

International Journal of Health Science

LITERATURE REVIEW ON TESTOSTERONE

Lucas Antônio Morais de Abreu

Mariana Conte Brenner

João Pedro Barros Patrocínio

Ruy Emílio Dornelles Dias

Edinéia Melo Hoffmann

Vitória de Souza Endres

Michelle Tozo Zahr

Julie Any Araujo Bif

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).



Abstract : Testosterone plays an essential role in human physiology. Inappropriate use of anabolic steroids has led to bans, however despite the bans the use of this medication has continued to grow with clandestine schedules. Despite the abuse of this hormone bringing several health hazards, its use can be beneficial in some conditions if there are even certain indications. Proper follow-up is crucial to maximizing the benefits of testosterone use and minimizing side effects for the patient.

Keywords: testosterone, testosterone replacement therapy and steroids.

INTRODUCTION

Testosterone, an androgenic steroid hormone, plays a fundamental role in male and female physiology, exerting significant influences on several aspects of human health. Its production occurs predominantly in the testicles in men and in the ovaries and adrenal glands in women, and, to a lesser extent, in peripheral tissues through the conversion of androstenedione. Testosterone synthesis is mediated by the enzyme 17β -hydroxysteroid dehydrogenase and $5\text{-}\alpha$ -reductase, converting it into dihydrotestosterone (DHT), which has a greater affinity for androgenic receptors (; FREEMAN ER, et al., 2001) .

One of the first scientific references to Testosterone, even before its isolation in the laboratory, was made by Brown-Séguard, one of the most prominent physiologists of his time (1817-1894). In addition to his important discoveries related to the nervous system, he presented an experiment to the scientific community on June 1, 1889, seeking to convince that extracts from animal genital glands could act as an "elixir of life", capable of rejuvenating and prolonging health. of the individual (HOBERMAN JM, 2005).

At a meeting at the French Society of Biology in Paris, Brown-Séguard, then 72 years old, reported the results of his experiments

in which he administered subcutaneous injections of extracts derived from the testicles of dogs and guinea pigs to himself, in an attempt to reverse the effects of physical decline associated with aging. The impressive results, such as increased strength, disposition and physical and mental resistance, caught the attention of listeners present at the event. He later published the clinical results of these extracts in the renowned English magazine *The Lancet*, generating great international repercussion (HOBERMAN JM, 2005; FREEMAN ER, et al., 2001).

Only in 1970, after realizing the indiscriminate use of these substances for doping purposes, the International Olympic Committee began to develop awareness campaigns and implement detection tests among athletes. Consequently, many countries have banned the sale of most Anabolic Androgenic Steroids (AAS), which has triggered a wave of discrimination against those who use them, whether in sporting competitions or for recreational purposes. This prohibition also boosted the production and sale of these hormones clandestinely by the pharmaceutical market, resulting in syntheses without proper health supervision and, often, in counterfeiting and contamination of products (BEZERRA A, et al, 2022).

Despite the criminalization of the sale and production of testosterone and Anabolic Androgenic Steroids (AAS), the use and abuse of these substances is common, especially by resistance training practitioners, such as bodybuilding, who often use them without due technical knowledge and without supervision. appropriate doctor. The inappropriate use of these substances can lead to several side effects related to testosterone and EAAs, such as acne, testicular atrophy, gynecomastia, increased libido, oligospermia, changes in the lipid profile, high blood pressure, premature closure of the epiphyses in young people,

mood changes and aggressiveness. In women, side effects may include masculinization, hair growth, deepening of the voice and clitoral hypertrophy (ABRAHIM O, et al., 2013; BEVILACQUA G, et al., 2016).

There is no doubt about the danger of inappropriate use of testosterone and EAAs, since their side effects and complications are already widely documented in the scientific literature. This fact creates a great taboo regarding the use of these hormones by medical professionals, which creates obstacles to their use for therapeutic purposes. However, it is necessary to explore the most recent information in scientific publications on the use of these substances in clinical practice, in order to determine whether, with appropriate and judicious indication, these medications could find their place in the therapeutic arsenal for the treatment of various diseases, reversing its unfavorable courses.

