TESTOSTERONE REPLACEMENT THERAPY IN LATE ONSET HYPOGONADISM

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Thesis mentor: Assist. Prof. Antun Gršković, MD, PhD

This graduation thesis was graded on _____ in Rijeka, before the Committee composed of the following members:

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The graduation thesis contains 27 pages, 2 figures, 1 table, 29 references.

Contents

List of abbreviations and acronyms

BMD: bone mineral density

FSH: follicle-stimulating hormone

GnRH: gonadotropin-releasing hormone

HPG axis: hypothalamic-pituitary-gonadal axis

Hct: Hematocrit

LH: luteinizing hormone

LOH: late-onset hypogonadism

nmol/L: Nanomoles per liter

PSA: prostate-specific antigen

SHBG: sex hormone-binding globulin

T: testosterone

TC: testosterone cypionate

TE: testosterone enanthate

TRT: testosterone replacement therapy

TU: testosterone undecaonoate

WHO: World Health Organization

fT: free testosterone

tT: total testosterone

1. Introduction

1.1. Definition of testicles

Testicles, also referred to as testes or male gonads, form a crucial part of the male reproductive system. Found in pairs within the scrotum beneath the penis, these glands perform an exocrine function by producing sperm and an endocrine function by secreting various hormones (1).

1.2. Functions of testicles:

1.2.1. Endocrine function/Hormone Production:

Testosterone (T), the primary hormone produced by the testicles, is regulated by the hypothalamic-pituitary-gonadal (HPG) axis. The process begins in the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH). This, in turn, signals the pituitary gland to produce two key hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH specifically targets Leydig cells located in the interstitial space of the testicles, stimulating them to produce T (2). On the other hand, FSH drives the Sertoli cells in the seminiferous tubules to generate inhibin B, further facilitating spermatogenesis (3). The production of GnRH and LH is inhibited by T (4), whereas FSH secretion is suppressed by inhibin B (3).

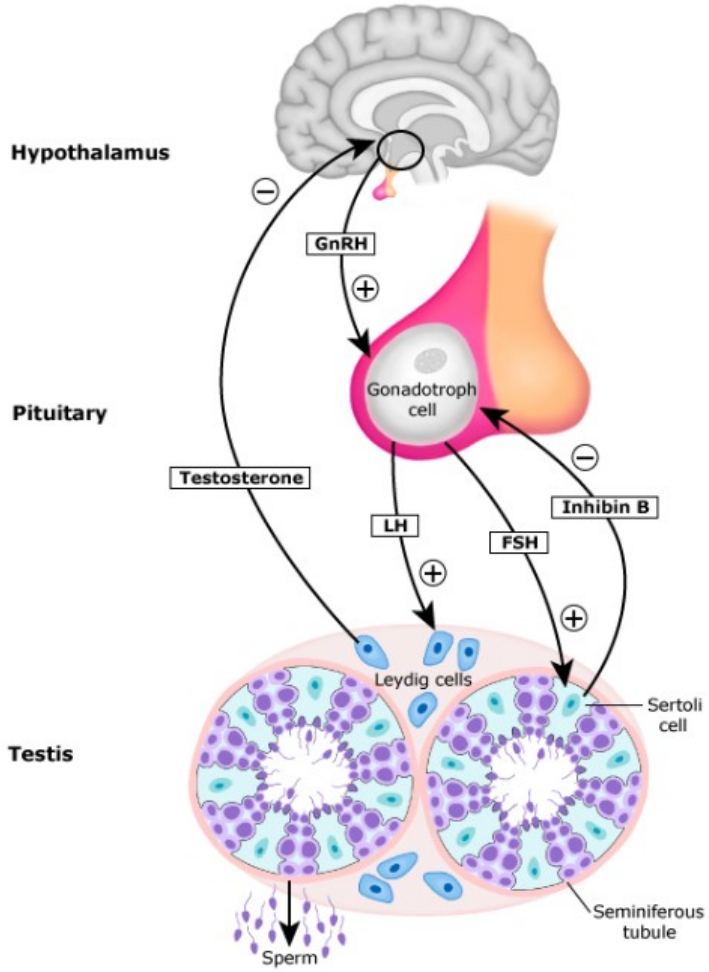

Figure 1: *Illustration of the HPG axis.*

Source: "Snyder PJ. Clinical features and diagnosis of male hypogonadism [Internet]. Matsumoto AM, Martin KA, editors. UpToDate; 2024. [accessed March 3, 2024]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-male-hypogonadism?search=clinical%20features%20and%20diagnosis%20of%20male%20hypogonadism&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1#H23"

1.2.2. Exocrine function/Sperm Production:

The testicles function at a cooler temperature, around two degrees Celsius lower than the rest of the body's temperature, aiding in the process of sperm production, known as spermatogenesis, within the seminiferous tubules. Mature sperm cells take approximately 74 days to develop (1).

