APPLICATIONS AND SAFETY OF TESTOSTERONE CREAMS: A SYSTEMATIC REVIEW OF TOPICAL FORMULATIONS, CLINICAL EFFICACY, AND POTENTIAL RISKS

APLICAÇÕES E SEGURANÇA DOS CREMES DE TESTOSTERONA: REVISÃO SISTEMÁTICA SOBRE FORMULAÇÕES TÓPICAS, EFICÁCIA CLÍNICA E RISCOS POTENCIAIS

APLICACIONES Y SEGURIDAD DE LAS CREMAS DE TESTOSTERONA: REVISIÓN SISTEMÁTICA SOBRE FORMULACIONES TÓPICAS, EFICACIA CLÍNICA Y RIESGOS POTENCIALES

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ABSTRACT

Testosterone creams and gels have been widely used in clinical practice for hormone replacement and for use without formal clinical indication, mainly among middle-aged and elderly men. This study aims to systematically review the evidence on the composition, mechanisms of action, efficacy, safety, and risks associated with the use of topical testosterone formulations, including creams, gels, ointments, and transdermal patches. Studies indexed in PubMed, Scopus, and SciELO databases between 2010 and 2025 were included. Comparative analysis shows that creams exhibit variable absorption depending on the area applied, the vehicle, and the contact time, while gels offer more stable bioavailability, and transdermal patches maintain continuous release. Although effective in raising serum testosterone levels, these products can cause adverse events, including acne, gynecomastia, alopecia, and possible stimulation of prostate or breast cells. It is concluded that, even with topical use, the systemic risk is significant, and they should be prescribed under rigorous medical evaluation.

Keywords: Topical Testosterone. Testosterone Cream. Hormone Therapy. Androgen Replacement. Skin Safety.

RESUMO

Os cremes e géis de testosterona vêm sendo amplamente utilizados na prática clínica para reposição hormonal e uso sem indicação clínica formal, principalmente entre homens de meia-idade e idosos. Este estudo tem como objetivo revisar sistematicamente as evidências sobre a composição, mecanismos de ação, eficácia, segurança e riscos associados ao uso de formulações tópicas de testosterona, incluindo cremes, géis, pomadas e patch transdérmico. Foram incluídos estudos indexados nas bases PubMed, Scopus e SciELO entre 2010 e 2025. A análise comparativa mostra que os cremes apresentam absorção variável conforme a área aplicada, o veículo e o tempo de contato, enquanto os géis oferecem biodisponibilidade mais estável, e os adesivos transdérmicos mantêm liberação contínua. Embora eficazes na elevação dos níveis séricos de testosterona, esses produtos podem causar eventos adversos, incluindo acne, ginecomastia, alopecia e possível estimulação de células prostáticas ou mamárias. Conclui-se que, mesmo de uso tópico, o risco sistêmico é relevante, devendo ser prescritos sob rigorosa avaliação médica.

Palavras-chave: Testosterona Tópica. Creme de Testosterona. Terapia Hormonal. Reposição Androgênica. Segurança Cutânea.

RESUMEN

Las cremas y geles de testosterona se han utilizado ampliamente en la práctica clínica para la terapia de reemplazo hormonal y para su uso sin indicación clínica formal, principalmente en hombres de mediana edad y ancianos. Este estudio busca revisar sistemáticamente la evidencia sobre la composición, los mecanismos de acción, la eficacia, la seguridad y los riesgos asociados con el uso de formulaciones tópicas de testosterona, incluyendo cremas, geles, ungüentos y parches transdérmicos. Se incluyeron estudios indexados en las bases de datos PubMed, Scopus y SciELO entre 2010 y 2025. El análisis comparativo muestra que

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las cremas presentan una absorción variable según la zona de aplicación, el vehículo y el tiempo de contacto, mientras que los geles ofrecen una biodisponibilidad más estable y los parches transdérmicos mantienen una liberación continua. Si bien son eficaces para elevar los niveles séricos de testosterona, estos productos pueden causar efectos adversos, como acné, ginecomastia, alopecia y posible estimulación de las células prostáticas o mamarias. Se concluye que, incluso con el uso tópico, el riesgo sistémico es significativo y su prescripción debe realizarse bajo rigurosa evaluación médica.

Palabras clave: Testosterona Tópica. Crema de Testosterona. Terapia Hormonal. Reemplazo de Andrógenos. Seguridad Cutánea.

1 INTRODUCTION

The use of topical testosterone has expanded in recent decades, with an increasing variety of formulations in creams, gels, ointments, and transdermal patches (patches). These presentations aim to promote controlled skin absorption, providing stable plasma levels without the need for frequent intramuscular injections (Corona et al., 2023; ANVISA, 2024).

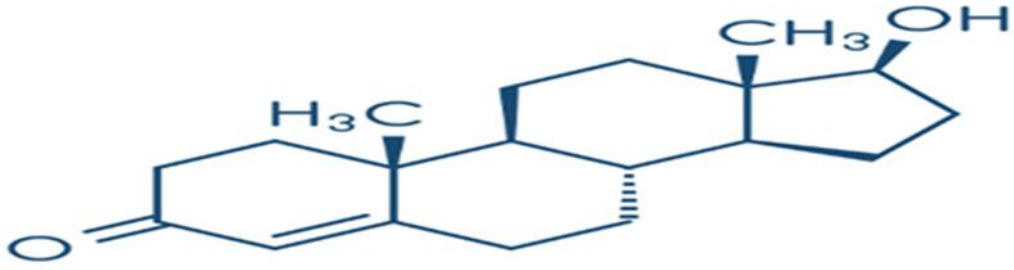
From a pharmacotechnical point of view, the different formulations have distinct characteristics that influence the profile of cutaneous release and absorption of the hormone. The creams consist of oil/water emulsions, associated with rapid absorption and lower oiliness; gels correspond to transparent hydroalcoholic solutions, with rapid evaporation and more uniform absorption, reducing the risk of transfer to third parties (Saad, 2023); ointments have an oily base and a more occlusive action, resulting in prolonged absorption; and transdermal patches (controlled-release skin patches) allow continuous release of testosterone over time (FDA, 2022).

Testosterone is the main human androgenic hormone. In men, it is produced predominantly by Leydig cells (≈95%) and, to a lesser extent, by the adrenal glands; in women, it originates mainly in the ovaries and adrenal cortex, playing a fundamental role in libido, bone mass, and metabolic balance (Bhasin et al., 2018; Saad, 2023).

