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USE OF TESTOSTERONE IN PALLETS IN HYPOGONADIC MEN: A NARRATIVE REVIEW

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Abstract: Late-onset hypogonadism (LOH) or male aging androgen decline (MAAD) or andropause is a clinical condition characterized by the presence of symptoms and/or signs associated with biochemical evidence of decreased serum testosterone levels, either in the form of total testosterone or free testosterone, and is increasingly common in men. This clinical situation presents with a compilation of symptoms and signs that are divided into: clinical symptoms and signs of androgen deficiency, sexual symptoms, and cognitive and neurovegetative symptoms. There is a wide range of therapies for replacing serum testosterone levels in patients with LTA or MAAD, with different therapeutic forms, each with advantages and disadvantages. This study is a narrative review that aimed to investigate the specialized health literature of the last 20 years on testosterone replacement therapy (TRT) in men through subcutaneous testosterone pellets in hypogonadal men from 2004 to 2024. The articles were searched in the databases of the Medical Literature Analysis and Retrieval System Online (Medline), Latin American and Caribbean Health Sciences Literature (LILACS), and the Scientific Electronic Library (Scielo). Of the 269 articles found, after reading the abstracts, 37 articles met the inclusion criteria and were analyzed according to the specific theme of this review. The studies show that this is a safe and effective therapeutic modality, with low comorbidity complications, with the experience of the medical professional, insertion technique, insertion geometry, and physical activity after the procedure being significant factors in the occurrence of extrusion and infection. The cost of medication alone is equal to or lower than other therapeutic options, and in the total aggregate, considering the minimally invasive procedure, it is higher, offset by routine medical follow-up. Publications show that the method is highly effective and efficient, with a high patient satisfaction rate and high clinical safety promoting improvement in clinical signs and symptoms, rehabilitation of sexual components, and optimization of neurovegetative signs.

Keywords: Testosterone replacement therapy, pellets, male hypogonadism, testosterone therapy, testosterone replacement, andropause.

INTRODUCTION

Late-onset hypogonadism (LOH) or male androgenic decline (MAD) is a clinical syndrome characterized by hypogonadal symptoms with or without associated signs, along with low serum testosterone levels, and can adversely affect multiple organ functions, quality of life, and even mortality (Fig. 1) (1,2,3) .

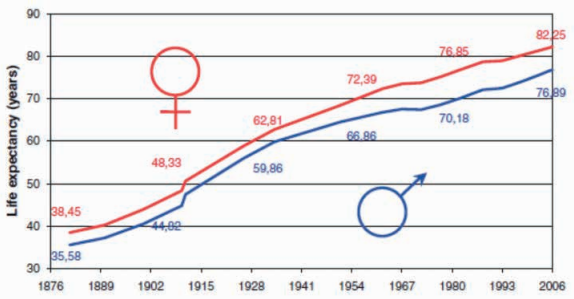

Figure 1: Increase in overall life expectancy Nieschlag, 2010(3) .

Achieving healthy old age is an individual condition, with 30% associated with improved HDI parameters across society as a whole. However, this is counterbalanced by the senescence of internal organs and systems, which suffer daily damage from endocrine disruptors, free radicals, and other factors. However, regardless of this, life expectancy is increasing worldwide, and caring for this population requires an understanding of the physiology of human aging and the longevity inherent in the new human reality (Fig. 2)(3) .

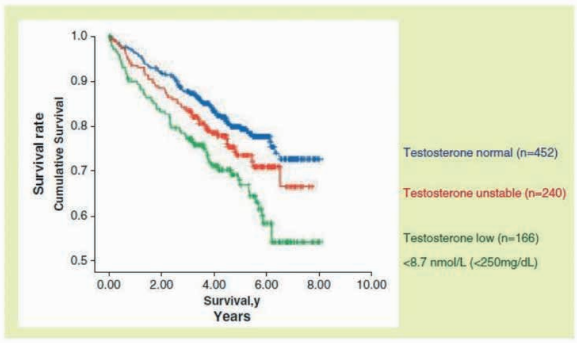

Figure 2: Association between overall survival and serum testosterone levels.

Nieschlag, 2010(3) .

Testosterone production involves the interaction of three self-regulating organs, which are the hypothalamus, the pituitary gland, and the testicles, constituting the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis is related to male development and maturation, as well as the conditions of senescence and senility. The hypothalamus, through the pulsatile secretion of gonadotropin-releasing hormone (GnRH), stimulates the anterior part of the pituitary gland, or pituitary gland, to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), glycoprotein polypeptide hormones that represent the exogenous metabolites of the pituitary gland (Fig. 3)(1) .

LH acts on the Leydig cells in the testicles, with gonadal testosterone and insulin-like growth factor 3 (INSL3) as coadjuvants, thus promoting the development and differentiation of male genitalia in their phenotypic characterization. The action of FSH is to maintain testicular exocrine activity, as it acts on Sertoli cells, generating spermatogenesis. Two other hormones act together in these testicular cells: inhibin B and anti-Müllerian hormone (AMH) (Fig. 4); the former regulates FSH secretion through a negative feedback mechanism, and the latter regulates genital masculinization from the fetal period through puberty and into adulthood(3) .

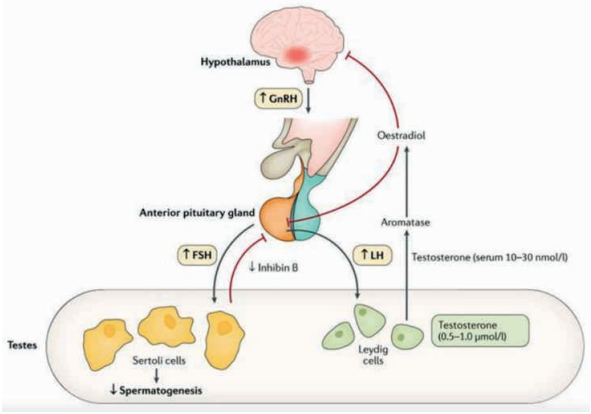

Figure 3: Hypothalamic-pituitary axis

Salonia, 2019 (1)

The impairment of the hypothalamic-pituitary-gonadal axis, whether congenital or acquired, characterizes the patient's hypogonadal condition. and in a broader pathophysiological concept, it is not only a reduction in male steroid hormones and their fractions, but also a reduction in inhibin and anti-Müllerian hormone with impaired sperm production or not.(1) .

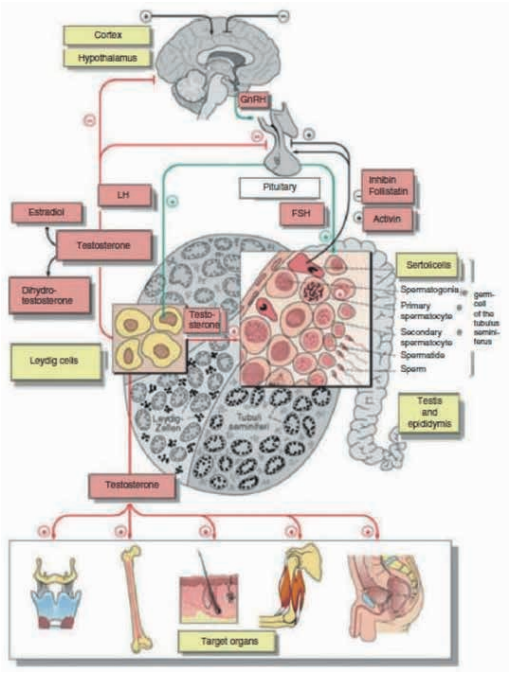

Figure 4: Neurophysiology of testosterone production and action and its target organs.

Nieschlag, 2010(3) .

Testosterone deficiency may be asymptomatic or lead to a wide range of physical symptoms such as: changes in body composition with increased body fat and decreased muscle mass, reduced testicular volume, reduced bone mineral density, among others; sexual symptoms such as reduced libido, morning erections, erectile dysfunction; and even neurovegetative symptoms such as fatigue, depression, lack of concentration(4,5) .

It is also important for medical professionals to identify hypogonadal conditions in patients outside the usual range, since when one thinks of hypogonadism, the first association is with patients after the fourth or fifth decade of life or a syndromic patient. In pediatric or prepubescent patients, serum testosterone decreases after the third month, and the laboratory parameter that guides the diagnosis is "lost," which requires attention and measurement of anti-Müllerian hormone and inhibin B in this patient profile. If these hormones are low, with gonadotropins not elevated, it may be a case of secondary hypogonadism or hypogonadism ((1)) (Fig. 5).

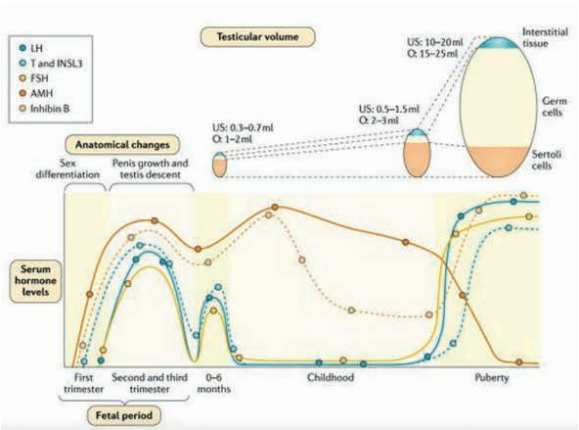

Figure 5: Anatomical changes and sexual differentiation in men.

Salonia, 2019 (1)

As detailed above, elevated gonadotropins are indicative of primary hypogonadism. However, up to one-third of boys with complete absence of testicular tissue have normal FSH and LH in childhood, showing that primary hypogonadism is not always associated with elevated gonadotropin levels in childhood(1) . When this condition establishes itself during childhood, clinical symptoms are not evident and are therefore limited, and medical professionals should be alert. As a result, secondary hypogonadism or primary hypogonadism may not be diagnosed unless Sertoli cell function is evaluated. Viable trisomies (chromosomal disorders characterized by extra chromosomes), such as Klinefelter syndrome and Down syndrome, are the most common causes of primary hypogonadism(1) .Gonadal dysfunction is present from early childhood in most boys with Down syndrome, while it usually appears during intermediate puberty in patients with Klinefelter syndrome(1) .

HTA or DAEM can be classified into: primary hypogonadism (PH), secondary hypogonadism (SH), and androgen resistance (AR)(6,7,8,9). The patient presents signs and symptoms that, according to common sense and from an individual perspective, seem to be a natural part of male aging, as they are common and a frequent social pattern in men over 50 years of age, but it is a disease condition that can be corrected (Fig. 6).