1.3. Testosterone

1.3.1. Role of testosterone

Testosterone is essential for:

- male sex differentiation (5),
- contributing to male characteristics like muscle strength, body hair, deeper voice (1),
- supporting normal sexual functions, such as libido, erectile capability,
- regulating a lower body fat percentage,
- enhancing bone density,
- initiating and maintaining spermatogenesis and erythropoiesis (6).

Additionally, it suppresses the secretion of both LH and FSH (4).

1.3.2. SHBG

In plasma, gonadal steroids are primarily protein-bound. In males with normal health, only about 0.5 to 3% of T in plasma exists in a free or unbound state, called free Testosterone (fT). Yet the majority is attached to proteins such as sex hormone-binding globulin (SHBG), albumin, corticosteroid-binding globulin, and orosomucoid (7). The fT and protein-bound T together comprise the total Testosterone (tT) (3).

The free hormone hypothesis suggests that 30 to 44 percent of T in circulation, which is strongly bound to SHBG, is not accessible to body tissues and hence is considered not "active". While the fT hypothesis is not yet conclusively proven, the limited existing data there is so far supports this theory (6,7).

1.4. Definition of Hypogonadism - primary and secondary

In males, hypogonadism is characterized by a reduction in either one or both of the key functions of the testes: the production of T and/or the production of sperm (3).

Primary hypogonadism is characterized by dysfunction originating in the testes themselves, whereas secondary hypogonadism stems from irregularities in the hypothalamus (GnRH) or the pituitary gland (LH, FSH).

Primary hypogonadism most commonly originates from Klinefelter syndrome, cryptorchidism, chemotherapy and radiation, certain medications like glucocorticoids, trauma, testicular torsion (8) and infections like mumps orchitis and epididymo-orchitis (9).

Causes for secondary hypogonadism include genetic disorders (e.g. Kallmann syndrome, Prader-Willi syndrome), as well as lesions of the hypothalamus and/or pituitary gland (e.g. neoplasms, physical trauma, surgery, irradiation) (10).

1.5. Obesity and hypogonadism

Research indicates that obesity might be the primary contributor to T deficiency in developed countries, with a significant number of obese men exhibiting below-normal testosterone levels. The interplay between obesity and hypogonadism is complex and bidirectional. Obesity leads to reduced testosterone while low testosterone can contribute to fat accumulation (11).

1.5.1. How obesity leads to low testosterone

Adipocytes produce the enzyme aromatase, which converts T to estradiol. With an increased fat mass the T levels decline as more T becomes transformed. Furthermore, the increasingly synthesized estrogen initiates negative feedback to the hypothalamus, suppressing GnRH secretion, causing a decrease in LH and hence T levels (11).

1.5.2. How low testosterone leads to obesity

On the other side, low T leads to an increase in fat tissue, but the exact mechanisms are still uncertain. Theories suggest it could promote lipolysis, reduce lipogenesis, and block lipid absorption. T specifically promotes the accumulation of visceral fat. Individuals undergoing androgen deprivation therapy, such as prostate cancer patients, often experience increased central obesity, higher body fat percentages, and reduced lean muscle mass (11).

1.6. Late-onset hypogonadism

Late-onset hypogonadism (LOH) refers to the development of T deficiency (below the reference range of healthy young adult males) and its characteristic symptoms in association with aging. The production of T by the testes reduces annually by 1% to 2% starting from the age of 40 (12). The cause of T deficiency in aging men is a mixture of primary and secondary hypogonadism (13). As part of the natural aging process, the hypothalamic-pituitary function and Leydig cell function in the testes deteriorate. As men age, the pulsed secretion of GnRH becomes disordered and the amplitude and frequency of LH pulses reduce. The decline in the number and function of Leydig cells occurs due to the degenerative alterations within the Leydig cells themselves. Furthermore, with aging, the SHBG levels rise, leading to a reduction in the amount of bioavailable fT (14).

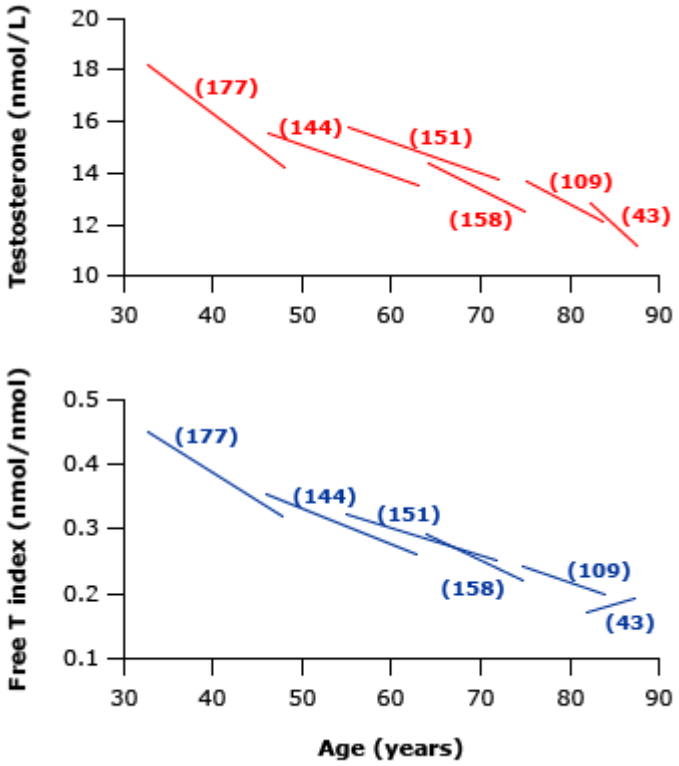

Figure 2: *Longitudinal effects of aging: Graphs depicting the relationship between tT and fT concerning age*

