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**To cite this article:** Giovanni Corona, Giulia Rastrelli, Clotilde Sparano, Linda Vignozzi, Alessandra Sforza & Mario Maggi (13 Jun 2024): Pharmacological management of testosterone deficiency in men current advances and future directions, Expert Review of Clinical Pharmacology, DOI: [10.1080/17512433.2024.2366505](https://doi.org/10.1080/17512433.2024.2366505)

**To link to this article:** <https://doi.org/10.1080/17512433.2024.2366505>



Published online: 13 Jun 2024.



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REVIEW



# Pharmacological management of testosterone deficiency in men current advances and future directions

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## ABSTRACT

**Introduction:** Testosterone deficiency (TD) is relatively common in aging men, affecting around 2% of the general population. Testosterone replacement therapy (TRT) represents the most common medical approach for subjects who are not interested in fathering.

**Areas covered:** This review summarizes advances in TRT, including approved or non-approved pharmacological options to overcome TD. When possible, a meta-analytic approach was applied to minimize subjective and biased interpretations of the available data.

**Expert opinion:** During the last decade, several new TRT formulations have been introduced on the market, including oral, transdermal, and parenteral formulations. Possible advantages and limitations have been discussed appropriately. Anti-estrogens, including selective estrogen modulators or aromatase inhibitors still represent further possible off-label options. However, long-term side effects on sexual function and bone parameters constitute major limitations. Glucagon-like peptide 1 analogues can be an alternative option in particular for massive obesity-associated TD. Weight loss obtained through lifestyle modifications including diet and physical exercise should be encouraged in all overweight and obese patients. A combination of TRT and lifestyle changes can be considered in those subjects in whom a reversal of the condition cannot be expected in a reasonable time frame.

## ARTICLE HISTORY

Received 26 January 2024

Accepted 6 June 2024

## KEYWORDS

Testosterone; hypogonadism; late onset hypogonadism; erectile dysfunction; weight loss

## 1. Introduction

Testosterone deficiency (TD) is a condition related to a reduction in the testicular production of the male hormone, testosterone (T). This condition is relatively common in middle-aged and older men, affecting 14% of the European general population during adulthood, when a threshold of less than 10.5 nmol/L in total T is considered [1]. In the majority of cases, TD is related to inappropriate stimulation from the hypothalamus-pituitary (HP) axis to the testis, resulting in hypogonadotropic (or secondary) hypogonadism (HG). In that case, luteinizing hormone (LH) levels are low or inappropriately normal (i.e. below 9.4 mU/L) [1]. Conversely, only 10% of those with TD showed elevated LH levels (i.e.  $\geq 9.4$  mU/L), such as in hypergonadotropic (primary) HG [1]. In hypogonadotropic HG, any treatment able to stimulate or restore the HP axis is able to reverse the condition, which can also be treated by replacing the TD with T replacement therapy (TRT). At variance, the latter (TRT) is the unique pharmacological treatment when the testis is dysfunctional and unable to release adequate amounts of androgens, such as in primary HG. Male TD can also be categorized according to the time of origin, whether congenital or acquired, or according to the time of symptom onset, that is, prenatally (very-early-onset HG), during childhood (early-onset HG), or in adult life (late-onset HG, LOH) [2]. Clinical symptoms and signs of congenital or early

acquired HG are dramatically more severe than those manifested in midlife (LOH) [2]. Treatment of HG is essentially dictated by three main determinants: i) the site of origin of the disease (see before); ii) the time of origin of the disease; and iii) the patient-related outcomes and needs [3]. For instance, in secondary HG, if fertility is desired, TRT is the wrong option, because it further depresses the HP testis (HPT) axis, due to the negative feedback exerted by the exogenous T [3]. Treatment of HG can also be affected by the potential reversibility of the HG, the so-called functional HG. In functional HG, due to its reversibility, treating the underlying condition is strongly encouraged, while a straightforward pharmacological intervention is reserved for organic HG, where irreversible damage to the HP-testis axis (HPT) is demonstrated [4]. This view was substantially accepted by the Endocrine Society of the U.S.A. [5] and of Australia [6], but not by all [7].

According to all the available guidelines released by several dedicated societies [5–11], TD should be treated only when specific symptoms are present. The main symptoms potentially associated with TD are rather nonspecific and vague and include sexual dysfunction, infertility, fatigue, sadness, poor concentration and memory, hot flashing, and decreased vigorous activity [12]. Signs that could be associated with a TD are increased waist circumference and fat mass, reduced body

### Article highlights

- New FDA-approved oral T formulations, based on the self-emulsifying delivery system technology, allow a better pharmacokinetic profile when compared to the older oral preparation.
- According to available evidence nasal T preparation is less often associated with side effects such as hematocrit increase or suppression of the hypothalamus pituitary testis axis. More controlled trials are advisable to confirm these preliminary results.
- Data derived from the use of anti-estrogens such as selective estrogens receptor modulators (SERM) or aromatase inhibitors are still conflicting.
- GLP-1 analogues represent a new putative tool for the treatment of functional hypogonadism in particular for massive obesity-associated hypogonadism.

hair, small testes, low trauma fractures, gynecomastia, reduced muscle mass and bone density, and anemia [7]. A study by the European Male Aging Study (EMAS) team indicated that only three sexual symptoms (erectile dysfunction, loss of libido, and reduced spontaneous erection) were segregated in a syndromic form with a TD, while other psychological or physical symptoms were not [12]. By using the EMAS definition for LOH, i.e. low T (<11 nmol/L) along with the aforementioned sexual symptom, the resulting prevalence of symptomatic male HG in the European general population is a fair amount less, i.e. 2% [12]. Nonetheless, even symptomatic LOH affects a considerable portion of European aging males (one out of fifty adult men).

The aim of this review is to summarize advances that occurred in the last ten years in the treatment of TD, including approved or non-approved pharmacological options to overcome the condition. We are aware that LOH, in particular in its functional form, can be successfully treated with non-pharmacological options, including lifestyle measures; however, this is behind the aim of this study and it has been reviewed elsewhere, also by our group [13,14].

## 2. Methods

A comprehensive review was performed using Medline, Embase, and Cochrane searches and including the following words: (('testosterone'[MeSH Terms] OR 'testosterone'[All Fields] OR 'testosteron'[All Fields] OR 'testosterones'[All Fields] OR 'testosterone s'[All Fields]) AND ('deficiencies'[All Fields] OR 'deficiencias'[All Fields] OR 'deficiency'[MeSH Subheading] OR 'deficiency'[All Fields] OR 'deficient'[All Fields] OR 'deficients'[All Fields]) AND ('men'[MeSH Terms] OR 'men'[All Fields])) AND ((humans[Filter]) AND (male[Filter]) AND (english[Filter])). Publications from 1 January 1969, up to NaN Invalid Date NaN, were included. In addition, to minimize subjective and biased interpretation of the available data, when possible a meta-analytic approach was applied. Meta-analysis was performed using Comprehensive Meta-analysis Version 2, Biostat, and (Englewood, NJ, USA).

Clinical data were derived from a consecutive series of more than 3900 patients seeking medical care at the University of Florence as previously described [13,14].

Multivariate analyses as well as other analyses were performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows, 25.

## 3. Approved medications for the treatment of TD

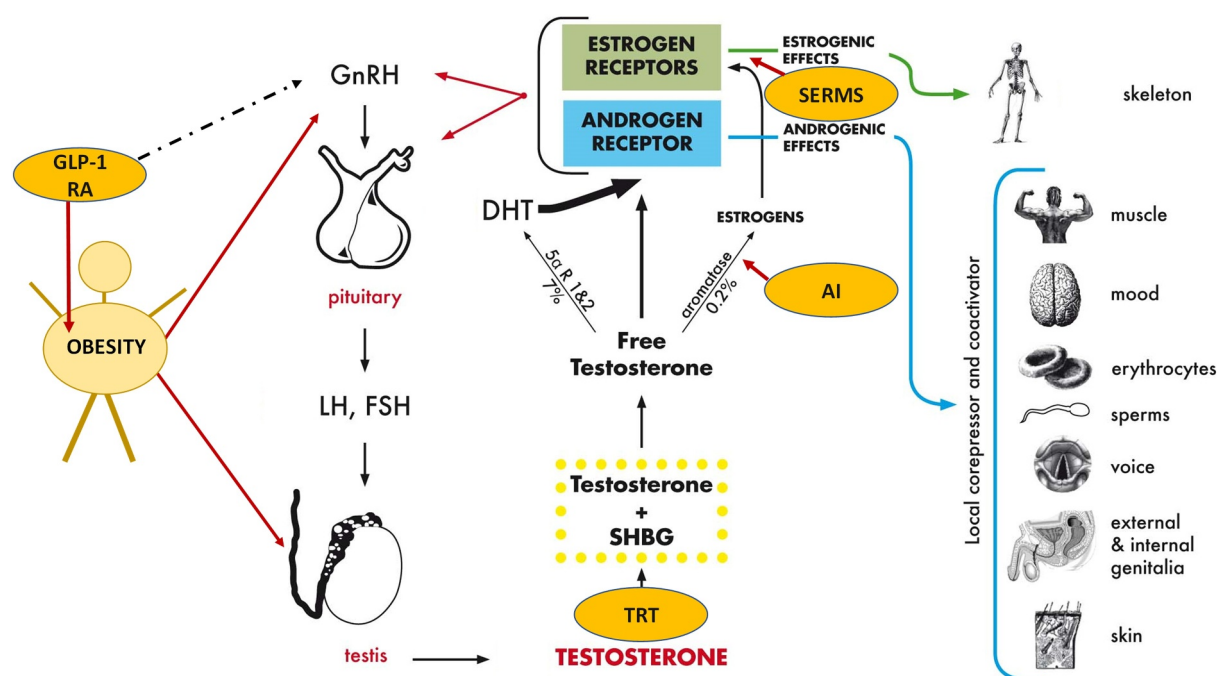
Considering that there are no major, recent developments on Gns in the treatment of male secondary HG, this topic will not be covered in this review, also because it has been recently covered by us elsewhere [15].