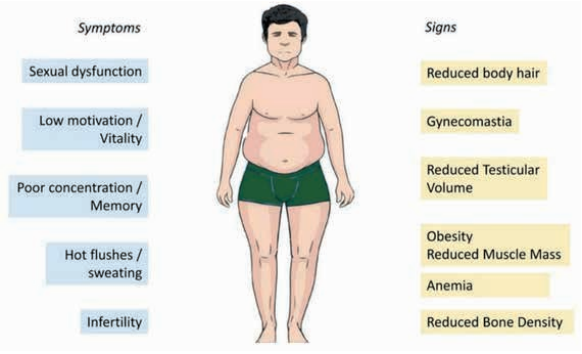

Figure 6: Signs and symptoms of late-onset hypogonadism in adults.

Isidori, 2022 (9)

HP or hypergonadotropic hypogonadism (HHyG) can be congenital or acquired. Among the causes of congenital HHyG,

the most common is Klinefelter syndrome, and among the less common are trisomy 21, 47XYY syndrome, 48 XXYY syndrome, Noonan syndrome, testosterone biosynthesis defect, LHR gene mutations, myotonic dystrophy types I and II, adrenal leukodystrophy, among others. Acquired causes of HHyG can be further subdivided into: drug-induced, diseases or systemic conditions that impact the hypothalamic-pituitary axis (HPA), and specific conditions that lead the patient to develop this clinical situation(6,7,8,9,10).

Drugs that induce HHyG are: chemotherapeutic agents, alkalizing agents, methotrexate, ketoconazole, aminoglutamines, metyrapone, and mitotane, the latter four being steroidogenesis inhibitor medications. Systemic diseases that lead to HHyG due to EHH impairment are: type 2 diabetes mellitus (DM2), metabolic syndrome (MS) (Fig. 7), human immunodeficiency virus (HIV) infection, chronic inflammatory arthritis (CIA), chronic organ failure (COF), and xml-ph-0 (Fig. 8). (MS) (Fig. 7), human immunodeficiency virus (HIV) infection, chronic inflammatory arthritis (CIA), chronic organ failure (COF), Cushing's syndrome, age, severe eating disorders, resistance exercises, lymphomas, vasculitis, and spinal cord trauma. Specific causes include testicular irradiation, testicular torsion, alcoholic cirrhosis, autoimmune testicular failure, and surgical castration, for example(6,7,8,9,10).

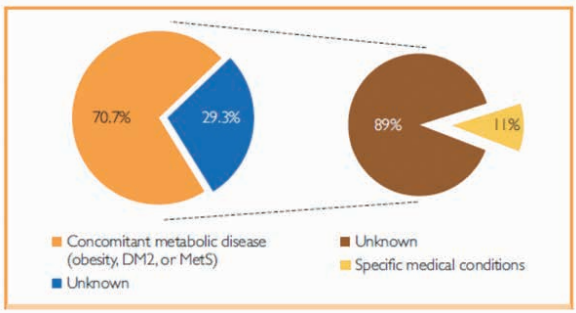

Figure 7: Association of hypogonadism in patients with metabolic diseases. Khera, 2016 (2)

HS or hypogonadotropic hypogonadism (HHoG) can be congenital and/or developmental disorders or acquired. The most common congenital causes or developmental disorders of HHoG are hemochromatosis and, less frequently, combined hypopituitarism (HPC), idiopathic hypogonadotropic hypogonadism (HHoGI), Indian Hedge Hog syndrome (IHHS), an autosomal recessive disease that affects chondrocytes and its variants, Kallmann syndrome, Prader-Willi syndrome, among others. The acquired etiopathogenesis of HHoG can be subdivided into drug-induced and specific problems. Drug-induced causes include the use of estrogens, anabolic androgenic steroids, progestogens (including cyproterone acetate), drugs that promote hyperprolactinemia, use of opiates – agonists (a worldwide endemic), GnRH antagonists, and glucocorticoids. Specific conditions that promote HHoG include: pituitary neoplasms, hypothalamic tumors, encephalitis, Wegener's granulomatosis, brain trauma, Langerhans cell histiocytosis, etc. (6,7,8,9,10).

Androgen resistance correlates with a decrease in testosterone bioactivity and, like HHoG, is divided into congenital and/or developmental disorders or acquired disorders. The first situation includes aromatase deficiency, Kennedy's disease, partial or complete androgen insensitivity, and type II 5α reductase deficiency (5aR). In the acquired condition of AR, it can be subdivided into drug-induced and specific problems. Among the drugs that can cause AR are: antiandrogenic steroids, cyproterone acetate and spironolactone, flutamide, bicalutamide, nilutamide, finasteride, dutasteride, clomiphene, tamoxifen, raloxifene, letrozole, anastrozole, exemestane, and idiopathic increase in sex hormone-binding globulin (SHBG) . As a specific cause of RA, it is important to note the correlation with celiac disease(6,7,8,9,10).

Testosterone production decreases with aging. The European Male Aging Study reported a 0.4% per year decrease in total testosterone (TT) and a 1.3% per year decline in free testosterone (FT). Late-onset hypogonadism is the term often used to describe this phenomenon and the detection of hypogonadism in adulthood. Evidence indicates that several associated diseases and chronic comorbidities, such as obesity (Fig. 8), diabetes, metabolic syndrome, liver disease, HIV, and age can interfere with the HHF axis, leading to the development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, significantly influencing the age--dependent physiological decline in testosterone(3,6,9).

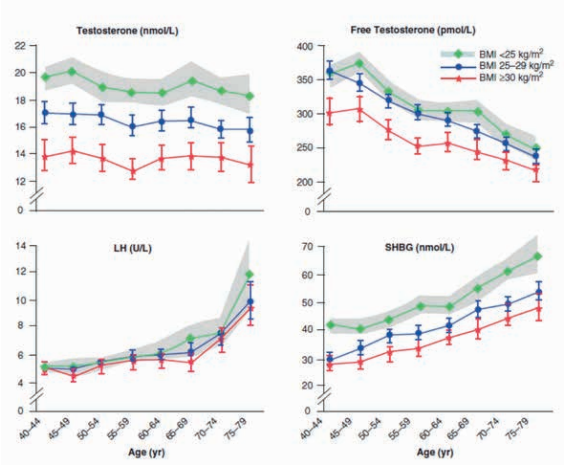

Figure 8: Correlation between obesity and late hypogonadism

Nieschlag, 2010(3) .

However, this condition does not occur in all aging men, does not manifest itself in a specific age group, can occur with low total or free testosterone levels, and, as described above, presents specific and general or nonspecific signs and symptoms, in which it is not possible to differentiate between senescence and senility in the process of increased life expectancy and male longevity (Fig. 9), which generates specific care and assistance for these patients, still causing discredit by medical professionals and underreporting (Fig. 10), and that of the 4 to 5 million hypogonadal men in 2004, only 10% were treated. In Brazil, Nardozza et al. estimate that 26.4% of men over 40 are affected, and for men over 70, the frequency was 51% in this sample.

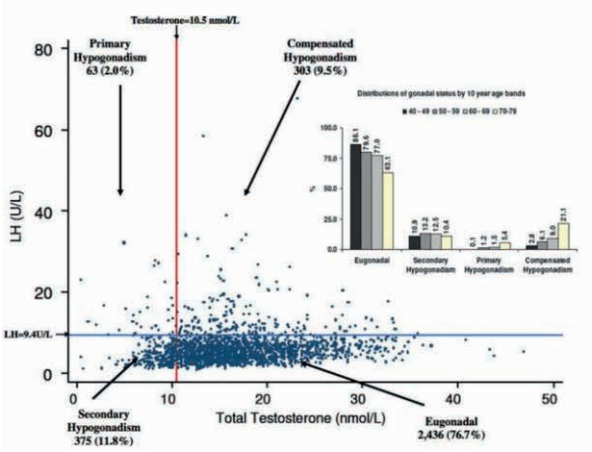

Figure 9: Distribution of frequency and increase in the incidence of late hypogonadism with age compared to secondary hypogonadism, which remains stable.

Tajar, 2010 (7)

We can describe the signs of late-onset hypogonadism in adults as: changes in body composition, with increased central fat; gynecomastia; testicular atrophy; muscle atrophy; osteoporotic fractures; weight loss; reduction in facial, axillary, and pubic hair. Symptoms of late-onset hypogonadism in adults include mood swings, sleep disturbances, reduced libido, decreased energy for usual activities, fatigue, reduced muscle strength, hot flashes, reduced ability to concentrate, muscle pain, memory loss, loss of morning erections, reduced penile rigidity, reduced sperm volume, and infertility. One should be aware of risk conditions in which the prevalence of low serum testosterone levels is higher: obesity, type 2 diabetes, dyslipidemia, obstructive sleep apnea, coronary heart disease, congestive heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease, osteoporosis,

HIV, use of antiretroviral therapy for HIV, chronic use of opioids, chronic use of corticosteroids, chemotherapy, and radiotherapy in general(7,10).

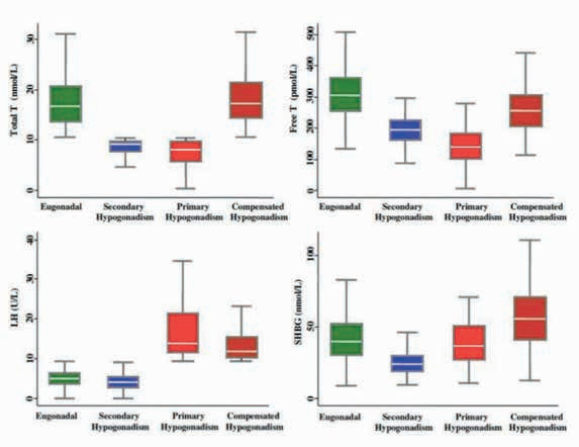

Figure 10: Serum levels of primary hypogonadism are lower than serum levels of secondary hypogonadism.

Tajar, 2010 (7).

Testosterone production is regulated by the HHS, resulting from the stimulation of follicle--stimulating hormone (FSH) and luteinizing hormone (LH), which act on the testicular and adrenal tissue. 98% of testosterone is produced by the testicles, representing nmol/day (69.2 g/day), and 2% is produced by the adrenal glands, i.e., 0.002 nmol/day (0.58 g/day).

Circulating testosterone, which is an androgen receptor, acts on muscle, bone marrow, bones, brain, and adipose tissue. When it undergoes the action of 5-alpha reductase, it is converted into dihydrotestosterone, another active form, which is also an androgen receptor acting on the external genitalia, prostate, skin, and hair. However, a small portion undergoes physiological action by aromatase, generating estradiol, which acts on the bones, brain, and breasts (Fig. 11)(11) .

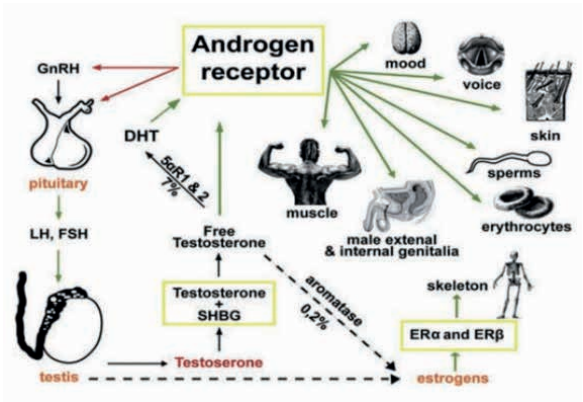

Figure 11: Distribution of testosterone receptors in the human body

Corona, 2011(4) .