Chemically, it is a steroid derived from cholesterol, belonging to the C-19 androgens, with a characteristic tetracyclic structure. **Figure 1** illustrates the molecular structure of testosterone, highlighting the 17-hydroxyl group, directly related to its biological activity and lipid solubility, a characteristic that favors absorption by the transdermal route.

Figure 1

Molecular structure of testosterone



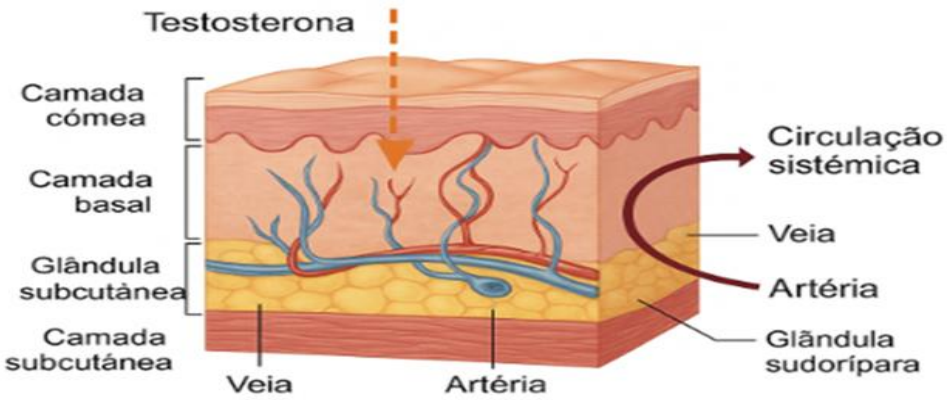
Source: Prepared by the authors based on Bhasin et al. (2018) and Saad (2023).

After endogenous secretion or topical application, testosterone circulates partially bound to sex hormone-binding globulin (SHBG) and albumin, with only the metabolically active fraction remaining free. Its metabolization occurs mainly in the liver, through oxidation and conjugation processes.

In topical preparations, testosterone progressively diffuses through the stratum corneum, the epidermis, and the vascularized dermis until it reaches the systemic circulation. This process of cutaneous penetration is schematized in **Figure 2**, which represents the layers of the skin and the gradient of diffusion of the hormone from the cutaneous surface.

Figure 2

Cutaneous absorption scheme of topical testosterone



Source: Prepared by the authors from Handelsman (2022) and FDA (2024).

In Brazil, the National Health Surveillance Agency (ANVISA) authorizes magistral and industrialized formulations of testosterone under medical prescription, classified as substances subject to special control (class A5) (ANVISA, 2023). In the United States, the Food and Drug Administration (FDA) has approved topical products such as AndroGel®, Testim®, and Axiron® since the early 2000s (FDA, 2024). Recent studies indicate a progressive increase in the use of topical testosterone, especially among middle-aged men, motivated by clinical complaints related to androgen deficiency and quality of life (Mulhall, 2023; Leão, 2024).

In recent decades, the use of topical hormonal formulations has extrapolated the traditional medical context, reaching self-medication practices and applications outside formal clinical indications, which raises concerns about the appropriate indication, safety, and clinical follow-up of these therapies.

Thus, this article aims to offer an updated systematic review that contributes to good clinical practices and to the rational use of topical testosterone in medical practice and in contemporary society. The review seeks to synthesize current scientific evidence and provide subsidies for the critical evaluation of the potential risks associated with the indiscriminate use of these formulations.

2 METHODOLOGY

This is a systematic review of the literature, conducted in accordance with the recommendations of PRISMA 2020.

2.1 SEARCH STRATEGY

Searches were performed in **the PubMed, Scopus, Web of Science and SciELO** databases, using terms in English and Portuguese: *"topical testosterone", "testosterone cream*", *"transdermal testosterone patch*", *"androgen replacement therapy transdermal", "topical testosterone cream"* and *"testosterone plaster".*

The period considered was **2010 to 2025**, including articles in English, Portuguese, and Spanish. The strategy sought to identify recent publications on topical testosterone formulations, both **industrialized** and **magisterial**.

2.2 INCLUSION AND EXCLUSION CRITERIA

The following were included:

- clinical trials;
- pharmacokinetic studies;
- systematic reviews and meta-analyses;
- research involving topical testosterone in cream, gel, ointment or plaster;
- studies with human participants (healthy or hypogonadistic);
- studies that reported bioavailability, Cm_{ax}, Tm_{ax}, AUC, application site, and adverse events.

The following were excluded:

- studies with oral **or** injectable **testosterone**;
- use of anabolic steroids other than testosterone;
- isolated case reports ($n < 5$);
- preclinical experiments in animals without translation to humans.

2.3 SELECTION OF STUDIES

Two independent reviewers performed the initial screening of titles and abstracts. Potentially eligible articles were fully evaluated according to the established criteria. Divergences were resolved by consensus or by a third evaluator.

The selection process followed the steps of **PRISMA 2020**: identification → removal of duplicates → screening → eligibility → final inclusion. The selection flow is represented in figure 3.

Figure 3

Selection flow of studies according to PRISMA 2020

Source: Prepared by the authors based on the PRISMA guidelines (2020).

There was no previous registration of the protocol in international databases for the registration of systematic reviews, such as PROSPERO.

2.4 DATA EXTRACTION

From each included study, the following were extracted:

- author/year and country;
- formulation (cream, gel, ointment or plaster);
- applied dose (mg);
- application site (abdomen, shoulder, scrotum, etc.);
- number of participants;
- duration of use;
- pharmacokinetic parameters (Cm_{ax}, Tm_{ax}, AUC);
- estimated bioavailability;
- adverse effects;

- clinical indication;
- follow-up time.

The variables were organized into **comparative tables**, allowing the observation of pharmacotechnical and pharmacokinetic differences between the formulations (Tables 1 and 2).

