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REVIEW

Pharmacological management of late-onset hypogonadism

Giulia Rastrelli[a], Mario Maggi[a,b] and Giovanni Corona[a,c]

[a]Sexual Medicine and Andrology Unit Department of Experimental Clinical and Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy; [b]I.N.B.B.—Istituto Nazionale Biostrutture e Biosistemi, Rome, Italy; [c]Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Bologna, Italy

ABSTRACT

Introduction: The frequency of late-onset hypogonadism (LOH) ranges between 2 and 15%. Up to 85% of LOH is due to a functional impairment of the hypothalamus–pituitary–testicular axis, mostly secondary to metabolic conditions.

Areas covered: This paper provides a comprehensive review of all the available medications for treating LOH, including antiestrogens, gonadotropins and testosterone therapy (TTh). In addition, the evidence on clinical outcomes of these treatments is provided by meta-analyzing the results from the available randomized clinical trials.

Expert commentary: The present data indicate that antiestrogens are able to increase testosterone levels without changing gonadotropins or even increasing them. Therefore, they may maintain, and even to stimulate spermatogenesis. However, their efficacy in treating LOH-associated symptoms has been scarcely tested and their use in LOH is off-label. In contrast, gonadotropins are indicated for hypogonadism, in particular when fertility is required. Information on the effects of gonadotropins on LOH is scanty and the impractical administration limits their use. TTh can be administered with different modalities, making it a suitable option for LOH, when fertility is not desired. The available meta-analyses show that TTh is able to improve sexual function and body composition, with more evident results obtained with transdermal and injectable preparations.

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Late-onset hypogonadism; treatment; testosterone therapy; selective estrogen receptor modulators; aromatase inhibitors; meta-analysis; randomized clinical trials

1. Introduction

Late-onset hypogonadism (LOH) is a medical condition essentially characterized by hypogonadism (HG), i.e. testosterone (T) deficiency, with an exordium in adulthood. Spermatogenesis may be also affected, although infertility is not the main complaint and it is not required to define the condition [1–3].

When T deficiency orchestrate its effects during early prenatal life (very early onset hypogonadism, VEOH), the associated symptoms can be very severe, ranging from an almost complete feminine body shape (complete androgen insensitivity) to minor defects in virilization, including micropenis, cryptorchidism and hypospadias, as sometimes in the case of congenital hypogonadotropic HG [4–6]. Hence, the resulting phenotype is severely affected. However, the prevalence of VEOH is relatively low (1:10.000–100.000). In the case of the more common (1:500–1000) peripubertal appearance of HG (early-onset hypogonadism, EOH), because of central conditions (e.g., pituitary tumors, as germinoma) or testicular failure (e.g., Klinefelter's syndrome), there might be a slowing or delaying of puberty progression, with an eunuchoid habitus, including long legs and arms, scant body hair, high-pitched voice, small testis and prostate [4,5].

In the case of an adulthood onset of HG (LOH), the symptomatology is often vague and the phenotype almost superimposable to that of eugonadal men. Symptoms and signs associated with LOH could be physical (weakness, decreased muscle mass, visceral obesity, osteoporosis), psychological (depression, fatigue, impaired memory) or sexual (decreased libido and impaired spontaneous or sexual-related erections). In a cross-sectional survey of the European general population (European Male Aging Study; EMAS), it was found that only sexual symptoms specifically clustered with low T [7]. This has been confirmed in a longitudinal extension of the same study, where it was demonstrated that worsening or developing sexual symptoms were associated with incipient secondary [8] or primary [9] HG (SHG and PHG, respectively). In line with these and previous results [8,9] almost all the andrology Scientific Societies recommend the presence of sexual symptoms, along with the biochemical demonstration of low T, to define a clinically relevant LOH [1–3]. Symptomatic LOH is a relatively common condition (1:50–100) and it can be due to a central (hypogonadotropic or secondary HG) or a peripheral (hypergonadotropic or primary HG) impairment in T synthesis. The former is six time more common than the latter in both the general population [10] and in subjects consulting for sexual dysfunction [11].

Recently, HG has also been classified according to its reversibility and to the demonstration of an organic perturbation in the hypothalamus–pituitary–testis (HPT) axis [12]. When the latter condition is verified, HG is termed *organic*; otherwise, HG is considered *functional*. In particular, functional HG is

CONTACT Giovanni Corona jocorona@libero.it Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Largo Nigrisoli, 2-40133 Bologna, Italy

characterized by 'no recognizable structural intrinsic HPT axis pathology' and by the lack of 'pathologic etiologies' [12]. Hence, it is a diagnosis of exclusion. Because of its functional nature, it may be reversible, if due to SHG [12]. Functional HG is often due to a deterioration of the HPT activity, due to morbidities impairing HPT axis function or to aging [12,13]. Recently, the role of aging in determining T deficiency has been questioned, in particular for SHG [12]. In fact, the mild decline in T associated with age is considered mostly related to a time-dependent accumulation of morbidities. Metabolic disturbances, such as type 2 diabetes mellitus (T2DM), obesity and metabolic syndrome (MetS), are the main morbidities associated with functional HG [12–15].

In a large series (n = 4220) of subjects consulting for sexual dysfunctions––and, therefore, potentially characterized by low T––LOH (i.e. total T below 10.4 nmol/L) was found to be very common [16]. In fact, 17.4 and 3.2% of the patients satisfied criteria for SHG and PHG, respectively. Of those, only 15% had organic HG, whereas the majority (85%) were allocated into the functional category, due to the lack of a specific etiology. Metabolic disturbances (T2DM, obesity and MetS) were present in 2/3 of the subjects with functional HG [16].

2. Non-pharmacological management of LOH

Since LOH in subjects consulting for sexual dysfunction (and therefore symptomatic) is often related to metabolic disturbances––such as T2DM, MetS or obesity––treating the underlying metabolic condition may be the most rationale approach. This view has been formalized by Grossman & Matsumoto in the already cited perspective paper [12], where, in subject with obesity-related functional HG, weight loss is strongly suggested before considering T substitution. Weight loss can be achieved through intensive lifestyle modification with or without anti-obesity medications or through bariatric surgery. A meta-analysis on the effect of low-calorie diet (LCD) on total T (TT) indicates that LCD can induce an average increase of 2.87 (1.68–4.07) nmol/L [17]. Unfortunately, the success of LCD is low and ranges between 2 and 20%, and it is often difficult to maintain in the longer term [18]. A greater T increase can be achieved through bariatric surgery, which results in an average increase of 9.19 (6.75–11.64) nmol/L and 88.85 (62.99–114.72) pmol/L in TT and calculated free T (cFT), respectively, as derived from a recent meta-analysis [17]. The increase in T was accompanied by an increase in gonadotropin (Gn) levels of more than one unit per liter [17], thus suggesting that weight loss partially restores HPT axis. This effect might be related to the decrease in circulating estradiol (on average 23 pmol/L), which could result in a decreased negative feedback on the axis [19,20], although this hypothesis was questioned in cohort studies from general [10] or diabetic [21] populations. In obese men, also physical activity, in particular moderate-intense aerobic exercise, induces an increase in TT and cFT levels [22–24]. Although reported by only one study, this was associated with an improvement in sexual functioning [25]. The effect of physical activity on T seems to be greater than LCD [26]. Hence, lifestyle changes (exercise more, eat less and adopt a healthier lifestyle) are strongly suggested as the first intervention in subjects with HG, particularly those with metabolic disturbances.

3. Pharmacological management of LOH

The pharmacological management of T deficiency, including LOH, essentially lies in increasing T. As mentioned before, this can be achieved by removing the underlying conditions causing HG (e.g. combating obesity or treating prolactinoma) or using pharmacological approaches able to overcome the deficiency. Concerning the latter, the scenario may change according to the nature of HG. In PHG, the only possible pharmacological therapy is administering exogenous T [27,28]. Several options are available for treating SHG (the most common form), including increasing endogenous Gns [pulsatile Gn-releasing hormone (GnRH), antiestrogens], treating with Gns themselves or treating with T [27,28]. The first two options favor reproduction and fathering, whereas the latter does not. In fact, exogenous administration of T suppresses the HPT axis, including follicle-stimulating hormone (FSH) and, therefore, spermatogenesis is usually impaired.

3.1. Antiestrogens

The rationale for the use of antiestrogens in HG is that estrogens down-regulate the HPT axis by binding to their cognate receptors (estrogen receptor α and β; ERα and ERβ) on the hypothalamus and pituitary. Antiestrogens prevent estrogens from performing this physiological action by inhibiting their binding to the receptor, as in the case of selective ER modulators (SERMs), or by downregulating the enzymatic activity of aromatase, as in the case of aromatase inhibitors (AI). In both cases, the blockage of estrogen activity on HPT axis results in an increased stimulation of the testes and, consequently, in increased T levels. From these mechanisms, it follows that antiestrogens can be successfully used only in SHG; however, their use for this indication is still 'off-label'.

In men, they have been studied for their effects on spermatogenesis and fertility outcomes in either idiopathic infertility or T deficiency [29,30]. A further application in andrology is the treatment of obesity-related SHG. In fact, although there is not total agreement on the matter, it has been hypothesized that the excess of adipose tissue could lead to increased aromatase activity with higher estrogen levels, which could affect, in turn, the HPT function [31,32]. However, the possibility that adipokines such as TNFα could have a direct role on obesity-related SHG cannot be excluded. Accordingly, a recent study using human fetal hypothalamic GnRH neurons indicates that TNFα could impair Kiss1 signaling by interfering with Kiss1 receptor activity [33].

3.1.1. Selective estrogen receptor modulators

SERMs are characterized by a nonsteroidal structure, which, however, allows for the binding to ERs with an agonist or antagonist effect, depending upon the target tissue.

Available SERMs are now classified into two main groups: the first-generation triphenylethylene derivatives, which include clomiphene citrate (CC), tamoxifene and toremifene,

and the second-generation benzothiopene derivatives, which include raloxifene. Further SERMs more recently introduced are basedoxifene, ospemifene, and losofoxifene. All the aforementioned molecules have been approved only in women.