According to the guidelines of endocrine and urological societies, only men with symptoms and/or signs of testosterone deficiency with repeatedly low serum testosterone concentrations in morning blood samples, collected under standardized conditions, should be diagnosed with hypogonadism. The serum total testosterone value should be < 10.4 nmol/l or 300 ng/dl, and the calculated free testosterone should be < 0.255 nmol/l or 7.35 ng/dl.

When choosing a therapeutic model, it should release enough testosterone into the circulation to restore physiological levels in adipose tissue for as long as possible, avoiding supra- and infra-physiological levels. The physician should be familiar with the advantages and disadvantages of each presentation and recommend the one that best suits the patient's needs. The objectives are: to restore parameters to eugonadal levels; improve sexual function; increase muscle strength and mass; recover and/or maintain bone mineral density, reducing the risk of fracture; improve neuropsychological aspects; and improve quality of life(11) .

Among the testosterone replacement models available in the medical literature, some of which are not available in Brazil, the medical professional has the option of following a line that promotes the stimulation of endogenous testosterone production in patients who

have absolute contraindications or a desire to preserve fertility, with *off-label* use, but historically practiced use of selective estrogen receptor modulators or aromatase inhibitors; in this group of patients, there is also the option of using gonadotropins: human chorionic gonadotropin (HCG), LH, and FSH.

The other therapeutic approach, and the most widely used worldwide, is the use of exogenous testosterone. In terms of chemical structure and similarity to what we find in human physiology, it is available in crystalline or *natural* form, with a bioidentical or native chemical structure, through compounding or patented formulations, or through the use of synthetic testosterone, chemically modified by the pharmaceutical industry, TEs are testosterone derivatives that comprise at least one substitution in the hydroxyl group of the cyclopentyl ring of the steroid nucleus by an acyl functional group or a substituted acyl functional group, and it is these variations, according to the structural alteration promoted by the pharmaceutical industry, that will generate variable action times, as described in the package insert for these drugs(12,13)

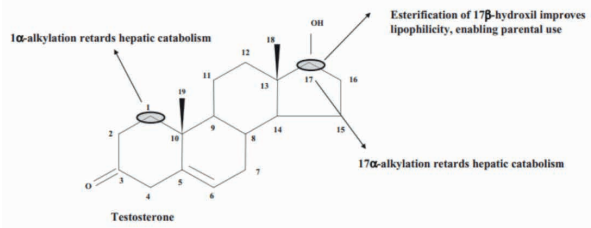

Figure 12: Chemical structure of testosterone esters .

Corona, 2011(4) .

The route of administration may be: oral; trans-mucosal, buccal or nasal; transdermal, compounded or patented form; parenteral (also in compounded or patented form), subcutaneous, intramuscular short-acting, medium-acting, and long-acting; and finally, but not least, the first to be approved by the FDA in 1972(14) and the only one approved for hypogonadal adolescents(15,16) , subcutaneous deposits (magistral or patented): absorbable (pellets) or non-absorbable (silastic devices), which have been used in female-to--male transgender patients due to the regularity and stability of serum hormone levels, ensuring better metabolic and hormonal adaptation and increasing clinical safety for the chosen transsexuality(12,13)

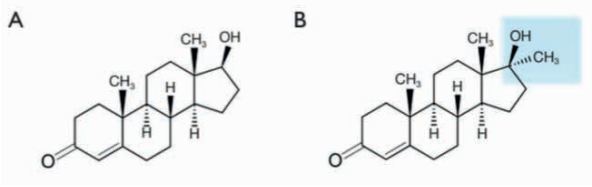

Figure 13: Chemical structure of testosterone (A) and methyl testosterone (B).

Shoskes, 2016(20)

Oral presentations of testosterone include: testosterone undecanoate, testosterone undecanoate with chrono release (Solid Self-Emulsifying Drug Delivery Systems) (Fig. 14)(17) , and masterolone, with this chrono release and conservation model being applied in various areas of medicine(18)

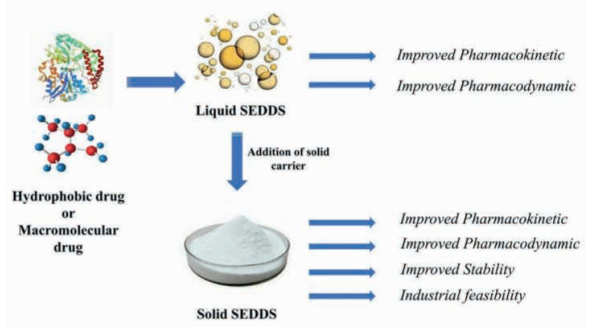

Figure 14: Solid Self-Emulsifying Drug Delivery Systems) Chrono-release system by self-emulsification.

Maji, 2021(18)

In the transdermal presentation, it has a patented formulation in testosterone patches, testosterone gel, testosterone solution, all with a bioidentical or native chemical structure, and dihydrotestosterone in gel, also with a chemical

structure bioidentical or native to this chemical composition; in the magistral presentation, it comes in the form of testosterone cream. In the trans-mucosal presentation, it is only available in the patented oral and nasal forms with the chemical presentation of bioidentical or native testosterone(12,13)

In parenteral presentations of testosterone, we have the following compositions: isolated and associated. In the parenteral presentation of isolated composition, we have patented and magistral: patented we have testosterone enanthate, testosterone cypionate, testosterone propionate, testosterone undecylate, and magistral, bioidentical testosterone or base (Fig. 15). In parenteral presentations of combined compositions or mixes, we have: patented combinations of testosterone propionate, testosterone fempropionate, testosterone isocaproate with testosterone decanoate, and in compounded formulations, we have combinations of testosterone propionate, testosterone cypionate with testosterone undecanoate(12,13, 18,19,20,21)

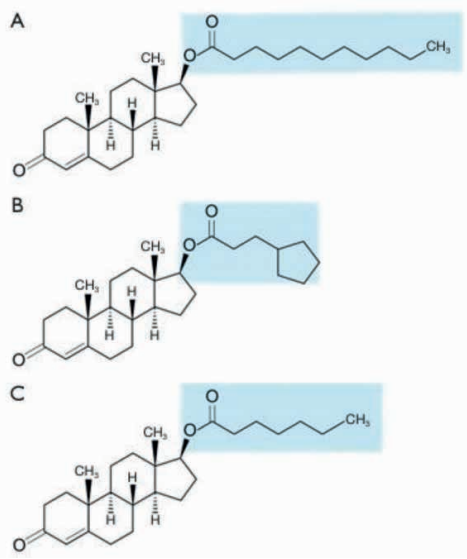

Figure 15: Chemical structure of testosterone undecanoate (A), testosterone cypionate (B), and testosterone enanthate (C)

Shoskes, 2016(20)

This parenteral presentation includes subdermal devices for minimally invasive surgical implantation by trocar puncture, which is the only one whose chemical composition is not modified. It is also called crystalline testosterone due to its bioidentical or native composition and its stabilizers.

When comparing intergroup, the most prescribed patented intramuscular formulation, which does not use the ideal biological terrain for replacement therapy, and crystalline testosterone pellets, for every 250 mg of testosterone undecylate/undecanoate there is 157.9 mg of the drug, with 36.84% of excipients added by dilution of the product, while for each 78 mg testosterone pellet, there are 75 mg of the drug and only 3.8% of excipients added by melting the product (12,13,18,19,20,21).

METHODOLOGY

This is a narrative review of the literature, which is broad in scope and aims to describe, from a historical, contextual, and theoretical perspective, through the analysis and interpretation of available scientific articles on the guiding question of this monograph entitled: *Use of testosterone pellets in hypogonadal men. A narrative review.* Would it have a place and indication in current medical practice? What have been the vicissitudes over the last 20 years?

For the present study, articles were searched in the databases of the Medical Literature Analysis and Retrieval System Online (Medline), Latin American and Caribbean Health Sciences Literature (LILACS) in the Scientific Electronic Library (Scielo). The search was conducted using the advanced mode between May 2, 2024, and July 4, 2024, in these databases, using the search terms testosterone replacement therapy **and/or** pellets, male hypogonadism **and/or** pellets, testosterone therapy **and/or** pellets, andropause **and/or** pellets, testosterone **and/or** pellets as descriptors in the last 20 years, characterizing this process in search activities, selection, filing of studies, mapping, and analysis, considering the

time frame, as it is a safe and effective form of replacement, but until five years ago, it was not very common in the medical profession. however, there has been a growing number of procedures and professionals who are interested in qualifying for this therapeutic model without having experience and expertise in the subject, causing the non-specialized media to demonize this therapeutic approach due to medical malpractice and recklessness, associated with scientific prejudice from traditional medical teaching centers and regulatory and Cartesian entities of medical conduct.

After this stage, the abstracts of the articles were read and subsequently selected, with the following exclusion criteria: experimental articles, articles whose subjects of study were non-human, case reports, book chapters, editorials, duplicates, annals, and articles from non-indexed journals. Some articles outside the predetermined period were added due to their academic relevance and historical context. Of the 1,943 articles found, 617 articles were applicable to the time frame, and after reading the abstracts and applying the exclusion criteria, 51 articles were selected that met the inclusion criteria and were analyzed according to the specific theme of this review (Fig. 18).

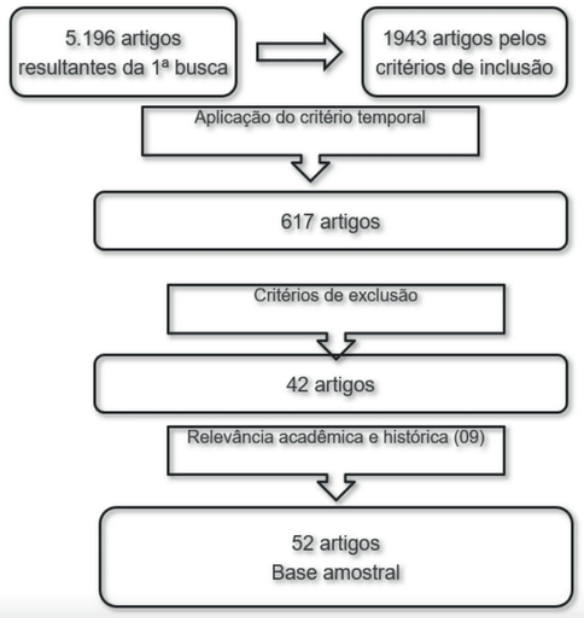

Figure 16: Description of article selection

Barros, 2024, author himself

DISCUSSION

CLINICAL PICTURE

Signs and symptoms suggestive of hypogonadism include reduced testicular volume, male infertility, hair loss, gynecomastia, reduced lean body mass and muscle strength, visceral obesity, metabolic syndrome, peripheral insulin resistance and type 2 diabetes mellitus, decreased bone mineral density, and anemia. Sexual symptoms include reduced sexual desire and frequency, erectile dysfunction, and reduced and decreased nocturnal erections (Fig. 17). Cognitive and psychocognitive symptoms include hot flashes, mood swings, fatigue and anger, sleep disturbances, depression, and decreased cognitive function.