Source: "Snyder PJ. Clinical features and diagnosis of male hypogonadism [Internet]. Matsumoto AM, Martin KA, editors. UpToDate; 2024. [accessed March 3, 2024]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-male-hypogonadism?search=clinical%20features%20and%20diagnosis%20of%20male%20hypogonadism&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1#H23"

Not to be confused with LOH, older men can experience the same well-known causes of primary hypogonadism that are observed in younger men, such as for instance previous treatment for testicular cancer, past testicular infection, medications exerting a gonadotoxic effect including chemotherapy, etc. Certain medications commonly prescribed to older men may also play a role in the onset of T deficiency. Notably, the often prescribed 5-α reductase inhibitors used for treating prostate enlargement can lead to moderate hypogonadal symptoms (13).

1.7. Symptoms of LOH

Most symptoms of hypogonadism in older men fall into two categories: sexual and non-sexual. Sexual symptoms encompass reduced sex drive, less frequent sexual thoughts, less frequent or firm nighttime erections, and erectile dysfunction. Non-sexual symptoms include tiredness,

low energy and concentration, reduced overall well-being, feelings of depression, and a general lack of vitality. Other signs commonly associated with hypogonadism are obesity, decreased muscle strength and mass, lower BMD and osteoporosis, hot flashes, and slight anemia. Physical examinations often don't reveal specific signs. Still, they might show smaller or uneven testicles, varicoceles, abnormalities in the penis, reduced pubic hair, breast tissue growth in men, abdominal fat accumulation, and a smaller prostate gland. However, some men with T deficiency might maintain a larger prostate. Many of these signs are not exclusive to this condition. A low sex drive though is closely associated with lower T levels in the blood (13).

1.8. Diagnosis of Hypogonadism

In diagnosing male hypogonadism, testing the level of T in the serum is considered the most critical test (3). The serum T level varies depending on the time it is measured. This is because, in healthy men, the circadian rhythm influences GnRH secretion and hence causes the levels of T to change over the course of the day. Typically, T levels peak in the morning and begin to decline after 10 am (15). Testing the tT level in the serum is generally a reliable indicator of T production. The typical range for this measurement in adult men is around 10 to 28 nmol/L (3). An early morning serum tT level below 8.5 nmol/L suggests hypogonadism. To verify this diagnosis, the tT measurement needs to be repeated (15). When serum T levels are low in two separate tests, the concentration of LH and FSH is measured to differentiate between primary and secondary hypogonadism. The normal range in adult men for LH and FSH is 1 – 8 mIU/mL (3).

In primary hypogonadism, T levels are low with high levels of LH and FSH. In secondary hypogonadism, T levels are low with normal-low levels of LH and FSH (16). For men undergoing infertility evaluation, semen analysis is the most important test (3).

1.9. Diagnosis of LOH

Serum T levels are not typically tested as a standard procedure in older males. Yet, older males should undergo the same diagnostic evaluation as younger males if they present with lab results of for example anemia or reduced BMD, or exhibit signs such as reduced libido, depression, diminished body hair, erectile dysfunction, metabolic syndrome suggestive of low T (17,18).

Current guidelines also advice to assess the fT levels if the tT levels are close to the lower normal threshold since the levels of SHBG is possibly higher, hence contributing to a decreased level of fT, in elderly males (12). Several questionnaires have been developed to surveil the

symptoms of LOH and the effects of T therapy. These tools include the Ageing Male Symptom Score (AMS), the Androgen Deficiency in Aging Men (ADAM), and the Massachusetts Male Aging Study Questionnaire. Despite their utility in monitoring symptoms, these questionnaires are not advised for diagnosing LOH due to their lack of specificity (12).

2. Aims and objectives

This paper aims to find out the utility of testosterone replacement therapy (TRT) in managing LOH, focusing on its implications for muscle mass, strength, bone density, sexual function, mood, cognitive abilities, cardiovascular health, and prostate well-being. LOH, characterized by diminished levels of T due to aging, contributes to a range of physical and psychological challenges.

With an aging male population, understanding and harnessing the potential benefits of TRT could significantly improve quality of life and reduce health risks associated with lowered T levels. This thesis will review the current literature on TRT's metabolic benefits and its role in muscle and bone health, sexual function, mood stabilization, cognitive function, and its cardiovascular and prostate effects.