CC is a non-racemic mixture of two stereoisomers, enclomiphene (ECC)––the trans-isomer that represents 62% of the mixture––and zuclomiphene––the cis-isomer that represents 38% of the mixture [34,35]. ECC exhibits a pure antiestrogen effect, whereas zuclomiphene has a mixed action [34,35]. In addition, ECC has a shorter half-life than zuclomiphene (10 h vs. 30 days) [34,35]. CC is currently approved for attainment of pregnancy in women with ovulatory dysfunctions and its action relies on the increase of Gn secretion, obtained by the inhibition of estrogen activity on the hypothalamus and pituitary. The same mechanism is able to increase T levels in men and, for this reason, CC is used 'off-label' also for treating male HG. The pure antiestrogen effect, together with its shorter half-life, makes ECC the ideal molecule for treating gonadal dysfunctions in both sexes. In fact, the use of ECC alone could maximize the desired effect and minimizing the unwanted ones [36]. Indeed, ECC is currently in the pre-registration phase and undergoing review by the FDA and the European Medicines Agency for its use in male HG.

In males, all SERMs have a similar biological profile, showing an antagonistic effect on ERs in hypothalamus and pituitary [27,28]. In addition, they could have agonistic effects on bone, thus preventing from osteoporosis, which may occur in HG men. On the other hand, their agonistic effect on venous vessels could predispose men to the development of venous thromboembolic disease, which represents the most important side effect in men, although its absolute risk appears quite limited [37,38].

3.1.2. Aromatase inhibitors

AIs prevent androgens from being converted into estrogens by aromatase. They are classified into steroidal (testolactone and exemestane) and nonsteroidal (anastrozole and letrozole). While testolactone is not commercially available, exemestane, anastrozole, and letrozole are currently used for treatment of breast cancer in women. In men, the reduction in estrogen levels has been hypothesized as a possible mechanism for increasing T levels without blunting Gns [27,28,31,32]. This characteristic allows us to hypothesize their clinical application for improving spermatogenesis and fertility and for increasing T levels in HG men, particularly those with obesity-related SHG.

3.2. Gonadotropins

Gns stimulate the endogenous production of T by the testis without affecting its oestrogen-mediated actions. In this view, they represent the most physiologic therapy for LOH, when testicular function is intact (SHG). T production is stimulated by luteinizing hormone (LH); hence, molecules mimicking its action are sufficient for treating HG men who are not concerned about fertility [39]. However, since parenthood is increasingly sought later in life, FSH therapy could be required also in LOH.

LH actions could be mimicked by using human chorionic Gn (hCG), which has a longer half-life than native LH, thus allowing a viable schedule for clinical practice [27,28]. It could be obtained by the purification of urine from pregnant women. This represents a widely used source of hCG with limited costs of production/purchase. A more expensive alternative is represented by recombinant hCG (rhCG) or LH [27,28]. However, both the recombinant molecules are registered for treatment of female infertility; hence, any use in men is 'off-label'. Extractive hCG is registered for the use in male HG with a dose ranging between 1000 and 2000 UI injected intramuscularly or subcutaneously up to three times a week. hCG therapy is safe and generally well tolerated. Adverse events are infrequent and they are mainly represented by gynecomastia and acne, which occur in less than 10% of cases [40]. Despite the excellent safety profile, the use in LOH is limited––unless fertility is required––because of the cumbersome administration and treatment schedule.

3.3. Testosterone preparations

Since native T undergoes a prompt hepatic metabolism, it cannot be administered by oral or intravenous route. Hence, chemical modifications were developed to improve T bioavailability and pharmacokinetics, essentially retarding liver catabolism or enhancing T availability.

In LOH, the goal of T therapy (TTh) is to restore serum T levels to the mid-normal range approximating the natural, endogenous production of the hormone, without significant side effects or safety concerns and alleviating the symptoms suggestive of LOH [1–3]. Since T plasma production rate was estimated as 6.9 mg/day in normal men [41], the same amount of T should be replaced, when there is a deficiency. However, in the elderly, there is a physiological decline of T production rate [42,43], which is smoothed by a reduction in its metabolic clearance rate [44]. In addition, in the aging male, the biological activity of T is also decreased by a physiological rise in sex hormone binding globulin (SHBG). SHBG is a protein that binds tightly to T, therefore impairing its effects on target tissues, as evidenced by a SHBG-induced reduction in hematocrit and prostate specific antigen (PSA) levels [45]. Hence, the actual dose needed for T substitution in LOH is a matter of debate.

At present, different T formulations are available for TTh. They can be administered orally, by injection (transdermal or subcutaneous implantation), transdermally (gels, axillary solution and patches) or transmucosally (buccal and nasal systems).

3.3.1. Available oral testosterone preparations

3.3.1.1. Testosterone undecanoate. T-undecanoate (TU) is a long chain fatty acid ester of T, absorbed by the intestines into lymphatic system lacteals, therefore bypassing the liver and enabling T delivery into the systemic circulation. Oral TU has been available since the end of the 1970s in oleic acid (Andriol) or, as recently reformulated, in a mixture of castor oil and propylene glycol laureate (T undecanoate caps), to allow the drug to be maintained at room temperature without any degradation of the product. TU is formulated in gel capsules to make up 40 mg. When ester weight is subtracted, the dose comes out to 25 mg of raw T per capsule. Its bioavailability is relatively poor: around 7%. Hence, a 40 mg capsule will theoretically deliver 1.75 mg of active T. However, the absorption with this

formulation via lymphatic route is rather unpredictable because it strongly depends upon the dietary fat content, with 20 g of dietary fat the minimum for a proper absorption [1–3,5]. In fact, when oral TU is taken on an empty stomach, studies have demonstrated an extremely low absorption and bioavailability. Oral TU dosages should be split into two or three evenly spaced administrations because it produces short-lived peaks of a few hours duration. Hence, one or two 40 mg caps should be taken twice or thrice daily during meals. Oral TU has the advantages of flexible dosage, self-administration and immediate decrease in T serum levels after interruption of treatment. Oral TU might be particularly suited to elderly patients because the oral administration route is convenient, the dose can easily be titrated to individual needs and the preparation can be discontinued quickly as needed.

3.3.1.2. Mesterolone. Mesterolone (1α-methyl-4,5α-dihydrotestosterone) is a derivative of 5α-dihydrotestosterone (DHT), the most active ligand for the androgen receptor. The methyl group in 1α position enhances its resistance to hepatic metabolism. Similar to DHT, mesterolone cannot be converted to estrogen through the activity of P-450 aromatase, hence it does not share the full spectrum of biological actions of native T. Accordingly, mesterolone relatively maintains Gns and this can represent an advantage in some contexts, such as fertility preservation. However, the lack of a full spectrum of T bioactivity––and in particular on bone metabolism––strongly limits its attractiveness. Mesterolone is prescribed at a daily dose of 50–100 mg and should be taken in two to three evenly spaced dosages [1–3,5].

3.3.2. Available injectable testosterone preparations

Subdermal implantations and intramuscular injectable preparations of T are the earliest employed routes of T administration. In fact, they have been used since the first half of the last century.

3.3.2.1. Subdermal implantation of T pellets. The subdermal implantation of T pellets is nowadays available only in few countries, such as the US, UK and Australia. The pellets, made of pure crystals of T compressed into short rods, are implanted, under local anesthesia, into the subdermal fat through an incision in the lower abdominal or upper buttock skin [1–3,5]. One commercially available pellet preparation (TESTOPEL) contains 75 mg of pure T. Implants of 2–6 pellets (150–450 mg) subcutaneously every 3 to 6 months are recommended. Implant site infections (cellulitis and abscess) and/or pellet extrusion are quite frequent (5–10%) adverse events. Overall, the procedure is invasive and may be unattractive for patients. However, subdermal T implants still offer the longest and most stable T release with prolonged steady-state delivery characteristics.

3.3.2.2. Intramuscular injectable preparations. Intramuscular injectable T preparations can be categorized according to their half-lives into short-, mid- and long-lasting preparations [1–3,5].

T propionate (TP) belongs to the first category. TP was the first ester introduced on the market, supplied as Testoviron by Schering AG since 1937. TP is a short-term formulation, requiring the administration of 2–3 doses weekly (usually 50 mg every two or three days). This limits its attractiveness, although it is still available on the market worldwide. Wide fluctuations in T plasma levels upon TP administration represent a further problem. In fact, some patients perceive these fluctuations as a bothersome feeling of variations in well-being, sexual capacities, and emotional stability [46].

Similar problems are shared by longer chain esters, such as T cypionate (TC) and enanthate (TE) that belong to the second category of mid-lasting T preparations. Thanks to the longer aliphatic chain in 17β-position, TC and TE are injected every 2–4 weeks at a dose of 200–250 mg [1–3,5]. TE has been the most widely used form of TTh for decades. After the intramuscular administration, TC and TE are hydrolyzed in site to release testosterone slowly over time, justifying their relative long half-life. However, serum T levels have large fluctuations, as they are even supraphysiological in the first few days, and then decline to subphysiological levels in the last few days. Besides their consequences on symptoms, the supraphysiological levels of T could frequently result in dangerous side effects, such as polycythemia [46–48]. In addition, rare post-marketing reports [49] have described the urge to cough, coughing fits, and respiratory distress immediately after TE injection, due to the oil-based depot preparation reaching systemic circulation accidentally.