METHODOLOGY

The present study aims, through a systematic bibliographic review, to reevaluate the history and use of testosterone. The study followed the following orders; elaboration of the question regarding the topic covered; search and selection of primary studies; data extraction from studies; critical and analytical evaluation of the studies included in the review; synthesis of studies and preparation of the review. To carry out the research, publications were used through the Google Scholar search tool, Latin American and Caribbean Literature in Health Sciences (LILACS) and the SciELO database. The search was carried out in Portuguese, Spanish and English, using the descriptors: "testosterone" and "testosterone review".

The analysis was carried out analytically, based on various explanations and lines of research from the most diverse studies. 40 articles relevant to the topic were selected for full reading. National and international

studies, articles involving the objective of the research were applied as inclusion criteria; as exclusion criteria, the following were removed: theses and dissertations, case reports or experience articles, letters, editorials, scientific articles duplicated among the databases and subjects that did not address the subject to be studied. At the end of the research, 21 articles were selected in order to argue the proposed theme. As it is secondary data in the public domain, the project was not submitted to the Research Ethics Committee.

DISCUSSION

In order to understand more about this hormone, it is necessary to reinforce how testosterone is formed

TESTOSTERONE FORMATION AND REGULATION

Most sexual functions in both men and women begin with the pulsatile secretion of Luteinizing Hormone Releasing Hormone (GnRH) by the cell bodies of neurons located in the arcuate nucleus of the hypothalamus. This peptide stimulates the anterior pituitary gland to produce two gonadotropic hormones: Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). FSH is secreted linearly, while LH follows the pulsatility patterns of GnRH, being known as LH Releasing Hormone (HALL, John E. Guyton, 2011).

FSH and LH are glycoproteins and exert their effects on target tissues of the testicles, activating the cyclic adenosine monophosphate second messenger system, which, in turn, activates specific enzyme systems in target cells. Testosterone is secreted by interstitial Leydig cells in the testicles only when stimulated by LH. This production is directly proportional to the amount of LH available in the body. The hypothalamus is inhibited by the negative feedback promoted

by circulating testosterone. High levels of this hormone decrease the pulsation of GnRH by the hypothalamus, while low levels have the opposite effect: they increase the frequency of pulses (HALL, John E. Guyton, 2011).

In the clinical context, exogenous testosterone administration has been widely used to correct hormonal deficiencies in cases of hypogonadism and other related endocrine disorders. In Brazil, several types of testosterone are sold, including immediate, prolonged and transdermal release formulations. These formulations differ in their pharmacokinetics and, consequently, in the frequency of administration and blood concentrations achieved. However, it is essential to emphasize that the use of testosterone as hormonal therapy requires adequate medical supervision, since inadequate or unmonitored treatment can pose significant risks to the individual's health (HALL, John E. Guyton, 2011).

Testosterone biosynthesis in Leydig cells occurs from cholesterol. When Luteinizing Hormone (LH) binds to membrane receptors, it induces the synthesis of cAMP from ATP. Cholesterol is transported by other enzymes into the inner mitochondrial membrane, where it is converted into pregnenolone. This metabolite is then transported to the smooth endoplasmic reticulum, where it undergoes several enzymatic reactions that culminate in the release of testosterone into the circulation (HALL, John E. Guyton, 2011).

Leydig cells are practically non-existent during childhood, but they become numerous in adult men after puberty, a period in which the testicles secrete a large amount of testosterone. Most testosterone in the blood binds weakly to plasma albumin or strongly to sex hormone-binding globulin (GLHS), circulating for minutes to hours. Subsequently, testosterone is transferred to tissues or degraded, with only the free

serum or albumin-bound form considered bioavailable (HALL, John E. Guyton, 2011).

When testosterone is fixed in tissues, it is converted into its active form, dihydrotestosterone, in the local cells, or is aromatized into estradiol by some specific tissues, such as adipose tissue. Testosterone performs several functions in the body, including the proper positioning of the testicles in the scrotum, increased distribution of body hair, thickening of the skin, greater protein formation and muscle development, calcium retention, increased basal metabolism and the number of red blood cells, as well as hypertrophy of the laryngeal mucosa, which leads to the widening of the voice and the acquisition of the typical adult voice.