Table 1

Comparison of topical testosterone formats

Formato	Tipo de veículo / resumo	Local típico de aplicação	Vantagens principais	Desvantagens principais
Creme	Emulsão óleo/água	Ombros, abdômen, antebraço	Boa cobertura e flexibilidade	Absorção variável, possibilidade de transferência
Gel	Base hidroalcoólica transparente	Ombros, abdômen	Absorção linear, fácil limpeza	Risco de contágio secundário
Pomada	Base oleosa e oclusiva	Áreas de pele espessa	Absorção prolongada	Textura oleosa, menor aceitação cosmética
Emplasto (patch)	Fita adesiva impregnada	Braço, costas, flanco	Liberação contínua (24 h)	Irritação local, custo elevado

Source: Prepared by the authors based on Swerdloff et al. (2000) and Saad (2023).

It is observed that creams have greater versatility, but less predictable bioavailability, while gels have more linear absorption and plasters release the hormone continuously.

Table 2

Selected Pharmacokinetic Data from Clinical Studies

Estudo (autor/ano)	Formato	Dose aplicada	Local de aplicação	Biodisponibilidade / observação relevante	T_{max} (h)
Fooladi et al. (2015)	Creme	5–10 mg	Braço superior (mulheres pós-menopausa)	Dobrar a dose ↑ ~30 % C_avg (PubMed 24845394)	4–6
Iyer et al. (2017)	Creme (escroto)	12,5–50 mg	Pele escrotal	Absorção rápida, $T_{max} \approx 2$ h (Wiley Online Library)	1,9–2,8
Swerdloff et al. (2000)	Gel / patch	50–100 mg gel; patch 5 mg/dia	Ombros/abdômen	Bioabsorção 9–14 %; steady-state 48–72 h (PubMed 11134099)	48–72 *
Davis et al. (2014)	Solução tópica	—	Braço vs axila	Local de aplicação altera farmacocinética (Clinical Therapeutics 2014)	Variável

Source: Prepared by the authors based on Davis et al. (2014), Fooladi et al. (2015), Iyer et al. (2017) and Swerdloff et al. (2000).

2.5 EVALUATION OF METHODOLOGICAL QUALITY

The quality of the studies was assessed using the **Cochrane Risk of Bias 2 (RoB 2)** for controlled trials and a **checklist adapted for pharmacokinetic studies**, including:

- randomization;
- blinding;
- intention-to-treat analysis;
- data integrity;
- full report of the results.

A risk of bias chart was designed to represent the consistency of the evidence.

2.6 SUMMARY OF THE DATA

The synthesis combined **quantitative and qualitative** approaches. Figures and comparative tables were elaborated showing differences between creams, gels, ointments and plasters.

When available, **weighted means of bioavailability and Tm_{ax}** (exploratory meta-analysis) were calculated. Adverse effects and clinical implications were analyzed narratively **and critically**.

2.7 LIMITATIONS

Limitations inherent to the heterogeneity of the included studies are recognized, especially regarding variations in formulation, dose, area of application, and methodological design. There is also **potential publication bias** and paucity of long-term controlled trials capable of assessing **carcinogenic risks** or late effects of topical therapy.

2.8 FUTURE PERSPECTIVES *(OPTIONAL AND RECOMMENDED)*

Current evidence indicates the need for multicenter studies with standardized formulations, comparing bioavailability, oncological safety, and long-term metabolic effects. Randomized controlled trials are also needed to evaluate differences between industrialized and magistral products, as well as the impact of recreational, self-medicated and vulnerable populations.

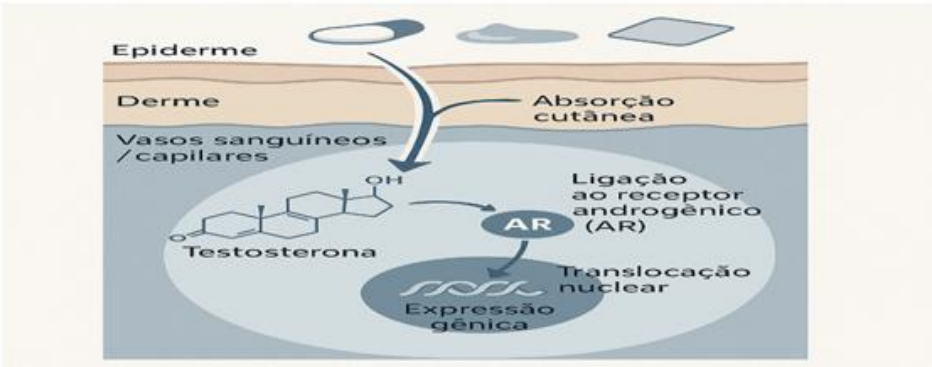
3 RESULTS

3.1 MECHANISM OF ACTION

Topical testosterone crosses the stratum corneum by passive diffusion, reaches the dermal capillaries, and enters the systemic circulation. In the cell interior, it binds to the androgen receptor (AR), forming the hormone-receptor complex, which migrates to the nucleus and activates genes related to muscle mass, libido, bone density, and protein metabolism (Nassar & Swerdloff, 2021; Handelsman, 2022), as shown in Figure 4 illustrative:

Figure 4

Mechanism of action of topical testosterone



Source: Prepared by the authors from Nassar; Swerdloff (2021) and Handelsman (2022).

Testosterone crosses the cutaneous layers (epidermis → dermis → blood vessels), reaches the circulation, and penetrates the target cell, where it binds to the androgen receptor (AR) in the cytoplasm. The hormone-receptor complex is then translocated to the nucleus,

promoting the activation of gene expression responsible for the anabolic and metabolic effects characteristic of androgenic action.

In transdermal formations, the skin acts as a reservoir, releasing the hormone gradually over 24 hours or more, depending on the type of vehicle.

According to the label of AndroGel® 1%, "each application provides circulating levels close to normal and continuous delivery for up to 24 hours after application on intact and dry skin" (FDA, 2024, n.p.).

Topical therapy aims to restore physiological serum levels (~300–1000 ng/dL in healthy men) and correct symptoms associated with testosterone deficiency, such as reduced libido, erectile dysfunction, loss of lean mass, depressed mood, and reduced bone density (Bhasin et al., 2018; Corona et al., 2023).

Skin absorption depends on local factors, such as the type of vehicle, area of application, skin thickness, presence of hair, and vascularization.

Studies show that application to the scrotal skin results in faster absorption, with Tm_{ax} between 1.9 and 2.8 h (Iyer et al., 2017).

At the molecular level, testosterone can be converted to dihydrotestosterone (DHT) by the enzyme 5-α-reductase or aromatized to estradiol, which results in androgenic or estrogenic effects depending on the tissue (Swerdloff et al., 2000; Saad, 2023).