More recently, a long-lasting injectable formulation of TU has been introduced [46,50]. TU is prepared through the esterification of the 17β position with undecanoic acid, a straight chain, 11-carbon-saturated medium-chain fatty acid. The fatty acid medium length side-chain increases half-life in comparison to other esters. Injectable TU in tea seed oil was first marketed in China, where TU 500 mg was administered every 4 weeks [46,50]. TU was then reformulated in 250 mg/ml castor oil (corresponding to 157.9 mg/ml of T), which further improves its duration. It was first developed and produced by Bayer HealthCare Pharmaceuticals. A depot preparation of 1000 mg in 4 mL is distributed under the trade name of Reandron 1000 in Australia, Reandron in Spain, Nebid in Italy, and Nebido in most of other countries. This 4 ml preparation should be administered every 12 weeks following a booster 6-week loading dose. In the US, a 3 ml ampulla containing 750 mg is available under the trade name of Aveed (Endo International plc). For this formulation, the loading dose is administered after 4 weeks, and afterwards every 12 weeks. TU should be injected intramuscularly slowly into the buttock, where it forms a reservoir. The reservoir gradually releases T into the bloodstream, keeping serum levels within the normal range, without supra or subphysiological levels. Thus, side effects due to T serum fluctuation are rarely observed, and both polycythemia and bouts of coughing were seldom reported [50]. When compared to other injectable preparations, TU requires six times lower administration frequency (i.e., 4–5 injections/year vs. 24) and this represents an aspect, which is greatly appreciated by patients.

3.3.3. Available transdermal testosterone preparations

3.3.3.1. Testosterone gels. Considering that the skin easily absorbs steroids such as T, transdermal application represents

an ideal way for gradual systemic T delivery. Indeed, transdermal T gels at different concentrations (1%, 1.62% and 2%) are the most popular formulations for TTh in LOH [1–3,5]. T gels can be applied to different skin areas, such as the shoulders and/or upper arms, and require a few minutes to get dry. The gel is quickly absorbed by the stratum corneum and it creates a reservoir within the subcutaneous tissues from where T is released. The steady state is reached one or two hours after the application. Only about 8–14% of the applied gel is absorbed, with absorption rates, which vary according to the application site and skin structural differences [1–3,5]. Hence, according to T production rate, 50–100 mg of T gel should be applied daily. Commercially available gels are supplied in sachets (usually containing 50 mg of T) or in a metered-dose pump, which further improves the dose flexibility. Skin irritation and erythema are seldom observed. Gels may also be considered inconvenient because there are restrictions on bathing/swimming within the first several hours after application [1–3,5]. Another potential side effect of T gel application may be the transfer of T during close contact with the skin's surface. To overcome this problem, an alcohol-based T solution (2%) was developed as an underarm application for topical administration under the axilla (Axiron, Eli Lilly & Company). The underarm T solution is available in two forms: pump actuated or twist actuated metered-dose pump [1–3,5].

3.3.3.2. Testosterone patches. T administration through thin, flexible and self-adherent patches were the first T transdermal formulation available, firstly using scrotal systems and, later on, through non-scrotal ones [1–3,5,46]. T-patches deliver T into systemic circulation constantly over the day. Scrotal patches were not popular because they require shaving and adhere poorly to the skin. The use of transdermal systems on non-genital skin was therefore developed [46]. They need different forms of alcoholic enhancers to guarantee sufficient skin absorption; however, these permeation enhancers are responsible of frequent adverse skin reactions at the application site. Hence, these preparations are characterized by a low compliance and they have not yet been marketed [1–3,5,46].

3.3.3.3. DHT gels. In some European countries, DHT is available as a hydroalcoholic 2.5% gel with a dosage of 5 or 10 g/day [1–3,5,46]. This gel must be applied to a large area of skin (chest, shoulders or thighs), where it is rapidly absorbed. After 2–3 days of application, DHT levels reach a steady state. Similar to mesterolone, DHT is not aromatized; hence, it works as a partial androgen, not replacing the full spectrum of T bioactivity, which includes oestrogen actions [1–3,5,46]. DHT gel is mainly used for treating particular conditions, such as gynecomastia and microphallus [51–53].

3.3.4. Available transmucosal testosterone preparations

Transmucosal delivery systems have been developed for improving T absorption because mucous membranes are more permeable than skin [1–3,5,46].

3.3.4.1. Transbuccal testosterone preparations. A T buccal system is available in several countries (Striant, Columbia Laboratories, Inc). It is a tablet designed to adhere to the gum or inner cheek, providing a controlled and sustained release of T through the buccal mucosa as the buccal system gradually hydrates. The tablet does not dissolve completely and must be removed and replaced every 12 h. Each buccal system contains 30 mg of T. This formulation has been proven to restore the physiological range with minimal or transient local problems, including gum edema, blistering and gingivitis [1–3,5,46].

3.3.4.2. Transnasal testosterone preparations. A gel containing 5.5 mg of T in 122.5 mg for intranasal administration was developed and it is available in some countries, including the US and Canada (Natesto, Acerus Pharmaceuticals Corp. Mississauga, ON Canada). The recommended dose is 11 mg of T (two pump actuations, one per nostril) administered intranasally three times daily for a total daily dose of 33 mg [1–3,5,46]. The nasal gel is available as a metered dose pump containing 11 g of gel dispensed as 60 metered pump actuations. The application is rapid, non-invasive, convenient, and avoids secondary transference observed with other topical products.

4. Antiestrogen outcomes

To evaluate the available evidence on clinical outcomes of antiestrogen (SERM or AI) therapy in HG men, we performed a meta-analysis of the available placebo-controlled randomized clinical trials (RCTs). In order to gather all the available evidence on the use of antiestrogens in men with LOH, we performed a Medline search considering the change in hormones as the primary outcome. The search terms for the meta-analyses are reported in Table 1. The primary outcome of the meta-analyses was the change in TT and gonadotropins. Data on symptoms and signs of androgen deficiency were collected, if available.

4.1. SERMs outcomes

The search provided 30 articles, of which only four [54–57], accounting for five studies, were eligible for the present meta-analysis. Completed but not published studies were searched for in the Clinical Trials database (search terms: 'hypogonadism, male' AND 'selective estrogen receptor modulators'). It allowed identifying eight studies with results available [NCT01880086, NCT01534208, NCT01270841, NCT00706719, NCT01532414, NCT01739595, NCT01386606, NCT01191320] to be identified, however, none of these provided sufficient data for meta-analysis.

The five retrieved studies [54–57] included overall 314 HG men with mean age of 49.5 ± 4.9 years, mean baseline TT of 7.4 ± 0.6 nmol/L and body mass index (BMI) of 29.6 ± 1.4 kg/m2. Of these, 159 men received an SERM (24 received CC 25 mg daily, 17 CC 50 mg daily, 33 ECC 25 mg daily and 85 ECC 12.5 mg with dose titration up to 25 mg based on T levels achieved). The study duration ranged between 8 and 16 weeks.

4.1.1. Effect of SERMs on hormones and SHBG levels

Figure 1 Panel A reports the difference at the end of the trial between SERM and placebo treated men in TT levels. SERM-treated men had higher TT than placebo, with a mean difference of 7.6 [6.6–8.6] nmol/L. The increase in TT was accompanied by increased Gns (Figure 1 Panel C and D). No differences were

Table 1. Search terms used for retrieving the available placebo-controlled randomized clinical trials on the use of selective estrogen receptor modulator or aromatase inhibitors in male hypogonadism.

	Search terms
Selective Estrogen Receptor Modulator	('selective estrogen receptor modulator'[All Fields] OR 'selective estrogen receptor modulators'[Pharmacological Action] OR 'selective estrogen receptor modulators'[MeSH Terms] OR ('selective'[All Fields] AND 'estrogen'[All Fields] AND 'receptor'[All Fields] AND 'modulators'[All Fields]) OR 'selective estrogen receptor modulators'[All Fields] OR ('selective'[All Fields] AND 'estrogen'[All Fields] AND 'receptor'[All Fields] AND 'modulator'[All Fields]) OR 'selective estrogen receptor modulator'[All Fields]) AND ('men'[MeSH Terms] OR 'men'[All Fields] OR 'man'[All Fields]) AND ('testosterone'[MeSH Terms] OR 'testosterone'[All Fields]) AND ('randomized controlled trial'[Publication Type] OR 'randomized controlled trials as topic'[MeSH Terms] OR 'randomized clinical trials'[All Fields] OR 'randomized clinical trials'[All Fields])
Aromatase Inhibitors	('aromatase inhibitors'[Pharmacological Action] OR 'aromatase inhibitors'[MeSH Terms] OR ('aromatase'[All Fields] AND 'inhibitors'[All Fields]) OR 'aromatase inhibitors'[All Fields] OR ('aromatase'[All Fields] AND 'inhibitor'[All Fields]) OR 'aromatase inhibitor'[All Fields]) AND ('men'[MeSH Terms] OR 'men'[All Fields]) AND ('testosterone'[MeSH Terms] OR 'testosterone'[All Fields]) AND ('randomized controlled trial'[Publication Type] OR 'randomized controlled trials as topic'[MeSH Terms] OR 'randomized clinical trials'[All Fields] OR 'randomized clinical trials'[All Fields])

found between SERMs and placebo for SHBG (Figure 1 panel B). The sperm concentration did not differ between the active study arm and the controls (mean difference in sperm concentration between SERMs and placebo: 8.0 [−13.5;29.5] per milliliter of semen). However, it should be noted that both for SHBG [55,56] and sperm concentration [57], only two studies provided sufficient data for the meta-analysis.

4.1.2. Effect of SERMs on sexual symptoms

Among the studies included in the meta-analysis, only one had sexual function among its outcomes [54]. The Guay et al. study [54] enrolled 17 patients (mean age 60.1 ± 8.6) with SHG and erectile dysfunction (ED) who received CC 50 mg daily for 8 weeks. The same group represented also the comparator, according to the cross-sectional design. During the treatment with CC, a significant increase in TT was observed. However, none of the proxies for erectile function (questionnaires and RigiScan) was significantly changed by CC. Besides the Guay et al. study [54], the effectiveness of SERMs in improving sexual complaints has not been assessed by other placebo-controlled RCTs so far. More recently, a RCT designed for comparing 12 weeks of treatment with CC 25 mg daily with anastrozole 1 mg daily in 26 SHG men aged 34.0 ± 5.2 years (13 for each study arm) showed that, in the CC group, no significant change in Androgen Deficiency in Aging Male questionnaire (ADAM) or International Index of Erectile Function (IIEF) score occurred [58].