During the last ten years several new formulations of the testicular hormone T for TRT have been available (see also Figure 1). TRT can be obtained in hypogonadal men through several routes of administration, including oral, parenteral, transdermal, intranasal, and implants. The specific analysis of the well-established TRT preparations is behind the aim of the present paper and has been revised elsewhere [15,16]. Similar considerations should be done for patient evaluation and monitoring during TRT therapy [5,7,9–11]. Briefly, although no general agreement has been reported in the different guidelines, patients should be evaluated after three months of treatment and then every six months or annually, according to patient characteristics and blood examinations [5,7,9–11].

### 3.1. New oral formulation for TRT

The oral route for drug delivery is often considered the most convenient way for several reasons, including safety considerations, convenience of administration, suitability for long-term use, and flexibility in dosage adjustment. Hence, it is the one most often desired, even at the patient level [17–20]. Native T administered via oral route passes through the small intestinal wall and reaches the liver before being transported via the bloodstream to its target site. However, after the first-pass through the liver, T is substantially metabolized into inactive byproducts, and, therefore, only a minimal amount reaches the systemic circulation [16–18,20]. Its alkylation in the 17 $\alpha$  position increases its bioavailability, but it results in liver toxicity [15,16,19]. Adding a mid-chain length fatty acid at the 17 $\beta$  position of the D ring strongly increases its lipophilicity, allowing absorption in part through the lymphatic system of the small intestine, therefore bypassing liver metabolism and, finally reaching the internal jugular or subclavian veins [16,21]. Although a T undecanoate (TU) preparation (Andriol®) has been available in Europe for more than 50 years, it was never approved by the United States Food and Drug Administration (FDA) because of its erratic absorption, which is essentially possible only when administered with fatty meals. In the last ten years, several other lipid-based formulations of native T were developed and introduced on the market with improved efficacy than Andriol (Table 1).

The first FDA-approved TU preparation is JATENZO (Tolmar Pharmaceuticals, Inc., Buffalo Grove, IL, USA), whose absorption is based on a self-emulsifying delivery system (SEDDS) ([22], Table 1). SEDDS is a technology consisting of a mixture of lipophilic and lipophobic matrices able to increase the solubility and bioavailability of poorly soluble substances, such as TU. Endogenous esterases allow the liberation of T from the



**Figure 1.** Hypothetic sites of action of the different medications for the pharmacological management of male hypogonadism (yellow circles). All the available preparations of testosterone for replacement therapy (TRT) increase the pool of circulating testosterone, that can be further converted in other active metabolites, including dihydrotestosterone (DHT) and estrogens. Selective estrogen receptor modulators (SERMS) act as antagonists of the estrogen receptors, therefore decreasing the negative feedback exerted by estrogens on hypothalamus and pituitary. Aromatase inhibitors (AI) can sort a similar effect by blocking estrogen formation. Glucagon-like peptide-1 receptor agonists (GLP-1RA), by decreasing obesity, halted the negative effects of this condition on the entire hypothalamus-pituitary-testis axis. In addition, a hypothetical positive effect of these compounds on the hypothalamus has been also envisaged by preclinical studies. The figure is modified from reference #3.

prodrug TU. JATENZO is available in three dosing formulations (158, 198, and 237 mg) that should be taken b.i.d. and need titration. At variance with Andriol, it does not need a fat meal for absorption, although it should be taken with meals. Two open-label randomized trials, reviewed elsewhere [23,24], demonstrated that eugonadal T levels were obtained in more than 80% of the treated hypogonadal men (total  $T < 10.4$  nmol/L) for up to one year. In addition, JATENZO was able to improve body composition, bone mineral density, at the spine, and hip, mood and sexual complaints (Psychosexual Daily Questionnaire, PDQ), similar to what was observed with the comparator (T gel formulations) [23,24]. Considering that sex hormone binding globulin (SHBG) decreased more in the JATENZO arm than in the T gel arm, calculated free T levels were higher in the former arm [23]. Accordingly, the mean increase of hematocrit was higher (6.8%) in the JATENZO arm than in the T gel arm (3.1%). A 12-month extension of a previous one-year JATENZO arm [25] further demonstrated significant increases from baseline in sexual enjoyment, mood, and satisfaction with erection [26]. In addition, an open-label study enrolling a small number of hypogonadal subjects previously treated with other T formulations, suggests that patient satisfaction was higher upon JATENZO than with previous other routes of T administration [27].

Another TU preparation, based on a different SEDDS technology (predigested triglycerides), is Tlando (Lipocine, Salt Lake City, UT, USA), approved by the FDA in March 2022 (Table 1). At variance with JATENZO, Tlando does not need dose titration and is available in 112.5 mg capsules that should be taken

twice daily with regular meals, without the need for a high-fat content. In a small trial enrolling 95 hypogonadal men (total  $T < 10.4$  nmol/L), eugonadism was reached in up to 80% of the treated subjects with a 450 mg daily dose for 28 days. In a preliminary open-label study (reviewed in [28,29]) involving 315 hypogonadal subjects for 52 weeks, Tlando was not inferior to topic T in improving patient-reported outcomes in sexual and mental domains with an equal proportion of subjects reaching the eugonadal state. An increase of 3.2% in hematocrit was observed after dosing 450 mg of Tlando for 4 months [30].

The most recent FDA-approved TU preparation is Kyzatrez (Marius Pharmaceuticals, Raleigh, NC; USA), a TU preparation dissolved in a combination of lipids and other solubilizers contained in a softgel capsule. It has been approved in three dosages: 100, 150, and 200 mg (Table 1), with the recommended starting dose of 200 mg twice a day at meals, followed by dose titration [29]. It is reported that this formulation is able to normalize serum T in up to 88% of the treated hypogonadal subjects [29].

Common side-effects of these recently approved three TU formulations are mild gastrointestinal symptoms along with a 2–5 mm HG increase in systolic 24-hour ambulatory blood pressure (ABP) and a minor elevation in diastolic blood pressure (BP) [23,24,28,29]. In a study with Tlando, a greater increase in ABP was observed in those showing a more sustained increase in hematocrit upon TU dosing, whereas in a study with Kyzatrez no relationship was observed [31]. In the Kyzatrez study [31], the ABP increase was relatively less evident than in other studies and greater in those taking anti-hypertensive medications [31].

**Table 1.** Available oral testosterone preparations.

Formulation (Commercial name)	Chemical structure	t 1/2	Standard dosage	Advantages	Disadvantages	FDA Approval
<b>AVAILABLE ORAL TESTOSTERONE PREPARATIONS</b>						
Testosterone undecanoate castor oil/propylene glycol vehicle (Andriol)	17- $\alpha$ -hydroxylester	2–5 hours	40–160 mg 2 times daily	– Reduction of liver involvement – Oral convenience – Modifiable dosage – Quick reversal	– Unpredictable absorption depending on dietary fat content – Must be taken with fatty meals	No
Testosterone undecanoate self-emulsifying delivery system (Jatenzo)	17- $\alpha$ -hydroxylester	2–5 hours	158, 198, 237 mg 2 times daily	– Reduction of liver involvement – Oral convenience – Modifiable dosage – Quick reversal	– Need titration – Must be taken with meals – Gastrointestinal side effects – increase in blood pressure	Yes: April 2019
Testosterone undecanoate self-emulsifying delivery system (TLANDO)	17- $\alpha$ -hydroxylester	2–5 hours	225 mg 2 times daily	– Reduction of liver involvement – Oral convenience – No titration – Quick reversal	– Must be taken with meals – Gastrointestinal side effects – increase in blood pressure	Yes: March 2022
Testosterone undecanoate self-emulsifying delivery system (Kyzatrez)	17- $\alpha$ -hydroxylester	2–5 hours	100, 150, 200 mg 2 times daily	– Reduction of liver involvement – Oral convenience – Modifiable dosage – Quick reversal	– Must be taken with meals – Gastrointestinal side effects – increase in blood pressure	Yes: August 2022

Considering that in recent meta-analyses of randomized controlled trials (RCTs) a TRT-induced BP increase was never observed [32,33], these results are surprising. However, a modest (0.3 mm Hg), although significant, increase in mean systolic blood pressure was observed in the recently published TRAVERSE study, a large trial investigating the cardiovascular (CV) effects of T gel administration in subjects at high CV risk [34]. Interestingly, however, in that trial no signal for an increased rate of major CV events (MACE, primary endpoint) was reported in the treated arm [34]. Hence, it is possible that these modest increases in BP are clinically insignificant. Nonetheless, the FDA required a black box warning that these drugs can induce a BP rise that might increase the risk of MACE. Due to this risk, the use of oral TU preparations should be limited to hypogonadal conditions associated with structural or genetic etiologies (the so-called organic hypogonadism; see before).

