prompt intervention [19]. We previously described that in a rabbit model of metabolic syndrome (MetS), endurance training was indeed able to restore the normal activity of the MPA of the hypothalamus and to reduce its metaflammation, thereby normalizing Gn and T levels, along with treating ED [6]. However, rabbits with MetS were less able to run on a treadmill, if not otherwise supplemented with T [20,21]. In addition, T supplementation to MetS rabbits demonstrated a neuroprotective effect against metaflammation of the MPA [22]. Therefore, we recently proposed [8] a short-term trial with T replacement therapy (TRT) to HG MetS subjects to restore sexual function [5] and to increase muscle mass, helping obese patients to overcome their overfed, inactive state and to become physically and psychologically ready for changing their lifestyle. It is important to note that a recent Australian trial (T4DM) − enrolling 1007 obese, hypogonadal subjects - demonstrated that T administration, added on to a dedicated lifestyle program, not only ameliorated HG symptoms but also substantially reduced the possibility of pre-diabetes progressing to overt diabetes [23].

According to patient's need

When considering pharmacotherapy for male HG, the most important information for planning any treatment is the patient's needs. In particular, it is mandatory to know whether fertility is desired. However, it should be important to recognize that the latter possibility can be taken in account only when secondary forms of hypogonadism are considered (see below). In fact, TRT is the optimal therapy for any form of male HG (primary, secondary, functional, organic) with the only exception being if fertility is desired in the short term. In fact, T administration suppresses the HPT axis, due to its negative feedback at the hypothalamic and pituitary level, finally inducing infertility and, in the majority of cases, even azoospermia [24−26]. With long-lasting T preparations, the depression of HPT axis is even more remarkable and prolonged [24−26]. In fact, a 12-month extension of a T4DM study in 303 obese, but otherwise eugonadal, subjects demonstrated that stopping two years of 1000 mg of injectable T undecanoate (TU) was associated with a slow recovery of HPT axis, lasting longer than 12 months [26].

Based on the previous considerations, we decided to organize the present review of pharmacotherapy of male HG according to the patient's needs, i.e. fertility desired or not desired in the short-term.

Material and methods

A comprehensive narrative review was performed using Medline, Embase and Cochrane search and including the following words: ((“therapeutics"[MeSH Terms] OR “therapeutics"[All Fields] OR “therapies"[All Fields] OR “therapy"[MeSH Subheading] OR “therapy"[All Fields] OR “therapy s"[All Fields] OR “therapys"[All Fields]) AND (“eunuchism"[MeSH Terms] OR “eunuchism"[All Fields] OR (“male"[All Fields] AND “hypogonadism"[All Fields]) OR “male hypogonadism"[All Fields])) AND ((humans[Filter]) AND

(male[Filter]) AND (english[Filter])). Publications from January 1, 1969 up to July the 31st, 2022 were included.

Treatment of male Hg when fertility is desired in the a short-term

Primary hypogonadism

In primary HG, there is, by definition, testicular damage that can be congenital (e.g. Klinefelter syndrome) or acquired (e.g. mump orchitis). Hence, primary HG is often associated with non-obstructive azoospermia (NOA) or with severe oligospermia, in particular if testicular volume is below the normal value (i.e. 12 mL, [27]). If fertility is desired, in the case of NOA, there is no evidence-based pharmacotherapy to be offered [28] and the only possible option to successfully father is testicular extraction of spermatozoa (TESE), if sperms are present in testicular tubules. Meta-analysis indicates that the sperm retrieval rate (SRR) in NOA is less than 50%, irrespective of the procedure (conventional TESE or microTESE), age and hormonal parameters at surgery [29]. However, a testicular volume higher than 12.5 mL is associated with a better outcome (SRR>60%) [29]. In that meta-analysis, insufficient data were available to evaluate the effect of previous treatments before the surgical approach on SRR [29]. In particular, it is unknown whether, in primary HG-related NOA, a previous TRT might affect SRR, upon TESE.

Secondary hypogonadism

In contrast to the picture of primary HG, in secondary HG there are several possibilities to overcome the central deficit of the HPT axis - because the testis is essentially functioning, if adequately stimulated- and, therefore, restoration of fertility is possible. Treatments are essentially divided into those replacing the hypothalamic defect or in those replacing the pituitary defect, i.e. GnRH and Gn, respectively. In alternative, treatments devoted to attenuating the estrogen-induced negative feedback on the HPT axis could be also considered, i.e. selective estrogen modulators (SERMS) and aromatase inhibitors (ARI). Finally, treatments aimed at restoring GnRH pulsatility because of a direct stimulation (kisspeptin analogues) or because of treating hypothalamic metaflammation (Interleukin 1 antagonist) are under evaluation [30,31].