MOST COMMON TYPES OF TESTOSTERONE SOLD

INJECTABLE TESTOSTERONE

Injectable testosterone is one of the most traditional forms of testosterone hormone replacement therapy. It is available in different esters such as cypionate, enanthate and undecylate. These esters have different durations of action, which influences the frequency of administration. Cypionate and enanthate are usually given every two to three weeks, while undecylate can be given every 10 to 14 weeks.

THE BENEFITS OF USING INJECTABLE TESTOSTERONE INCLUDE

Stability of Hormone Levels: Due to the interval of administration, injectable testosterone can provide more stable hormone levels compared to other forms of administration.

Ease of Administration: The injection is administered by healthcare professionals or by the patient themselves, making application

relatively easy.

TRANSDERMAL TESTOSTERONE

Transdermal testosterone is available in the form of a gel, patch or lotion, which are applied to the skin. This form of administration allows testosterone to be gradually absorbed into the bloodstream, providing a controlled release of the hormone over time.

THE BENEFITS OF USING TRANSDERMAL TESTOSTERONE INCLUDE

Prevents First Pass Hepatic Metabolism: Unlike oral forms, transdermal testosterone is not processed by the liver before entering the bloodstream, which may reduce the risk of hepatic side effects.

Flexible Administration Options: Transdermal testosterone is available in different formulations such as gel, patch or lotion, allowing patients to choose the option that best suits their preferences.

Oral: Oral testosterone is less common due to its extensive hepatic metabolism, which can lead to inactivation of the hormone before it reaches systemic circulation. However, there are formulations available, although they are less used compared to other forms of administration.

THE BENEFITS OF USING ORAL TESTOSTERONE INCLUDE

Convenience: For some patients, especially those who have difficulty tolerating other forms of administration, oral testosterone may be a more convenient option.

MAIN HEALTH BENEFITS OF TESTOSTERONE

Improvement of sexual dysfunction: Sexual dysfunction is a prominent symptom of hypogonadism, affecting up to 23-36% of men with sexual complaints. The use of hormone replacement therapy can reverse this situation, as demonstrated in recent studies. TRT significantly improved libido in patients with total testosterone below 230 ng/dL and erectile dysfunction in patients with testosterone below 350 ng/dL. (TSAMETIS, et al, 2018).

Muscle mass gain: Loss of muscle mass is a common complaint related to male aging, and hormone replacement therapy can be effective in combating this problem. Studies have shown that men treated with TRT showed an increase in lean mass and a decrease in fat mass, resulting in better adaptation of the epithelial tissue and reducing the risk of developing sarcopenia. (MAGNUSSEN, L. V. et al, 2017).

Increased bone mineral density: In addition to maintaining muscle mass, hormone replacement therapy can also increase bone mineral density in elderly men with hypogonadism. Studies have shown that TRT significantly increased bone mineral density compared to the control group, suggesting that it can prevent the onset of osteoporosis (AVERSA, Antonio et al, 2012).

Prevention of metabolic syndrome and DM2: Hormone replacement therapy can prevent the onset of metabolic syndrome and type 2 diabetes in men with low testosterone levels. Obesity and a sedentary lifestyle contribute to a reduction in testosterone production, leading to chemical changes in the body that can lead to peripheral insulin resistance and the development of DM2. Studies have shown that men with higher testosterone levels are less likely to develop diabetes (FINK, et al, 2018; KRIMPHOVE,

Marieke J. et al, 2020).

These are some of the benefits associated with the appropriate use of hormone replacement therapy in men with hypogonadism. It is important to remember that TRT must be prescribed and monitored by a qualified healthcare professional to ensure safe and effective results.

SIDE EFFECTS AND NEED FOR MEDICAL MONITORING

Testosterone replacement therapy (TRT) has some important contraindications that should be considered before starting treatment. One of them is obstructive sleep apnea (OSA), which is related to serum testosterone concentration. Low levels of this hormone can result in sleep disorders, with OSA being a direct cause of this problem. However, it is important to highlight that, although there is a relationship between OSA and testosterone levels, there is still not enough and consistent evidence to completely prove this connection. Even so, current guidelines maintain OSA as a relative contraindication for TRT, and it is recommended to treat this sleep disorder before considering hormone replacement (KIM, et al, 2019).

Another relevant aspect to be considered is the issue of fertility. Exogenous testosterone suppresses LH secretion, which results in a reduction in the high levels of intratesticular testosterone required for spermatogenesis. In around 25% of cases, azoospermia (absence of sperm in semen) can be irreversible. Therefore, patients who wish to have children should be advised to undergo semen cryopreservation before starting TRT treatment.