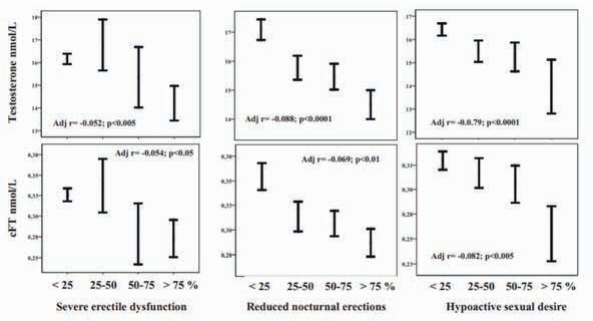

Figure 17: Relationship between serum total and free testosterone levels and severity of sexual symptoms.

Corona, 2011(4) .

When serum testosterone levels are stratified for patients with hypogonadal symptoms and correlated with sexual symptoms, publications show that sexual frequency is reduced when TT is below 8.0 n/mol, 8.5 for erectile dysfunction, 11 for reduced frequency of morning erections, and 13 for reduced vigor, especially in younger patients, since patients aged 40 to 70 were considered

It is known that androgen deficiency correlates with metabolic syndrome, which is directly correlated with erectile dysfunction, which is also associated with androgen deficiency itself. If we look at another correlation, androgen deficiency is related to diabetes, which is related to peripheral insulin resistance, which is in turn related to androgen deficiency. Androgen deficiency is also related to obesity, obesity is related to metabolic syndrome, which is again associated with androgen deficiency.

Peripherally, if we place androgen deficiency as ground zero, obesity is present along with peripheral insulin resistance, which is linked to diabetes, which is linked to erectile dysfunction, which is linked to metabolic syndrome, and back to obesity, closing an endless circle that feeds back and amplifies complications, with male androgen deficiency at the center of this mental map, and perhaps this is why there is a misconception that testosterone replacement would solve everything and is linked to the fountain of youth (Fig. 17).

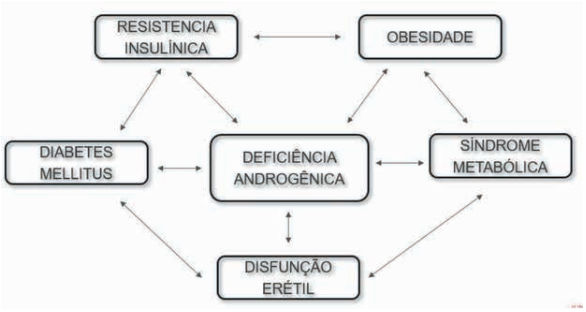

Figure 18: Basic mind map of the benefits of testosterone replacement and its various metabolic interactions with conditions common to longevity.

Barros, 2024, author

PHARMACOKINETICS

The first information on the pharmacokinetics of testosterone pellets dates back to 1998, when two groups were compared, one using intramuscular ET every 14 days, oral testosterone undecanoate twice a day, and another group using testosterone implants(22) .

This study, in which testosterone pellets were implanted in the abdominal wall of participants, showed efficacy and stabilization of serum levels of total testosterone, free testosterone, and SHBG using 600 mg of crystalline testosterone pellets(22) .

This study showed efficacy and effectiveness in both groups, considering both serum testosterone values and improvement in patients' signs and symptoms. Even in patients who presented extrusion, this did not compromise their clinical condition or the need for reimplantation to maintain serum levels and clinical improvement(22) . The maximum mean value achieved in the testosterone implant group was 781 ng/dl, which did not promote a supraphysiological dose . (22)

Another study from 1990 shows a regular and constant pattern of testosterone pellet pharmacokinetics(23) . The study consisted of three groups: one with six 100 mg testos-

terone implants, another with six 200 mg testosterone implants, and the third group with three 200 mg testosterone implants(23) . It was found that the maximum concentration reached on the 30th day was related to the initial amount implanted, with a higher total concentration of implants inserted leading to a supraphysiological peak and that, regardless of the number and size of the implants, the release was linear, with an estimated release of 0.65 mg/day for a 100 mg testosterone implant and 1.3 mg/day for a 200 mg testosterone implant(23) .

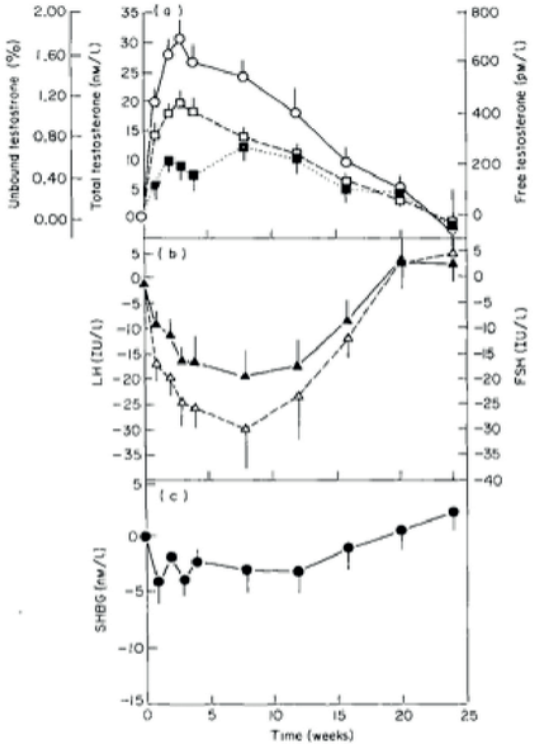

Figure 2: Distribution of serum concentrations of total testosterone, free testosterone, and SHBG

Conway, 1998(22) .

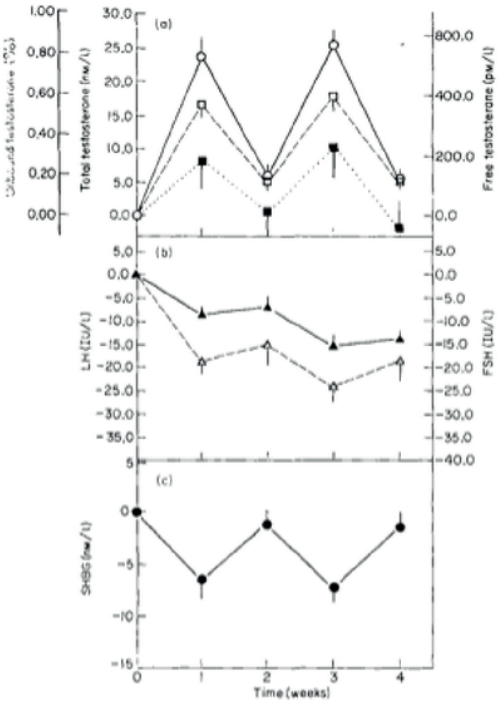

Figure 2: Fluctuation of serum concentrations of total testosterone, FSH, and LH with HT use

Conway, 1998(22) .

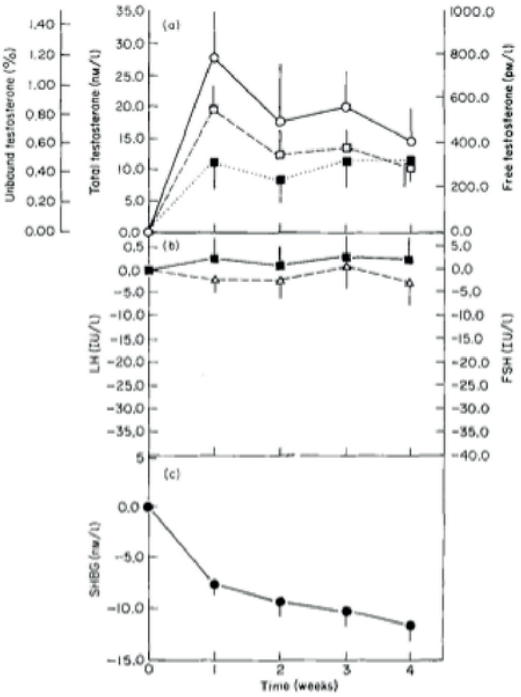

Figure 2: Fluctuation of serum concentrations of total testosterone, FSH, and LH with the use of oral testosterone undecanoate

Conway, 1998(22) .

Another study in 2004 corroborates the above data, as it considered testosterone implants to be degraded, fragmented, or not considering the dry weight of these implants before placement, and pharmacokinetic follow-up estimated a release rate of 1.31 mg/day (+/- 0.02) by linear regression of the least squares, with a 95% confidence interval(24) bearing in mind that testosterone is metabolized in approximately 90% by hepatic CYP3A4, with approximately 10% by 5-alpha reductase and 1% metabolized by other aromatase inhibitors(25)

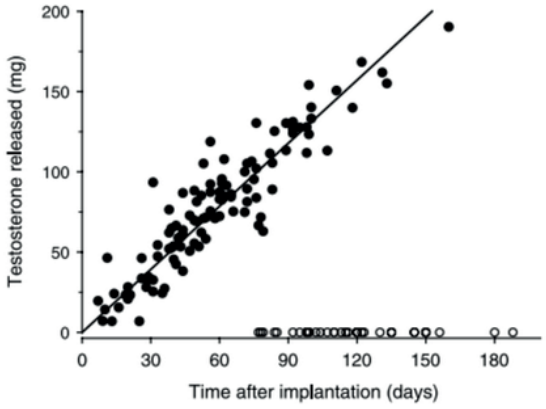

Figure 2: Comparative graph of testosterone release rate as a function of pellets destroyed.

Kelleher, 2004(24)

In obese patients with a body mass index (BMI) above 30 kg/m2, a higher number of implants should be considered, as the volume of distribution in the tissues is proportional to the BMI, which can even be used as a parameter for monitoring, along with the measurement of salivary testosterone(26, 27)

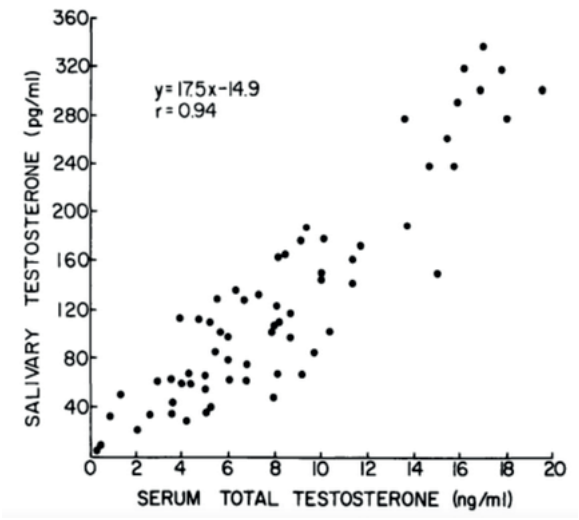

Figure 2: Comparative graph between salivary testosterone and serum testosterone.