4.1.3. Effect of SERMs on bone

Despite SERMs having a known positive effect on bone––such that raloxifene has been approved for treatment of osteoporosis in women––their efficacy in HG men has been scarcely investigated. None of the studies included in the present meta-analysis considered bone safety. A RCT comparing raloxifene 120 mg daily vs. placebo randomly administered to 43 middle-aged men (mean age 56 years) with low sex hormones for 6 weeks showed that the active treatment arm was able to improve markers of bone turnover only in men with the lowest estradiol and T [59]. This outcome has been specifically assessed in men receiving androgen deprivation therapy for prostate cancer. In this population, raloxifene 60 mg daily for 6 months was able to improve total hip and lumbar spine bone mineral density (BMD) as compared with no therapy [60] and toremifene 80 mg daily for 2 years, as compared with placebo, showed a significant reduction in incidence of new vertebral fractures [61].

4.2. Aromatase inhibitor outcomes

Fifty articles were found, of which nine were eligible for the meta-analysis. After excluding duplicates (i.e. articles referring to the same RCT), data were extracted from five RCTs [32,62–69]. Completed but not published studies were searched for in the Clinical Trials database (search terms 'hypogonadism, male' AND 'aromatase inhibitor'). Two studies with results available were identified [NCT00136695; NCT00179517]. However, none of these provided sufficient data for meta-analysis.

The five retrieved studies [32,62–69] included overall 192 HG men with mean age of 61.3 ± 11.8 years, baseline mean TT of 10.2 ± 1.1 nmol/L and mean BMI of 32.6 ± 6.1 kg/m^2. Of these, 97 men received placebo and 95 AIs (59 treated with anastrozole 1 mg daily, 18 with anastrozole 1 mg daily plus T cypionate 300 mg twice a week and 18 with letrozole 2.5 mg once a week with titration up to 2.5 mg daily). The study duration ranged between 12 and 52 weeks.

4.2.1. Effects of AIs on hormones and SHBG

Figure 2 Panel A shows that HG patients treated with AIs have higher TT levels (difference in means vs. placebo: 7.5 [5.0; 9.9] nmol/L, $p < 0.0001$). As expected, estradiol was significantly lower in AI treated patients, with a mean reduction of 40.6 (24.8; 56.3) pmol/L (Figure 2 Panel B). The meta-analysis of Gn levels at the end of the treatment did not show a significant difference in LH or FSH between AI and placebo arms (Figure 2 Panels C and D). Similarly, AI therapy was not associated with any change in SHBG (Figure 2 Panel E).

4.2.2. Effects of AIs on sexual function

Among the RCTs included in the meta-analysis, three [32,62,67] evaluated the change in sexual symptoms upon AI therapy, even though a formal quantitative meta-analysis for these outcomes was not possible. In a population of 37 elderly men (aged 62–74 years) with low T treated with anastrozole 1 mg daily or placebo, Leder et al. [62] did not find any significant change in sexual symptoms over 12 weeks of

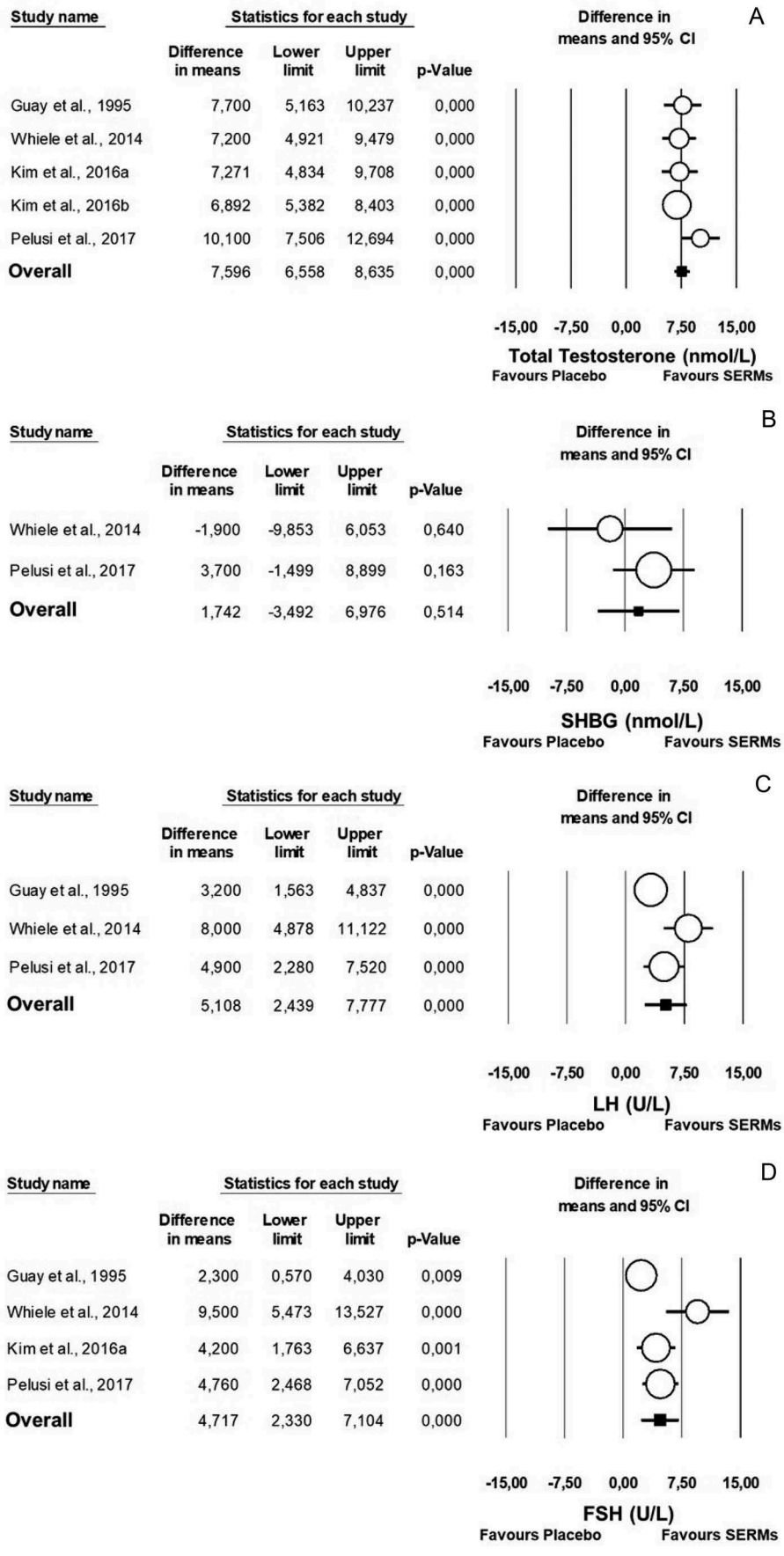

Figure 1. Unstandardized mean difference (with 95% confidence interval [CI]) of selective estrogen receptor modulators (SERMs) vs. placebo on total testosterone (A), SHBG (B), LH (C), and FSH (D).

SHBG: sex hormone binding globulin, LH: Luteinizing hormone, FSH: follicle stimulating hormone

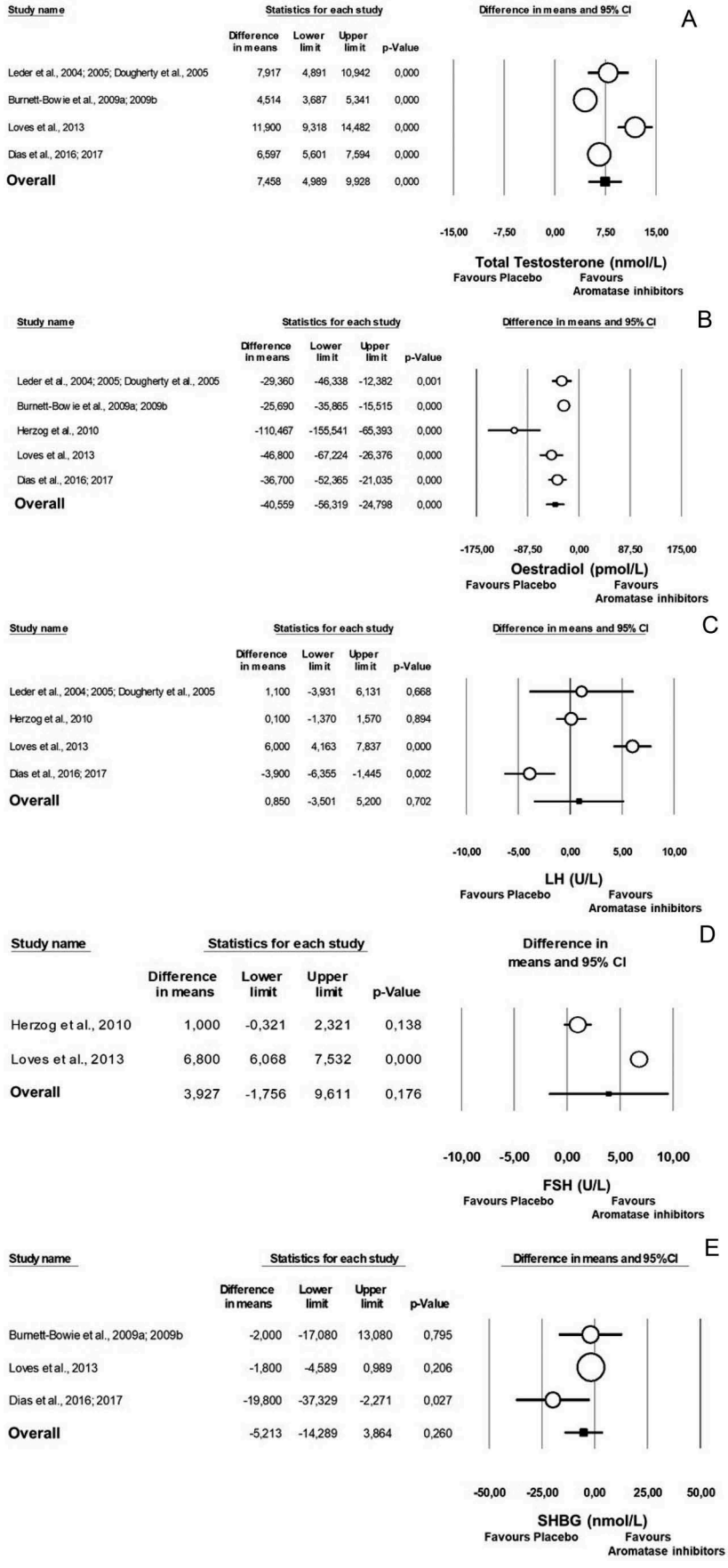

Figure 2. Unstandardized mean difference (with 95% confidence interval [CI]) of aromatase inhibitors vs. placebo on total testosterone (A), estradiol (B), LH (C), FSH (D), and SHBG (E).