Evidence indicates that TRT can enhance muscle mass and strength, bone mineral density (BMD), sexual function, and mood in men with LOH. However, the implications of TRT on cardiovascular and prostate health remain controversial, with studies presenting mixed outcomes. This research seeks to provide a comprehensive overview of TRT's multifaceted roles, addressing its mechanisms, benefits, and potential risks in the treatment of LOH.

3. Literature review: Testosterone replacement therapy in late-onset hypogonadism

3.1. Treatment of LOH/TRT

Male hypogonadism comes with a variety of physical, social, and psychological symptoms. Most patients will need long-term T therapy, and advanced age should not prevent starting this treatment. Due to the complexity of T therapy, it's important for patients to be well-informed and actively involved in their treatment process, including self-monitoring to identify and address any side effects (19). TRT should only be given to men with a verified diagnosis of hypogonadism (20). The clinician should assist the patient in choosing an appropriate T therapy option by conducting a comprehensive needs evaluation and explaining the advantages and disadvantages of each available T treatment (19).

There exist multiple options on how to administer the T. In Europe, the T preparations allowed are injections, pellets, transdermal patches and gels, buccal tablets, pills, and nasal gels (20,21).

3.1.1. Injections

3.1.1.1. Esters

Testosterone esters are injected intramuscularly either into the upper thigh or gluteal muscle (19). They work by attaching a lipophilic fatty acid to the 17-beta hydroxyl group of T, enhancing the lipophilicity of T. TEs are administered in oil-based vehicles and gradually get released into the blood hence, thus extending the duration of T in the blood (17).

Approved preparations for the therapy of hypogonadism are T cypionate (TC), T enanthate (TE), and T undecanoate (TU) (22).

3.1.1.1.1. Short-acting

TC comes in concentrations of 100 mg/mL and 200 mg/mL. The typical dosing for male hypogonadism ranges from 75-100 mg per week to 200 mg every two to three weeks.

The available concentrations of TE are 100, 200, or 250 mg/mL. It should be administered at 200 mg every two weeks or 300 mg every three weeks to be an effective therapy (22). Following an intramuscular injection of 200 mg of TE or TC, serum T levels elevate to a supraphysiological level within 24-48 hours and then slowly decrease to the low-normal range over a period of 2 weeks (20). Serum T levels should be tested one week following a dose of either TC or TE (22).

3.1.1.1.2. Long-acting

TU is noted for its extended half-life, around 34 days, which is longer compared to other intramuscular T treatments.

Clinical use of TU includes a single 1000 mg. After the initial dose, a second 1000 mg injection is administered six weeks later. Subsequent doses are then given every 10 to 14 weeks. The timing between injections is adjusted based on serum T levels, which are checked right before each injection and annually. If these levels are higher than the desired range, the interval between injections is extended; if lower, the interval is shortened (22).

3.1.2. Pellets

Testosterone pellets are surgically implanted into the subcutaneous tissue. They are typically prescribed in doses of two to six 75 mg pellets, to be administered every three to six months (22). Serum T reaches its highest level at one month and stays within the normal range for 3 to 6 months, varying by the preparation used (23). These pellets are inserted into the subdermal fat located in the buttocks, lower abdomen, or thigh. The implantation is performed with a trocar in a sterile environment and involves the use of local anesthesia (24). The pellet's surface undergoes even erosion, allowing T to be absorbed (22).

3.1.3. Transdermal

3.1.3.1. Patches

Transdermal patches with either 2 mg or 4 mg of T are placed on areas of the skin other than the scrotum. Within 4 to 12 hours, T in the serum attains the mid-normal range, and physiological levels of dihydrotestosterone are reached. For some men, a single 4 mg patch may not adequately increase T levels, necessitating a higher dosage (22).

3.1.3.2. Gels

Transdermal gels come in concentrations of 1%, 1.62%, or 2%. For the 1% gel, the typical dosage ranges from 50 to 100 mg. In the case of the 1.62% gel, dosages vary between 20.25 to 81 mg, and for the 2% gel, the amount applied should be between 40 and 70 mg (23). It is applied once daily, preferably in the morning, to dry, intact skin in areas other than the genitals. It is absorbed quickly, usually in 5–10 minutes, and raises T levels to the normal range values within 2–4 hours of application. The dosage is adjusted to achieve mid-normal tT levels, guided by blood tests taken 2–6 hours after applying the gel, avoiding the area where the gel was

applied. It can take up to 6 hours for the gel to be fully absorbed, so it's advised to avoid showering or swimming during this period.

Significant fluctuations in serum T levels have been observed among individuals using transdermal gel. Consequently, periodic monitoring of T levels is necessary (20).

3.1.4. Oral

3.1.4.1. Buccal tablets

Buccal tablets are positioned in the gum depression above the incisors. Following absorption through the buccal mucosa, T enters the systemic circulation, bypassing the liver (20,22). By avoiding liver processing, the bioavailability enhances. Applying a 30 mg T tablet every 12 hours leads to peak T levels in the bloodstream within 10-12 hours after the first dose and achieves a stable state in 24 hours.T levels return to their initial baseline within 4 to 6 hours following the tablet's removal (20).