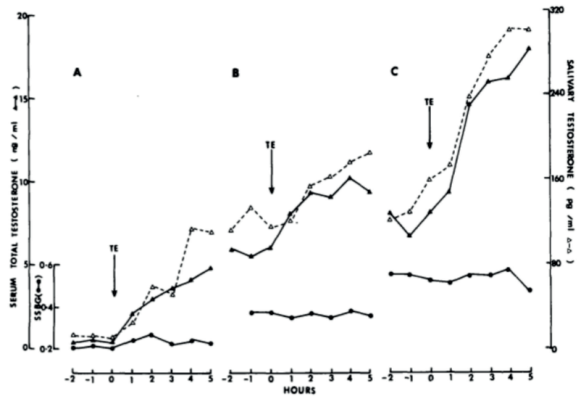

Figure 2: Comparative graph between salivary testosterone and testosterone enanthate.

This situation should be monitored, not least because of the relationship between sex hormones and the patient's age and weight(1) . Total testosterone is found at lower serum levels in overweight and obese men compared to non-obese men, when comparing all ages; free testosterone, similar to total testosterone, is also decreased in overweight and obese men compared to non-obese men at all ages, while LH increases with age, showing no association with body mass index (BMI), and SHBG increases with age(1) (Fig. 10).

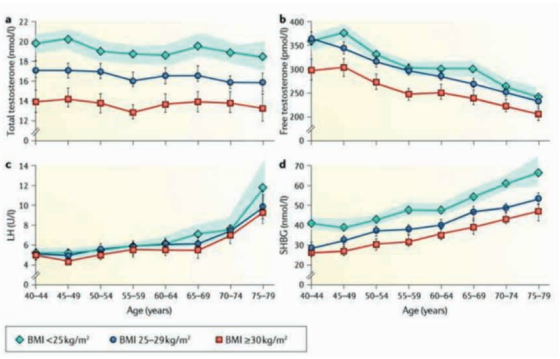

Figure 10: Relationship between SHBG and sex hormones with age

Salonia, 2019 (1)

Among the most prevalent symptoms are decreased physical vigor, mood swings, reduced sexual desire and activity, and erectile dysfunction. Other factors overlap and constitute a bias in the diagnosis and care of this patient, such as obesity, a condition that is increasingly prevalent in the Brazilian and global population, and the patient's general health status and coexisting chronic disease. (28) Precisely because of the patient's clinical condition and the time it took to diagnose and treat hypogonadism, we find in the literature different times for clinical response to the most diverse complaints presented by patients(29) .

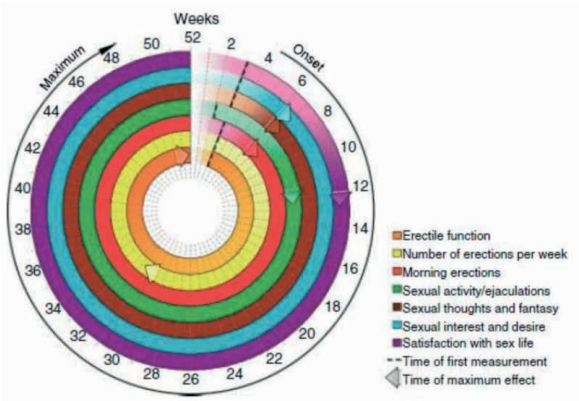

Figure 10: Changes in sexual function with testosterone replacement

Saad, 2011(29) .

Studies have shown that after testosterone administration, there is a positive effect

The correlation between blood testosterone concentrations and *leg press* strength, increased thigh muscle volume, quadriceps, and increased hemoglobin and IGF1 levels, and the effects of testosterone on muscle mass/strength are mainly short-term. In a study that combined testosterone with GH, muscle mass increased, as did appendicular lean tissue and maximum voluntary strength of the upper and lower body muscles, which increased after 16 weeks.

In another study investigating the effect of a long-acting testosterone drug administered for 12 weeks, maximum exercise capacity and muscle strength showed an increase in isometric quadriceps strength, maximum voluntary contraction, and isokinetic strength (peak torque). Testosterone administration for 20– s was associated with dose-dependent increases in skeletal muscle mass, leg strength, and power.

In another 180-day study of testosterone therapy, average muscle strength in *leg press* exercises increased after 90 days. A similar study found an increase in lean body mass and improvement in lower limb muscle strength after 6 months. Another study using higher doses of testosterone observed significant increases in *leg press* strength, chest press strength, and power to climb stairs with a load within 6 months. It can be concluded that the effects of testosterone on muscle strength are demonstrable after 12–20 weeks, depending on testosterone levels, and maximum effects are achieved after 6 or 12 months . (29)

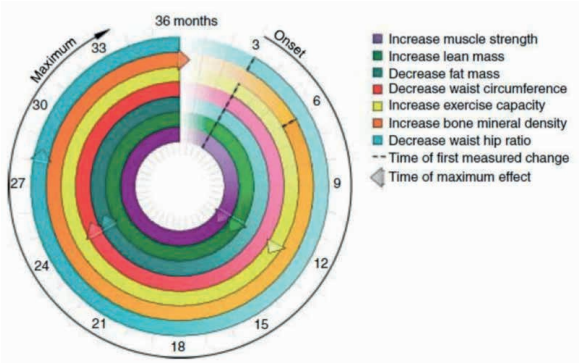

Figure 10: Changes in body composition with testosterone replacement

Saad, 2011(29) .

The effects of testosterone on bone mineral density are partly mediated by estrogens, derived from testosterone via aromatization(4) (Fig. 22). Testosterone improves bone mineral density in the lumbar spine compared to placebo, but improvements are less evident in the femoral neck. Testosterone reduces markers of bone resorption. Effects on bone mineral density have been demonstrated in 6-month, 8-month, and 1-year studies, showing further improvement. (29)Studies analyzing the effects of testosterone administration for up to 36 months also observed an increase during this period, and it is unclear whether the maximum effect of testosterone on bone mineral density had reached its peak.

The effects of testosterone replacement on the metabolic profile are well demonstrated in the articles, and what is identified is a reduction in the first thirty days, which continues until the ninth month and may reach the twelfth month. Similarly, serum triglyceride levels also follow this pattern(29) .

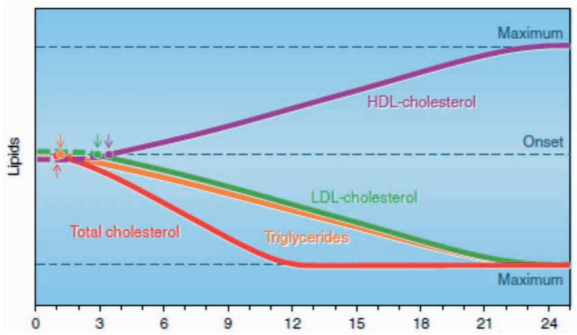

Figure 10: Effect of testosterone replacement on the lipid profile in months.

Saad, 2011(29) .

The result of testosterone replacement on glycemic function is not as immediate as that on lipids, and there are other physiometabolic associations to be considered. The reduction in serum glucose, glycated hemoglobin, and insulin levels occurs after three months, taking into account that patients with lower serum testosterone levels and higher serum estradiol levels tend to have a delay or even greater effectiveness of this improvement, even with bodily changes, as this may be correlated with more severe mitochondrial dysfunction.(29)

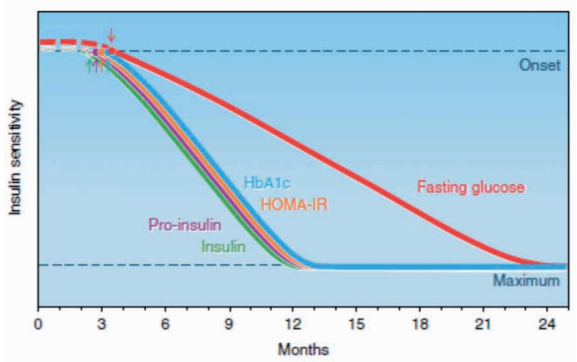

Figure 10: Effect of testosterone replacement on the glycemic profile over months.

Saad, 2011(29) .

Testosterone replacement therapy still faces concern and resistance in the medical community, largely based on old, award-winning articles that used different therapeutic

models, doses, and dosages than those used today. Regarding the physiology of hematocrit, its rise is dose-dependent and occurs in the first three months, stabilizing during replacement. As for the prostate-specific antigen, an increase may also occur, but this is compatible with the serum levels of eugonadal patients and does not characterize a complication of the therapy. Long-term follow-up studies have proven the safety and rationality of testosterone therapy, even in patients with benign prostatic hyperplasia(29) .

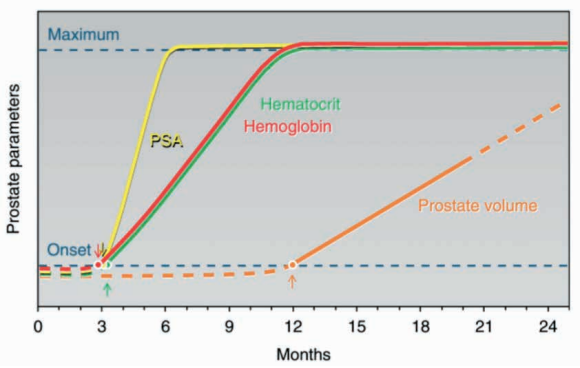

Figure 10: Effect of testosterone replacement on the lipid profile over months.

Saad, 2011(29) .

INSERTION TECHNIQUE

Early publications show that they were initially placed in the abdomen, originating from the umbilical scar, and the implants were positioned up to 5 cm from the entry hole, then in the lateral region of the hip, and finally, at the waistline, the anatomical line connecting the superior iliac spines(23, 24, 28, 30) . The implants can be placed using the single-line technique (TecL), which limits the number of units to be implanted(23, 28) , or using the "V" technique (TecV), in which two linear paths, in different geospatial planes, with a single access, allow for a greater number of units to be implanted(30) . The number of units implanted using TecL was 8 [Δ 6 to 8] and 10 units implanted using TecV [Δ 10 to 13](30) .

Description of the single-line technique (TecL), or single track the patient is placed in a lateral decubitus position with the knees semiflexed toward the abdomen, or fetal position; the implantation site is in the upper outer quadrant of the posterior gluteal region; the skin site is marked 3 cm below the start of the imaginary line and halfway between the iliac crest and the sacroiliac joint, extending 10 cm parallel to the femur; Antisepsis was performed using alcohol and polyvinylpyrrolidone (PVPI). A fenestrated sterile field was placed. Infiltration with 2% lidocaine associated with a vasoconstrictor, epinephrine (1:100,000), was performed. creation of an anesthetic button, in papule, and progression of the distribution of the anesthetic to a depth of 1 to 2 cm using a 25 to 27 gauge needle (G), in a fan shape(28) (Fig. 11).

