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## REVIEW

# Male hypogonadism: therapeutic choices and pharmacological management

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## ABSTRACT

Male hypogonadism, defined as an inadequate testosterone production, recognizes a testicular (primary hypogonadism) or a hypothalamic-pituitary dysfunction (central hypogonadism), although combined forms can also occur. Moreover, it has been known that intensive exercise training might be a cause of functional hypogonadism. Many therapeutic choices are currently available, depending on the timing of hypogonadism onset and fertility issue. The aim of this review was to comprehensively supply therapeutic options and schemes currently available for male hypogonadism, including pharmacological management of primary and central forms. Evidence on testosterone formulations, human chorionic gonadotropin, selective estrogen receptor modulators and aromatase inhibitors will be provided.

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KEY WORDS: Hypogonadism; Testosterone; Hormone replacement therapy; Chorionic gonadotropin; Selective estrogen receptor modulators.

Male hypogonadism is a clinical syndrome characterized by failure of the testes to produce an adequate amount of testosterone (T) and/or a normal number of spermatozoa. It can be classified according to the site of hypothalamic-pituitary dysfunction, the involvement of testicular cell population, and the time of its onset. Also, hypogonadism can be organic or dysfunctional. The former is caused by congenital, structural or destructive disorders, whereas the latter refers to potentially reversible conditions.<sup>1</sup> Hypogonadism is further classified into primary or central forms, based on the presence of a dysfunction at the testicular or the hypothalamic-pituitary level.<sup>1, 2</sup> Combined hypogonadism is characterized by low serum T levels and/

or impaired spermatogenesis, with gonadotropin levels which vary depending on whether primary or secondary hypogonadism predominates. Late onset hypogonadism (LOH) is an example of combined hypogonadism. It is a clinical and biochemical syndrome associated with advancing age characterized by symptoms indicative of androgen deficiency and a decline in serum T levels. Accordingly, several cross sectional and longitudinal studies have shown a gradual decline in T levels with increasing age, at an average rate of 1-2% per year,<sup>3, 4</sup> which varies among men on the basis of the presence of adiposity, pharmacological therapies and chronic diseases. Among a cohort of 3219 participants from Europe aged 40-79 years, LOH was identified in

2.1%, whereas 17% has shown isolated T deficiency (total T < 11 nmol/L [317 ng/dL]).<sup>3, 4</sup> Finally, a new classification of hypogonadism has been proposed by using data from the European Male Ageing Study (EMAS), which presents the issue of “compensated hypogonadism,” a further clinical subgroup characterized by normal total T levels combined with higher LH values, especially in the ageing population. This category of patients may develop infertility, since their testicular dysfunction carries on an increased risk of low total motile sperm count, low testicular volume and azoospermia.<sup>5</sup>

Diagnosis of male hypogonadism is established when the presence of specific symptoms and signs are associated with decreased serum T levels. So far 12.1 nmol/L (350 ng/dL or 3.5 ng/mL) is considered the lower limit of the normal range for total T level.<sup>6</sup> However, due to individual differences in T sensitivity, some men may exhibit symptoms of hypogonadism with total T concentrations above this threshold.<sup>6</sup>

Evidence strongly supports that low T is an important biomarker for morbidity and mortality in men. It is now clear that low T levels correlate significantly with certain conditions, such as age, obesity, poor general health and with some diseases, such as metabolic syndrome and cardiovascular disease (CVD).<sup>7</sup> Epidemiological studies identified T deficiency as a risk factor for CVD.<sup>8</sup> Low levels of T may have important long-term negative health consequences, such as premature death, in presence of CVD, due to high rate of myocardial infarction, ischemic stroke and other adverse cardiovascular events. It seems that patients with low T have a 24-124% increased risk for all-cause mortality during an average 4 to 16-year follow-up period.<sup>9, 10</sup> Moreover, low T is significantly associated with respiratory mortality and to cancer mortality.<sup>10, 11</sup> Lastly, normal serum T levels favor glycemic homeostasis through a better glucose uptake, utilization and disposal, and the general improvement of metabolism. For this reason, T deficiency favors hyperglycemia which, in addition to being the hallmark of diabetes mellitus, is an important component of the metabolic syndrome and increases the risk of CVD.<sup>12</sup> T deficiency has also been shown to alter the lipid profile and

to change, by causing insulin-resistance, body composition favoring the accumulation of visceral fat.<sup>13</sup>

Complications of untreated hypogonadism include worsening of sexual symptoms, bone damage, systemic symptoms and long-term metabolic complications. This strongly highlights the importance of a proper pharmacological treatment of male hypogonadism. Therefore, the aim of this review is to provide a comprehensive and updated overview of the available therapeutic options for male hypogonadism, including: T, human chorionic gonadotropin (hCG), selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and their management.

### **Treatment of primary hypogonadism: Testosterone formulations**

The goals of testosterone replacement therapy (TRT) are to restore serum T levels within the mid-normal physiological range, generally considered to be between 400 and 700 ng/dL, and to improve the well-being of the hypogonadal patient.<sup>14, 15</sup> Several T preparations are currently approved by the Food and Drugs Administration (FDA, USA) and by EMEA. These can be generally classified by the route of delivery and include oral, buccal, nasal, subdermal, transdermal and intramuscular (IM) preparation.