### 3.2. New nasal formulation for TRT

The nasal mucosa shows interesting properties for drug delivery because it is not subject to first-pass metabolism, therefore allowing high bioavailability of the applied medications [35]. Natesto (Acerus Biopharma Inc.,) is a nasal formulation of T for treating male hypogonadism, approved by the FDA almost 10 years ago. Natesto nasal gel is available as a metered-dose pump. One pump actuation delivers 5.5 mg of T. The recommended dose of Natesto is 11 mg of T (2 pump actuation; 1 actuation per nostril) administered intranasally three times daily for a total daily dose of 33 mg. Natesto should be administered once in the morning, once in the afternoon, and once in the evening (6 to 8 hours apart), preferably at the same time each day [36]. At this recommended dosage, 90% of hypogonadal subjects (total T < 10.4 nmol/L) reached eugonadism in a ninety-day, randomized, open-label study [37]. A phase IV, prospective, randomized, non-blinded, multi-institutional study is ongoing to compare results with the aforementioned dosage of Natesto and intramuscular administration of 200 mg of T cypionate (TC)

twice a month (ClinicalTrials.gov ID NCT04439799, <https://clinicaltrials.gov/study/NCT04439799?cond=male%20hypogonadism&rank=11>) In a preliminary release of that study, Natesto administration for four months was associated with a lower risk of polycythemia and an overall lower hematocrit increase than TC [38]. This positive finding could be associated with the intrinsic properties of Natesto, i.e. a rapid, transient, rise and fall of circulating T upon nasal administration [36]. For the aforementioned characteristics it was postulated that nasal T (NT) administration could be associated with lower suppressive activity on the HPT axis and, therefore, on spermatogenesis. In a short-duration (six months) single-center, uncontrolled trial, NT (11 mg t.i.d) maintained spermatogenesis in the majority of the 60 hypogonadal (T < 12 nmol/L) men enrolled, reducing in a non-significant manner serum Gn levels [39,40]. According to this hypothesis, NT induced, after 16 weeks, a lower suppression of 17-hydroxyprogesterone (17-OHP, taken as a surrogate marker of testicular activity) than other T preparations, i.e. subcutaneous pellets and TC [41]. Considering that an increase in hematocrit and reduced fertility are the major problems with TRT [16], these results could be of interest. However, their uncontrolled nature, short duration, and enrollment in small cohort of hypogonadal subjects are the main limitations of the aforementioned studies that need confirmation. In addition, the number of patients who dropped out of the study [40] due to azoospermia or severe oligospermia was not included in the final analysis. An alternative explanation of the positive results on hematocrit and spermatogenesis is that NT has lower biological activity than other T preparations, therefore resulting in less effectiveness in rescuing hypogonadal symptoms. However, two uncontrolled trials reported a significant increase in International Index of Erectile Function (IIEF) scoring over baseline [40,42] which was in line to that derived from available meta-analyses [43,44]. The most common side effects of Natesto are associated with its route of administration and include headache, rhinorrhea, epistaxis, nasal discomfort, and nasopharyngitis [36].



### 3.3. New intramuscular formulation for TRT

Although TU intramuscular formulations have been available worldwide for more than 20 years and are approved in more than 100 countries and marketed in more than 80 parts of the world, including Europe (Nebido, originally by Bayer AG, Kaiser-Wilhelm-Allee 1 51,373 Leverkusen, Germany [45]), in the USA injectable TU was FDA-approved only in 2014 with the brand name AVEED (Endo Pharmaceuticals Solutions Inc.). The main difference between Nebido and AVEED is in their single-use vial dose, i.e. 1000 mg in 4 mL for the former and 750 mg in 3 mL for the latter. At variance with Nebido, following the first intramuscular injection of 3 mL of AVEED (750 mg), a second 3 mL dose is injected four weeks later, and then 3 mL is injected every ten weeks thereafter. The approval of AVEED is based on data from an 84-week Phase 3 trial of hypogonadal men in the USA. The men enrolled in the study had an average age of 54 years and a serum total T level of less than 10.4 nmol/L. In the Phase 3 study, AVEED increased mean serum T levels, maintaining them for up to 10 weeks at a steady state (between weeks 14–24) [46]. Clinical experience in the USA with TU 750 mg provides evidence for good patient satisfaction and persistence with treatment, together with a favorable safety profile [47]. However, its prescription is available only through a Risk Evaluation and Mitigation Strategies (REMS) program. In addition, AVEED carries a black box warning for serious pulmonary oil microembolism (POME) reactions (the urge to cough, dyspnea, throat tightening, chest pain, dizziness, syncope) and episodes of anaphylaxis. However, of the 633 individual case safety reports in the Endo Pharmaceuticals Inc. safety database, 28 spontaneously reported adverse events were classified as POME, for a yearly spontaneously reported adverse event per injection rate of <0.1% [48]. Most (21/22) events resolved, and of those with a resolution time reported, most (13/17) were resolved in less than 30 minutes (32). More than 60% (13/21) of patients required no medical intervention [48]. In a meta-analysis of injectable TU preparations, it was found that in either controlled or uncontrolled trials, injectable TU was associated with a reduction of fat mass and HbA1c and an improvement of erectile function, without an increased risk of prostate cancer or severe CV events [45]. A recent Australian RCT [49] – the T4DM trial enrolling more than 1,000 men aged 50 years with prediabetes or newly diagnosed type 2 diabetes mellitus (T2DM) with a mild TD (total T < 14 nmol/L) – reported that a two-year treatment with TU 1000 mg, along with a lifestyle program, reduced the likelihood of T2DM diagnosis by 40% compared to placebo. This effect was accompanied by a decrease in fasting serum glucose and was associated with favorable changes in body composition, hand grip strength, bone mineral density, skeletal microarchitecture, and sexual function [49,50]. Interestingly, a recent network meta-analysis showed that the rate of hematocrit increase upon injectable TU is lower than with other injectable preparations and similar to that associated with gels, patches, or oral TU preparations [51].

### 4. Non-approved preparations for the treatment of TD

Several non-approved medications are frequently used for the management of male hypogonadism (Figure 1). Some classes,

such as selective estrogen modulators (SERMs) or aromatase inhibitors (AIs), are frequently used in an off-label manner to treat patients with functional secondary hypogonadism, particularly in subjects with metabolic derangements, to preserve fertility and sperm count [52]. Conversely, other medications such as glucagon-like peptide 1 (GLP-1) analogues are still not routinely used. The following section will better analyze these possible approaches.

#### 4.1. Selective estrogen modulators

Selective estrogen receptor modulators (SERMs) represent a diverse group of molecules with varying levels of estrogenic agonist and antagonist activity in target tissues. Although these molecules were approved in different countries for the treatment of several female conditions, including breast cancer, osteoporosis, or ovulatory dysfunction, none of them have been approved or licensed for the treatment of any male disorders. Nonetheless, they were often used for treating male infertility and hypogonadism [3]. The rationale for their use in males for these indications is that SERMs, by blocking estrogen action in the hypothalamus and pituitary, have the potential to increase serum follicular stimulating hormone (FSH), LH, and T levels in men with low or inadequate levels of low gonadotropins (Gns), restoring physiological endogenous T secretion, while maintaining testicular volume and, possibly, increasing spermatogenesis. Accordingly, three different meta-analyses [53–55] suggested a positive effect of the triphenylethylene derivatives clomiphene citrate (CC) and tamoxifen on several sperm parameters and even on pregnancy rate in different cohorts of infertile men. Similarly, other meta-analyses have shown a statistically and clinically significant increase in Gns levels, along with an increase in circulating T, upon administration of those SERMs [53–57] (Table 2; Figure 2).

A previous meta-analysis from our group on RCTs exploring the effect of SERMs on hormonal levels in subjects with hypogonadism, showed a mean increase of 7.5 nmol/L in total T and of 5 and 4.7 mU/L in LH and FSH, respectively [56] (Figure 2). Similar results were confirmed by Huijben et al. in a further meta-analysis on CC including not only RCTs but also observational studies [55] (Figure 2). The same group recently reported results from a prolonged observational study with clomiphene in 153 subjects with secondary and primary hypogonadism [58]. Overall, they found a biochemical increase in total T in 89% of the treated subjects, being more efficient in those with low baseline Gns levels (as expected) than in those with primary HG, although, in the latter small group ( $n = 16$ ), one in three showed a T increase over baseline levels. In a meta-analysis, including obese men treated with SERMs for HG in seven observational studies, a mean 9.7 nmol/L increase in total T was reported [57]. That increase was higher in those treated with CC than with enclomiphene citrate (EC). The latter is the transisomer of CC that shows only antagonistic and short-acting efficacy at variance with the cis-isomer zuclophene which has mixed properties and a prolonged half-life [3,56]. For those properties, EC was developed under the trade name Androxal for the treatment of male HG and/or infertility by Repros