Figure 5

Enzymatic conversion of testosterone into dihydrotestosterone (DHT) and estradiol

Source: Prepared by the authors based on Swerdloff et al. (2000), Bhasin et al. (2018) and Handelsman (2022).

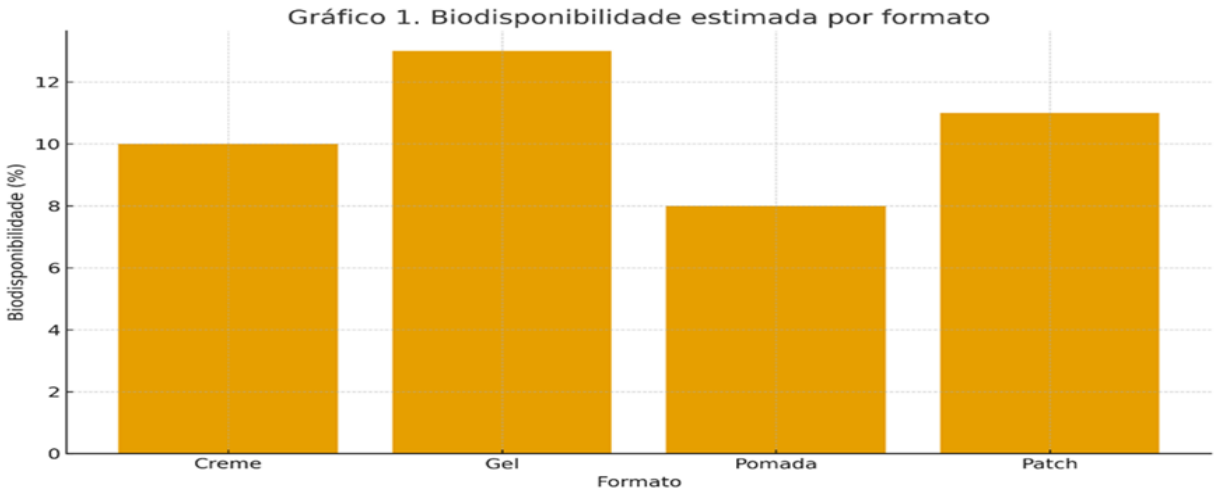
3.2 COMPARISON OF FORMULATIONS: BIOAVAILABILITY

Bioavailability varies by pharmacotechnical vehicle. Gels show more stable absorption (~13%), followed by transdermal patches (~11%), while creams and ointments show greater inter-individual variation (~10% and ~8%).

Figure **6** presents the comparison between the main vehicles used in topical testosterone formulations.

Figure 6

Estimated bioavailability by format of topical testosterone



Source: Prepared by the authors based on Swerdloff et al. (2000); Handelsman (2022); Saad (2023).

It can be seen in Figure 1 that:

- gels exhibit more linear and predictable absorption (≈ 13%)
- transdermal patch ≈ 11%
- creams ≈ 10%
- Ointments ≈ 8%

These data reinforce that the choice of vehicle directly interferes with the amount of bioavailable testosterone and the serum stability of the hormone (Swerdloff et al., 2000; Handelsman, 2022; Saad, 2023).

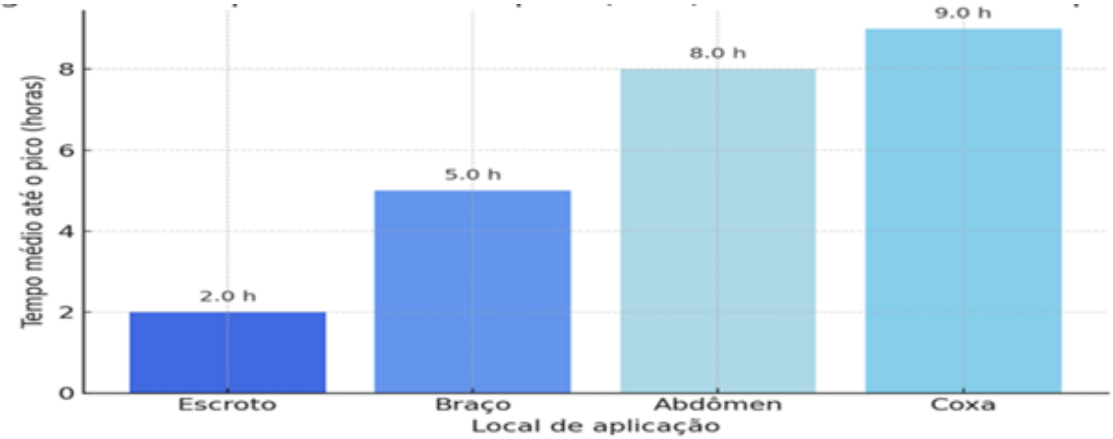
3.3 INFLUENCE OF THE ANATOMICAL SITE ON Tm_{ax}

The site of application significantly affects the time to peak serum. Scrotal application produces rapid Tm_{ax} (~2 hours), while arm and abdomen peak between 5–8 hours; the thigh, around 9 o'clock.

Figure 7 shows the impact of the anatomical site on absorption kinetics.

Figure 7

Mean time to peak (Tm_{ax}) according to application site



Source: Prepared by the authors from Iyer et al. (2017); Handelsman (2022); Saad (2023)