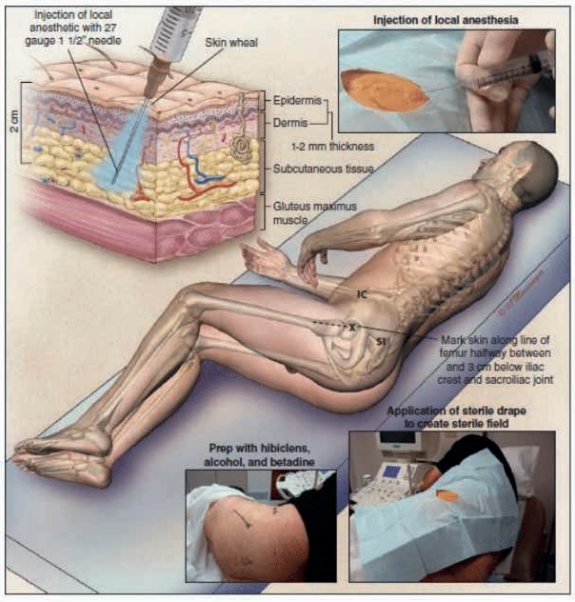

Figure 11: Description of the single-track insertion technique

Cavender, 2009 (28)

After the site is properly anesthetized, a small incision of 3 to 4 mm in length is made in the skin and subcutaneous tissue (, SCT) using a No. 11 scalpel blade; The trocar with a sharp mandrel is then inserted at a 30-degree

angle to the skin surface, penetrating 1 to 2 cm into the subcutaneous tissue; this progression follows the trajectory of the femur; the trocar and stylet are advanced to their full length of 10 cm(28) (Fig. 12).

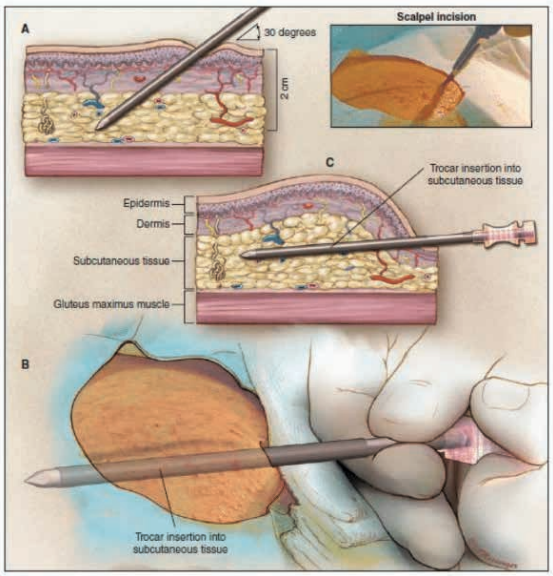

Figure 12: Arrangement and progression of the trocar for pellet insertion

Cavender, 2009 (28)

After the trocar has been advanced to its maximum length (10 cm), the inner mandrel is removed, and the testosterone pellets or implants are placed individually in the trocar through the trocar slit or the central slit. (28) After all pellets have been placed in the trocar, the internal mandrel, which was previously removed, is advanced inward while the trocar is simultaneously withdrawn, pushing the pellets one by one into the path formed by the trocar within the subcutaneous tissue and the trocar (Fig. 13).

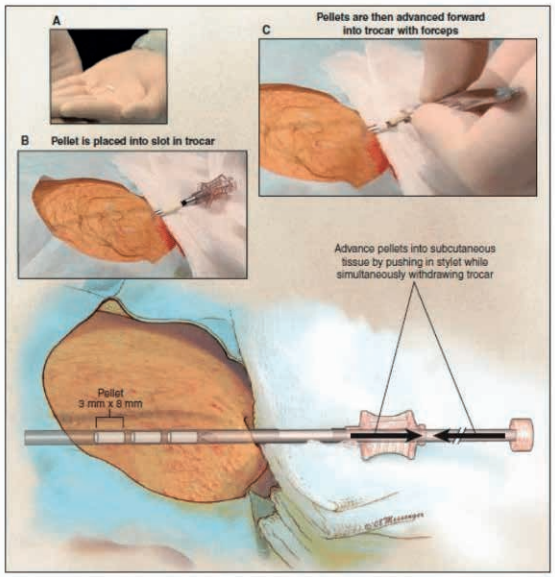

Figure 13: Insertion of pellets into the TSC through the trocar

Cavender, 2009 (28)

After all pellets have been placed and the trocar removed, an adhesive and degreasing solution, in this case benzoin tincture, is applied to the skin; a surgical dressing is made using a sterile dressing to protect the area. (28)The patient is then placed in the opposite position, contralateral, and the implant site is subjected to cold compression ( ) using the patient's own body weight, and while still under the effect of the anesthetic infiltration, in an ice bag for approximately 10 minutes (Fig. 14).

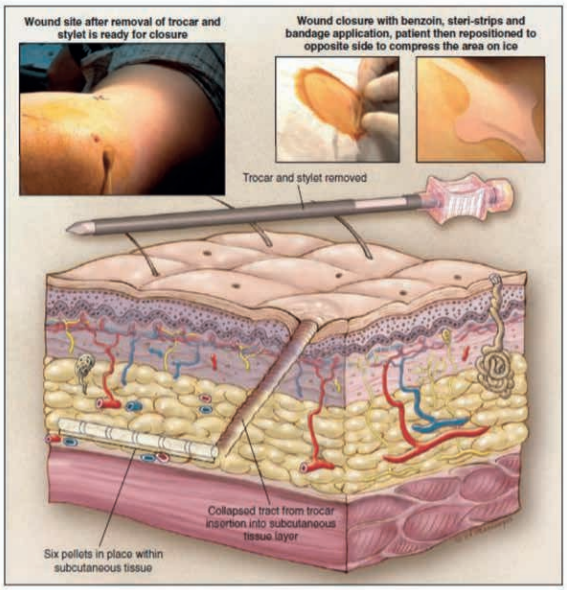

Figure 14: Application of the final dressing

Cavender, 2009 (28)

In the V technique, the patient is also placed in a lateral decubitus position, with the legs slightly flexed; the side of implantation is normally rotated for each individual procedure, as this allows both sides to be done simultaneously; local anesthetic (10 ml of 2% xylocaine with epinephrine) is also used; extensive infiltration of the planned area. for incision and future implantation; normally, 2–3– r injections are necessary; this is followed by an incision with a 11 blade made at the level of the upper margin of the gluteal cleft, following the line of the lateral margin of the prominence of the gluteus maximus muscle or greater (this area corresponds approximately to the lateral edge of the back pocket of a pair of pants)(30) .

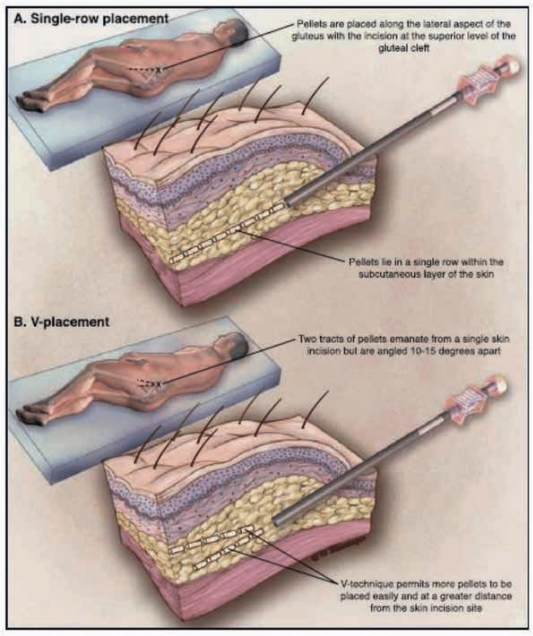

Figure 15: V-technique, with two tracks

Conners, 2011(30) .

The trocar with the mandrel is then inserted into the wound at an angle of approximately 30 degrees, positioning it parallel to the skin surface, deep enough to avoid ripples on the skin surface; the inner mandrel is then removed, and the testosterone pellets or implants are placed in the inner sheath of the trocar; after all pellets have been placed in the sheath, the inner mandrel is advanced into the inner sheath while the trocar is pulled out of the subcutaneous tissue in a reverse motion but in the same direction so that the pellets are arranged in the mechanically created space where they will act without completely protruding from the surgical site(30) .

After placing the first set of pellets as described, the trocar is completely removed from the incision site or withdrawn to leave only the tip of the trocater remains inside the wound before starting the second path, below or above the first track; the trocar is then tilted 10 to 15 degrees from the first line of pellets; the second set of pellets is then inserted into the trocar and arranged along this new track, with the new angle; Finally, a surgical dressing is applied with a sterile dressing and(30) e (Fig. 15).

COMPLICATIONS

Complications are related to the replacement procedure itself, rather than the treatment, and include the following: extrusion, which is spontaneous and rare(31) , but estimated to occur in 8% of cases and related to physical activity(32) ; local hematoma and cellulitis(31,32) , which can reach 5.4%(27) . In the article produced in 2011, with the standardization of insertion by TecV of the 40 participants submitted to TecL and 241 participants submitted to TecV, and with a total of 281 procedures, the extrusion rate was 7.5% with TecL and 0.8% with TecV, the occurrence of cellulitis at the surgical site was 7.5% with TecL and 0.8% with TecV, however, there was no hematoma with TecL and 1.2% of hematomas occurred with TecV, of which 3 patients were using anticoagulants, which was not reported to the team, but it was a comorbidity with low morbidity and no clinical repercussions(30) . The occurrence of pain that led to discontinuation of therapy was observed in 7.5% of patients undergoing TecL and 1.7% of patients undergoing TecV. Significant pain without interruption was observed in patients undergoing TecL and 1.2% of patients undergoing TecV . (30)

In another article published in 2021, in a retrospective review, more consistent data were found based on the number of participants studied, totaling 1,204,012 procedures involving 376,254 patients, including 185,496 hypogonadal men, with <3% extrusions, <1% cellulitis, and <1% overall bleeding(33). Extrusions were more common in patients with a BMI lower than 25; immediate bleeding was considered very rare (<0.1%) and post--procedure bleeding was related to the use of non-steroidal anti-inflammatory drugs, aspirin, omega-3 supplementation, and higher BMI(33).