#### **Oral administration**

The administration of super-physiological doses of oral T has been proven unsuccessful due to extensive first pass metabolism through the liver despite a good gastrointestinal absorption. Therefore, the assumption of supra-physiological doses is required to overcome this and to reach measurable serum T levels.<sup>16</sup> Alkylation of T at the carbon 17 $\alpha$  results in 17 $\alpha$ -methyl-T. This compound has the ability to overcome the first pass hepatic metabolism. However, this modification has generated a compound with significant liver toxicity and capable of lowering HDL cholesterol.<sup>17</sup> Esterification at carbon 17 $\beta$  yields testosterone undecanoate (TU) which is absorbed via the lymphatic system and bypasses liver degradation. This formulation requires a high capsule burden due to low bioavailability

along with gastrointestinal and liver adverse effects.<sup>17, 18</sup> It has been used in Europe for decades but it was never approved for use in the United States. The advantages of TU administration include convenience of administration and a relatively safe profile, but its short half-life causes T serum levels fluctuations, that require repeated daily intake.

### **Buccal administration**

The permeability of the oral mucosa has been used for slow-release T for trans-buccal formulations. Muco-adhesive tablets are applied to the gums of the mouth and provide controlled and sustained release of T as the buccal system hydrates. This preparation delivers T directly into the systemic circulation and bypasses the liver, avoiding first pass metabolism thus increasing T bioavailability. Each tablet contains 30 mg of T and one tablet has to be applied every 12 hours, alternating the side of the mouth above the incisor teeth. Levels of circulating T peak within 10 to 12 hours of initial administration and reach the steady state within 24 hours. When the product is discontinued, T levels drop below the lower range limit within 2 to 4 hours, allowing for quick withdrawal if necessary. The preparation mimics the physiological circadian T rhythm, with serum levels quickly increasing after insertion and peak levels obtained by the second dose with no accumulation over time.<sup>19</sup> It is recommended to evaluate T levels between 4 to 12 weeks after therapy initiation prior to the morning dose. Buccal T has been found to be well tolerated in clinical trials with the most common adverse effect being gum-related.<sup>20, 21</sup> Approximately 18% of subjects reported irritation, inflammation, or gingivitis. Advantages of buccal T include non-invasive administration with minimal risk for secondary transfer to women or children.

### **Nasal administration**

Another T formulation that may be used for TRT is the nasal gel formulation (Natesto™, Endo Pharmaceuticals, Malvern, PA, USA), which was approved by FDA in May 2014. This product utilizes a metered dose pump applicator, allowing patients to self-administer into the nostrils.

Each pump delivers 5.5 mg of T, at the recommended dosage of two pumps (one per nostril) three times a day, for a total daily dose of 33 mg. Doses should be separated by 6 to 8 hours. Absorption occurs through the nasal mucosa, avoiding first pass metabolism, and the  $C_{max}$  is reached within 40 minutes of administration. Treatment is well tolerated. Adverse effects include increased PSA, headache, rhinorrhea, nosebleed, nasal discomfort, upper respiratory tract infection, sinusitis, bronchitis, and nasal scab. T nasal gel is another non-invasive alternative with simple administration, low total daily dose, and no concern for secondary transfer. Currently, T nasal gel is not commercialized in Italy.

### **Subdermal administration**

Subdermal T pellets were the first effective formulation for TRT, developed many decades ago.<sup>22</sup> T pellets consist of crystalline T and are created through high-temperature molding and designed for consistent and prolonged release. Absorption occurs through uniform erosion of the pellet's surface associated with the solubility of T in extracellular fluid. The dosage varies upon patient age and diagnosis and is adjusted to the patient response and manifestation of adverse reactions. The dose recommended ranges from 150 to 450 mg implanted sub-dermally in the hip area or another fatty area at 3- to 6-month intervals. T pellets are generically available in 12.5, 25, 37.5, and 50 mg dosages. A 75 mg pellet is also available as Testopel® (Auxilium Pharmaceuticals Inc., Malvern, PA, USA). The most common adverse event is pellet extrusion. Other adverse events include site infections, bleeding, and fibrosis at the insertion site. Potential advantages of pellet usage include the infrequency of dosing, guaranteed compliance, and lack of transference. However, administration is invasive requiring skin incision and local anesthesia. There are also concerns regarding pellet removal for patients experiencing androgen related side effects. Subdermal T administration is not available for TRT in Italy.

### **Transdermal testosterone**

Transdermal TRT is delivered in the form of a transdermal patch or gel. It requires daily ad-

ministration and has the benefit of mimicking T normal circadian rhythm, peaking in the morning and declining slowly to its nadir at night.

#### *Transdermal patch*

This application allows for a maximal absorption through a thin-skinned area. Disadvantages include smaller skin surface area and application challenges (hair clipping). Non-scrotal transdermal patches, Androderm®, (Actavis, Parsippany, NJ, USA) were approved by FDA in 1995. The patches are available in either 2 or 4 mg/day formulations. The recommended starting dose is one 4 mg/day patch every 24 hours applied nightly. The patch has to be applied to the back, abdomen, upper arms or thighs. Sites should be rotated and not re-used within 7 days. Two weeks after initiation of therapy, serum T level should be measured (early in the morning after patch application the night prior) and patch dosing adjusted as necessary. Levels <400 ng/dL require a dose escalation to 6 mg/day (1×4 mg/day patch plus 1×2 mg/day patch), while levels >930 ng/dL should be reduced to 2 mg/day. The efficacy of the transdermal patch is often limited by lack of adherence or discontinuation due to skin blistering, pruritus, or irritation. This is due to permeation enhancers included in the transdermal system, which are necessary to increase absorption. Topical corticosteroid application to the affected area is recommended for alleviation of symptoms.