LH: Luteinizing hormone, FSH: follicle stimulating hormone, SHBG: sex hormone binding globulin

treatment. Sexual function represented a primary outcome in the RCT conducted by Herzog et al. [67]. In this trial, 40 epileptic HG men with sexual complaints (aged 18–50 years) were randomized to TC 300 mg twice weekly plus anastrozole 1 mg daily or TC (same dosage) plus placebo for 12 weeks. Sexual interest, sexual function and satisfaction increased significantly in both groups; however, the change was not significantly different between them. Sexual desire and erectile function was assessed, although without validated instruments, also in the RCT conducted by Loves et al. [32]. Among 39 obese men (mean age 44.6 ± 1.6 years) with low serum T randomly receiving placebo or letrozole 2.5 mg (dose titrated from one tablet a day to one table a week) for 24 weeks, ED at the end of the trial was reported with similar frequency in the two study arms [32]. These findings suggest that the increase in T levels found in men treated with AIs is associated with a slight, if any, improvement in sexual function. However, these results, deriving from few RCTs involving small samples, are largely insufficient for providing evidence of the positive or at least neutral effect of AIs on male sexuality. Despite the role of estrogens on male sexual function is still incompletely known, a trial conducted by Finkelstein et al. [70] in almost 200 healthy volunteers with an experimentally induced hypogonadism has shown that the exclusion of estrogen action by the addition of anastrozole 1 mg daily to T replacement is associated with an impairment in sexual desire and erectile function.

4.2.3. Effects of AIs on bone

Bone health is a concern when using AIs, due to the well-known role of estrogens on bone turnover in both men and women. Only two of the meta-analyzed RCTs provided data on BMD useful for the meta-analysis (Table 2). As shown in Table 2, after 52 weeks of AI therapy, both femoral and lumbar spine BMD were not significantly different from placebo (Table 2), however, in one of the two meta-analyzed RCTs [65,68], performed in elderly HG men, a significantly greater decrease of lumbar spine BMD was found in AIs as compared with placebo. Besides the RCTs reported in the meta-analysis, BMD has been evaluated by Leder et al. [63] and Loves et al. [32], without showing any significant difference between the active treatment and placebo groups. It could be argued that all the aforementioned results on BMD are affected by the relatively short follow-up (52 weeks). Markers of bone turnover are earlier signs of bone damage. They have been evaluated in two [63,65] (osteocalcin, osteoprotegerin, N-terminal telopeptide of type 1 collagen; NTX) or three [32,63,65] (Procollagen I Intact N-Terminal; PINP) RCTs among those meta-analyzed, without reporting any change associated with AI treatment (Table 2).

4.2.4. Effects of AIs on body composition and serum metabolic parameters

Two RCTs considered the effect of AIs as compared to placebo on lean body mass [66,68], whereas three evaluated the fat mass [32,66,68]. Meta-analyzing the results, AIs did not show any significant effect on body composition (Table 2). Similarly, no differences between AIs and placebo were found with regard to lipids and Homeostatic model assessment (HOMA) index [32,64,67] (Table 2).

Table 2. Results of the meta-analysis of the available the randomized clinical trials (RCT) comparing aromatase inhibitors to placebo for the treatment of male hypogonadism.

	Standardized difference in means and 95% CI	# RCT
BMD femor (g/cm^3)	0.84 [−1.42; 3.10]; p = 0.467	2
BMD lumbar spine (g/cm^3)	−2.43 [−6.99; 2.13]; p = 0.296	2
	Difference in means and 95% CI	
PINP (ng/mL)	2.38 [−1.27; 6.02]; p = 0.201	3
NTX (nmol/L)	0.06 [−0.40; 0.52]; p = 0.796	2
OC (ng/mL)	−1.33 [−6.43; 3.76]; p = 0.608	2
OPG (pmol/L)	0.12 [−0.15; 0.39]; p = 0.376	2
	Standardized difference in means and 95% CI	
Fat mass (kg)	−0.11 [−1.09; −0.88]; p = 0.827	3
Lean mass (kg)	−0.27 [−0.69; 1.15]; p = 0.202	2
	Difference in means and 95% CI	
Total cholesterol (mg/dL)	−14.46 [−33.88; 4.95]; p = 0.144	2
HDL-cholesterol (mg/dL)	−0.00 [−0.01; 0.01]; p = 0.999	3
LDL-cholesterol (mg/dL)	15.19 [−14.08; 44.46]; p = 0.309	3
Triglycerides (mg/dL)	14.43 [−38.62; 67.48]; p = 0.594	3
HOMA-index	0.33 [−0.29; 0.95]; p = 0.297	2

Abbreviations: PINP, N-terminal pro-peptide; NTX, Serum N-telopeptide of type 1 collagen; OPG, osteoprotegerin; OC: osteocalcin.

4.2.5. Effects of AIs on strength and muscle

Few data are available for the effect of AIs on physical strength. Dias et al. [68] compared anastrozole one mg daily with either placebo or TTh, randomly administered for 12 months to older men (mean age 71 years) with low T. Anastrozole treated men significantly increased their knee flexor and extensor strength early during follow-up, whereas TTh showed a significant improvement only at the end of the study, and placebo did not show any change. Despite the improvement being meaningfully greater in anastrozole than TTh or placebo, the values did not reach the statistical significance. In a previous RCT [66], thigh muscle was measured using computed tomography and no difference was found between the values measured in men treated for 12 months with anastrozole one mg/day or placebo. Accordingly, this study did not find any significant difference in lower extremity strength between anastrozole and placebo.

4.2.6. Effects of AIs on mood and psychological health

The effect of AIs on mood was investigated by two of the RCTs retrieved [32,67]. Both of them did not find a significant difference between AI and placebo treated men in any of the investigated areas. However, it should be noted that both the studies had a relatively short follow-up (three or six months) and the longer lasting study slowly up-titrated the dosage so that the full dose was used for only two months.

5. GnRH and gonadotropin outcomes

Data in LOH men on Gn therapy are scanty, while those on GnRH are completely lacking. Only three RCTs assessed the effects of Gn treatment in comparison with placebo [71–73] or TTh [74]. The earliest study [71] was conducted in 40 men older than 60 years with low TT (<15 nmol/L) receiving placebo or rhCG 5000 UI subcutaneously twice weekly for 3 months with the aim of assessing the change in inflammatory serum markers. A following study [72,73] used the same treatment on a population with similar inclusion criteria but it was aimed at evaluating

the change in metabolic and physical performance parameters. Finally, the most recent study [74] compared urinary derived hCG 2000 UI twice a week with different formulations of TTh (TU 1000 mg every 12 weeks, T gel 60 mg daily and TE 250 mg monthly) administered for 6 months to 40 men (10 per study arm) with a median age of 50 years.

5.1. Effects of gonadotropins on hormone levels

The administration of rhCG 5000 UI twice weekly was consistently associated with the increase in TT, free T and estradiol [71–73]. No change in SHBG occurred, whereas, as expected, endogenous LH and FSH were significantly lower than the placebo arm [71–73]. A lower dose of 2000 UI twice weekly showed an increase in TT similar to T gel or TE injectable, but significantly lower than TU injectable [74]. The increase in estradiol was significant as compared with baseline but lower than all the other T preparations [74].

5.2. Effects of gonadotropins on sexual function

Concerning sexual function, two RCTs yielded conflicting results. In the first one, rhCG 5000 UI twice weekly for three months did not show any significant improvement as compared to placebo [72]. Conversely, hCG 2000 UI twice weekly for 6 months improved erectile function and other symptoms of androgen deficiency similarly to TTh [74].

5.3. Effects of gonadotropins on physical strength

Only one RCT assessed the efficacy of hCG on physical strength [72]. Among the different functional tests for the assessment of physical performance, none proved to be significantly affected by hCG therapy. The measurement of upper and lower extremity muscle strength showed a small (3%) overall improvement due to hCG treatment.

5.4. Effects of gonadotropins on body composition and serum metabolic parameters

Increased lean mass and decreased fat mass were detected by both the RCTs assessing these outcomes [72,74]. In particular, the favorable change in body composition was significant as compared to placebo [72] and similar to what was observed in TTh [74]. As compared to placebo, hCG 5000 UI for three months significantly improved total and low density lipoprotein (LDL) cholesterol as well as triglycerides but it did not affect glucose and insulin sensitivity [73]. La Vignera et al. [74] found that hCG 2000 UI twice weekly for six months improved lipid, glucose and insulin levels similarly to TTh.

5.5. Effects of gonadotropins on vascular reactivity

Ng et al. [71] evaluated the effect of hCG 5000 UI for three months on several biochemical markers of inflammation and endothelial function, without finding any significant difference from placebo. Similar results were found by Liu et al. [73] who did not show a difference in flow mediated dilation between hCG and placebo treated men.