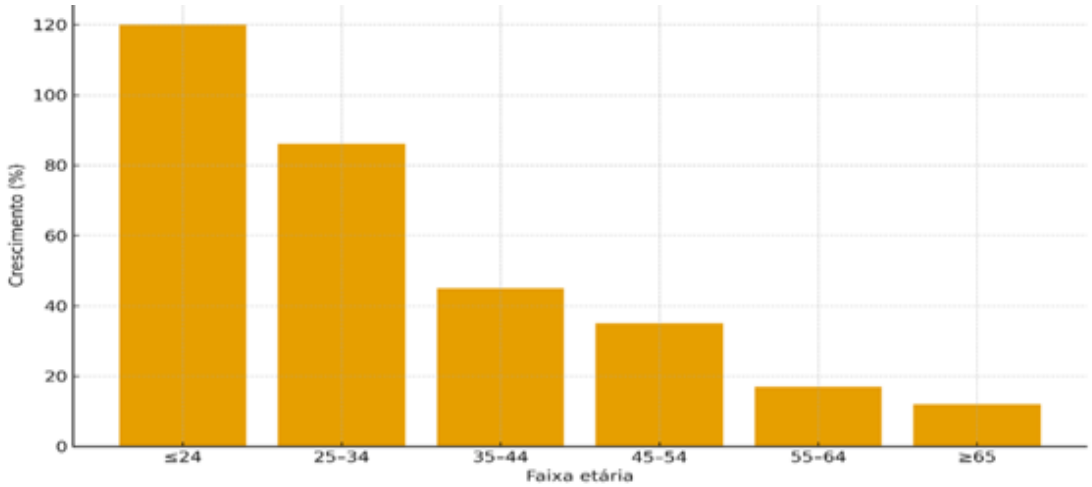
The scrotal skin is more rapidly absorbed, with a mean time to serum peak (Tm_{ax}) of around 2 hours, attributed to high vascularization and lower epidermal thickness. In comparison, applications performed in regions such as the arm and abdomen result in Tm_{ax} values between 5 and 8 hours, while application in the thigh is associated with a later serum peak, approximately 9 hours. These differences reinforce the need to individualize the area of application according to the therapeutic objective and the patient's skin tolerance.

3.4 USAGE GROWTH: DEMOFIGUREIC PROFILE

The use of topical testosterone has increased sharply, especially among young individuals. As illustrated in Figure 8, the highest percentage increase occurred among users aged 24 years or younger (+120%) and in the age group of 25 to 34 years (+86%), a pattern compatible with non-therapeutic use and self-medication. Data derived from U.S. and Canadian epidemiological reports compiled between 2018 and 2022.

Figure 8

Percentage growth of testosterone use by age group (2018–2022)



Source: Prepared by the authors based on North American and Canadian epidemiological reports (2018–2022).

A more pronounced growth in the use of topical testosterone was observed among individuals aged 24 years and under, with an estimated increase of approximately 120%, followed by the age group of 25 to 34 years, which showed an increase of about 86%. In contrast, individuals over the age of 55 exhibited proportionally more modest increases.

From a geoFigureical point of view, the United States and Canada concentrate the highest rates of topical testosterone consumption. It is estimated that approximately 25% of users obtain the product without a regular medical prescription, characterizing self-medication.

3.5 INTEGRATED SYNTHESIS OF FINDINGS

The main findings of this study, bringing together the pharmacological, clinical, and demoFigureic dimensions of topical testosterone therapy, are summarized in Table 4.

Table 4

Summary of the main findings

Item	Resultado principal
Mecanismo de ação	Ligação ao receptor androgênico → expressão gênica → absorção transepidérmica → conversão a DHT/estradiol.
Proposta de uso	Reposição em pacientes com hipogonadismo; aplicação diária em pele limpa e seca.
Frequência típica	Uma vez ao dia (géis, patches e cremes).
Duração	Contínua enquanto houver indicação e ausência de efeitos adversos; estudos até 180 dias.
Exames de controle	Testosterona total, LH/FSH, hematócrito, PSA, função hepática, perfil lipídico.
Idades principais de uso	40–54 anos (uso estético ou clínico leve); 55–69 anos (reposição formal); ≥ 70 anos (uso cauteloso).
Prescrição vs uso leigo	Requer receita médica; há uso informal sem monitoramento.
Países / mercado principal	EUA e Canadá, co[illegible]escimento contínuo; dados brasileiros ainda limitados.

Source: Bhasin et al. (2018), AUA (2022), US Pharmacist (2022), Corona et al. (2023), FDA (2024).

4 DISCUSSION

4.1 CLINICAL USE OF TOPICAL TESTOSTERONE

The main clinical indication for topical testosterone is hormone replacement therapy in men with primary or secondary hypogonadism, properly diagnosed based on clinical and laboratory criteria, as established by international guidelines (Bhasin et al., 2018; AUA, 2022).

Although the literature predominantly describes the use of gel formulations and transdermal patches, topical creams follow similar pharmacological principles, differing mainly by vehicle, absorption variability, and dosage flexibility. Pharmacokinetic studies demonstrate that daily topical testosterone administration is able to maintain relatively stable serum levels over prolonged treatment periods, with consistent hormonal stability data over 30, 90, and even 180 days of continuous use (Corona et al., 2023).

4.2 PRESCRIPTION PROFILE AND MEDICAL SPECIALTIES

The use of topical testosterone, particularly in gel formulations and in magisterial cream preparations, has been most frequently prescribed by physicians specializing in Endocrinology and Urology. In specific contexts, its use also extends to the practice of

gynecologists, especially in the management of postmenopausal women with complaints of sexual dysfunction, and to dermatologists involved in hormonal therapies. However, recent reviews point to a significant increase in prescriptions made by general practitioners and aesthetic clinics, especially in Brazil and the United States, often without the adoption of standardized laboratory criteria for the diagnosis of hypogonadism (AUA, 2022; Corona et al., 2023).

Data from a North American survey published in JAMA Internal Medicine indicate that approximately 25–30% of testosterone prescriptions were not preceded by adequate serum hormone dosage, and that a similar proportion of users did not return for clinical or laboratory follow-up after the start of therapy, evidencing relevant weaknesses in the prescription and monitoring process (JAMA Internal Medicine, 2020; AUA, 2022).

In specialized practice, magisterial cream preparations tend to be used when greater dosage flexibility and individualization of the dose and area of application are sought. On the other hand, industrialized gel formulations, such as AndroGel® and Testim®, are preferred in more stable therapeutic regimens, due to their more predictable bioavailability and lower inter-individual variability. Classic and contemporary pharmacokinetic studies confirm that transdermal gels and patches offer more linear absorption and more consistent serum levels, while creams and ointments have greater interindividual dispersion of response (Swerdloff et al., 2000; Iyer et al., 2017).

4.3 USE IN THE ELDERLY AND ASSOCIATED RISKS

In the elderly, the prescription of topical testosterone is usually motivated by symptoms of fatigue, loss of libido, decreased muscle strength and bone density. However, replacement in advanced age groups requires extra caution, since aging is naturally associated with a higher prevalence of benign prostatic hyperplasia and latent prostate cancer, greater cardiovascular susceptibility, and metabolic alterations that interfere with hormone clearance (Bhasin et al., 2018; AUA, 2022; Handelsman, 2022).