3.1.4.2. Pills

Natural T is quickly neutralized due to first-pass metabolism in the liver, rendering oral administration an ineffective method for delivering unaltered T. However, esterifying T at the 17-beta carbon position results in the production of TU (22).

TU is taken orally and gets absorbed via the intestinal lymphatic system. Uniquely, they avoid the initial hepatic metabolism that earlier oral T products underwent (24). It is prescribed at dosages of 40 to 80 mg, to be taken orally two or three times a day alongside meals (23). Other oral T derivatives, such as 17-alpha-methyltestosterone and fluoxymesterone, are known for their hepatotoxic effects and have been excluded from the European market (22).

3.1.5. Nasal gel

This gel is applied into the nostrils using a metered-dose pump. Each pump action releases 5.5 mg of T. The advised dosage is 11 mg, achieved by two pump actions (one for each nostril), administered three times a day, amounting to a total daily dose of 33 mg (24). The T is absorbed via the nasal mucosa, thereby avoiding first-pass liver metabolism (22). The positive outcomes of administering testosterone involve enhancing sexual traits, libido, muscle power, lean body mass, and bone density. On the downside, T can lead to unwanted complications such as acne, problems with the prostate including symptoms of benign prostatic hyperplasia, sleep apnea, and an increase in red blood cell count (24).

3.2. Effects of testosterone replacement therapy in LOH

3.2.1. Lean muscle mass

Lower T levels are linked to the loss of lean muscle and the increase of visceral fat. Starting from the third decade, muscle mass starts to decline by 1–2% annually, accompanied by a decrease in muscle strength at a rate of 1.5–3% per year, due to a simultaneous reduction in muscle quality (25).

Research indicates that TRT can lead to an increase in lean muscle mass among elderly males, though data are limited compared to younger populations with hypogonadism. Different studies have indicated that older individuals, specifically those aged over 65, who underwent TRT, experienced notable improvements in their lean muscle mass and reductions in fat mass. These studies utilized different T delivery methods, including transdermal patches, injections, and gels, across treatment durations from six months to three years (26).

3.2.2. Muscle strength

Research on the impact of T therapy on older adults has yielded varied results, particularly in terms of enhancing muscle strength and overall physical capabilities. While certain studies observed an increase in muscle mass, they did not find a corresponding rise in muscle strength or overall physical function measured by the Tinetti Balance Test, Tinetti Gait Test, 6-min walking test, knee flexion, and extension exercises. Conversely, other research demonstrated notable enhancements in muscle strength, particularly in the legs and chest, using chest-press and leg exercises (26).

3.2.3. Bone

Testosterone deficiency due to aging contributes to diminished BMD and a greater likelihood of fractures. Several studies highlight TRT's beneficial effects on BMD. Despite the positive findings, the overall impact of TRT on bone density and fracture prevention remains debated, with a recent meta-analysis finding no significant enhancement in overall BMD in comparison to placebo. There is a need for further long-term research to conclusively determine TRT's role in bone health (25).

3.2.4. Sexual function

TRT plays a crucial role in enhancing sexual function in hypogonadal men (25). Studies over one year have demonstrated significant improvements in sex drive and energy in men with an average age of 55 (26).

Additionally, older men receiving T gel showed marked enhancements in sexual activity (24,26). These studies underscore the positive impact of T on libido and sexual function. However, a three-year study involving men with varied health issues, including hypertension and diabetes, did not find T therapy to improve overall sexual function, highlighting the variability in T's effects on sexual health across different populations (26).

3.2.5. Mood and cognitive function

Testosterone's impact on mood and cognitive function in humans is still under investigation, with mixed results (20,26). Some studies suggest a link between low T levels in young men and depressive disorders, but this connection is not consistently supported across all research, especially in older men with low T levels where only modest benefits for mood and depressive symptoms have been observed.

The relationship between T and age-related cognitive decline is also debated (20). While some epidemiological studies found higher fT levels associated with better cognitive performance in certain areas, this finding is not universal. Clinical trials on T treatment in older men have shown controversial outcomes, with some reporting no effect on memory and others noting improvement in cognitive tests.

Recent trials have not demonstrated improvement in cognitive function in men over 60 with low to normal-low T levels (26).

3.2.6. Cardiovascular system

The effects of TRT on the cardiovascular system in older men have been inconsistent (25). Some early studies indicated that TRT might lower cholesterol levels without affecting high-density lipoprotein. Despite several trials not showing significant adverse cardiovascular outcomes, concerns persist due to the small size of these studies and their varied demographics and duration. Notably, TRT has been observed to mitigate the age-related increase in QTc interval, suggesting potential cardiac benefits. Its impact on atherosclerosis progression seems negligible, with no change in carotid artery thickness or coronary calcium observed.