#### *Transdermal gel/liquid solution*

Transdermal gel was designed to further improve transdermal delivery systems. Although it is one of the most expensive TRT modalities, transdermal gel is currently the most commonly used, followed by injections, patches, and oral tablets. The gel, containing 1% T, is available in 2.5, 5, or 10 g tubes or packets and as a 75 g pump delivering doses of 1.25 g per compression. Generally, the gel is applied to dry skin on the shoulder, abdomen or upper arm after bathing. It dries within 10 minutes. Patients are advised to cover the application site with clothing for at least 2 hours after application to prevent transferring the gel to others by contact and to avoid bathing or swimming for 2 to 6 hours after application, de-

pending on the brand. Approximately 10% of the gel is absorbed into the stratum corneum of the skin, which serves as a reservoir for the T, allowing its slow release over several hours. T levels peak in 16 to 22 hours, reaching the steady state in 1 to 2 days and tends to remain stable thereafter. Levels return to baseline within 4 days after discontinuation. Compared with the patch, the gel rarely causes skin irritation. It also allows for greater flexibility of dosing compared with other modalities, as it is available in variable doses and as a pump. Levels of DHT, however, seem to be significantly higher than those attained with patch use.<sup>23</sup> This is likely due to the fact that the gel covers a greater skin surface area than the patch, causing more testosterone to be converted into DHT. PSA levels are elevated with gel use but remain within the normal range.

#### **Intramuscular administration**

IM T has been used for years due to its effectiveness and low cost. Whereas free T has a half-life of only 10 minutes, the esterification process renders T less polar and more lipid soluble, thereby prolonging its duration of action. Delivery of these esters through an oil-based depot injection allows their slow release. T enanthate (TE) and T cypionate (TC) have similar pharmacokinetic profiles. Both produce peak, often supra physiologic levels within 2 to 3 days of injection and decline slowly, often to subnormal levels in 1 to 2 weeks. Such saw-toothed pharmacokinetics cause swings in mood, energy level, sexual function, and libido. The most commonly recommended dosage regimen for TE or TC is 100 to 250 mg IM every 2-4 weeks or, as the American Association of Clinical Endocrinologists (AACE) recommends, when T levels are just above the lower limit of normal, in the range of 250 to 300 ng/dL.<sup>24</sup> The Endocrine Society recommends measuring levels midway between injections and adjusting dose or frequency to achieve levels in the mid normal range.<sup>1</sup> We suggest to monitor serum T levels the same day, but before, the next T IM injection is given.

T propionate is rarely used in an injectable form because its pharmacokinetic profile requires administration every 2 to 3 days. IM T injections are deep and may produce pain, site reactions, or



pruritus. As with all forms of T that undergo aromatization to  $E_2$ , administration may cause gynecomastia early in the treatment process, mild cases of which usually resolve within a few months. Some reports also have described short episodes of coughing following injections. Such episodes are thought to result from pulmonary micro embolisms caused by the oily vehicle. A long-acting IM injection of T in form of TU has currently been approved for use in Europe. TU is the first injectable T to be taken every 3 months. It maintains stable physiologic levels for 12 weeks and appears to be well accepted. Compared with TE, TU produces a more stable rise, modest maximal concentration and gradual decline of T, thereby minimizing the mood and libido fluctuations compared with TE. As reviewed elsewhere,<sup>25</sup> its safety and tolerability profile is also favorable: incidence and severity of common adverse effects are not greater than those associated with TE and no serious adverse event has been noted. The recommended dose is 1000 mg every 10 to 14 weeks, with an additional loading dose of 750 mg to be administered at 4 weeks. Because TU has a long half-life and its safety in older men is yet to be reported, it may have a greater role in treating younger patients. For older men, the switch to TU may be considered if transdermal agents have been used for 3 to 6 months, thus ensuring tolerability.

### Treatment of central hypogonadism

Central hypogonadism results from an impairment of the hypothalamic (GnRH)-pituitary (LH and FSH) axis function. Hence, the rationale of the treatment is to restore the gonadotropin deficiency, raising their serum levels either directly or indirectly. The molecules able to achieve this goal include both FDA-approved (hCG) and off-label drugs (selective estrogen receptor modulators [SERMs] and aromatase inhibitors [AIs]).<sup>26</sup> These drugs have to be taken into consideration only when fatherhood is desired and after an accurate search of the causes of central hypogonadism, as recommended by the Endocrine Society.<sup>1</sup> Indeed, TRT is currently suggested by the scientific Societies guidelines in adult patients with central hypogonadism when no other treatment

(e.g. surgical removal of a pituitary mass, treatment of hyperprolactinemia, etc.) can revert the deficiency.<sup>1, 27-30</sup>