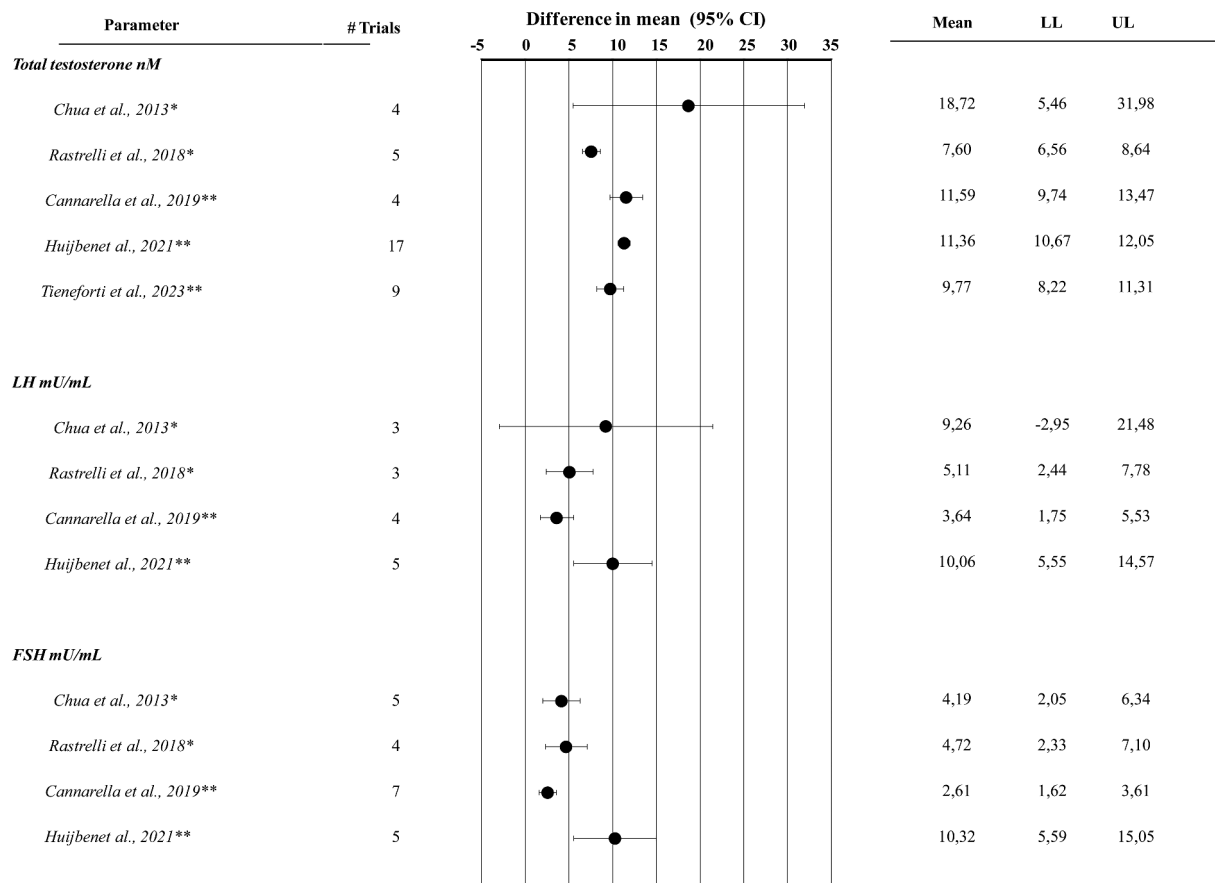
**Table 2.** Comparisons of the available meta-analyses evaluating the relationship between total testosterone, luteinizing hormone and follicular stimulating hormone after selective estrogen modulators (SERM) treatment or when compared to controls at endpoint. Data are related to only those studies investigating hormonal parameters.

Inclusion criteria	Chua et al., 2013 [53]	Rastrelli et al., 2018 [56]	Cannarella et al., 2019 [54]	Huijben et al., 2021 [55]	Tienforti et al., 2023 [57]
Number of trials included	5	5	7	17	7
Number of patients analyzed	381	314	298	274	292
Comparison with placebo or no treatment	x	x			
Data at endpoint after SERM treatment			x	X	X
<b>Outcomes evaluated</b>					
Total testosterone	X	X	X	X	X
Follicular stimulating hormone	X	X	X	X	-
Luteinizing hormone	X	X	X	X	-

Therapeutics. Although EC demonstrated efficacy in small RCTs and in observational study in improving T levels and maintaining spermatogenesis in hypogonadal men (recently reviewed in [59,60]), it was never approved by the FDA.

Considering that the diagnosis of male HG relies not only on the T deficiency but also on specific symptoms and signs [5,7,10,11], it is surprising that the effect of SERMs on these parameters was not extensively investigated, apart from the effect on sperm production. Sexual symptoms are considered the most specific symptoms of male functional HG (LOH) [12,61]. It is therefore surprising that only a few studies [60,62] investigated the effect of CC using the International Index of Erectile Function-5 scoring (IIEF-5 [63]). While in a small, uncontrolled trial some improvement was observed in

IIEF-5 [64], in another controlled study, comparing the efficacy of CC to that of an aromatase inhibitor, the results on IIEF were completely negative [62], despite a sharp increase in total T in both studies. It is important to recognize that the majority of investigations used the Androgen Deficiency in Aging Males (ADAM) questionnaire [65], a tool consisting of 10 questions that help determine if a male patient suffers from androgen deficiency, but with very low specificity [66] and only two questions dedicated to sexual dysfunctions. A meta-analysis of four observational studies using ADAM scoring reported a significant mean difference of 3.13 [2.1–4.16] in ADAM scoring from baseline upon CC administration [55]. A double-blind, placebo-controlled, cross-over study by Guay et al. [67] enrolled 17 patients with erectile dysfunction (ED) who were



**Figure 2.** Weighted mean differences (with 95%CI) on hormonal parameters after selective estrogen modulators (SERM) treatment (\*\*) or when compared to controls (\*) at endpoint. LH= luteinizing hormone; FSH= follicular stimulating hormone.

found to have secondary hypogonadism. They were treated with CC or placebo for two months each. During the treatment with CC, a significant increase in total T was observed. However, none of the proxies for erectile function (questionnaires and RigiScan) were significantly changed by CC. Negative results in ADAM scoring were also observed in a more recent RCT on obesity-associated secondary HG, comparing CC to placebo, with similar scoring on questions concerning libido and erection, even though T and Gns levels were higher in the active arm [68]. Furthermore, no differences were observed between CC and placebo on a number of sexual intercourses or sexual satisfaction [68]. Interestingly, the placebo-induced improvement in ADAM scoring at the study end of the Soares et al. [68], trial, i.e.  $3.12 \pm 2.63$ , was similar, if not identical, to that reported upon CC in several observational, uncontrolled studies meta-analyzed in [55]: 3.13 (2.1–4.16). In addition, in a small sub-analysis [69] of a larger randomized, double-blind, placebo-controlled study [70] on the effect of CC as an add-on to metformin in hypogonadal subjects with prediabetes or T2DM, it was demonstrated, in an adjusted between-treatment difference, an improvement in ADAM scoring, but no change in IIEF-EFD, despite an increase in libido [69].

T administration to hypogonadal subjects is associated with an improvement in body composition, either in observational [71] and controlled [32] studies. These positive effects are also apparent in subjects with prediabetes, diabetes, and HG [72]. Hence, it is conceivable that SERMs, by increasing circulating T, might also improve body composition. In the Pelusi et al. [70] crossover RCT, no significant improvement was found in body composition or other metabolic parameters upon CC administration for 3 months when compared to placebo. However, in a sub-analysis including only subjects with prediabetes (IFG), significant improvements in body mass index (BMI), waist circumference (WC), fasting glucose, insulin, and HOMA-IR were observed that were not apparent in those with overt T2DM. In an RCT enrolling obese subjects with secondary HG [68], after 12 weeks, it was found a significant improvement in the CC arm in body composition, i.e. increase in fat-free mass (FFM), skeletal muscle mass (SMM) and lean body mass, without significant changes in BMI and WC between groups.

No specific trial addressed the issue of the effect of SERMs on bone health in hypogonadal men. In a double-blind RCT with crossover enrolling forty-three healthy eugonadal men receiving either raloxifene 120 mg/day or placebo for six weeks, a decrease in biochemical markers of bone turnover was found in men in the active arm with the lowest baseline values of total T and estradiol [73]. In addition, raloxifene has been reported to prevent bone loss in men with prostate cancer upon treatment with GnRH analogs [74], but not in elderly men [75]. In an observational study enrolling 46 hypogonadal men (mean age 44 years) treated with CC for more than one year, it was reported that there was a significant increase in mean femoral neck and lumbar spine bone mineral density (BMD) scores over baseline values [76]. However, in another retrospective study [77], BMD increased in 54 hypogonadal men treated with T but significantly decreased in 17 treated with CC, as well as in the four treated with anastrozole alone or in combination with CC.

## 4.2. Aromatase inhibitors

Aromatase inhibitors (AIs), by blocking all aromatase-mediated estrogen formation, are approved in several countries for the treatment of estrogen-dependent tumors, such as breast cancer. The most widely used are the third generation AIs, including letrozole, anastrozole, and exemestane. As for SERMs, by halting the negative feedback exerted by estrogens at the HP level, AIs can increase Gns levels in both sexes and stimulate gonadal production of sex steroids. Therefore, AIs represent a potential tool for treating male secondary HG, in particular in its functional form. However, at variance with SERMs, which still play some agonistic activity in selected tissues, all estrogen-mediated actions are blocked by AIs, resulting in overt hypoestrogenism. Considering that T transformation into estrogens is an important way to explain full T biological action, AI-induced hypoestrogenism raised several concerns for the treatment of secondary HG [78]. Due to the relevant role of estrogens in bone metabolism, not only in the female but also in the male, most of the concerns related to the employment of AIs in treating secondary HG are related to the potential deleterious effect of these medications on bone safety [78–80].

All the meta-analyses so far published, collecting the few RCTs available and other observational studies, reported a significant reduction in estrogen and an increase in T levels upon short-term treatment with AIs [56,81,82] (see also Table 3 and Figure 3). In two meta-analyses, upon AIs administration, LH and FSH were increased [81,82] (Figure 3). Most of the available studies focused on the effects of AIs on spermatogenesis. Two meta-analyses of observational studies enrolling infertile men found a significant increase (standardized mean difference) in total sperm count [81,82] and sperm motility [81,82], whereas a positive effect on normal morphology was reported in one [82].