5.6. Effects of gonadotropins on semen parameters

The only RCT assessing semen parameters in LOH men was performed by La Vignera et al. [74] who found a trend toward a significant improvement in progressive motility and normal forms over six months of treatment with hCG 2000 UI twice a week. Sperm concentration was not changed during six months hCG treatment, whereas TTh, as compared to hCG, produced a significant worsening in sperm concentrations and progressive motility.

6. Testosterone preparations outcome

Considering the pivotal role in LOH of sexual impairment and metabolic alterations [7,13,19,75–79], the role of TTh on sexual function, body composition and glycometabolic control will be reviewed in detail in the following sections. In particular, data derived from available meta-analyses on RCTs will be scrutinized, categorizing outcomes according to the different T preparation (oral, transdermal and parental) employed, when possible. Finally, available data of TTh on other outcomes including bone function, mood, and cognition will be also analyzed.

6.1. TTh and sexual function

Since 2005, six meta-analyses evaluating the effect of TTh on sexual function have been published [80–85]. However, two of them [81,82] did not report specific Forest plots with standardized mean outcomes. In addition, the last meta-analysis produced by us [80] was based on a limited number of trials all using IIEF as an outcome. Hence, in order to present more comparable data, we focused the present analysis only on the meta-analyses including placebo-controlled RCTs, independently of the sexual inventory used for the assessment of sexual function, and reporting data as effect size. The trials included range from 17 to 29 and the number of subjects considered from 657 to 1,930 (Table 3). All meta-analyses reported outcomes on erectile function and libido, whereas two [83,85] investigated the effect of TTh on morning erections and sexual satisfaction and only our study evaluated orgasmic function as an outcome [83] (see also Table 3). In addition, whereas two studies [84,85] used a threshold of 10.4 nmol/L of TT at enrolment for defining HG, Corona et al. considered 12 nmol/L [83] (Table 3). Results categorized according to the T preparation used was reported only by Corona et al. [83] (Table 3).

Figure 3, Panel A shows that, when trials involving eugonadal patients were considered, no effect on erectile function and libido was observed, although Isidori et al. [85], documented a medium effect on libido also in this population (Figure 3, panel A). Similarly, in the same population of eugonadal subjects, no effect of TTh on orgasmic function and sexual satisfaction was documented. All available meta-analyses found a positive effect of TTh on morning erections (Figure 3 panel A). When the analysis was limited to HG patients, TTh resulted in a significant improvement in all the evaluated sexual parameters (Figure 3, panel B). Finally, when the results in HG subjects were stratified according to the use of the different T formulations, oral preparations did not show a positive effect

Table 3. Comparisons of the available meta-analyses evaluating the relationship between testosterone therapy (TTh) on several sexual parameters. TT = total testosterone.

Inclusion criteria	Isidori et al., 2005		Bolona et al., 2007		Corona et al., 2014	
Number of trials included	17		17		29	
Number of patients analyzed	657		862		1,930	
Hypogonadism definition used (TT)	10 nmol/L		10.4 nmol/L		12 nmol/L	
	Yes	*No*	***Yes***	*No*	***Yes***	*No*
Outcomes according to T preparation		X		X	**X**	
Sexual parameter analyzed						
Erectile function	**X**		**X**		**X**	
Libido	**X**		**X**		**X**	
Morning erections	**X**			X	**X**	
Orgasmic function		X		X	**X**	
Sexual satisfaction	**X**			X	**X**	

on erectile function, whereas they showed only a small effect on libido (Figure 3, Panel C). Conversely, no difference in the positive efficacy of both transdermal and parental T preparations was documented (Figure 3, Panel C). No sufficient data were available to evaluate possible differences among specific transdermal and parental preparations. In particular, no comparison between the older short-term injectable T formulations and the newer long-acting injectable TU is feasible.

6.2. TTh body composition and glycometabolic control

Since 2005, four systematic meta-analyses have evaluated the effect of TTh on different parameters related to body composition and glycometabolic profile [86–89] (see also Table 4). The number of trials considered ranged from 19 to 59 including from 1,083 to 5,078 subjects. The meta-analyses differed in body composition and metabolic outcomes considered (Table 4). Three meta-analyses [87–89] considered only placebo-controlled RCTs, whereas Corona et al. [86] included also non placebo-controlled RCT (Table 4). In addition, data according to the presence of HG at enrolment were available only in three studies [86,88,89]. In particular, whereas two studies [88,89] used a threshold of 10.4 nmol/L of TT for the definition of HG, Corona et al. considered 12 nmol/L as a cut-off [86] (Table 4). Finally, only Corona et al. reported metabolic and body composition outcomes according to the preparation used [86] (Table 4). When the overall population was considered, TTh caused similar modifications in fat mass and lean mass without any changes in BMI (Figure 4, Panel A). Similar results were confirmed when only HG patients were considered (Figure 4, Panel B). In addition, in the whole population, Corona et al. reported that TTh significantly improved fasting glycaemia. This finding was not observed by Fernandez-Balsells et al. [87], although they considered a lower number of trials (Figure 4, panel C). Corona et al. reported data on fasting glycaemia restricted to HG men [86], whereas no information in this subpopulation was reported by Fernandez-Balsells et al. [87], (Figure 4, panel D). Conflicting results were detected for the effect of TTh on lipid profile (Figure 4, Panel C). When results on lipids were restricted to HG subjects, a trend toward or a full significant reduction was observed for both total cholesterol and triglycerides in the TTh arm (Figure 4, panel D). Conversely, no effect was observed for both high-density lipoprotein (HDL) and LDL cholesterol (Figure 4, panel D). Finally, when body composition and metabolic profile outcomes were evaluated according to the use of the different T preparations, oral preparations did not show a positive effect on lean mass and glycometabolic profile, but only in fat mass (Figure 4, Panel E). However, the latter association was not confirmed when only placebo-controlled RCTs were considered (standardized difference in mean = −0.29[−0.61; 0.04]; p = 0.08). Conversely, no difference between transdermal and parental testosterone preparations was documented (Figure 4, Panel E). No sufficient data are available to evaluate possible differences among specific transdermal and parental preparations. In particular, no comparison between the older short-term injectable T formulations and the newer long-acting injectable TU was possible.

6.3. Other outcomes

6.3.1. Osteoporosis

T plays a major role in regulating male bone health, mainly through its aromatization to estradiol [78,80]. However, some reports indicated a possible independent link between reduced T levels and the risk of bone fractures, suggesting a possible direct role of androgen receptor in increasing bone health [78,80]. In line with the latter evidence, two independent meta-analyses showed a positive effect of TTh on BMD [89,90]. Conversely, insufficient data have been published to calculate the effect of TTh on the risk of bone fractures [91].

6.3.2. Mood and cognition

Several observational studies have documented a possible relationship between depressive symptoms and reduced T levels [92]. However, the relationship between low T and the incidence of clinical depression is still unclear [92]. A first meta-analysis of seven placebo-controlled RCTs reported a significant positive effect of TTh on depressive symptoms [93]. However, this was not confirmed in a more recent study [94].

A possible contribution of reduced T levels to the age-dependent cognitive deterioration has been hypothesized. Subjects treated with androgen deprivation therapy for prostate cancer have a higher risk of cognitive deterioration when compared to controls [95]. Similarly, in a meta-analysis of seven prospective studies [96], low T was associated with a 50% higher risk of developing Alzheimer's disease. However, it is important to recognize that the effects of TTh on the improvement of cognitive disorders remain not entirely conclusive, although some recent trials seem to show encouraging results [97].

7. Conclusions

LOH is the most frequently occurring form of T deficiency in both general and symptomatic populations [4,5]. Considering that its prevalence in the aging male is estimated to range from 2–15%, it is one of the most frequently occurring hormonal deficiencies along with thyroid hormone deficiency.