There is theoretical evidence that androgen stimulation can accelerate the progression of preneoplastic prostate cells, although meta-analyses (Frontiers in Endocrinology, 2023; PMC 8596965, 2023) do not indicate a statistically significant increase in the risk of prostate cancer with replacement therapy.

Thus, in men over 60 years of age, prior prostate evaluation (PSA, digital rectal examination, and prostate magnetic resonance imaging) and biannual reassessment are recommended, according to AUA (2022) guidelines.

4.4 FEMALE USE: INDICATIONS, RISKS AND PRECAUTIONS

Among women, topical testosterone use has been indicated primarily for the management of hypoactive sexual dysfunction in the postmenopausal period, for decreased libido associated with aromatase inhibitor therapy, and, in specific contexts, for improved muscle tone and general well-being. These indications stem from the recognition of the physiological role of androgens in female sexual function and in the maintenance of lean mass (Bhasin et al., 2018; AUA, 2022).

Recent clinical studies report that low doses of testosterone gel, usually between 2 and 3 mg/day, are able to improve sexual function in postmenopausal women, without promoting a significant increase in serum estradiol levels, suggesting a relatively stable hormonal profile when used in a controlled regime (European Journal of Breast Health, 2023; BioMed Central, 2024).

However, data from large observational cohorts indicate that chronically elevated androgen levels in women are associated with increased risk of breast cancer, with odds ratios of approximately 1.5 in the top quartiles of total testosterone. This finding reinforces the need for caution in the indication and follow-up of therapy, especially in higher-risk populations (JAMA Network Open, 2023; European Journal of Breast Health, 2023).

4.5 OVER-THE-COUNTER USE AND SELF-MEDICATION

Self-medication with topical testosterone is a growing phenomenon in different population contexts. North American and Brazilian reviews estimate that approximately 20 to 25% of men and about 10% of women who use testosterone do so without a regular medical prescription, often outside of appropriate diagnostic and clinical monitoring protocols (AUA, 2022; PMC 8596965, 2023; Brazilian Journal of Endocrinology and Metabology, 2024).

There are even reports of self-prescription among physicians and other health professionals, motivated by nonspecific complaints of fatigue, performance, or aesthetic goals, often without systematic monitoring of essential parameters, such as PSA, blood count, and liver function. This behavior suggests a trivialization of hormone use even among individuals with technical training, which increases the risk of avoidable adverse events (AUA, 2022; Frontiers in Public Health, 2023).

Qualitative studies indicate that some of these professionals recognize the risks associated with testosterone therapy, but tend to underestimate the real magnitude of the carcinogenic and cardiovascular potential, configuring a phenomenon described as therapeutic cognitive dissonance, in which knowledge of the risk does not translate into preventive conducts proportional to its severity (Frontiers in Public Health, 2023).

4.6 USE IN GYMS, POPULATION PREVALENCE AND SPORTS PRACTICES

4.6.1 Prevalence and characteristics of use in gyms

The non-medical use of testosterone and anabolic steroids in gym settings is widely documented in the literature, although there are still limited data specifically on the employment of topical formulations. Population studies indicate that between 6% and 12% of regular gym-goers use testosterone or anabolic derivatives, often without medical supervision and without adequate laboratory monitoring, which characterizes a relevant health risk scenario (Revista Brasileira de Medicina do Esporte, 2023; Frontiers in Public Health, 2023).

In this context, topical testosterone is often perceived by users as a "milder" or "less dangerous" alternative to injectable formulations. However, available evidence indicates that, when used irregularly, manipulated, or without clinical monitoring, this route of administration may carry systemic risks comparable to those observed with other hormonal presentations (Handelsman, 2022; Brazilian Journal of Endocrinology and Metabology., 2024).

Self-medication is particularly prevalent among individuals aged between 25 and 40 years, an age group characterized by greater involvement with sports practices and greater susceptibility to aesthetic discourses of "acceleration of results" and body optimization, a phenomenon already described in recent reviews on the non-therapeutic use of testosterone (AUA, 2022; Frontiers in Public Health, 2023).

4.6.2 Recreational and sports use: modalities, patterns and risks

The recreational use of testosterone is a growing practice in gym environments and in different sports. Recent data indicate an approximate prevalence of 15–20% among men who practice bodybuilding and 2–3% among women, reflecting a predominantly non-therapeutic consumption pattern and often disconnected from regular medical follow-up (Revista Brasileira de Medicina do Esporte, 2023).

Among men, injectable formulations predominate, usually associated with muscle mass gain and body fat reduction objectives. Among women, the use tends to occur more discreetly, with a higher frequency of topical gels and creams, perceived as "less aggressive" alternatives, although they present hormonal and metabolic risks similar to those observed with other routes of administration (Revista Brasileira de Endocrinologia e Metabologia, 2024).

Recent reports also describe the use of testosterone creams by athletes in aerobic and collective modalities, such as running, athletics and soccer, under the allegation of improved performance, accelerated muscle recovery and increased physical vigor. However, there is no robust scientific evidence to support the relevant ergogenic benefit of testosterone

in these modalities, particularly when used outside of formal clinical indications (Handelsman, 2022; Frontiers in Public Health, 2023).

On the contrary, the literature points to significant risks associated with the recreational use of testosterone, including suppression of the hypothalamic–pituitary–gonadal axis, with reduced endogenous production of the hormone, hepatotoxicity, especially in prolonged or combined regimens, dermatological disorders, virilization in women, potentially persistent hormonal imbalances, and increased cardiovascular risk in chronic users (Handelsman, 2022; Frontiers in Public Health, 2023).

Among older individuals active in gyms, recreational use has been motivated by the idea of "hormonal rejuvenation". This group, however, has greater prostate and cardiovascular vulnerability, which makes close monitoring essential when there is a formal clinical indication and establishes an absolute contraindication for recreational or non-therapeutic use of testosterone in this age group (AUA, 2022; Bhasin et al., 2018).

4.7 ONCOLOGICAL RISKS AND CLINICAL PRECAUTIONS

4.7.1 Pathophysiological foundations of oncological risk

The figures and Figures presented above visually reinforce this context: Figure 5 illustrates the mechanism of hormonal conversion of testosterone into DHT and estradiol, while Figure 3 demonstrates the significant growth in use by age group, especially among young men and in aesthetic contexts. (Swerdloff et al., 2000; Handelsman, 2022; JAMA Network Open, 2023).