### hCG

hCG is a glycoprotein produced by placental trophoblastic cells starting from the 10<sup>th</sup>-12<sup>th</sup> embryonic day, and it is required for the maintenance of the fetus in the first trimester. The  $\beta$ -subunit of hCG shares with that of LH 82% amino acid homology.<sup>31</sup> On this basis, hCG extracted from urine of pregnant women or produced *in vitro* using recombinant DNA technology is currently used for the treatment of central hypogonadism.<sup>32</sup> It enhances T synthesis by stimulating Leydig cell function. hCG, administered by IM or subcutaneous injection, has a biological half-life of 8 hours. On the other hand, due to the above-mentioned chemical differences with LH, the latter has a half-life of only 30 minutes and, therefore, it is not used in the clinical practice. Doses of hCG ranging from 2000 IU twice/week in patients with LOH<sup>33</sup> to 1500-2000 IU three times/week in patients with central hypogonadism<sup>34, 35</sup> have been successfully used to raise T levels for up to 24 months.<sup>35</sup> One of the advantages of hCG administration is the increase of intra-tubular T levels, which, on the opposite, are suppressed in patients on TRT. The raise of intra-tubular T levels is better accomplished using low-dose schemes (125 IU every other day)<sup>36</sup> and it is crucial to sustain spermatogenesis. However, hCG at high doses has been also found compatible with the achievement of spontaneous pregnancy.<sup>35</sup> Indeed, among 20 patients with central hypogonadism treated with 1500-2000 IU three times a week, 10 searched paternities and 7 of them achieved it naturally.<sup>35</sup> Accordingly, hCG has been showed to stimulate the recovery of spermatogenesis in patients with central hypogonadism who have been treated with TRT.<sup>37</sup> Treatment with hCG has been also observed to increase vitamin D levels. However, this topic requires further investigation since only few evidence is available so far.<sup>33, 38, 39</sup>

### SERMs

SERMs act as estrogen agonists or antagonists in a tissue-specific manner.<sup>40</sup> At the hypothalamic

TABLE I.—*Main therapeutic schemes reported in the literature.*<sup>43</sup>

Drug	Therapeutic scheme
Clomiphene citrate	25 mg on alternate days for 3-6 months 25 mg daily for 3-6 months 50 mg daily for 3-6 months
Tamoxifen	10 mg twice a day for 3-6 months 20 mg daily for 3-6 months 30 mg daily for 3-4 months
Toremifene	60 mg daily for 3 months
Raloxifene	60 mg daily for 3 months

and pituitary levels, they block estrogen receptors. This stimulates GnRH and, in turn, LH and FSH secretion.<sup>41, 42</sup> SERMs include several molecules, such as tamoxifen, clomiphene citrate (CC), raloxifene and toremifene. They are orally-administered and rapidly metabolized in a  $P_{450}$ -dependent manner. CC has a half-life of 5 days and is mainly eliminated through feces. The more commonly adopted therapeutic scheme in men is 25-50 mg daily. Tamoxifen has a half-life of 7 days and is removed by the gallbladder. It is more frequently administered at the dose of 20-30 mg daily.<sup>43</sup> The main therapeutic schemes reported in literature are shown in Table I.<sup>43</sup> The available evidence suggests the effectiveness of CC and tamoxifen for the treatment of T deficiency in patients with central hypogonadism. In particular, CC showed its efficacy in prospective trials when used at the dose of 25 to 50 mg every other day for up to 19 months,<sup>44</sup> 25 mg daily for 4-6 weeks<sup>45</sup> or 50 mg three times a week for 4 months<sup>46</sup> in 86, 36 and 228 patients with hypogonadotropic hypogonadism (HH), respectively. Similar results have been reported for tamoxifen<sup>47-50</sup> and a recent meta-analysis reported a raise in LH and total T serum levels after treatment with this molecule.<sup>43</sup> SERMs also improve sperm parameters and the pregnancy rate by increasing FSH serum levels as meta-analytic data have shown,<sup>43</sup> thus making their choice of particular usefulness in patients searching for fertility. Despite the above-mentioned evidence, SERMs are currently considered off-label drugs for the treatment of central hypogonadism.<sup>26</sup>

### AIs

AIs inhibit the conversion of T into  $E_2$  by targeting the aromatase enzyme. The consequent

decrease in estrogen serum levels results in a decrease of the negative feedback exerted by these hormones on the hypothalamic-pituitary-axis. Therefore, aromatase inhibition results in a direct and indirect raise in T serum levels.<sup>51</sup> AIs are orally-administered drugs, metabolized in a  $P_{450}$ -mediated manner. Anastrozole and letrozole, both showing a half-life of 48 hours, have been rarely adopted for treatment of central hypogonadism.<sup>26</sup> Administration of anastrozole (1 mg once daily or 1 mg twice/week) showed its efficacy in raising T concentrations after 12 weeks of treatment in a randomized controlled trial.<sup>52</sup> Likewise, a randomized placebo-controlled trial compared letrozole 2.5 mg (once day) with placebo in healthy young and elderly patients reported a significant raise of T levels in both groups after 28 days of treatment.<sup>51</sup> However, due to the paucity of data, this topic needs to be further investigated and no definitive conclusions can be made. Currently, AIs are off-label drugs for the treatment of central hypogonadism.