Other secondary reactions described were: histamine reaction resulting from the use of anesthetic for insertion, hyperpigmentation at the implant insertion site, and subdermal fibrosis identified on palpation, which resolved spontaneously(33). Of the hypogonadal men in these studies, 68,564 were followed for seven years, and retrospective analysis also describes the occurrence of 100 complications or general health events with higher morbidity, representing 0.14% of this subgroup: 46 patients who had non-fatal acute coronary events [0.067%]; 37 patients who obtained a diagnosis of mitotic process in the prostate ( ) [0.054%]; 09 patients diagnosed with a thrombotic event in the deep venous system [0.013%]; and 08 patients with a non-fatal acute neurological event [0.012%](33) . When compared with the medical literature, these rates are lower when comparing the clinical profile of the patients studied.

To reduce the occurrence of extrusion or cellulitis at the implant insertion site, impregnation with antibiotics prior to the procedure was considered. but despite a lower occurrence in the gentamicin-impregnated group, it was not significantly important. However, this study highlights the possibility that antisepsis of the site with topical polyvinylpyrrolidone appears to be a protective factor in reducing this situation(34) . Due to the similarity in pathophysiology, the use of topical gentamicin could reduce the incidence of cellulitis at the implantation site(35) .

The importance of medical guidance before and after the procedure, the patient's clinical condition, individualized dosage, and the physical specificity of the implant do seem to influence the occurrence of cellulitis after implantation, as none of the 292 patients who followed medical guidelines presented spontaneous extrusion(36) . In this study, the cellulitis rate was 0.3%, and the extrusion rate was also 0.3%, with one negative event for 292 cases in the same patient. When compared with historical data from Organon, the rates are 1.4 to 6.8% for cellulitis and 8.5 to 12% for extrusion, respectively(36) .

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As already mentioned, the arrangement in two tracks, TecV versus TecL, reduces the occurrence of cellulitis and extrusion(30) , but the location of the implants can lead to more or less complications, and when the implants are placed in the hip, they generate more complications than when placed in the abdominal flank, in the direction of the waist, with statistical significance of $p < 0.006$ and a 95% confidence interval, as the design of this study was prospective(37) .

CLINICAL AND LABORATORY EFFICACY

The use of testosterone pellets or implants dates back to the 1930s(38,39)and since then, publications and their use have increased, with satisfactory clinical results and normalization of laboratory levels(40) . Having been approved since 1972 by the FDA(14) , the use of testosterone implants has not been widely used by the medical profession, being more common in some centers in the United States of America (USA) and Australia.

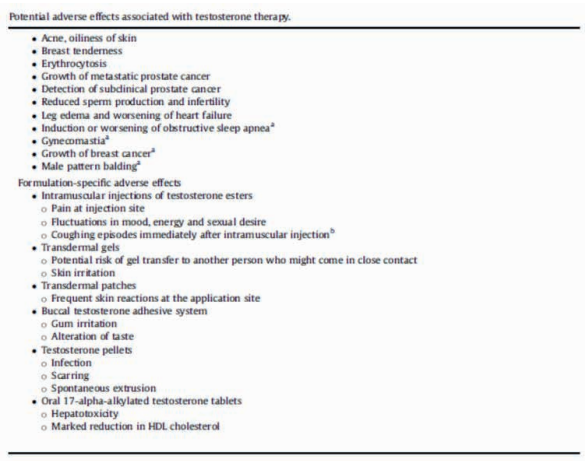
However, after 2008, there has been an increase in testosterone replacement prescriptions and a greater number of professionals interested and qualified to insert the implants, both due to publications that demonstrated the safety of this presentation and the medical community's understanding of the need to treat andropause and its clinical repercussions on male health and longevity. However, the dosage was higher than historically suggested, increasing from six 75 mg pellets to ten 75 mg pellets, without causing supraphysiological levels(41,42,43) .

The implantation of pellets provided the most prolonged effect, with elevated levels of free and total testosterone for up to 4 months(36) . This was accompanied by an immediate and sustained suppression of plasma LH and FSH, an increase in plasma estradiol levels, but no change in sex hormone-binding protein levels (SHBG(23) . In contrast, intramuscular injections induced marked but reproducible weekly fluctuations in free and total testosterone, which resulted in a small decrease in plasma SHBG levels, less marked suppression of LH and FSH, and a smaller increase in plasma estradiol levels(24,31,32,44).

Oral testosterone undecanoate produced the most variable plasma levels of free and total testosterone, with a peak in the first week of treatment and a decline thereafter(45,46). Despite maintaining testosterone levels within the physiological range, there was no significant suppression of plasma LH and FSH levels, and estradiol levels remained unchanged, but SHBG and total cholesterol levels decreased, along with other parameters, including neurovegetative symptoms(47,48).

Improved sexual function is also described, and the combination of 5-phosphodiesterase inhibitors [5PDE](49)and side effects were lower with parenteral treatments compared to oral treatments, including urinary symptoms in patients with benign prostatic hyperplasia. A meta-analysis produced in 2023, with 12 years of follow-up, also shows improvement in these symptoms(50) .

Contraindications for testosterone replacement therapy, regardless of the route of administration, are: locally advanced/metastatic prostate cancer; desire to maintain fertility; male breast cancer; hematocrit above 54% and severe chronic heart failure, class IV(9,31,32,49). With the advent of the importance of patient choice in the conduct of their treatment, when possible, some articles show that considering cost, efficacy, safety, and convenience, patients tend to opt for testosterone implants (11 ,27,33,51)



Potential adverse effects associated with testosterone therapy.

- Acne, oiliness of skin
- Breast tenderness
- Erythrocytosis
- Growth of metastatic prostate cancer
- Detection of subclinical prostate cancer
- Reduced sperm production and infertility
- Leg edema and worsening of heart failure
- Induction or worsening of obstructive sleep apnea[a]
- Gynecomastia[a]
- Growth of breast cancer[a]
- Male pattern balding[a]

Formulation-specific adverse effects

- Intramuscular injections of testosterone esters
  - Pain at injection site
  - Fluctuations in mood, energy and sexual desire
  - Coughing episodes immediately after intramuscular injection[b]
- Transdermal gels
  - Potential risk of gel transfer to another person who might come in close contact
  - Skin irritation
- Transdermal patches
  - Frequent skin reactions at the application site
- Buccal testosterone adhesive system
  - Gum irritation
  - Alteration of taste
- Testosterone pellets
  - Infection
  - Scarring
  - Spontaneous extrusion
- Oral 17-alpha-alkylated testosterone tablets
  - Hepatotoxicity
  - Marked reduction in HDL cholesterol

Figure 16: Contraindications for testosterone replacement and specifications for each modality.

Bassin, 2011(11) .

The use of a conventional dosage of 600 mg allows for 4 to 5 months of effectiveness with eugonadal levels for the patient, while implanting a dose of 1,200 mg only increases the peak maximum concentration in 30 days, but does not prolong the treatment's effectiveness, based on total testosterone (Fig. 16), free testosterone (Fig. 17), SHBG (Fig. 18), FSH (Fig. 19), and LH (Fig. 20)(23) .

In the three therapeutic models of testosterone implants, highly predictable time intervals were obtained for total and free testosterone levels, with a clear dose-response relationship between the pellet dose and plasma testosterone levels. Testosterone peaks in the first month and gradually decreases until it returns to baseline values found 6 months before implantation in the two 600 mg dosage regimens, whether with 100 mg (06 units) or 200 mg (03 units), but remained statistically significantly elevated after 6 months when using the 1200 mg dose(23) (Fig. 16).

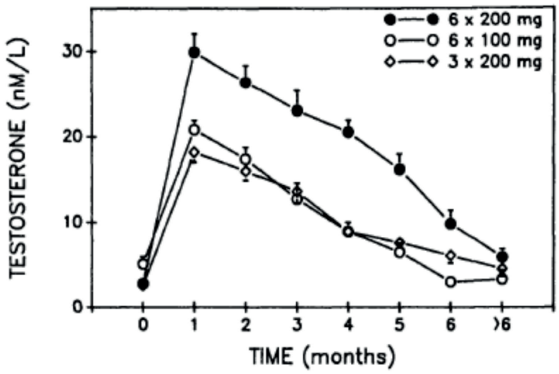


Figure 16: Serum total testosterone values at 180 days

Handselman, 1990(23) .

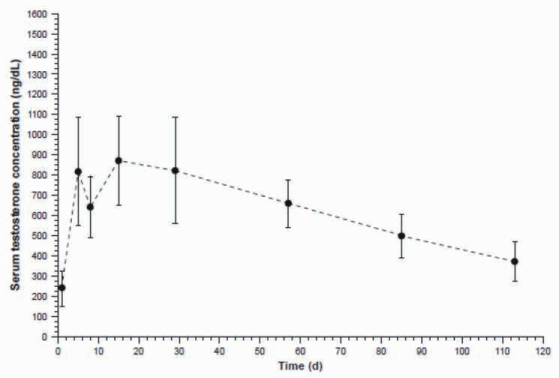


Figure 16: Total serum testosterone values at 180 days

McMahon, 2017 (5)

The group of patients who used 1200 mg as a therapeutic model had higher total testosterone levels when compared to the groups that received either 06 units of 100 mg or 03 units of 200 mg, with a higher average concentration of 137.8, with a P <0.0001; When comparing the two groups receiving 600 mg, they had a similar time course, with total plasma testosterone varying on average by 0.4 mg, with P = 0.5(23) (Fig. 16).

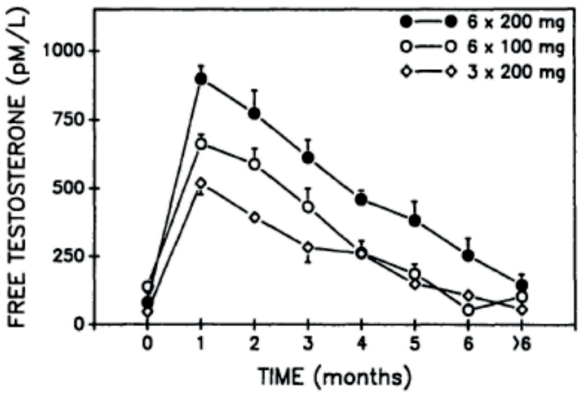


Figure 17: Serum free testosterone values at 180 days

Handselman, 1990(23) .

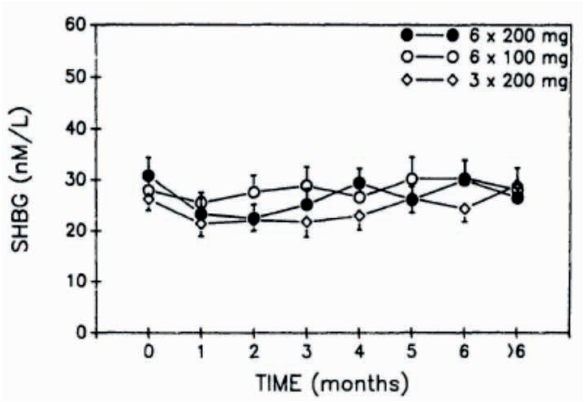


Figure 18: Serum SHBG values at 180 days

Handselman, 1990(23) .