Another relevant adverse effect of androgen therapy is the increase in erythrocyte mass, known as polyglobulinemia. This can lead to an increase in hematocrit and consequently increase the risk of deep vein thrombosis (DVT), particularly in men with underlying

thrombophilia. Although some studies have shown an increased risk of DVT in the first 6 months of therapy, which decreases thereafter, more research is still needed to fully understand this relationship. However, it is important to investigate the presence of hematological diseases in patients who are candidates for TRT treatment and treat erythrocytosis before starting treatment (Cole AP, et al., 2018).

The increased risk of cardiovascular events in patients undergoing testosterone replacement therapy (TRT) is a topic that still lacks definitive conclusions. Some studies and meta-analyses have raised concerns about the increased risk of acute myocardial infarction and stroke in men treated with TRT, especially when the therapy is administered intramuscularly (XU, Lin et al., 2013).

However, a new meta-analysis that included 30 studies on TRT and 1642 men suggested that testosterone replacement in hypogonadal patients, maintaining their levels in the physiological range, does not increase the risk of cardiovascular outcomes. Furthermore, another study carried out in the United States with 3422 men from the American military service, who received TRT between 2006 and 2010, showed that those who received the treatment had an improved survival rate from cardiovascular events, a lower incidence of coronary heart disease and a higher risk of developing obstructive sleep apnea (OSA) (HADDAD, Rudy M. et al., 2007).

Despite these observations, there is still a lack of conclusive studies on the risk of cardiovascular events in patients undergoing TRT. Therefore, it is essential to adequately monitor the patient who wishes to continue treatment and take individual risk factors into account before making any therapeutic decision. It is recommended that treatment be conducted with adequate medical supervision and regular monitoring to assess the response

and possible side effects (ABRAHIN, et al., 2013).

The prevalence of acne in EAA users is high, reaching around 63.4% of cases. Stretch marks are another common side effect, affecting around 34% to 44.4% of users. These effects are related to the stimulation of the sebaceous glands and rapid muscle growth (ABRAHIN, et al., 2013).

In the endocrine aspect, the abusive use of EAA can result in hormonal imbalances, increasing the risk of gynecomastia, fluctuations in libido and, in some cases, sexual impotence. Users often believe that the use of antiestrogens can prevent gynecomastia, but this is not always effective (CISNEIROS, et al. 2021).

Regarding the lipid profile, the use of EAA can lead to an increase in total cholesterol and triglycerides, in addition to decreasing high-density lipoprotein (HDL) and increasing low-density lipoprotein (LDL). Suspension of use can minimize these negative changes in the lipid profile (CARVALHO, 2011).

The psychological changes caused by the use of EAA vary according to the individual profile. Some users may experience increased aggression, irritability, depression, mania and psychosis. Furthermore, EAAs can cause dependence syndrome in a minority of users, but this effect is still poorly understood (COSTA, 2020).

It is important to highlight that the side effects mentioned are related to the abusive

use of EAA and that treatment must be carried out under adequate medical supervision to minimize risks and complications (CALIXTO, 2021).

Adequate patient monitoring during testosterone replacement therapy is essential to ensure the success of the treatment with maximum benefit and fewer adverse effects. The effects of TRT can vary in terms of time of manifestation, with some, such as increased energy, sexual function and lean mass, being observed in the first three months, while others, such as increased bone mineral density, can take up to 24 months to manifest (ARAGÃO, et al. 2022).

It is recommended that the patient be clinically evaluated every three months, through anamnesis, physical examination and laboratory tests, such as hematocrit, serum testosterone and PSA. If there is an inadequate response, subnormal testosterone levels or the appearance of adverse effects, it is possible to adjust the dose or method of administration of the treatment (ARAGÃO, et al. 2022).

CONCLUSION

In conclusion, testosterone replacement therapy is an advantageous option for men with male aging androgen deficit, as long as it is appropriately monitored. Although there is still a need for more studies on some adverse effects, careful monitoring allows the treatment to occur safely and effectively, with significant benefits for the patient's quality of life.