### Treatment of prepubertal male hypogonadism: the induction of puberty

Treatment in young male with hypogonadism (both primary or central) and consequent pubertal delay is aimed to obtain a good virilization and to optimize bone mass accrual without compromising the final height. The induction of puberty is more commonly based on the administration of T by IM; more rarely oral or transdermal formulations are used, but the treatment protocols have not yet been standardized and there is no consensus on the optimal regime.<sup>53, 54</sup> Thus far IM T esters (enanthate, propionate, cypionate) have been used. TE is generally preferred as it has a longer duration of action.<sup>55</sup> Treatment should start at the age of 12 with 15-25% of adult dosage, hence 50 mg/month for 6 months, increasing the dose by 50 mg every 6-12 months.<sup>53, 55, 56</sup> After the dose of 100-150 mg of T esters monthly has been reached, the interval between dosages can be reduced to two weeks. The adult full replacement levels (250 mg every two-four weeks for TE; 1000 mg every 10-14 weeks for TU) are reached over about 3 years.<sup>55</sup> Other authors report a therapeutic scheme based on a first IM in-

jection of 125 mg of T esters at 125, 250 and 250 mg three weeks apart with the aim to induce the initial virilization. The same regimen, a second one of 250 mg after three weeks, and it can be repeated twice in the following 6 months. Thereafter, the complete achievement of puberty can be reached with monthly injections over 2 years.<sup>57</sup> Transdermal T formulations, in form of gel topically applied at the dose of 50 mg/m<sup>2</sup>/day or in form of patches, should be started when about 50% of the adult dose with IM T administration has been reached.<sup>55</sup> Transdermal T is usually preferred in patients with pubertal delay secondary to renal failure, although some authors showed that therapy with these formulations at bedtime simulated physiological T secretion and increased short-term growth and bone turnover in male with constitutional delay of growth and puberty (CDGP).<sup>53</sup> As for the oral formulation of T, there is a lack of experience and there are no formal guidelines about its use.<sup>56</sup>

In prepubertal boys with HH, puberty can be induced using hCG alone or in combination with FSH. These approaches result in better testicular growth and (probably) fertility outcome than the administration of T alone.<sup>58</sup> However, to date, there are no large studies evaluating the outcome of gonadotropin replacement therapy during adolescence. Patients with delayed puberty second-

ary to HH need a prolonged use of T for pubertal induction, thus it is still debated if this treatment could have negative effects on spermatogenesis.<sup>57</sup> A recent study suggests that hCG/FSH treatment in adolescent boys with HH results in an improvement of quality of life (QoL).<sup>59</sup> Conventionally, hCG is administered at the dosage of 500 IU twice/week for 6 months; subsequently, the dosage is increased to 1000 IU twice/week for 12 months and then 1500 UI twice/week for maintenance.<sup>57</sup> In case of azoospermia after 6-12 months of hCG treatment, FSH can be added at a dose between 75-225 IU (usually 150 IU) three times/week for 4-6 months. If azoospermia persists, FSH dosage can be increased at 300 UI three times/week. Some authors suggested that combination therapy of hCG plus FSH is more effective in inducing spermatogenesis than treatment with hCG alone.<sup>58, 60</sup>

Protocols for puberty induction are available in Table II.

## Follow-up

### Follow-up of primary hypogonadism

Hypogonadal patients who have started TRT should be monitored over time to assess both the efficacy and the safety of the treatment. Unfor-

TABLE II.—*Protocols for puberty induction in males.*

Treatment	Primary hypogonadism	Central hypogonadism
Testosterone enanthate, propionate, or cypionate	50 mg/months; increase of 50 mg every 6-12 months. Increase at 100-150 mg of testosterone ester first monthly, then every two weeks. Adult full replacement levels reached over about 3 years Some authors suggest administration of 125, 250 and 250 mg three weeks. The same regimen can be repeated in 6 months. Monthly injections over 2 years for a complete achievement of puberty	50 mg/months; increase of 50 mg every 6-12 months. Increase at 100-150 mg of testosterone ester first monthly, then every two weeks. Adult full replacement levels reached over about 3 years Administration of 125, 250 and 250 mg three weeks. The same regimen can be repeated in 6 months. Monthly injections over 2 years for a complete achievement of puberty
Transdermal testosterone	50 mg/mq/day of gel or 5 mg patches (experimental studies). To start when the about 50% of adult dose with intramuscular testosterone administration has been achieved	50 mg/m <sup>2</sup> /day of gel or 5 mg patches (experimental studies). To start when about the 50% of adult dose with intramuscular testosterone administration has been achieved
hCG	Not used	500 IU twice/week for 6 months. Then increase to 1000 IU twice/week for 12 months and then 1500 UI twice/week for maintenance
FSH	Not used	75-225 IU (usually 150 IU) three times/week for 4-6 months. Increase at 300 UI three times/week in case of azoospermia



tunately, TRT is frequently prescribed without appropriate patients' follow-up, as some studies have reported.<sup>61-63</sup>