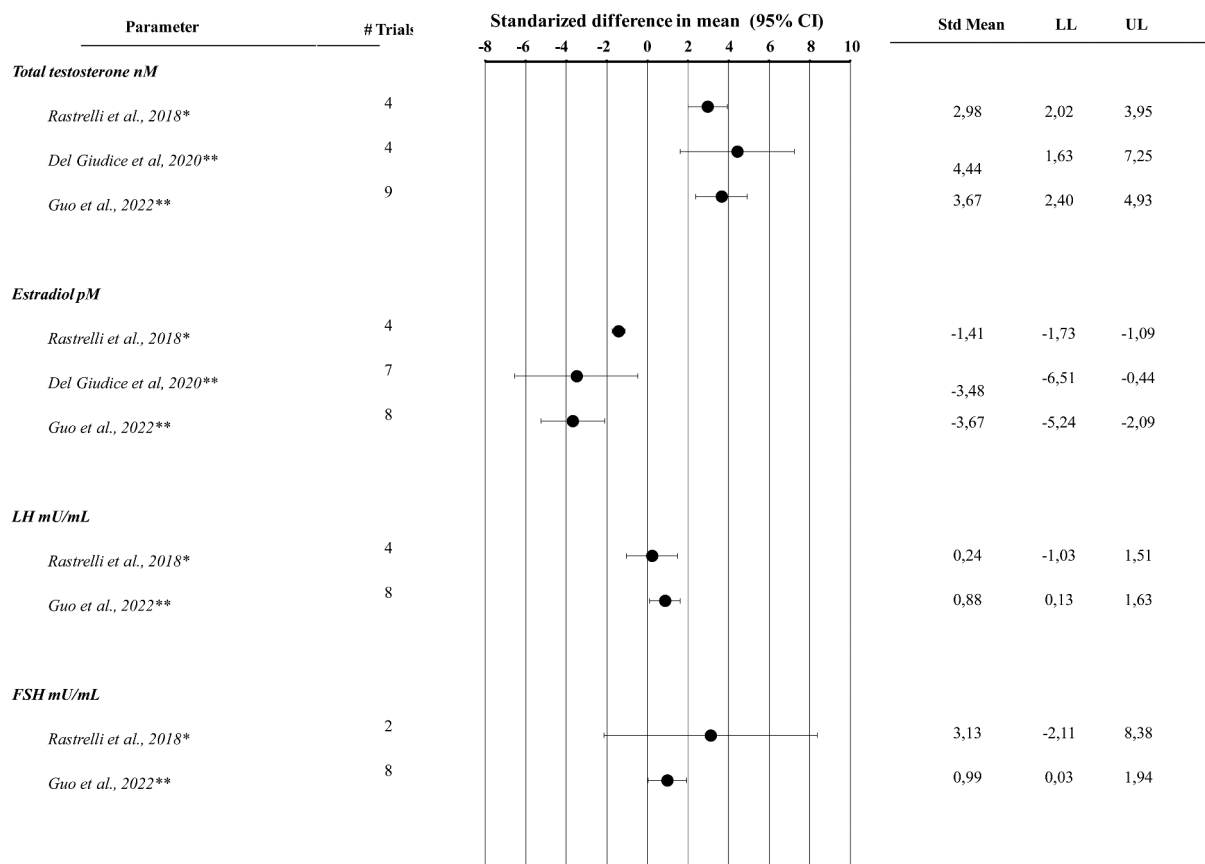
Interestingly, in both meta-analyses, one of the more common side effects in infertile men was a reduction in sexual desire, which was present in 2.5% [81] and 6.2% [82] of the cohorts. In one study [83], loss of libido was reported in more than half of the sample, despite an impressive increase (25 nmol/L) in T concentration.

Concerning symptoms of hypogonadism, a meta-analysis published in 2018 [56] did not show any significant effect of AIs in RCTs on body composition, body mass density (BMD), or markers of bone turnover. However, the maximal follow-up of the included RCTs was no longer than 52 weeks [56]. This finding is quite surprising because thresholds of 37–92 pmol/L serum estradiol have been suggested to be necessary for bone health in men [78,80] and, as derived from the available meta-analyses [56,81,82], with AIs, the level of estradiol at the end-point was often below these thresholds. In addition, in a double-blind, randomized, placebo-controlled trial on symptomatic hypogonadal, older men a significant decrease in spinal BMD, and bone turnover markers after one-year treatment with anastrozole (1 mg) or placebo was observed, in front of a marked increase in total T and a parallel decrease of estradiol [84]. Similar results were recently published in 271 obese subjects with functional secondary HG (total T <10.4 nmol/L) enrolled in a multicenter, double-blind RCT. Subjects were treated weekly with 0.1, 0.3, and 1 mg of the AI leflutrolole



**Table 3.** Comparisons of the available meta-analyses evaluating the relationship between total testosterone, estradiol, luteinizing hormone and follicular stimulating hormone after aromatase inhibitors treatment or when compared to controls at endpoint. Data are related to only those studies investigating hormonal parameters.

Inclusion criteria	Rastrelli et al., 2018 [56]	Del Giudice et al., 2019 [81]	Guo et al., 2022 [82]
Number of trials included	5	8	8
Number of patients analyzed	192	417	29
Comparison with placebo or no treatment	x		
Data at endpoint after SERM treatment		x	x
<b>Outcomes evaluated</b>			
Total testosterone	X	X	X
Estradiol	X	X	X
Follicular stimulating hormone	x	-	X
Luteinizing hormone	X	X	X



**Figure 3.** Weighted standardized mean differences (with 95%CI) on hormonal parameters after aromatase inhibitors treatment (\*\*) or when compared to controls (\*) at endpoint. LH= luteinizing hormone; FSH= follicular stimulating hormone.

or placebo for 24 weeks. It was observed a dose-dependent increase in total T and Gn levels, with a significant decrease in estradiol even below 40 pmol/L [85]. In front of these hormonal changes, body composition did not change, and BMD at the lumbar site significantly decreased with all the tested doses up to 2% [85]. Interestingly, even in the leflutrozolet trial, a significant improvement in semen parameters was observed in a subset of 139 men that provided semen samples [85].

In all the trials exploring sexual function with AIs, there was no significant amelioration of sexual functioning as measured by several tools, including IIEF [56]. In addition, data derived from leflutrozolet demonstrated a significant decrease in 'interest in sexual activity' [85]. The same trial did not report any significant change in fatigue or quality of life upon treatment,

despite a decrease and an increase in HDL and total cholesterol, respectively [85]. These findings are in keeping with an experimental study by Finkelstein et al. [86]. In a double-blind placebo-controlled experimental model of gonadotropin-releasing hormone (GnRH)-analogue-induced hypogonadism performed in 400 healthy men, it was shown that both estrogen and T deficiency contribute to the decline of sexual desire. In that study [86], 198 healthy men received a GnRH analog (goserelin acetate to suppress endogenous T and estradiol) and were randomly assigned to receive a placebo or increasing doses of T daily for four months. Another group of 202 healthy men received goserelin acetate, placebo gel or T gel, and anastrozole (to suppress the conversion of T to estradiol). In the groups that received T, the inhibition of estrogen synthesis through anastrozole was associated with significant

decreases in sexual desire when compared to the group not receiving the AI. Interestingly, body fat increased in all groups when the aromatization of T to estradiol was inhibited [86].

In order to better clarify the role of AIs on male sexual desire, we originally collected, and meta-analyzed available trials investigating the effect of AIs on libido at the end point. Overall, nine studies were collected including 457 subjects with a mean age and mean BMI of 42.9 years and 32.1 kg/m<sup>2</sup> [83,85,87–93] (Table 4). Overall, the use of AIs significantly increased the risk of low libido, up to 44% (Figure 4). Interestingly, meta-regression analysis showed that the risk of low sexual desire was inversely related to estradiol (E2) levels and increased as a function of the T/E2 ratio at the endpoint (Figure 5, Panel A-B). The latter findings were confirmed after the adjustment for age and BMI ( $r = -0.370$  and  $2.981$  for E2 and T/E2 respectively; both  $p < 0.0001$ ).