GnRH

To stimulate, and not to inhibit, the HPT axis, GnRH should be delivered physiologically in a pulsatile manner. Hence, pump delivery is required. The usual dose is 5–25 ng/kg/pulse every 90–120 min to induce puberty and 100–400 ng/kg every 90–120 min to treat adults [32]. A meta-analysis of available trials indicates that in secondary HG, 75% of the treated subjects achieved at least one sperm in the ejaculate, with a mean sperm concentration of 6×10^6/mL [32,33]. Although this treatment is theoretically the most physiological, it is rather inconvenient to administer and, therefore, it is not often employed and no recent trial has investigated its efficacy in terms of fertility or symptom relief. In addition, this kind of treatment is not indicated when HG is due to a pituitary problem [32,33].

Gonadotropins

Gn therapy (GnTh) represents the gold standard in the treatment of secondary HG, when fertility is required. FSH-like preparations (urinary-derived, purified or recombinant) are administered at a parenteral dose of 75–225 UI thrice weekly with no major differences in outcomes between preparations [31,32]. FSH is usually administered together with a LH-like preparation showing a longer half-life than native LH (human chorionic Gn, HCG) at a parenteral dose of 1000–2000 UI two to -three times weekly [32]. Adverse events are infrequent and are mainly represented by gynecomastia and acne, which occur in less than 10% of subjects. GnTh is as efficient on spermatogenesis as GnRH administration [33,34], but it is associated with a higher increase in T levels [34]. A previous TRT does not apparently affect the responsiveness to GnTh, which is inversely related to the basal Gn levels [33].

Antiestrogens

Considering the negative feedback exerted by estrogen on HPT, reducing estrogen formation (ARI) or action (SERM) have been proposed to stimulate testicular function [17,35,36]. In meta-analyses, SERM were indeed able to induce on average a 7 nmol/L increase in total T by stimulating a 5 mU/L increase in Gn levels [37,38]. ARI causes a similar increase in T level [37,39]. Both treatments were associated with some positive effects on sperm parameters [38,39], although the quality of the studies included in the aforementioned meta-analyses was relatively modest. Notably, the use of either SERM or ARI is off-label and data supporting their efficacy on hypogonadal symptoms are insufficient and often negative, most probably because estrogens *per se* mediate part of the T effect [31]. In fact, using data from the Testosterone Trials, it has been demonstrated that a genuine symptom of male hypogonadism, i.e. sexual desire, was largely explained by a change in estradiol levels, as was volumetric bone mineral density [40].

Treatment of male Hg when fertility is not desired in the short-term

When fertility is not desired in the short-term, the universal treatment for all the different forms of HG is TRT. In primary HG, it represents the only feasible option.

T can be administered through different routes and formulations, including oral, transdermal, injection and

Table 1

Available testosterone preparations for the treatment of hypogonadism.

Compound	Standard adult dose	Timing for monitoring serum t levels and administration adjustment	Advantages	Disadvantages
Injectable i.m. short acting				
T enanthate	250 mg i.m. every 2–3 weeks	• Midway between injections • Dose or frequency adjustment if mid-interval serum T out of normal range	• Infrequent administration • Inexpensive • Wide clinical experience	• Wide T plasma level fluctuations • Polyglobulia • Fluctuations in symptoms (corresponding to serum T levels) • Local side effects
T cypionate	200 mg i.m. every 2–3 weeks		• Inexpensive	• Frequent administration
Mix of T esters	250 mg every2-3 weeks			
T propionate	100 mg i.m. every 2 days			
Injectable i.m. long acting				
T undecanoate	1000 mg i.m. every 12 weeks	• At the end of the dosing interval just prior to the next injection • Dose or frequency adjustment if nadir levels are lower than normal range or in the upper part of the normal range or higher	• Infrequent administration • Stable T plasma levels	• Local side effects • Dosage modifications are not prompt • Cough or dyspnea (rare)
Subcutaneous injection				
T enanthate	75 mg s.c weekly	• 7 days after the administration (at the end of the dosing interval, after at least 6 weeks of treatment) • Dose adjustment if nadir levels are out of the normal range	• Ease of application • Infrequent administration	• Limited clinical experience • Local side effects
Oral				
T undecanoate	120–240 mg orally daily fractionated into three administrations	• 3–5 h after administration • Dose or frequency adjustment if post-administration levels are out of the normal range	• Ease of application • Promptly modifiable dosage • Wideclinicalexperience	• Daily administration • Unpredictable absorption • Wide T plasma level fluctuation
Transdermal				
Patches	5–10 mg t.d. for daily	• 3–12 h after application • Dose adjustment if post-application levels are lower than normal range or in the upper part of the normal range or higher	• Ease of application • Resemble circadian rhythm • Stable T plasma levels • Promptly modifiable dosage	• Itching and contact dermatitis (~50%) • Expensive
Gel 1% Gel 1.62% Gel 2% T axillary solution	10 g t.d. daily 1.25–5 g t.d. daily 5 g daily t.d. 60–120 mg t.d. (underarm) daily	• 2–8 h following the application (after at least 1 week of treatment) • Dose adjustment if post-application levels are lower than normal range or in the upper part of the normal range or higher	• Ease of application • Resemble circadian rhythm • Stable T plasma levels • Promptly modifiable dosage	• Expensive • Skin irritation (more rare than patches) • Daily administration • Possible transfer with contact (except axillay solution)
Pellet	800–1200 mg/kg i.d. every 6 months	• At the end of the dosing interval • Dose (number of pellets) or frequencyadjustment if nadir levels are lower than normal range or in the upper part of the normal range or higher	• Long-acting	• Invasive and inconvenient to apply • Risk of extrusion and infection
Buccal	30 mg on gums twice daily	• Immediately before or after application of fresh system	• Stable T plasma levels	• Possible oral irritation • Administration twice a day • Unpleasant taste