From the pathophysiological point of view, the potential carcinogenic risk of testosterone is related to the stimulation of the androgen receptor and the activation of hormone-sensitive tissues. DHT exerts a significant proliferative action on the prostatic epithelium, while estradiol, resulting from the peripheral aromatization of testosterone, participates in the proliferative regulation of breast tissue, especially in postmenopausal women (Bhasin et al., 2018; Handelsman, 2022).

4.7.2 Clinical Evidence in Testosterone Replacement Therapy

Despite this theoretical basis, recent systematic reviews and meta-analyses demonstrate that, when used at therapeutic levels and under appropriate medical supervision, testosterone replacement therapy (TRT**) is not associated with a statistically significant increase in the incidence of prostate cancer** (Frontiers in Endocrinology, 2023; PMC 8596965, 2023). These data support the relative safety of testosterone in well-indicated clinical settings.

4.7.3 Non-therapeutic use and elevation of potential risk

In contrast, the literature clearly distinguishes between monitored therapeutic use and uncontrolled use. Chronically high testosterone levels, observed in situations of self-medication, aesthetic use, or inappropriate manipulation of doses, can modify the prostate and breast microenvironment, favoring cell proliferation in previously susceptible tissues or with subclinical alterations (Frontiers in Public Health, 2023; Brazilian Journal of Endocrinology and Metabology, 2024).

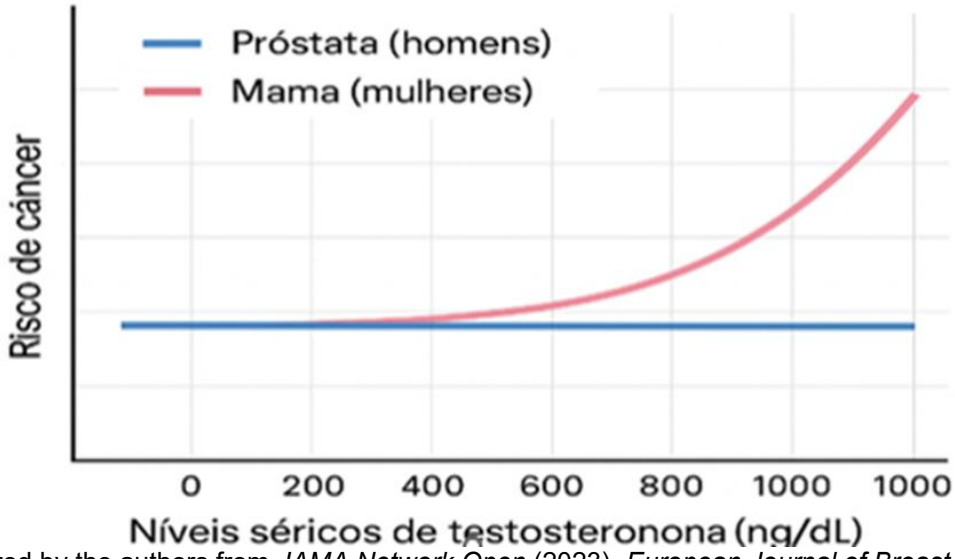
This risk is increased in individuals with predisposing factors, such as a family history of hormone-sensitive cancer, obesity, a condition associated with increased aromatase activity, and the absence of periodic clinical and laboratory monitoring. In these circumstances, increased peripheral conversion of testosterone to estradiol may contribute to unwanted proliferative stimulation, particularly in female breast tissue (European Journal of Breast Health, 2023; JAMA Network Open, 2023).

4.7.4 Epidemiological evidence in prostate and breast

The relationship between serum testosterone levels and cancer risk is summarized **in Figure 9**, in which there is no direct correlation between therapeutic testosterone levels and prostate cancer, but a slight trend towards increased risk of breast cancer in postmenopausal women in the upper quartiles of total serum testosterone (see Figure 7) (European Journal of Breast Health, 2023; BioMed Central, 2024).

Figure 9

Relationship between serum testosterone levels and risk of prostate (men) and breast (women) cancer

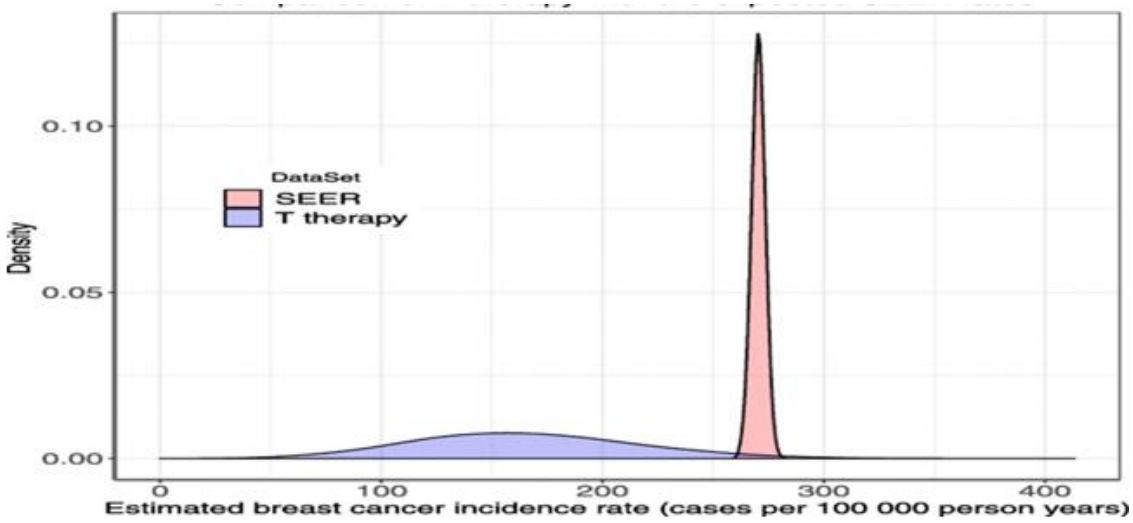


Source: Prepared by the authors from *JAMA Network Open* (2023), *European Journal of Breast Health* (2023) and *BioMed Central* (2024).

On the other hand, comparative cohort studies demonstrate that women using topical testosterone alone, at controlled doses and under medical monitoring, **do not have an increased incidence of breast cancer** when compared to the rates expected in the general population, as evidenced **in Figure 10** (European Journal of Breast Health, 2023).