The goals of TRT is the normalization of total T levels and the improvement of symptoms and signs of hypogonadism.<sup>30</sup> TRT should maintain serum T concentrations in the middle tertile of the normal physiological range of 450-600 ng/dL (4.5-6 ng/mL), using the smallest necessary dose.<sup>30</sup> Serum total T levels should be measured 3 to 6 months after initiation of therapy or changing in dose and then if stable, every 6-12 months to ensure maintenance of target levels.<sup>30</sup> The pharmacokinetics of the T formulations should guide the timing of therapeutic monitoring. Table III shows a summary of the timing for T levels measurements based on the T formulation according to the latest guidelines of the American Urological Association and the Endocrine Society. Improvement of the symptoms and signs of hypogonadism occurs at different times for different organ systems. Improvement of libido and in the QoL usually occurs within 3-6 weeks after starting TRT,<sup>64</sup> but maximal effects on depressive mood appear only after 18-30 weeks.<sup>65</sup> Effects of TRT on insulin sensitivity appear quickly but effects on glycemic control become evident

after 3-12 months. Effects on lipids appear after 4 weeks, with maximal effects after 6-12 months of treatment.<sup>66</sup> Decrease in fat mass and increase in lean body mass and muscle strength occur after 12-16 weeks of TRT starting and stabilize at 6-12 months, but can continue to improve over years.<sup>66</sup> A significant improvement in erectile and ejaculatory functions is achieved after 12 months of TRT. Improvement in bone appears after 6 months of TRT, while the full beneficial effect of TRT on bone mineral density may take 2-3 years<sup>65, 67</sup> or even 6 years.<sup>68</sup> In men with osteoporosis who are not considered to be at high risk for fracture, clinicians should repeat BMD measurements 1 to 2 years after initiating TRT (Table IV).<sup>1</sup> If, after the proper period of time, patients do not experience symptomatic improvement, despite the achievement of the specified T level target or remain T deficient in the setting of symptom/sign improvement, TRT should be stopped because, very likely, hypotestosteronemia does not play a pathophysiological role.<sup>1, 30, 66</sup>

Patients who receive TRT should be evaluated for possible adverse effects related to T itself or to the formulation used. Often these adverse effects can be minimized by dose adjustment,

TABLE III.—*Timing of testosterone measurements according to the testosterone formulation administered.*

Testosterone formulation	AUA 2018	ES 2018
Transdermal gel	At least 2-4 weeks after the start of the TRT Treatment must be applied on the day the blood is withdrawn	At least 1 week after the start the TRT Assess testosterone levels 2-8 hours after gel application
Transdermal patches	At least 2-4 weeks after the start of the TRT Treatment must be applied on the day the blood is withdrawn	Assess serum testosterone levels 3-12 hours after patch application
Buccal testosterone bioadhesive tablet		Assess serum testosterone levels immediately before or after application of fresh system
Oral testosterone undecanoate		Monitor serum testosterone levels 3-5 hours after ingestion with a fat-containing meal
Injectable testosterone enanthate or cypionate	No earlier than three to four cycles	Assess testosterone levels midway between injections
Injectable testosterone undecanoate	Assess testosterone levels halfway between the first two weeks injections	Assess testosterone levels at the end of the dosing interval just prior to the next injections
T pellets	Assess testosterone on two separate occasions: 2-4 weeks after initial implant to determinate if the number of inserted pellets needs to be increased or decreased to achieve the appropriate therapeutic level After 10-12 weeks to ascertain when the next administration should occur	Assess testosterone levels at the end of the dosing interval

AUA: American Urological Association; ES: Endocrine Society; T: testosterone; TRT: testosterone replacement therapy.

TABLE IV.—*Time-course of testosterone replacement therapy effects on the main symptoms/signs in hypogonadal patients.*

Symptoms	Time of improvement	
	Initial change	Maximal effect
Libido and QoL	3-6 weeks	12 months
Lipid metabolism	4 weeks	6-12 months
Glycemic metabolism	Few days	3-12 months
Erectile function	12 months	
Bone	6 months	2-3 years (even 6 years)

switching to an alternative formulation or discontinuation of T supplementation. According to the latest American Urological Association and Endocrine Society guidelines, follow-up of TRT should include periodic assessment of PSA, digital rectal examination (DRE), and hematocrit evaluation. Although obstructive sleep apnea (OSA) and severe LUTS are considered relative contraindications, a specific time monitoring is not indicated in guidelines.

Before starting TRT, patients should be carefully evaluated to rule out potential contraindications. TRT is not recommended in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a PSA level  $>4$  ng/mL, a PSA level  $>3$  ng/mL associated with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit ( $>50\%$ ), untreated severe OSA, severe LUTS, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months and/or thrombophilia.<sup>1, 69</sup>

For men between 55-69 years of age and for men between 40-69 years of age who are at increased risk for prostate cancers, clinicians should evaluate PSA levels and perform a DRE at baseline and at 3 to 12 months after TRT has been started. After 1 year of TRT, prostate monitoring should conform to guidelines for prostate cancer screening, depending on the race and the age of the patient. For patients who have an elevated PSA at baseline, a second PSA test is recommended to exclude the possibility of transient rises (*e.g.*, due to prostatitis or assay variability). In patients who have elevated PSA levels, suspicion for the presence of prostate cancers, and a prostate biopsy with/without MRI (if needed) should be considered before TRT starting. During follow-up, a urological consultation is rec-

ommended in three cases: 1) if during the first 12 months of TRT there is a confirmed increase in PSA concentration  $>1.4$  ng/mL above baseline; 2) a confirmed PSA  $>4.0$  ng/mL; or 3) a prostatic abnormality detected by DRE.<sup>1, 69</sup>

Periodic hematologic assessment is indicated before treatment, after 3, 6, and 12 months of TRT initiation, and thereafter annually. Prior TRT, all patients should undergo a baseline measurement of hemoglobin/hematocrit. If the latter exceeds 50%, TRT should be withheld until diagnosis is made and hematocrit values have been returned below 50%. While on TRT, if hematocrit increases to  $\geq 54\%$ , TRT should be temporarily stopped or dosage reduced.<sup>1</sup> If hematocrit cannot be kept below the upper limit of normal, even when the serum T levels are at the low end of the normal range, phlebotomy can be considered.