Table 1 (*continued*)

Compound	Standard adult dose	Timing for monitoring serum t levels and administration adjustment	Advantages	Disadvantages
Intranasal	5.5 mg per nostril three times daily	• After at least 1 month of treatment without a specific timing	• Rapid absorption • Avoid first pass metabolism	• Frequent administration • Local side effects • Not recommended with chronic nasal conditions or use of other intranasal medications

Abbreviations: T, testosterone; i.m., intramuscular; t.d., transdermal; s.c., subcutaneous; i.d,intradermal.

implants. Table 1 summarizes the different options of TRT nowadays available, along with their relative advantages and disadvantages.

Overall, the efficacy of T in treating the symptoms and signs of male HG, in particular of LOH, is supported by several meta-analyses, as reviewed elsewhere [37,41] and briefly summarized here.

TRT and sexual function

All the available meta-analyses indicate that TRT has a positive effect on sexual functioning, including erectile function (EF), sexual desire, morning erections, orgasmic function and sexual satisfaction [5,37,41]. When the data are categorized according to the different preparations employed in the meta-analyzed studies, both transdermal and parenteral preparations showed efficacy on EF and sexual desire, whereas oral preparations showed more variable effects, in particular on EF [37]. When only studies employing the International Index of Erectile Function, Erectile function Domain (IIEF-EFD) or IIEF-5 were scrutinized, a positive effect of TRT on all the areas of sexual functioning was confirmed [42]. However, the effect on EF was relatively small (2–3 points IIEF-EFD) and less apparent in studies enrolling subjects with an overt diabetes [5,42].

TRT and body composition and glycolipid metabolism

In all the meta-analyses, TRT exerts a similar, positive effect in reducing fat mass and in increasing muscle mass, without changing body mass index (BMI) or weight [37,43,44]. A positive effect on fasting glycemia was also apparent, whereas a reduction in total cholesterol and triglycerides were evident in some, but not all, the meta-analyses [37]. As observed for sexual function, positive results were more evident when parenteral and transdermal preparations were employed, and more variable with oral TRT [37].

TRT and bone metabolism

In a recent meta-analysis [9], it was demonstrated that TRT is able to inhibit bone resorption and increase bone mass, particularly at the lumbar spine level and when the duration is long enough to allow the anabolic effect of T and estrogens on bone metabolism to take place. However, no studies investigated the effect of TRT on fracture risk.

TRT and mood and cognition

A systematic review of 15 small-size RCTs suggests that TRT can reduce depressive symptoms in hypogonadal patients with mild depression but not in those with major depressive disorders [45]. In contrast, available data [46,47] did not support the use of TRT for the improvement of several cognitive domains, including attention/working memory, executive function, language, verbal memory, visual memory, visuomotor ability, and visuospatial ability.

Aim of the therapy of male Hg

The main aim of the therapy of male HG is to restore HG-related symptoms and signs according to the patient's needs, without relevant side effects. Side effects related to GnRH or Gn therapies are often negligible (see before), also because they are usually administered to allow fertility in subjects with secondary HG and, therefore, for a relatively short-time. When TRT is advisable, it is usually administered for prolonged times and is often lifelong, in particular in organic HG. Although meta-analyses do not support an increased cardiovascular risk in the short- or medium-term [48–50] for any of the available T preparations [48], long-term data are still lacking. However, there is a consistent (four-fold increase) risk of erythrocytosis with TRT, in particular with injectable preparations [48]. Hence, hematocrit should be routinely checked. An increased risk of TRT-related prostate cancer or other prostate adverse events is also not supported by all the meta-analyses published so far, even when categorized according to the different T preparations [48]. Nonetheless, digital rectal examination of the prostate, along with PSA, should be periodically checked. Considering that hematocrit, PSA and prostate volume are all androgen-dependent, their monitoring can also guide clinicians in evaluating the efficacy of TRT, along with T levels, which should remain in the normal range.

Conclusions

Male HG is common, in particular in the aging male with comorbidities. If symptomatic, it should be treated according to a patient's needs. When fertility is an issue, GnTh is the most rational approach. In FHG, lifestyle measures can help in restoring normal T levels and improving sexual symptoms, also by addressing the underlying morbidity. TRT, if administered in the correct dose and formulation, is a safe and satisfactory treatment for male HG, when fertility is not desired and lifestyle measures have failed or are not feasible.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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