Contrarily, some trials have linked TRT to a higher incidence of cardiovascular events, particularly in men over 65 with mobility limitations, where a significant number reported

cardiovascular-related adverse events. Studies also pointed to a higher short-term risk of non-fatal heart attacks following TRT initiation, especially in men with pre-existing cardiac conditions (26).

These findings highlight the need for caution and further research into the long-term safety of T therapy in older men, considering the high prevalence of cardiovascular risks among this population (24,25).

3.2.7. Prostate gland

The role of T in prostatic hyperplasia is well recognized, with reductions in prostate volume observed following castration. Earlier studies indicate that T supplementation does not exacerbate benign prostatic hyperplasia symptoms in men with initially low to moderate T levels. Despite this, the impact of T therapy on prostate cancer risk remains unclear due to insufficient studies.

A significant finding from a recent trial is the elevation of prostate-specific antigen (PSA) levels after three years of T treatment in older men, though this did not correlate with an increased detection of prostate cancer.

The current evidence suggests a need for large-scale clinical trials to thoroughly assess the risks of prostate cancer associated with TRT (26).

3.2.8. Erythrocyte count

Testosterone plays a key role in boosting the production of red blood cells, evident in the rise of hemoglobin levels during puberty and generally higher levels in men than in women. This relationship also links T levels with mild anemia in older men (24,26). Studies have shown that TRT in these men leads to higher hemoglobin and hematocrit (Hct) levels. While this increase can be advantageous for those with anemia, due to the increased blood viscosity it might elevate the risk of heart attacks and strokes in older individuals. Consequently, observing hemoglobin and Hct levels is crucial for older men receiving this therapy (26).

3.3. Contraindications to TRT/safety

Present guidelines advise against starting TRT in men who have:

- confirmed prostate cancer (either locally advanced or metastasized),
- a prostate nodule or hardening or if the PSA level exceeds 4 ng/mL, or is above 3 ng/mL alongside a heightened risk of prostate cancer,
- breast cancer,

- intense lower urinary tract symptoms with an International Prostate Symptom Score over 19,
- a Hct level above 50%,
- unmanaged severe sleep apnea,
- severe heart failure that is either uncontrolled or inadequately controlled,
- an active wish to father children (27).

3.3.1. Prostate cancer

Generally, men with a history of prostate cancer should not receive T treatment. An exception might be made for men with low T levels who underwent a radical prostatectomy for cancer that was contained within the prostate and who have shown no signs of the disease, with an undetectable PSA level, for a minimum of two years. Other men should undergo assessments to rule out the potential of undetected prostate cancer. Men older than 50 years of age should receive a digital rectal examination and a serum PSA test. Should a prostate nodule be found, or if the PSA levels exceed 4 ng/mL, or surpass 3 ng/mL in men at high risk, these men should be directed to a urologist for further evaluation (24).

Men with benign prostatic hypertrophy experiencing mild to moderate lower urinary tract symptoms can receive T treatment safely. However, for men with severe symptoms, close observation is necessary as even a minor enlargement of the prostate could worsen obstructive symptoms (20).

3.3.2. Breast cancer

Testosterone is converted into estradiol. Therefore, men with breast cancer should avoid T therapy (24).

3.3.3. Erythrocytosis

Since T enhances red blood cell production, it's important to check Hct levels before starting T therapy (24). Men receiving T in clinical trials have a fivefold higher risk of experiencing erythrocytosis compared to those given a placebo. This condition is more commonly observed in men receiving T through intramuscular injections, as well as in men over the age of 60, likely due to decreased T clearance. The occurrence of erythrocytosis is more common with injections than with transdermal applications, likely due to the higher levels of T in the bloodstream achieved through injections (20). Higher Hct levels correlate with a higher risk of venous

thromboembolic disease (27). If Hct is found to be high, the underlying cause must be identified and treated prior to beginning T treatment (24).

3.3.4. Sleep apnea

Untreated severe sleep apnea could potentially deteriorate further. Therefore, clinicians ought to ask about symptoms like significant daytime fatigue and episodes of apnea observed by a partner during sleep. Polysomnography should be conducted if indicated. Patients who effectively manage their sleep apnea with continuous positive airway pressure (CPAP) can be considered for T therapy (24).

3.3.5. Fertility

Exogenous T inhibits the secretion of LH, leading to reduced levels of T within the testes, which are crucial for the process of sperm production. Hypogonadal men should be informed about T's potential to inhibit sperm production. If they wish to maintain fertility, alternative treatment options should be explored (27).

3.3.6. Cardiovascular disease

Since T possesses mild sodium retention and hence water retention properties, it is important to manage severe heart failure prior to initiating T therapy (24,27). Other common side effects of TRT include oily skin and acne, whereas male pattern baldness is rare and has solely a weak link to this treatment (27).