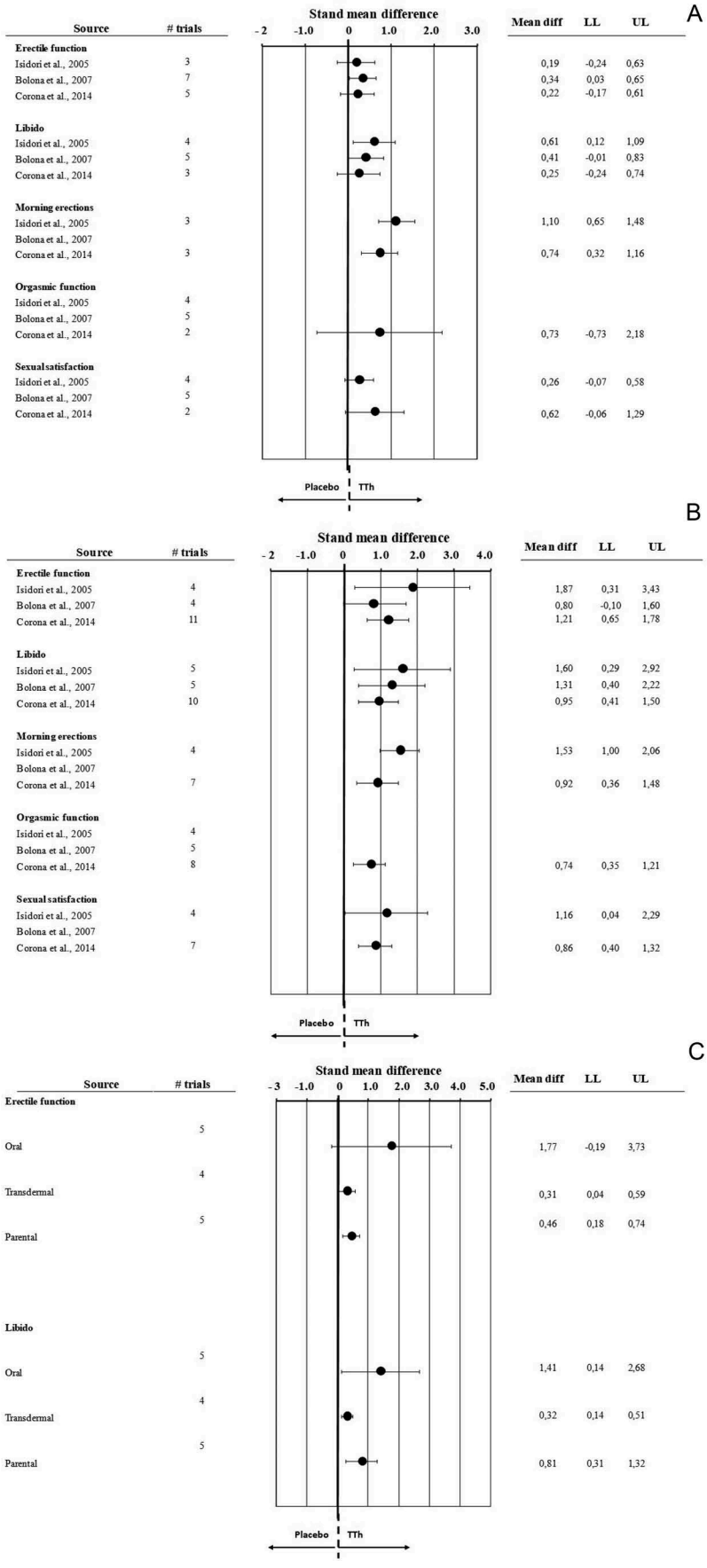

Figure 3. Effect size (with 95% confidence interval [CI]) of testosterone treatment (TTh) vs. placebo on several sexual parameters when eugonadal (A) or hypogonadal (B) subjects were considered. Panel C shows the effect of TTh on erectile function and libido according to different testosterone preparation. LL = lower limits; UP = upper limits.

Table 4. Comparisons of the available meta-analyses evaluating the relationship between testosterone therapy (TTh), body composition and glycometabolic profile. RCT = randomized controlled trials. HDL = high density lipoprotein; LDL = low density lipoprotein.

Inclusion criteria	Isidori et al., 2005		Haddad et al., 2007		Fernandez-Balsells et al., 2010		Corona et al., 2016	
Number of trials included	29		30		51		59	
Number of patients analyzed	1,083		1,642		2,679		5,078	
Hypogonadism definition used (TT)	10 nmol/L		10.4 nmol/L		NR		12 nmol/L	
	Yes	*No*	***Yes***	*No*	***Yes***	*No*	***Yes***	*No*
Only placebo controlled RCT	**X**		**X**		**X**			**X**
Outcomes according to T preparation		**X**		**X**		**X**	**X**	
Body composition parameter analyzed								
Body mass index		X		X		**X**	**X**	
Fat mass	**X**			X		**X**	**X**	
Lean mass	**X**			X		**X**	**X**	
Metabolic parameter analyzed								
Fasting glycemia		X		X	**X**		**X**	
Total cholesterol	**X**		**X**		**X**		**X**	
Triglycerides		X	**X**		**X**		**X**	
HDL cholesterol	**X**		**X**		**X**		**X**	
LDL cholesterol								X

Secondary HG is the leading form of LOH [10,11], because it is the form associated with metabolic disturbances, which are often present in the aging male. As mentioned before, the goal of any pharmacological treatment of LOH is not only to correct the hormonal deficiency, but also to relieve bothersome symptoms.

As in all hormonal deficiencies, LOH therapy includes strategies able to overcome the T deficiency, if the cause of the deficiency cannot be corrected. Testosterone replacement can be achieved through the stimulation of Leydig cell activity (when possible, as in the case of SHG) or through the substitution of the deficient hormones, i.e. testosterone or DHT.

8. Expert commentary

We strongly suggest a tailored approach for treating LOH subjects. This tailored approach should take into account the nature of HG (primary vs. secondary) and the patient needs, including bone safety or fertility. Nowadays, fathering in late adulthood––and even in the elderly––is a frequent request and this must be taken into consideration in the pharmacological management of LOH. When fathering is an issue, LOH characterized by normal or reduced gonadotropin levels (secondary HG) could be treated with medications able to replace the deficient hormones (GnRH or gonadotropins) or with medications that increase their levels, by blocking the estrogen-mediated negative feedback, such as SERMs or AIs. Present meta-analyses of available RCTs indicate that both SERMs and AIs are able to increase circulating T levels without impairing endogenous Gns (AIs) or even increasing them (SERMs). They show, therefore, the theoretical advantage not to impair, or even to stimulate, sperm formation [29,30]. However, their efficacy on treating LOH-associated symptoms has not been systemically tested, and results in contrasting outcomes, at least in the available RCTs. As stated before, the inconsistent effect of antiestrogens on sexual symptoms may be due to the interfering activity on the estrogen receptor, which an experimental study has demonstrated to positively regulate sexual desire and arousal [70]. In addition, AIs hamper estrogen activity and they have the potential risk of inducing or increasing osteoporosis, at least after long-term administration. It is important to mention that osteoporosis itself is characteristic of LOH. Therefore, further trials are, needed to clarify this point and several of them are ongoing. Another possible caveat to the use of antiestrogen medications is that they theoretically need an intact HPT axis, to respond to the estrogen blockade. However, the majority of LOH is of a functional nature [12], and, therefore, potentially treatable with antiestrogens. None of the antiestrogens on the market are indicated for LOH, and therefore their use is off-label, at least at the present time.

In contrast to antiestrogens, both GnRH and Gns have been indicated for treating HG, and, therefore, LOH, in particular when fertility is an option. However, information on the effects of GnRH administration on LOH-related symptoms are completely lacking and for Gns they are relatively few. The pulsatile administration of GnRH of through a subcutaneous infusion pump makes this form of treatment an obsolete opportunity, never investigated in LOH, most probably for practical reasons. In addition, GnRH therapy is not a real practical alternative to boost spermatogenesis in LOH. For Gns, some studies indicate positive effects on LOH symptoms, along with an improvement in circulating T [71–74], however, the number of published trials with Gns in LOH is still low and only few have investigated sexual outcomes. In addition, the unpractical way of administration (intramuscular or subcutaneous) and the required frequency of injections (two to three times a week) makes this option for LOH treatment not very popular, often prescribed only to those seeking fertility.

T preparations offer different ways and modalities of treatment, making them a suitable option for LOH subjects, when fertility is not desired. In all meta-analyses scrutinized, TTh was able to improve sexual function (spontaneous and sex-related erection, desire, orgasm and sexual satisfaction), in particular in HG subjects [80–85]. Results in eugonadal subjects were more inconsistent. Considering that TTh is also able to decrease fat mass and to improve muscle mass, it is obvious that they can ameliorate adiposity-associated LOH and assist

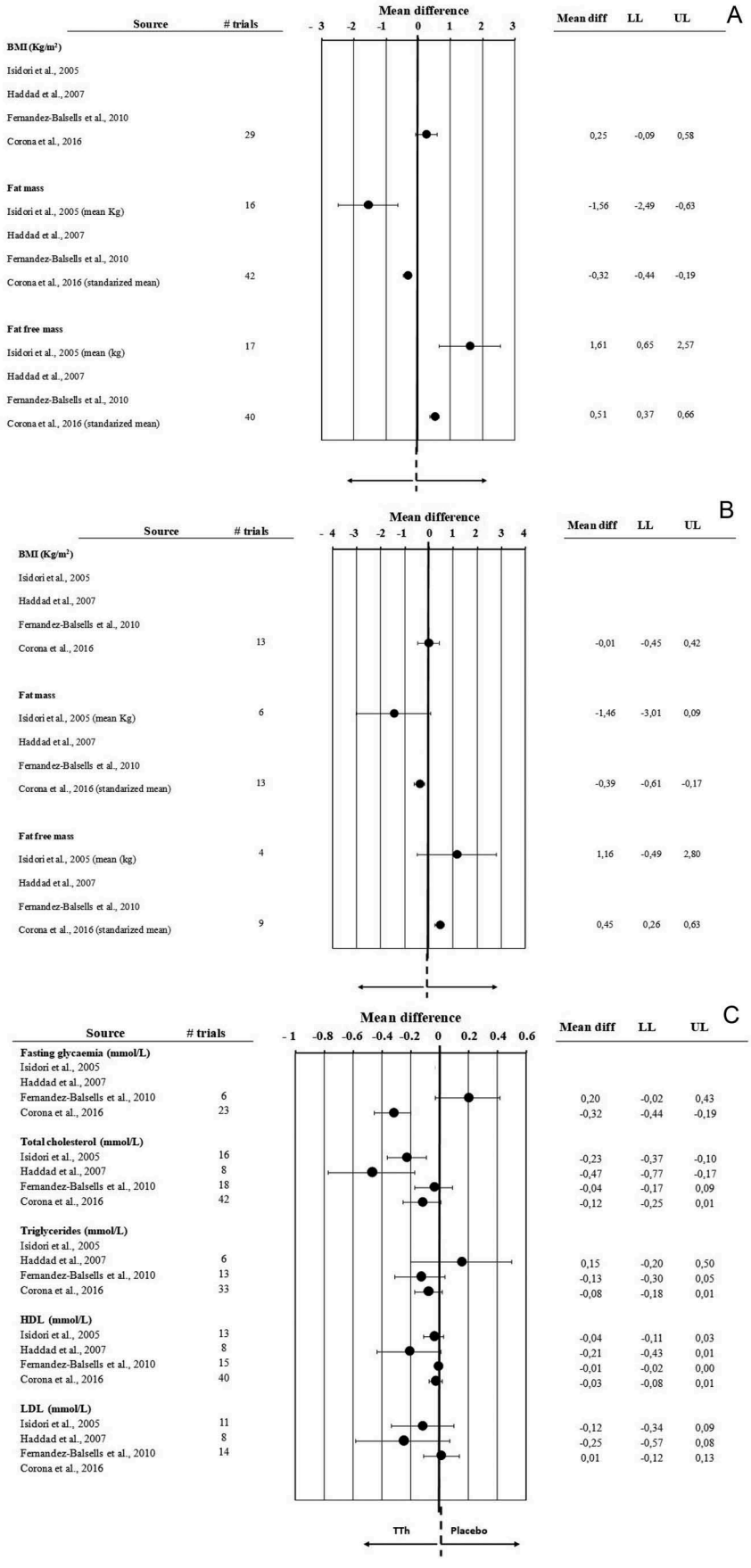

Figure 4. Standardized (fat mass and lean mass) or unstandardized mean difference (fasting glucose and total cholesterol, HDL and LDL cholesterol and triglycerides) (with 95% confidence interval [CI]) of testosterone treatment (TTh) vs. placebo on several body composition and metabolic outcomes when overall population (A, C) or when only studies enrolling hypogonadal patients at enrolment (B, D) were considered. Panel E shows the standardized (fat mass and lean mass) or unstandardized mean difference (fasting glucose and total cholesterol) according to testosterone preparation when only data derived from Corona et al. [86] meta-analysis were considered. HDL = high density lipoprotein; LDL = low density lipoprotein, LL = lower limits; UP = upper limits.* only studies enrolling hypogonadal subjects at baseline were considered.