Plasma free testosterone also behaved in the same way as total testosterone (r = 0.90) and, therefore, free testosterone levels rose in the first 30 days and gradually decreased at the end of treatment. The only exception was in patients in the group receiving 6 units of 100 mg, which was significantly higher in the first month but not in the others when compared to the group receiving 3 units of 200 mg; serum total testosterone levels were not correlated with age or physique (P > 0.15), but plasma free T was weakly inversely correlated with the patient's body surface area (r = -0.09, P = 0.06) and BMI (r = -0.13, P = 0.004), but not with age (P > 0.5)(23) (Fig. 17).

Plasma SHBG did not vary significantly between pellet regimens (P = 0.87) or over time (P = 0.18); it was moderately correlated with age (r = 0.44), body surface area (r = 0.40), and BMI (r = 0.25, all P < 0.001)(23) (Fig. 18).

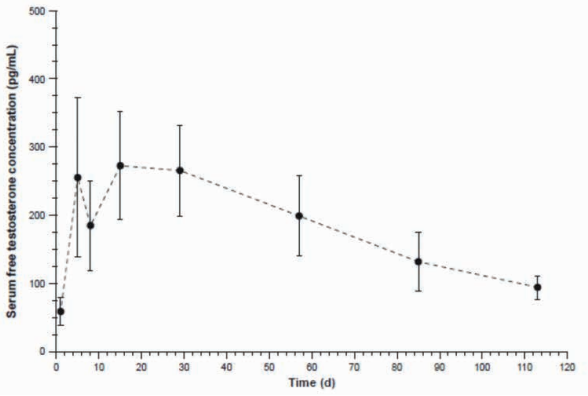


Figure 16: Serum free testosterone values at 180 days

McMahon, 2017 (5)

Plasma LH and FSH levels were markedly suppressed by all three regimens in men with primary hypogonadism (hypergonadotropic) with marked dose dependence, as the 1200 mg regimen produced significantly

greater and more sustained suppression of LH and FSH than the two 600 mg regimens with a P < 0.001 for both LH and FSH(23) .

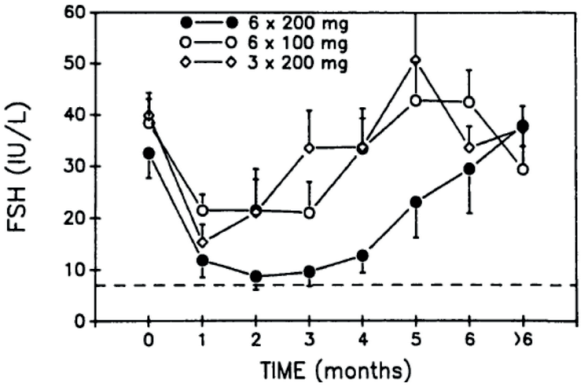


Figure 16: Serum LH values at 180 days

Handselman, 1990(23) .

The two 600 mg regimens produced similar results for plasma LH with a P = 0.32) and for FSH a P = 0.93. The 600 mg dosage regimens produced

lower LH levels between 1 and 3 months with a significant increase between the fourth month and returning to baseline in the fifth month. In contrast, the 1,200 mg dose produced the lowest point only in the sixth month(23) .

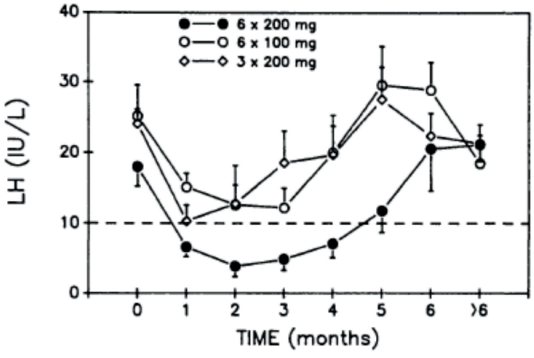


Figure 16: Serum LH values at 180 days

Handselman, 1990(23) .

These findings were reproduced in 2017, using a dose of 900 mg, with measurement of estradiol, total testosterone, free testosterone, and dihydrotestosterone (Fig. 26). but it is important to mention that serum values were compared with an international sexual function questionnaire, a questionnaire for assessing depression and mood swings, and the male aging questionnaire itself, and a positive relationship was found between serum values and clinical improvement reported and measured by the patient himself, with a satisfaction level of 76.7%(5) .

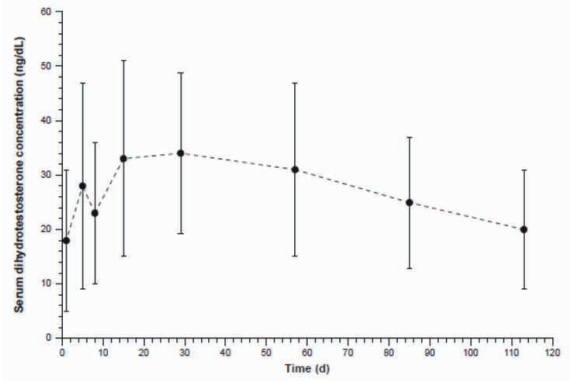


Figure 16: Serum dihydrotestosterone values at 180 days

McMahon, 2017 (5)

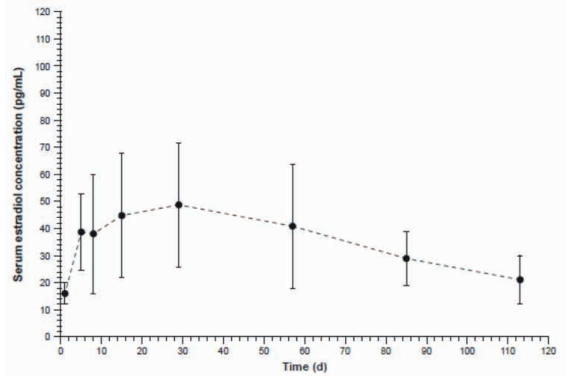


Figure 16: Serum estradiol values at 180 days

McMahon, 2017 (5)

In another publication in 2012, targeting patients with Klinefelter syndrome, four young men with secondary hypogonadism were evaluated to determine whether implantable pellets represented a viable treatment option for these patients. Participants received doses ranging from 300 to 750 mg of subcutaneous testosterone, and in all 4 patients, total and free testosterone levels improved during the study follow-up, although fluctuations between levels were inconsistent. All patients reported improved energy and concentration, and parents noted improved mood stability.

The mean baseline total T level of 108.3 ng/dl increased in all patients at the time of the second pellet implantation. Mean total T levels ranged from 325 to 587 ng/dl throughout therapy. There was significant variability in serum T levels while patients were on therapy. All patients eventually received a greater number of pellets at some point during their care. Subcutaneous implantation of testosterone pellets has been shown to be a viable and effective form of testosterone replacement therapy in young men with Klinefelter syndrome in whom adherence is a problem. However, the need to repeat implantation every 3 months and the increased cost of therapy mean that this strategy deserves consideration in non-adherent patients(16) .

Serum FSH levels in both 600 mg dosage regimens produced maximum decline between the first and second month, but after the third month, the effects of the combination of 6 units of 100 mg (which had a larger initial surface area) were sustained longer when compared to the group receiving 3 units of 200 mg. In contrast, the group that received 6 units of 200 mg produced a more prolonged suppression of FSH, with a return to baseline levels only after 6 months(23) (Fig. 19)

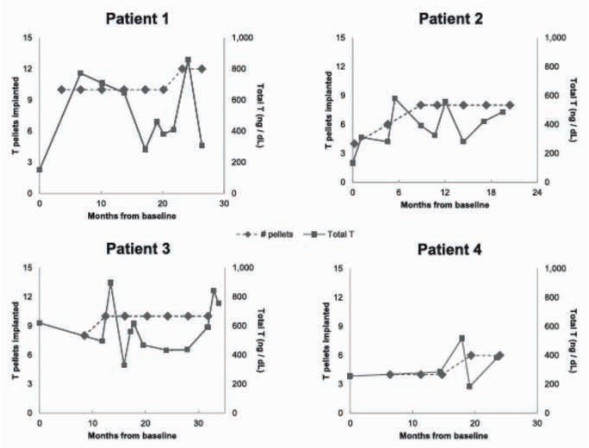


Figure 16: Serum testosterone values in a patient with Klinefelter syndrome

Moskovic, 2012 (16)

When comparing therapeutic forms of testosterone replacement, the use of implants allows serum testosterone levels to be > 40% above the start of treatment(52) (Fig. 20), considering the full metabolism of the drug, because if the medical professional doses during the cycle, will the serum values found be normal due to the use of the medication or the recovery of endogenous testosterone production? The question remains.

Add to this the fact that the description of EHH recovery, characterized by increased FSH and LH, associated with increased serum testosterone after the end of the cycle, is described in a few articles and, when described, occurs with the use of testosterone implants(23,52) , and because it shows a graphical trend in these studies(23,52) , it would allow the medical professional to restore the patient's health rather than just treating the patient's disease, in this author's opinion.

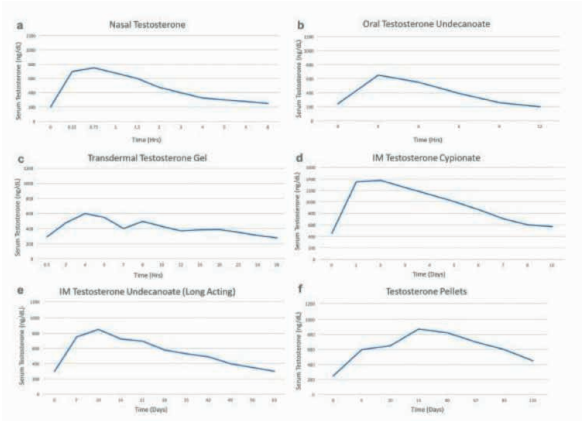


Figure 20: Comparative graph between forms of testosterone replacement

Kresch, 2021(52) .

CONCLUSION

The use of testosterone pellets or implants for hypogonadal male patients is a clinically safe, stable, and comfortable option for treating androgen decline in aging men. It is widely supported in the medical literature and has been recommended by the FDA since 1972 for its efficacy and effectiveness. The use of lower doses allows for a shorter duration of action, but does not generate supra-physio-

logical levels in the first thirty days. Patients with a higher BMI require higher doses. Medical complications are low in morbidity, related to the insertion of the pellets and not to the treatment itself, and occur at a low frequency, even for professionals on a learning curve, the most common being extrusion, which is also related to physical activity and the experience of the medical professional. This does not compromise treatment when it occurs. Finally, it is known that adopting healthy social and dietary habits are recommendations for patients with DAEM and common to all forms of testosterone replacement, but the choice of testosterone implants as treatment allows patients to recover their axis and eugonadal parameters by the end of the first cycle, with a tendency not to become dependent on chronic use of exogenous testosterone.

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