### 4.3. GLP-1 analogues

According to a recent meta-analysis on the prevalence of endocrine disorders in obese patients, a biochemical male HG resulted as the most frequent endocrine correlate to obesity, with a pooled prevalence of 42.8% and 32.7% for low total T or low free T, respectively [94]. Interestingly, total or free T deficiency was proportional to the BMI of the enrolled

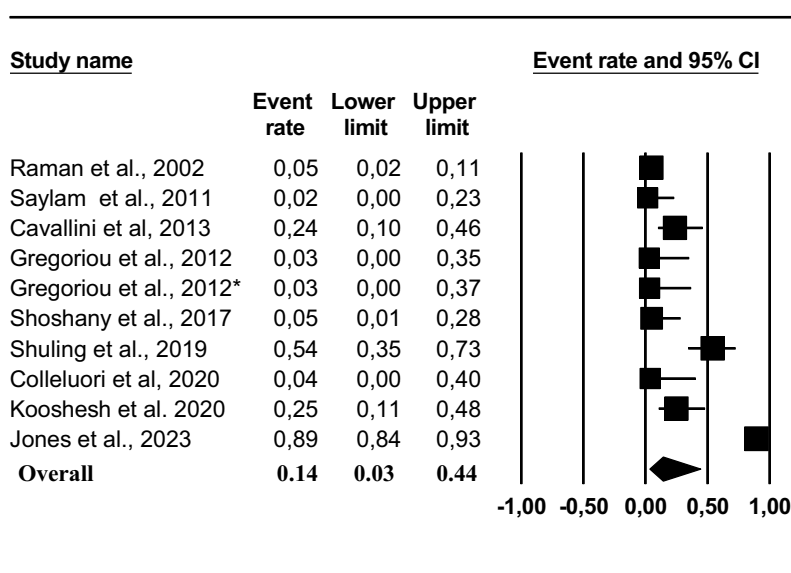
subjects [94]. Similar data were reported by our group in subjects complaining of sexual dysfunction (and therefore having a symptomatic HG). In fact, in a cohort of 750 obese subjects (BMI  $\geq 30$  kg/m<sup>2</sup>) with ED, 40.7% showed low total T ( $<10.4$  nmol/L) and 43.4% low calculated free T ( $<220$  pmol/L) [95]. In addition, in that cohort, the severity of obesity was tightly associated with the T decline (Supplementary Figure S1), even after adjusting for several confounders (age, lifestyle, chronic disease score) ( $\beta = -0.290$ ,  $p < 0.0001$ ). Mechanisms underlying the association between male obesity and HG are behind the aim of this review and were described by us elsewhere [95,96]. As a matter of fact, losing weight (any intervention) is associated with a dose-dependent increase in total and free T [13,14].

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) have been approved in several countries for the treatment of obesity and diabetes. In a recent meta-analysis examining 41 trials involving 15,135 obese participants, GLP-1RAs significantly reduced body weight (mean  $-5.319$  kg, 95% CI:  $-6.465$ ,  $-4.174$  kg) when compared to controls [97]. In particular, although direct comparisons are limited, a recent Network Meta-analysis documented that semaglutide 2.4 mg and liraglutide  $>1.8$  mg showed the best outcomes in weight loss over placebo [98]. More impressive results were obtained with tirzepatide, a dual glucose-dependent insulinotropic-peptide (GIP), and GLP-1RA (mean weight loss

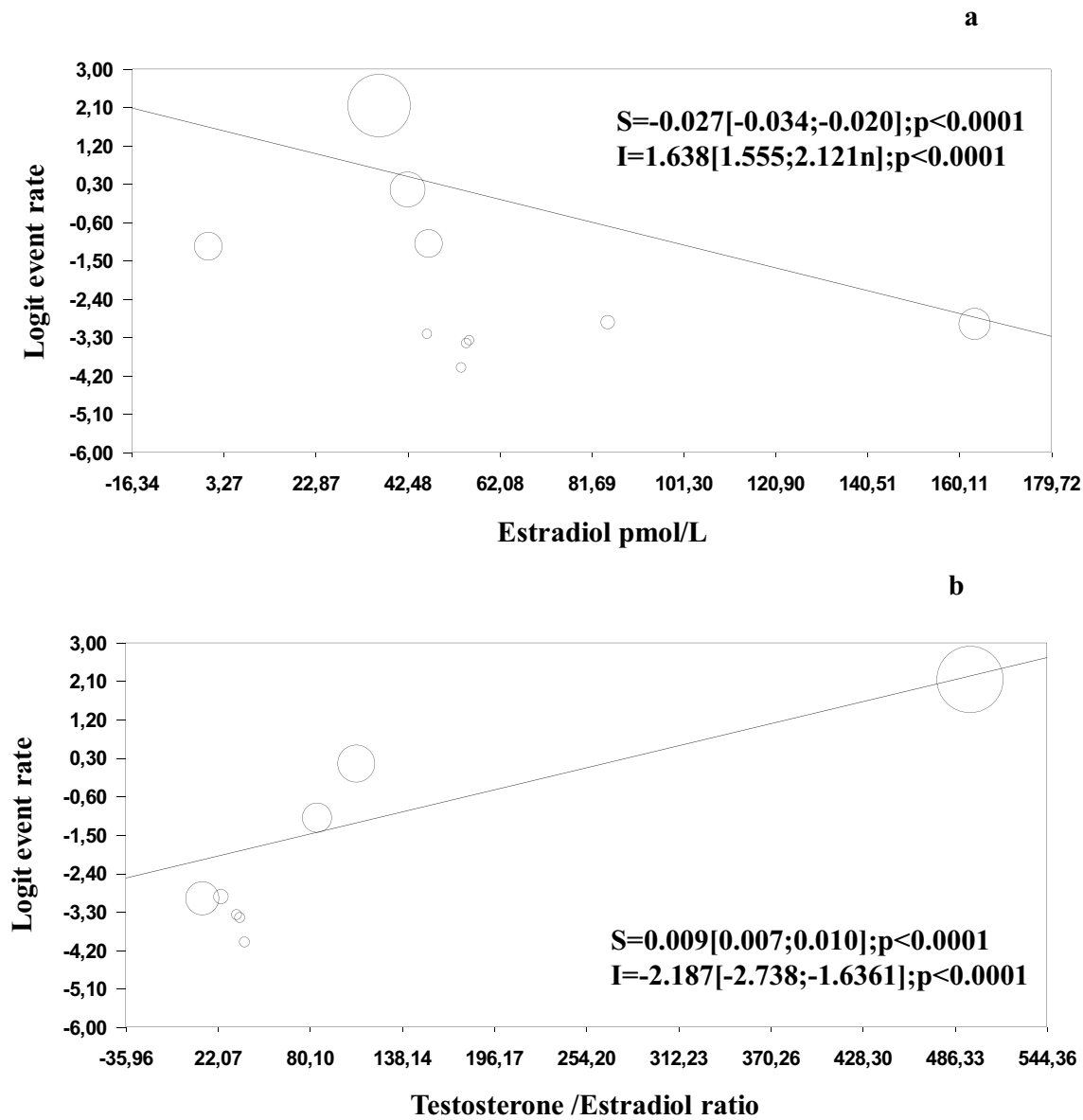
**Table 4.** Characteristics of trials on aromatase inhibitors included in the analysis.

Study	N° of subjects	Age (years)	BMI (Kg/m <sup>2</sup> )	Treatment regimen
Raman et al., 2002 [87]	104	-	-	Anastrozole 1 mg daily
Saylam et al., 2011 [88]	27	34.9	28.4	Letrozole 2.5 mg daily
Cavallini et al., 2013 [89]	22	44.0	31.2	Letrozole 2.5 mg daily
Gregoriou et al., 2012 [90]	15	-	29.9	Letrozole 2.5 mg daily
Gregoriou et al., 2012* [90]	14	-	30.2	Anastrozole 1 mg daily
Shoshany et al., 2017 [91]	20	37.0	-	Anastrozole 1 mg daily
Shuling et al., 2019 [83]	24	38.7	27.1	Letrozole 2.5 mg daily
Colleluori et al., 2020 [92]	12	52	39.6	Anastrozole 1 mg daily
Kooshesh et al. 2020 [93]	20	-	-	Letrozole 2.5 mg daily
Jones et al., 2023** [85]	199	50.9	38	Leflurozole 0.1, 0.3 and 1 mg daily

BMI = body mass index; \*same study different groups.



**Figure 4.** Rate of low sexual desire as derived from the use of Aromatase inhibitors in the meta-analyzed studies.



**Figure 5.** Effects of Estradiol (a) or Testosterone/estradiol ratio (b) on the incidence of low sexual desire after aromatase inhibitor use in the meta-analyzed studies.

with 5 mg:  $-12.47$  kg, 95% CI:  $-13.94, -11.00$  kg) [99]. With higher tirzepatide dosing (10, 15 mg), the effect was even greater [99]. Considering the efficacy of this class of compound on weight and the clear, dose-dependent, effect of losing weight on the activation of the HPT axis, we now report in a meta-analytic form the results of GLP-1 analogs on TD. The present meta-analysis is an extension of a previous one [13], considering that an additional trial has recently been published [100].

Six studies evaluating the effects of GLP-1RAs on the HPT axis were considered [100–105]. Overall, available studies accounted for 386 subjects with a mean age of  $47.1 \pm 11.1$  years, a mean BMI of  $35.2 \pm 3.9$  kg/m<sup>2</sup>, and a mean follow-up of  $31.4 \pm 19.1$  weeks (Table 5). Available studies used a mixed combination of GLP-1RAs. In particular, liraglutide and exenatide were used in two studies each, whereas one author compared the effects of liraglutide with dulaglutide, and one study enrolled a mixed population of patients treated with liraglutide or dulaglutide. Furthermore, only diabetic subjects were considered in four

studies, whereas a mixed population of diabetic and non-diabetic subjects, or only non-diabetic patients, was the objective of one study for each one (Table 5). Finally, metformin was used in combination with GLP-1 analogues in four studies (Table 5).

GLP-1RAs resulted in a significant increase in total T, cFT, and SHBG levels (Figure 6, Supplementary Figure S2 Panels A-C). Similarly, an increase in either LH or FSH levels was observed at the endpoint. (Figure 6 and Supplementary Figure S2, Panels D-E). Finally, an improvement in erectile function was also observed after GLP-1RA therapy (Figure 6, Supplementary Figure S2, Panel F). However, apart from the important improvement in IIEF-EFD scoring reported by the four available studies (more than 3 points) and the obvious changes in body composition (i.e. decrease in fat mass, visceral adipose tissue, and absolute lean mass), no other information is present up to now on other symptoms of HG, including bone health. A previous review demonstrated the positive effects of GLP-1RAs on bone turnover and strength in pre-clinical studies, but clinical studies on the topic are scanty and

often contradictory [106]. In addition, they were not focused on men with overt HG [106].