3.4. Monitoring of TRT

The goal of monitoring is to evaluate the effectiveness and safety of TRT (27). Patients undergoing T treatment should undergo regular monitoring to ensure that they achieve normal serum T levels. Monitoring should occur two to three months after starting treatment or adjusting the dosage. Once the dosage is stable, monitoring every 6 to 12 months should be adequate. Additionally, patients should be regularly assessed for any adverse effects (24).

The recommended serum tT target value is within the low-normal range observed in young males (e.g., 10 to 14 nmol/L) to reduce the risk of diseases associated with T (17). Enhanced sexual desire begins to manifest after three weeks and stabilizes at six weeks. Improvements in erectile function and ejaculation could take up to six months to occur (22). PSA levels should also be checked three to six months after starting T treatment. If PSA increases more than 1.4 ng/mL above baseline or exceeds 4 ng/mL, further urologic evaluation is recommended.

Additionally, Hct levels should be assessed three to six months after beginning treatment and annually thereafter (17). According to most guidelines, Hct levels should remain below 54% during TRT (22). If Hct levels rise to 54% or above, it's important to check the patient for contributing factors like smoking and sleep apnea. In such cases, it's advisable to either temporarily halt TRT, adjust the dosage, or switch from injectable to topical (transdermal) T forms, as these are associated with a lesser rise in Hct (22,27).

4. Discussion

Testosterone replacement therapy comes in various formulations, each with its distinct clinical pharmacology, advantages, and disadvantages.

Testosterone enanthate or TC are comparatively cheap, particularly if self-administered, and allow adjustable dosing (23). Yet, they require deep intramuscular (IM) injections every one to three weeks, often also associated with pain and inflammation at the injection site (22,24). Another disadvantage is the variations in serum T levels, which lead to fluctuations in energy, mood, and libido in numerous patients (24).

Long-acting TU injections offer the advantage of less frequent dosing and keep the serum T levels normal for the majority of men treated. Nevertheless, they require administering a significant volume and may lead to coughing episodes immediately following the injection in some cases (23). Furthermore, TU has rarely been linked to cases of pulmonary oil microembolism (POME) and anaphylactic reactions (22), with occurrences of 1.5 and 0.4 per 10,000 injections, respectively (22,24).

Transdermal patches offer benefits such as non-invasive and uncomplicated application and rapid reversal of T levels upon removal, without the risk of transferring the medication to others (22). However, some men might only achieve serum T levels at the lower end of the normal spectrum, potentially necessitating the application of two patches per day (23). Skin irritation, experienced by 19-66% of users, leads to discontinuation in 5-10% of cases. Applying 0.1% triamcinolone cream at the site before using the patch can lower the chance of irritation without reducing the absorption of T (20).

Transdermal gels elevate serum T levels back to the normal, physiological range for males. Compared to TE or TC there is less fluctuation in serum T concentration and less erythrocytosis (23). These gels offer adjustable dosing, straightforward application, and higher skin tolerance in comparison to transdermal patches (22,23). Skin irritation is reported by 7-10% of men. Other disadvantages are the risk of transferring T to others, most commonly partners or children, through direct skin contact and moderately elevated concentrations of dihydrotestosterone, for which the significance is yet unknown (20,23).

Buccal bioadhesive T tablets bring serum testosterone concentrations back to the normal range for men. The advantages of this treatment are the convenience and discretion of use (23). The disadvantages are the need for twice-daily application, irritation of the gums, taste alteration, and bad adherence to the buccal mucosa (20).

TU, when taken as a pill, offers the simplicity of oral administration (23). Yet the effectiveness of oral TU is reduced due to its inconsistent bioavailability when taken orally, variable serum

T levels both daily within the same individual and across different individuals, and brief half-life (22). It must be taken with a fatty meal to enhance absorption, with the fat content of the meal directly influencing the hormone's bioavailability (23). One ought to be cautious about these products regarding their potential to raise the blood pressure and the risk of cardiovascular incidents, such as heart attacks and strokes (24).

Testosterone pellets need to be administered infrequently but require a surgical insertion, carrying risks such as the pellets being expelled spontaneously, formation of local hematomas, and infection at the implantation site (23).

Nasal T gel maintains serum T levels within the normal range and compared to transdermal gels the likelihood of unintentional gel transfer to others is strongly reduced (23). The need for administration three times daily may be seen as inconvenient by some users. Additionally, individuals with allergies or pre-existing nasal or sinus issues might find the formulation challenging to use, as more than 3% of participants in clinical studies reported experiencing symptoms like runny nose, nosebleeds, inflammation of the nose or throat, sinusitis, and nasal crusts (24).