#### Management of central hypogonadism treatment

Alternative therapies to TRT (hCG, SERMs and AIs) can be used to promote the endogenous production of T, especially in patients who wish to maintain fertility. Among these, only hCG is approved by the FDA for use in men while AIs and SERMs are off-label. For this reason, clinical guidelines do not exist for the proper follow-up of patients treated with these drugs. A correct management of the treatment should include the evaluation of both efficacy and safety. As regard to efficacy, in most cases, the goal of these alternative therapies is not only the normalization of total T levels and the improvement in symptoms or signs, but also to restore fertility. Thus, a proper follow-up should include not only monitoring of serum T levels and assessment of symptoms/signs but also the evaluation of sperm parame-

ters. Concerning the safety, unluckily, few studies have evaluated the adverse effects of these drugs in hypogonadal patients.

hCG administration is generally well tolerated. Adverse events are infrequent and they are mainly represented by gynecomastia and acne, which occur in less than 10% of cases.<sup>70</sup> In order to ensure well-tolerated and optimal dosing, clinicians should monitor serum T levels, hematocrit and E<sub>2</sub> every 4-6 weeks to guide dose titration until a steady state has been achieved.<sup>71</sup> Moreover, safety may be superior to TRT because the risk of overtreatment is limited by Leydig cell capacity and reversal is rapid upon drug cessation, which is advantageous especially in the older population where adverse effects could be particularly hazardous. Liu and colleagues,<sup>72</sup> evaluated recombinant hCG (r-hCG) for the treatment of 40 old men with partial age-related androgen deficiency in a double-blind, placebo-controlled, randomized clinical trial. After three months of therapy, they found no difference in the number or severity of clinical (sleep, lower urinary tract symptoms, blood pressure, pulse) or biochemical (polycythemia, hemoglobin, PSA) adverse events between r-hCG and placebo treatment groups. Three months of r-hCG treatment significantly decreased testicular volume.<sup>72</sup> Volumes had not returned to baseline 1 month after the cessation of therapy, and this is consistent with male hormonal contraceptive studies in young men in whom up to 6 months may be required before testicular volume returns to normal.<sup>73</sup>

Among SERMs, CC is considered an effective and safe drug, although few studies have assessed adverse effects, especially compared with TRT. More common side effects include headache, gastrointestinal distress, dizziness, gynecomastia and weight gain.<sup>74, 75</sup> There is also a 1.5% risk of visual disturbances such as blurred vision, photophobia, and diplopia although they are reversible with cessation of the treatment.<sup>74, 75</sup> Taylor and Levine<sup>76</sup> assessed hemoglobin, cholesterol, and PSA levels after CC and TRT treatment and found no significant increase in either treatment group. Wheeler and colleagues<sup>16</sup> found a lower risk of secondary polycythemia among hypogonadal patients treated with CC than in patients on TRT (2% vs. 11%, respectively); no

patient treated with CC needed phlebotomy. Da Ros and colleagues<sup>77</sup> found no adverse events or statistically significant changes in pre- and post-treatment HDL-cholesterol, triglycerides, fasting glucose, or prolactin levels in 125 men receiving CC for hypogonadism. In women, there have been reports of exacerbation of psychiatric illness associated with CC treatment. In men more studies are needed to draw a final conclusion. In addition, SERMs could have agonistic effects on bone, thus preventing from osteoporosis, which may occur in hypogonadal patients.<sup>78</sup> On the other hand, their agonistic effect on venous vessels could predispose patients to venous thromboembolic development.<sup>79, 80</sup>

AIs are generally well tolerated with rare side effects including nausea, decreased libido, and decreased bone mineral density, probably due to their suppressive effects on estrogen levels.<sup>81, 82</sup>

Studies evaluated the long-term efficacy and safety of these agents for the treatment of hypogonadism are needed.

### Exercise-related hypogonadism

For convenience through this paragraph the term “exercise” will be used to indicate both physical activity (any bodily movements) and exercise (subset of physical activity characterized by a planned and purposeful training). It is important to remind that exercise might have an acute or chronic effect on hormones, and therefore also on T. Indeed, after a single bout of exercise training T levels tend to increase and this changing is proportional to the intensity and the volume of exercise training. Physical activity might be considered as non-invasive therapy for physical and mental health diseases.<sup>83</sup> However, to reach these positive health and physiological effects, the volume, the intensity, the frequency and the type of exercise should be planned to achieve the best clinical results. When these exercise parameters are not correctly planned or subjects practice the exercise beyond the recommendations for health and physical fitness improvement, it could be possible that exercise might induce health complications (*e.g.* musculoskeletal injury and psychological disease).<sup>84, 85</sup> Moreover, increasing levels of exercise training might negatively influ-