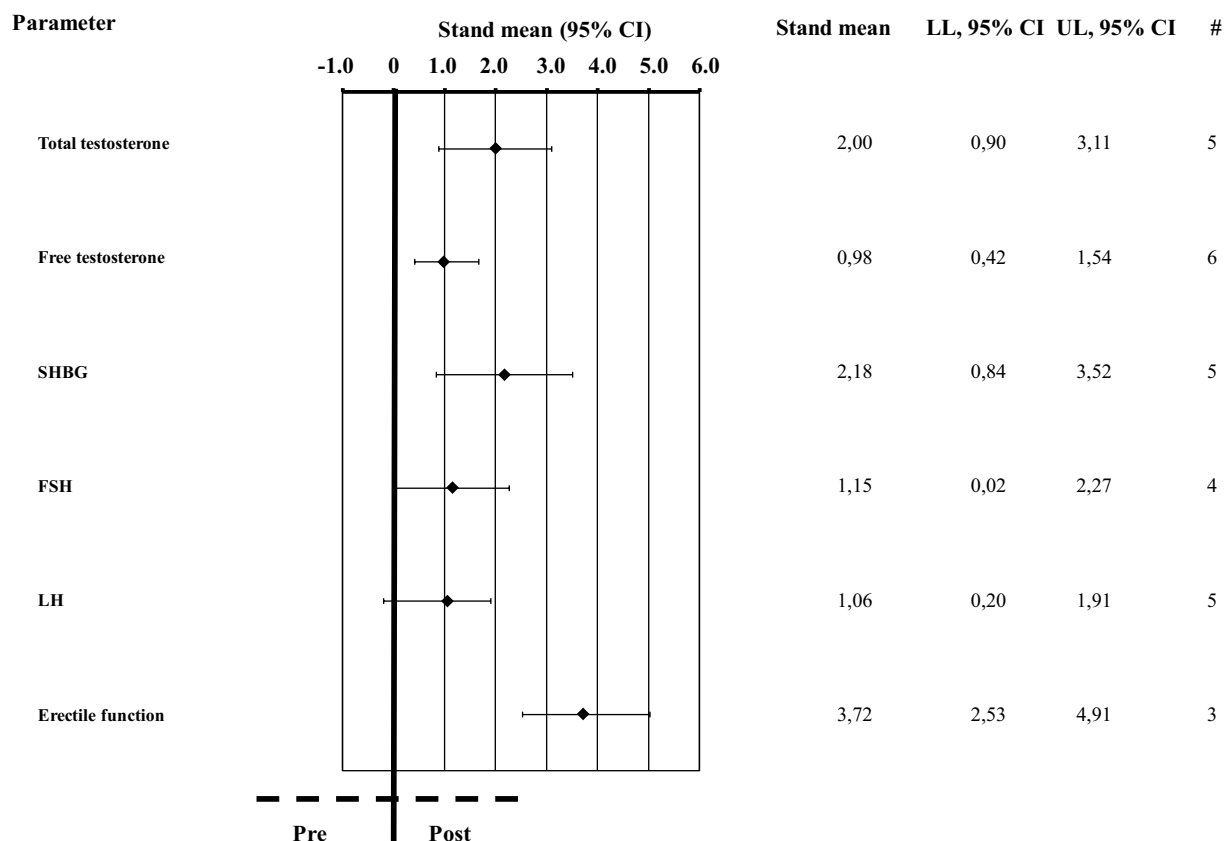
Considering that losing weight *per se* is associated with an improvement in the HPT functioning [13,14], it is obvious to speculate that the positive effect of GLP-1RAs on Gns and T is mediated by their impressive effect on body composition. Accordingly, meta-regression analysis demonstrated a positive relationship between GLP-1RA-induced weight loss and T rise ( $S = 0.361[0.249;0.472]$ ;  $p < 0.0001$  and  $I = -0.449[-1.562;-0.789]$ ;  $p = 0.429$ ; see also Supplementary Figure S3). However, several preclinical studies demonstrated the possible action of this class of medications on the hypothalamus. In the rat clonal hypothalamic cell line rHypoE-8, as well as in GT1-7 GnRH-producing neurons and in primary cultures of fetal rat brain, GLP-1 increased Kisspeptin-1 (KISS-1) gene expression, therefore increasing the

expression of GnRH mRNA [107]. A relative increase in hypothalamic gene expression of KISS-1, its receptor (KISS-1 R), and GnRH upon two months of liraglutide administration was also observed in a diabetes-induced secondary HG in male rats [108]. The same study also observed positive effects on diabetes-induced testicular dysfunctions [108]. It is interesting to note that similar results were also obtained by us in the rabbit model of metabolic syndrome (MetS) by just changing body composition through endurance physical exercise [109,110]. Hence, it is difficult to understand whether the positive effects of GLP-1RAs on HPT are mainly due to a direct effect on the hypothalamus or just related to a drug-related, positive effect on body composition. A recent study in humans failed to demonstrate any effect of eight hours of intravenous infusion of GLP-1 on HPT in 18 healthy men in single-blind, randomized, placebo-

**Table 5.** Moderators and outcome variables in individual studies included in the meta-analysis.

Study (Ref.)	Location	Type of study	FU (wk)	Age (yr)	BMI (kg/m <sup>2</sup> )	DM (%)	Type of drug	TT (nmol/L)	IIEF
Shao et al., 2018 (100)	Harbin, China.	CBA	12	43.0	30.5	100	Exenatide and metformine	12.9	-
Jensterle et al., 2019 (101)	Ljubljana, Slovenia	RCT	16	43.9	43.2	40	Liraglutide	7.6	-
Giagulli et al., 2020 (102)	Bari, Italy	CBA	52	51.1	33.5	100	Dulaglutide and metformine	9.4	IIEF5
Giagulli et al., 2020 (102)	Bari, Italy	CBA	52	48.9	34.0	100	Liraglutide and metformine	8.9	IIEF5
Graybill et al., 2021 (103)	Houston, TX, US	BA	24	57.6	34.9	100	Exenatide and metformine	11.5	-
La Vignera et al., 2023 (104)	Catania, Italy	CBA	12	26.0	36.0	0	Liraglutide	4.8	IIEF5
Lisco et al., 2023 (99)	Nary, Italy	BA	52	59.0	34.0	100	Liraglutide or Dulaglutide and metformina	10.4	IIEF5

All data are reported as mean  $\pm$  standard deviation. FU = follow up (weeks); DM = diabetes mellitus; BMI = body mass index; TT = total testosterone; IIEF = international Index of Erectile Function. BA = Controlled cohort before-and-after comparisons in the same group of patients; RCT = randomized controlled trials CBA = Controlled before-and-after study between two or more groups of participants receiving different interventions.



**Figure 6.** Weighted standardized mean differences (with 95%CI) on hormonal parameters and erectile function after Glucagon-like peptide-1 (GLP1) analogue treatment at endpoint. LH= luteinizing hormone; FSH= follicular stimulating hormone. Data were reported and standardized mean for graphical purposes.



controlled trials [111]. Similar negative results were also published previously [112].

One possible limitation regarding the use of GLP1RAs in the andrological field is related to limited information regarding the impact of these medications on sperm production. Preliminary data have shown that weight loss induced or maintained with liraglutide is associated with sperm parameters improvement [113]. Data derived from a mouse model of experimental induced diabetes concluded that liraglutide resulted in amelioration of sperm count and chromatin condensation and DNA integrity in diabetic animals [114]. No information related to semaglutide is available. However, a recent meta-analysis showed that weight loss whatever obtained resulted in sperm parameter improvement. Hence, an improvement or at least no modification in sperm parameters induced by the use of GLP1RAs is conceivable.

## 5. Conclusions

During the last ten years there have been important FDA approvals for new TRT formulations, including oral and nasal preparations. However, all these formulations are not still available in other countries. All three new oral formulations for TRT employ T undecanoate (TU) and are based on the self-emulsifying delivery system; (SEDDS) technology, although with differences in the relative constituents. The main advantage over the older oral formulation of TU (Andriol) is their independence from being tacked with a fat meal, although regular meals favor their absorbance. Besides class-associated side effects (increase in hematocrit), gastrointestinal side effects and a mild increase in blood pressure (BP) are reported in trials [23,24,28,29]. Hence, the FDA required a black box warning that these drugs can induce a BP rise that might increase the risk of MACE. According to the FDA, the use of oral TU preparations should be limited to hypogonadal conditions associated with structural or genetic etiologies (the so-called organic hypogonadism) [115]. However, all the trials available with these oral preparations did not enroll subjects with organic HG but subjects with the functional form [23–30]. In addition, a modest increase in BP was also noted in the recently published TRAVERSE trial employing a T gel formulation, although no increased MACE events over placebo were observed [34]. Both the JATENZO and Tlando trials showed improvement in HG symptoms, including sexual ones [23–28]. According to published trials, nasal T (NT) administration is less often associated with a hematocrit increase [38] and with suppression of the HPT axis [39–41], although 90% of treated subjects reached eugonadism [37]. However, these studies with NT are often uncontrolled, of short duration, and based on small cohorts of treated subjects. In addition, multiple administrations of NT are needed to reach physiological levels, therefore non-respecting physiological rhythms of T oscillation. The same problem is shared by the new oral TU preparations. Even the new injectable TU preparation, recently approved by the FDA (AVEED), does not respect the normal circadian rhythmicity of T, and although it guarantees a relatively constant level of T in the treated patients over a 10 week period [46]. This property of injectable TU preparations suggests its main employment in subjects with a chronic, often

irreversible, HG condition, as suggested by a recent guideline [7]. Although there is an FDA black box for POME with these injectable TU preparations, real-life data are reassuring [48]. Considering that the risk of forthcoming prostate cancer upon TRT seems not to be consistent according to all guidelines [5–11] hematocrit increase is the main concern with all TRT preparations, and clinicians should routinely check for it during any TRT treatment [51].