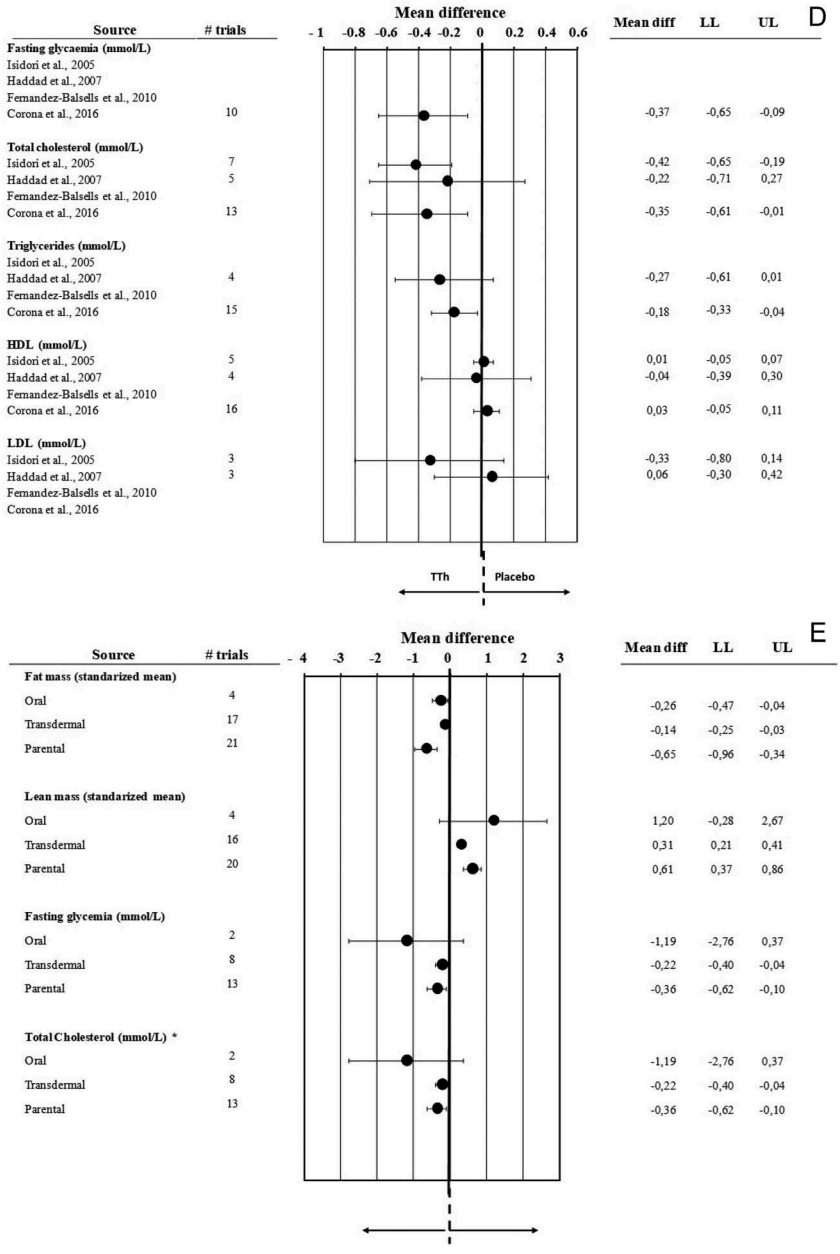

Figure 4. (Continued)

the obese subjects to further lose weight trough lifestyle changes. The positive effects of TTh on glucose and lipid metabolism are also interesting, although not apparent in all meta-analyses. All the aforementioned improved outcomes are evident with transdermal and injectable preparations, but less evident with the oral ones.

Although there was some clamor in the lay press and in some scientific reports [98–102] about an increase in cardiovascular (CV) risk associated with TTh in LOH, a critical, systematic analysis recently performed by our group [47] does not support this issue. In fact, both CV and prostate safety are not affected by TTh [47].

Considering that the vast majority of RCTs on TTh are performed selecting LOH patients, it is difficult to support the opinion that increasing T levels is without effect in the aging male with HG. In this review, we have reported results from several meta-analyses corroborating the advantages of increasing low T in LOH. It is obvious that, whenever it is possible, resolving or attenuating the underlying condition leading to T deficiency is the first choice; however, it cannot be the only one. In fact, we strongly believe that along with lifestyle changes a combined approach with a pharmacological intervention is the more rational approach, at least in the case of obesity-associated LOH. In fact, proposing just LCD and a generic advice to increase physical activity can generate, in the symptomatic LOH subjects, the inability to fulfill needs, frustration, disappointment and demotivation toward the medical intervention, because it is perceived as a waste of time, with a final effect of an elevated dropout from the medical support. In contrast, a pharmacological intervention can more easily generate positive effects, such as an overall increased fitness (improved muscle mass

and insulin resistance) and, more important, a significant improvement in sexual life, including spontaneous erection and sexual desire. These positive effects will increase self-esteem and satisfaction in marriage and relationships, thus reinforcing the patient's trust in the doctor. All these effects will prompt the patient to adhere more tightly to the entire medical intervention, including the lifestyle modifications suggested by the medical service. A meta-analysis involving the few controlled trials in the field demonstrate that supplementation with TTh improves the lifestyle-induced improvement in body composition and metabolic outcomes [19].

As a final message, we believe that TTh is effective only when offered to genuinely HG men, and that the variable and often disappointing results are due to poor diagnostic practices, where T is prescribed to men without properly diagnosed HG.

9. Five-year view

LOH has confirmed as a frequent finding in both general and specific populations. Even though its pathogenesis and clinical meaning is still unclear, in the last years the urgency of recommendations on its clinical management has emerged. TTh represents the most classical therapeutic approach for treating LOH. In the last years, many efforts have been done for evaluating the benefits of TTh in the treatment of LOH and several RCTs have been published with different outcomes. The meta-analysis of the available RCTs confirms that TTh is able to improve sexual function, body composition and glycolipid metabolism. In contrast, data concerning the effect of TTh on osteoporosis and mood or cognition are still scanty with insufficient or inconclusive results. Since LOH has often a functional nature; in the last years a non-pharmacologic approach, based on lifestyle, has been encouraged. However, despite there is evidence for an increase in serum T levels after weight loss, there is still no data of an associated improvement in clinical features of LOH. In secondary HG, gonadotropins and antiestrogens represent other possible treatments for LOH. Despite their mechanism of action is more respectful of HPT axis physiology than TTh, also allowing preserving fertility, their use in LOH men has been scarcely studied, in particular concerning sexual outcomes. Although showing a nice increase in serum T, antiestrogens carry the potential––and still not extensively studied––risk of worsening sexual function and osteoporosis. However, the need of acquiring more information on these medications for LOH has been apparently received by researchers, since several clinical trials are now ongoing.

At present, TTh seems to be the most reasonable treatment for LOH, because it is the most studied in terms of both advantages and disadvantages. However, it is conceivable that in the next few years further information will be available on these new options, which will make them more realistic alternatives to TTh.

Key issues

- LOH is the most frequent form of hypogonadism (HG) and it is characterized by low serum testosterone (T) together with symptoms consistent with HG. It often results from a mixed disruption of the HPT axis at central or peripheral level, without a clear structural lesion at either these levels. Thus, it is considered functional in about 85% of cases.
- A non-pharmacological approach with lifestyle improvements is the most rationale treatment because it removes the causing conditions, resulting in serum T increase. However, compliance is an issue. In addition, there is still limited evidence of its efficacy in improving the LOH-related symptoms.
- Estrogens can inhibit HPT axis and, despite conflicting evidence have been reported, they are deemed to have a role in pathogenesis of obesity-related HG. Antiestrogens (SERMs or aromatase inhibitors) can decrease estrogen activity on hypothalamus and pituitary, thus being an option for LOH therapy. Indeed, this treatment––used off-label for HG––is associated with a considerable increase in serum T. However, the improvement in LOH clinical features has been scarcely investigated. Due to the possible role of estrogens in physiology of sexual function and bone, concerns exist on the possibility that antiestrogens could have a deleterious, rather than beneficial, effect on sexual complaints and osteoporosis.
- Gonadotropins are on label treatments for HG and they are mainly used for improvement of fertility. They could represent an option in LOH for the increasingly later search of paternity during life. However, they have not been specifically studied in LOH and their advantages on its clinical features are largely speculative.
- T therapy (TTh) is available with a number of possible formulations, which can be tailored in the patient needs. In the last years, several randomized clinical trials have assessed its efficacy in improving clinical features of LOH. These have shown that TTh can ameliorate sexual symptoms, body composition and glycolipid levels. Uncertainness still exists on its role in improving mood and cognition as well as the risk of fractures.

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