REFERENCES

- ABRAHIN, Odilon Salim Costa et al. Prevalência do uso e conhecimento de esteroides anabolizantes androgênicos por estudantes e professores de educação física que atuam em academias de ginástica. **Revista Brasileira de Medicina do Esporte**, v. 19, p. 27-30, 2013.
- ABRAHIN, Odilon Salim Costa; SOUSA, Evitom Corrêa de. Esteroides anabolizantes androgênicos e seus efeitos colaterais: uma revisão crítico-científica. **Revista da Educação Física/UEM**, v. 24, p. 669-679, 2013.
- ARAGÃO, Guilherme Lima Britto et al. Uso clínico da testosterona e seus derivados químicos: uma revisão narrativa. *Revista Eletrônica Acervo Saúde*, v. 15, n. 7, p. e10608-e10608, 2022.
- AVERSA, Antonio et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. **The Aging Male**, v. 15, n. 2, p. 96-102, 2012.
- BEVILACQUA, Guilherme Guimarães et al. Percepções sobre risco e efeitos do uso e consumo de esteroides anabolizantes por praticantes de musculação. **Caderno de Educação Física e Esporte**, v. 14, n. 2, p. 21-27, 2016.
- BEZERRA A, et al. Riscos relacionados ao uso de anabolizantes esteróides para fins estéticos. *Research, Society and Development*, 2022; 11(7): e18811729983.
- CALIXTO, Igor Tupinambá; DE MELO PRAZERES, Tereza Cristina M. Terapia de reposição da testosterona na DAEM (deficiência androgênica do envelhecimento masculino): uma revisão de literatura. **Brazilian Journal of Health Review**, v. 4, n. 1, p. 3816-3830, 2021.
- CARVALHO, Marineuza Pereira de. O uso da testosterona como anabolizante e seus efeitos colaterais. 2011.
- CISNEIROS, Mirelly Grace Ramos et al. O uso de anabolizantes e suas consequências: revisão de literatura Anabolic steroids use and consequences: literature review. **Brazilian Journal of Health Review**, v. 4, n. 6, p. 27986-27997, 2021.
- COLE AP, et al. Impact of testosterone replacement therapy on thromboembolism, heart disease and obstructive sleep apnea in men. *BJU Int.*, 2018
- COSTA, Rian Lucas Aires; DE MELO, Amanda Teixeira. Disfunções anatomo-fisiológicas provenientes do uso indiscriminado de derivados sintéticos da testosterona (EAAs). **Brazilian Journal of Development**, v. 6, n. 12, p. 94256-94268, 2020.
- FINK, Julius; MATSUMOTO, Masahito; TAMURA, Yoshifumi. Potential application of testosterone replacement therapy as treatment for obesity and type 2 diabetes in men. **Steroids**, v. 138, p. 161-166, 2018.
- FREEMAN, Erica R.; BLOOM, David A.; MCGUIRE, EDWARD J. A brief history of testosterone. **The Journal of urology**, v. 165, n. 2, p. 371-373, 2001.
- HADDAD, Rudy M. et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. In: **Mayo Clinic Proceedings**. Elsevier, 2007. p. 29-39.
- HALL, John E. **Guyton y Hall. Tratado de fisiología médica**. Elsevier Health Sciences, 2011.
- HOBERMAN, John. **Testosterone dreams: Rejuvenation, aphrodisia, doping**. Univ of California Press, 2005.
- KIM, Sung-Dong; CHO, Kyu-Sup. Obstructive sleep apnea and testosterone deficiency. **The world journal of men's health**, v. 37, n. 1, p. 12, 2019.
- KRIMPHOVE, Marieke J. et al. Long-term testosterone therapy in type 2 diabetes is associated with decreasing waist circumference and improving erectile function. **The world journal of men's health**, v. 38, n. 1, p. 68-77, 2020.
- MAGNUSSEN, L. V. et al. Testosterone therapy preserves muscle strength and power in aging men with type 2 diabetes—a randomized controlled trial. **Andrology**, v. 5, n. 5, p. 946-953, 2017.
- TSAMETIS, Christos P; ISIDORI, Andrea M. Testosterone replacement therapy: For whom, when and how?. **Metabolism**, v. 86, p. 69-78, 2018.
- XU, Lin et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. **BMC medicine**, v. 11, n. 1, p. 1-12, 2013.