ence the endocrine system promoting changes in circulating hormone levels. Beside the most notable endocrine dysfunction named Female Athlete Triad, less is known regarding the negative effects of exercise training on the reproductive endocrinology of men (*e.g.* development of exercise relative hypogonadism). However, the type of exercise might also influence the T response (*e.g.* running *vs.* weight lifting).<sup>86, 87</sup> Conversely, after a long period of exercise training (chronic effect) T levels are commonly unchanged or reduced.<sup>88-90</sup> A consideration should be done for weight-restricted sports in which a remarkable T reduction was observed.<sup>91</sup> In these sports, the reduction in caloric intakes plus the high exercise intensity and volume lead to a suppression of the hypothalamic-pituitary-gonadal (HPG) axis. However, this negative condition could be reversible obverting the existing energy deficit to achieve a healthy body weight.<sup>88, 92</sup>

The term exercise-hypogonadal male condition (EHMC) has been used in scientific literature to indicate male athletes who showed a reduction of circulating T levels (functional HH), with unchanged performance and motivation.<sup>93</sup> This condition may be considered a potential adaptive response of the HPG axis in which a new set-point for normal T level develops due to a chronic and long-term exercise exposure.<sup>88, 89, 94</sup>

Differently from EHMC condition, overtraining syndrome is defined when in conjunction to a reduced T level there is a compromised physical performance with also negative health consequence. There are two main causes for T reduction: first, other hormones in a stress response cascade might inhibit the T production; second, inadequate energy intake disruption of the HPG axis regulatory function.<sup>94</sup> Exercise-related short-term cortisol elevations may disrupt T production negatively by impacting on LH/FSH, via GnRH suppression or affecting Leydig cell function through direct inhibition of steroidogenesis.<sup>94</sup> Moreover, the exercise-induced prolactin increase inhibits GnRH production and even inhibits the action of gonadotropins on the testis directly. Additionally, the inadequate energy intake in athletes may impact on HPG axis with a reduced GnRH release and hypothalamic suppression due to dysregulation of leptin, gh-

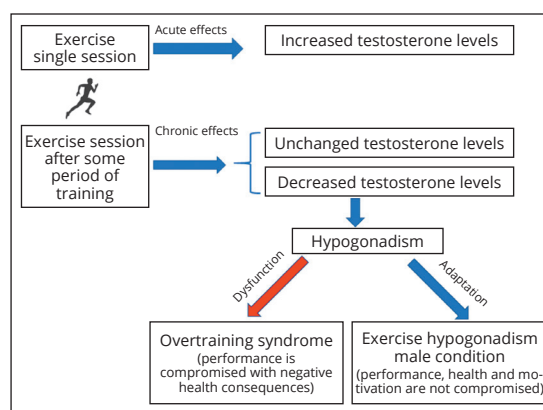


Figure 1.—Effects of exercise on testosterone levels.

erlin and pro-inflammatory cytokines. However, the T reductions found in trained athletes generally are in the lower limit of reference values.<sup>94</sup> The effects of exercise training on T are shown schematically in Figure 1.

#### Anabolic androgenic steroids use

The use of anabolic androgenic steroid (AAS) should be investigated when evaluating the causes of hypogonadism, especially in athletes. Indeed, the AAS use is associated with several side effects which may lead to variable and individually specific complication. In this situation, hypogonadism is a very common outcome and may appear during the AAS use as well as a long-term effect after the AAS withdrawal.<sup>94</sup> To stop AAS immediately and dynamic re-testing of the HPG axis after an appropriate wash-out period is advised.

#### Treatment of the exercise-related hypogonadism

The administration of the previously mentioned treatments for male hypogonadism in athletes is not allowed since the World Anti-Doping Agency (WADA) includes exogenous T and gonadotropins in the list of prohibited substances and methods (Anabolic agents; Peptide hormones, growth factors related substances, and mimetics).<sup>94</sup> WADA provides Therapeutic Use Exception options allowing the administration of some medications for health reason; but EHMC is not included in this list since low T is the consequence of exercise training, unless there is a documented pre-existing/acquired medical con-



dition.<sup>94</sup> Therefore, TRT or gonadotropin use is considered a violation of WADA code. So, in such cases it is advisable to choose non-pharmacological strategies including nutritional intervention or modifications in training volume in order to gain energy availability and a normalization of the HPG axis function.<sup>95, 96</sup> Indeed, evidences reported a rise in total or free T concentrations related with some legal supplements such as D-aspartic acid and fenugreek (*Trigonella foenum-graecum*).<sup>94</sup> However, the use of such nutraceuticals is rarely recommended since reported outcomes show minimal benefits. Furthermore, some nutraceuticals may contain illicit substances banned by WADA. In light of these issues, there are few treatment choices for exercise-related hypogonadism other than warning athletes that this is a transient condition that may/may not impact on their physical performance.

## Conclusions

In conclusion, several therapeutic schemes are available for the treatment of male hypogonadism, whose choice depends on the timing of disease onset and fertility issues. Exercise-related hypogonadism is still a controversial occurrence and it is unclear if a clinical intervention is warranted (or desired) since it is considered an adaptive condition with not reported negative health consequences. Timing of follow-up, including the assessment of serum T levels and markers of safety, depend on the drug pharmacokinetics.

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