Table 1: *Overview of testosterone formulations*

Formulation		**Standard dosage**	**Advantages**	**Disadvantages**
Injections	Testosterone cypionate	75-100 mg/week 200 mg/2-3 weeks	Cheap, adjustable dosing	Frequent deep IM injections Fluctuating T levels
	Testosterone enanthate	200 mg/2 weeks or 300 mg/3 weeks	Cheap, adjustable dosing	Frequent deep IM injections Fluctuating T levels
	Testosterone undecanoate	Injection of 1000 mg Injection of 1000 mg 6 weeks later Further injections every 10-14 weeks	Less frequent deep IM injections Less fluctuations in T levels	Coughing following injection POME Anaphylactic reactions
Pellets		2 - 6 x 75 mg every 3 - 6 months	Infrequent administration	Surgical insertion Spontaneous expulsion Local hematomas & infections
Patches		2 – 4 mg	Non-invasive & uncomplicated application Rapid reversal of T levels upon removal No risk of transfer	Low effectiveness Skin irritation
Gels		Once daily: 1%: 50 – 100 mg or 1,62%: 20,25 – 81 mg or 2%: 40 – 70 mg	Less fluctuations in T levels Adjustable dosing Straightforward application	Skin irritation Risk of transference
Oral	Buccal tablets	30 mg tablet/12 hours	Convenience & discretion of use	Gum irritation Taste alteration Bad adherence to buccal mucosa
	Pills	40 – 80 mg 2-3x/day alongside meals	Simple administration	Low effectiveness Fluctuations in T levels
Nasal gel		11 mg 3x/day	No risk of transfer	Frequent administration Irritation of nasal mucosa

5. Conclusion

Testosterone therapy is recommended for men exhibiting signs or symptoms of T deficiency and who have consistently low levels of T in their blood (28).

According to the World Health Organization (WHO) 'Guidelines for the use of androgens in men', the optimal T for TRT should meet several criteria: it ought to be safe and efficient in alleviating the symptoms and effects of T deficiency, cost-effective, simple to administer, and provide steady and long-lasting T levels in the blood. Furthermore, the dosing should be adaptable and maintain T levels at a natural physiological level. Various methods of administering TRT have been employed throughout the years, yet none fully meet the criteria for an optimal treatment as defined by the WHO (22). Several T formulations are available or being developed to treat T deficiency. T gels are often recommended due to their ability to maintain physiological and steady levels of serum T, with many patients favoring them over alternative options. When using T gels, the risk of transferring the medication to someone else is minimal if the patient adheres to the instructions provided in the package insert, which include:

- proper hand washing after applying the gel,
- avoiding skin-to-skin contact until the gel has fully dried,
- not letting the application area become wet for about five hours following the application,
- ensuring the application area is covered by clothing after the gel has dried (19,24)

Nonetheless, the selection of a treatment regimen is influenced by various factors such as personal preference, affordability, ease of use, and insurance coverage, which can differ across plans and regimens. Typically, the newest formulations (gels) are the most expensive, while injectable esters are the least costly (24). Worldwide, injections are the most commonly prescribed T preparation (28). Despite being clinically available for the past eighty years, it wasn't until the 1990s that T preparations capable of achieving physiological serum levels of the androgen began to enter and become increasingly popular on the market (22). The United States has seen a twentyfold increase in T sales since 1990. In contrast, when adjusted for population, sales figures have stayed relatively constant in Europe, Asia, and Australia. This significant difference is probably due to the influence of direct-to-consumer advertising in the U.S. for a medication with direct implications for sexual health. Notably, Australia led the way in creating national prescribing guidelines aimed at limiting the prescription of T for conditions related to aging in men (29). Doctors must thoroughly review both the advantages and potential risks of T therapy, including the potential for an elevated risk of cardiovascular incidents, with

their patients before initiating treatment. It's important for every patient to understand the potential hazards and weigh them against the established benefits of T therapy (28). Lifestyle adaptations should also be part of the therapy in obese men as reducing weight also raises T levels (11).

6. Summary

Gonads, including testes in males, are essential for producing reproductive cells and hormones like T, which is crucial for male physical characteristics, sexual function, and overall health. T production is regulated by the HPG axis and affects various bodily functions, from muscle and bone health to mood and cognitive abilities. Hypogonadism, characterized by reduced T production, can arise from issues within the testes themselves (primary) or from problems in the hypothalamus or pituitary gland (secondary). Diagnosing this condition involves measuring serum T levels.

Testosterone replacement therapy is explored as a treatment for LOH in older men, offering potential benefits for muscle mass, strength, bone density, sexual function, and mood. But TRT's impact on cardiovascular and prostate health remains controversial. Various TRT delivery methods exist, including injections, patches, gels, oral applications, and nasal gels, each with specific advantages, potential side effects, and monitoring requirements to manage risks effectively. Despite advancements, no TRT method fully meets all criteria for optimal treatment as defined by the WHO, with ongoing research and individualized patient considerations guiding therapy choices.

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8. CV

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After finishing elementary school in 2008, Antonia continued her education at the Camerloher Gymnasium Freising, Karl-Meichelbeck Realschule Freising, and Fachoberschule und Berufsoberschule Freising.

After graduating with a high school diploma in the year 2018, Antonia enrolled in the Faculty of Medicine in Rijeka. During her six years of medical school, Antonia completed multiple internships in the field of Anesthesiology in the clinics of Ingolstadt, Kitzingen, and Freising.