Another important concern for TRT is fatherhood desire in the future, and no TRT preparation is indicated in this case, with Gns treatment as the main indication for subjects with secondary HG [15]. Apart from Gns, off-label antiestrogen administration is widely used to treat male infertility in those with and without TD, with relative success. In fact, meta-analyses of infertile populations demonstrated improvement in semen parameters either with SERMs [53–55] or with Als [81,82]. Considering that with both SERMs and Als, an increase in HPT activity was often observed (see also Figures 2 and 3), these medications were also tried for the treatment of male HG. However, the available results were overall discouraging [15,84,85]. We here meta-analyzed the side effects reported by several trials with Als in male infertility and found that treatment increased the risk by 44% of any degree of low sexual desire (Figure 4). The effect of SERMs treatment on sexual symptoms is less clear. Upon SERMs, a meta-analysis of observational trials found some improvement in scoring in the ADAM questionnaire [55], a rather nonspecific instrument to evaluate HG symptoms [66]. However, three RCTs [67–69] did not confirm such a result, and in one RCT [68], the improvement in ADAM scoring in the placebo arm was similar to that reported in the meta-analysis of uncontrolled trials [55]. A similar figure was observed with body composition. In two RCTs, no significant amelioration was observed on metabolic parameters or on WC [68,70], while with TRT, the effect was clearly apparent [32,71,72]. In addition, results with SERMs on bone health were quite discordant [73–77], most probably depending on the rate of agonistic activity on the skeletal estrogen receptor (ER) of the SERMs tested.

Encouraging results were obtained with GLP-1RAs, a class of anti-diabetic medications approved for obesity treatment [97,99]. In particular, semaglutide (2.4 mg weekly subcutaneous injections) not only improved body composition but was also superior to placebo in reducing the incidence of a composite of death from CVD (including nonfatal myocardial infarction, or nonfatal stroke) at a mean follow-up of 39.8 months [116].

## 6. Expert opinion

During the last decade, several new formulations on TRT have been introduced in the market, including oral, transdermal, and parenteral formulations. Trials demonstrating their efficacy for FDA approval were often (if not always) enrolling subjects with functional HG, although the same FDA claimed that TRT is approved only for treating the organic form (however, we are not aware of any placebo-controlled trial with TRT enrolling just organic HG) [115]. In functional HG, several Societies suggest life-style changes as the main strategy to treat T deficiency [5–7]. In fact, weight loss and physical exercise (PhyEx) are able to increase

T levels in functional HG [13]. Preclinical studies in a rabbit model of MetS-related HG suggested that just doing endurance physical exercise is able to restore regular functioning of the HPT axis and is associated with amelioration of ED [109]. However, in a subsequent study [110], we demonstrated that rabbits with MetS were less able to perform PhyEx, than their regular diet (RD) counterparts, because of consistent weakness due to alterations in the lean, muscular mass. Interestingly, treating these rabbits with TRT restored regular functioning of the altered muscular compartment [110]. In particular, in MetS rabbits, TRT increased the expression of myogenic/differentiation markers and induced the expression of mitochondrial respiration enzymes, therefore restoring mitochondrial ultrastructure, succinate dehydrogenase activity, ATP production, and normalizing MetS-induced reduction in oxidative fibers [110]. As a final result, MetS rabbits treated with TRT were able to perform the same endurance performance as RD rabbits [110]. Interestingly, treatment of RD, eugonadal, and rabbits with T did not ameliorate physical performance, although it increased muscle fiber diameter [110]. These preclinical findings might justify the contradictory results on the effect of T administration on unselected elderly populations on muscle strength, as demonstrated by several meta-analyses (reviewed also in [7]). A recent meta-analysis involving only older men with TD at baseline indeed showed a significant improvement in muscle strength upon TRT at upper and lower extremities, as well as in handgrip, although to a limited extent (Hedges's  $g = 0.21$ ), with a major effect through intramuscular injection (Hedges's  $g = 0.74$ ) [117]. In addition, the beneficial effect was proportional to the severity of TD [117]. Another recent meta-analysis compared results on muscle strength obtained with androgen administration alone, PhyEx alone, or the combination of the two [118]. Although a significant improvement in muscle strength was observed with all treatments, the combination was superior to the two isolated interventions [118]. These findings suggest that TRT in functional HG might help to initiate changes in lifestyle, as performing PhyEx might, and that the two interventions might even be initiated even simultaneously. This point was essentially accepted in one recent guideline [7]. As soon as the change in lifestyle is adopted, TRT could eventually be discontinued. At this light, short-acting TRT preparations (e.g. gel, oral, intranasal) could be more useful than long-lasting preparations (as injectable TU), because it has been demonstrated that upon 2 years of treatment with injectable TU, the HPT axis required up to twelve months to be restored from the drug-induced suppression of HPT [119]. Among the new short-acting preparations recently available, NT seems more innocuous in term of endogenous HPT functionality [39–41]. However, all the studies released up to now are based on uncontrolled trials enrolling small cohorts of subjects. In addition, it is not clear whether NT will be, at a patient level, the more convenient way of administration and its relative suitability for long-term use. Published studies with the new oral preparations suggest that they can efficiently treat not only the biochemical TD but also its related symptoms, reaching eugonadism in more than 80% of the treated subjects [23,24]. However, considering the twice daily administration of the oral preparations, they do not respect the circadian variation of endogenous T, as gels did [16]. There is the same problem with NT (t.i.d. administration). Hence, the main short-term physiological

route of T administration is, in our opinion, the once-a-day, early morning, transdermal administration of TRT. Being the more physiological route of TRT administration, transdermal administration could even represent the most versatile way of discontinuation, in case lifestyle measures were adopted and body composition accordingly changed by the patient with functional HG. In our opinion, long-acting preparations should be mostly employed in patients with an organic, irreversible HG condition [7].

Antiestrogens are considered respectful treatments for conserving a functional HPT axis in subjects with functional secondary HG. SERMs and AIs increase seminal parameters in infertile subjects [53–55,81,82], along with an increase in HPT axis activity (Figures 2 and 3). Hence, during the last decade, they were tested as a possible treatment for functional HG. The results are somehow discouraging. Enclomiphene (Androxal) research was officially abandoned by Repros Therapeutics, and a recently published trial with AI leflutrolole reported quite negative results on HG symptoms, despite a consistent activation of HPT. IIEF did not increase, and libido was significantly reduced [85], as predicted by the Finkelstein trial [86]. Interestingly, low libido was the most common complaint reported in trials with AIs for infertility (Figure 4), and the frequency of this relevant side effect was proportional to the degree of estrogen suppression by the AI (Figure 5). This is not surprising either in light of preclinical studies. A recent study in sexually naive mice [120] strongly suggests that estrogen receptor- and TAC1-positive neurons in the bed nucleus of the stria terminalis (BNST), having aromatase (ARO) activity, after receiving chemosensory cues, project to the median preoptic area (MPA) of the hypothalamus, where receptors for TAC1 are present. In males, the aforementioned network of estrogen-sensitive, dedicated neurons in BNST has important activity in discriminating potential female mates. Thereafter, activation of dopaminergic VTA neurons modulates reward in the nucleus accumbens [120], therefore promoting rewarding sexual desire.

Obvious bone-related side effects were also reported in the leflutrolole trial [85]. Hence, in our opinion, AIs are not a useful tool for treating symptomatic male HG. As far as SERMs are concerned, results are more conflicting because meta-analysis of observational trials reported some improvement in HG symptoms [55] but results in RCTs were less encouraging [67–70].

GLP-1RAs represent a new putative tool for the treatment of functional HG in particular, for massive obesity-associated HG. Trials available till now all demonstrated efficacy in activating the HPT axis in obese subjects with TD [13], with an effect that is directly related to the entity of weight loss [13]. To treat obesity, subcutaneous liraglutide daily injection was FDA-approved in 2014 and subcutaneous semaglutide was FDA-approved in 2021 and is dosed once weekly [121]. Although these medications are very effective in inducing relevant weight loss during treatment [121], weight gain is often observed after drug discontinuation [122]. If lifestyle measures were not adopted, it is possible that also the beneficial effects of overcoming the obesity-related TD will be lost after GLP-1RA discontinuation, although dedicated studies are not yet available. It is, however, interesting to note that from the few available studies meta-analyzed here and before [13], the benefit of GLP1-RA in ameliorating erectile function (IIEF-

EFD) overcome those observed in a previous [123] and recent meta-analysis with TRT [124]. This could be most probably related to the beneficial effect of this class of compounds on the CV system (a conclusion), being penile erection a neuro-vascular event.

In conclusions, although different on-label and off-label options are available, the management of testosterone deficiency should be based on a tailored approach according to the type of hypogonadism (organic vs., functional), age, comorbidities and patient needs.

## Funding

This paper was funded by Next Generation EU grant DM 1557 11.10.2022.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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**Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*) to readers.**

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