Figure 10

Sample distribution of estimated breast cancer incidence rates in women on testosterone therapy compared to expected rates (SEER).



Source: Adapted from *European Journal of Breast Health*, 2023.

4.7.5 Clinical and ethical implications

In an integrated way, the available data indicate that the oncological risk profile associated with topical testosterone is **context-dependent, tissue-specific, and multifactorial**, being more influenced by age, obesity, family history, dose, and exposure time than by the topical route alone (Bhasin et al., 2018; Handelsman, 2022).

Thus, topical testosterone can be considered an effective and relatively safe therapeutic tool when indicated in patients with duly confirmed hypogonadism, prescribed by a qualified physician, and accompanied by periodic clinical and laboratory monitoring, in accordance with the guidelines of medical societies and the regulations of the Federal Council of Medicine (CFM, 2018; AUA, 2022).

On the other hand, aesthetic, recreational, or self-medicated use is associated with a higher risk of adverse events and may contribute to the progression of latent neoplasms, especially in elderly men and postmenopausal women. The scarcity of long-term studies involving magisterial formulations reinforces the need for greater regulatory rigor and additional clinical investigations on cancer safety (Frontiers in Public Health, 2023; Brazilian Journal of Endocrinology and Metabology, 2024).

4.8 RISK IN PATIENTS WITH A HISTORY OF PROSTATE OR BREAST CANCER

The scientific literature indicates that the prescription or use of topical testosterone in individuals with a history of prostate or breast cancer should be viewed with extreme caution, especially when performed outside of strictly monitored protocols, since it may be associated with high clinical risk and constitute potentially avoidable iatrogenic events (Bhasin et al., 2018; AUA, 2022).

A recent cohort study involving men undergoing radical prostatectomy evaluated the safety of testosterone replacement therapy in a postoperative setting and demonstrated no statistically significant increase in tumor recurrence among those who received testosterone under strictly controlled protocols (hazard ratio ≈ 1.07; p = 0.43) (PMC 11220914, 2024). These findings suggest that, in carefully selected patients, the therapy can be used relatively safely.

However, it is essential to emphasize that these results derive from highly selected populations, composed of individuals with low-risk tumors, negative surgical margins, persistently undetectable PSA levels, and absence of unfavorable prognostic factors. Thus, the data do not authorize extrapolation to scenarios of unrestricted, manipulated, aesthetic, or self-medicated use, which do not reproduce the rigorous conditions of research protocols and represent a methodologically inappropriate and clinically risky approach (AUA, 2022; Frontiers in Endocrinology, 2023).

From the pathophysiological point of view, androgen exposure can create a hormonal microenvironment favorable to tumor reactivation, either by the reexpression of androgen receptors in previously neoplastic tissues, or by the peripheral aromatization of testosterone into estradiol, particularly in individuals with obesity or metabolic syndrome (Swerdloff et al., 2000; Traish, 2022).

Thus, the introduction of testosterone replacement therapy in survivors of hormone-sensitive cancer without specialized oncological follow-up should be considered a high-risk approach with low clinical rationality. In these cases, the therapeutic decision should involve interdisciplinary evaluation, shared discussion of risks and benefits, and formal documentation of informed consent, in line with current ethical and legal guidelines (CFM, 2018; AUA, 2022).

In addition, the relationship between topical testosterone use and the risk of prostatic recurrence should be interpreted in light of the epidemiology of prostate cancer. As shown in **Figure 11**, based on data from North American cancer surveillance (SEER, 2023), the incidence of the disease increases exponentially from the age of 55, reaching its peak

between 70 and 74 years of age, the age group that concentrates the highest proportion of men undergoing testosterone replacement therapy for hypogonadism.

This age overlap between the highest incidence of prostate cancer and the population eligible for hormone replacement reinforces the need for rigorous clinical and laboratory surveillance. Even in contexts of therapeutic and supervised use, individuals with a previous prostate history may present an increased relative risk, requiring continuous follow-up with serial PSA measurement, specialized clinical evaluation, and careful risk-benefit analysis.

Figure 9

Age distribution of prostate cancer incidence

Source: Adapted from epidemiological data from North American cancer surveillance (SEER, 2023).

It is observed that the incidence rate exceeds 850 cases per 100,000 men-year between 70 and 74 years of age, followed by a progressive decline in the older age groups, a phenomenon attributed both to the increase in overall mortality and to the detection bias in very elderly populations.

5 CONCLUSION

Topical testosterone, in cream, gel or transdermal patch formulations, has established itself as an effective pharmacological alternative for androgen replacement, allowing more stable serum levels and greater convenience of use when compared to parenteral routes. Its adequate clinical application represents an important therapeutic tool in the management of male hypogonadism and in selected indications in the female context.

However, the safety of this therapy depends directly on careful medical indication, dosage standardization, and continuous clinical and laboratory monitoring. The available

evidence indicates that, at therapeutic doses and under appropriate medical supervision, topical testosterone is not associated with a proven increase in cancer risk. On the other hand, aesthetic use, manipulated without standardization or self-medicated configures a high risk scenario, especially in individuals with a history of hormone-sensitive neoplasms, such as prostate or breast cancer.

It is critical to recognize that the absence of evidence of harm does not equate to definitive evidence of safety. Thus, the use of topical testosterone should follow well-established clinical protocols, with informed consent and strict surveillance, especially in populations considered vulnerable, including the elderly, postmenopausal women, and cancer patients in remission.

From an ethical and professional point of view, prescription outside the indications supported by the scientific literature and the guidelines of medical societies exposes the patient to unnecessary risks and compromises good clinical practice, reinforcing the need for greater medical responsibility and health inspection.

Finally, relevant gaps persist in the literature, especially with regard to long-term studies and the safety assessment of magistral formulations. These aspects highlight the need for multicentric, prospective, and controlled research, capable of defining the oncological efficacy and safety profile of topical testosterone with greater precision.

6 MANDATORY DECLARATIONS

6.1 CONFLICTS OF INTEREST

The authors declare that they have no financial, commercial, institutional, or personal conflicts of interest related to the content of this manuscript.

6.2 FUNDING

This study did not receive financial support from funding agencies, public or private institutions, or non-profit organizations. The work was developed without external funding.

6.3 ETHICAL RESPONSIBILITY

This is a systematic review of the literature, without primary data collection and without direct involvement of humans or animals. Thus, it was not necessary to submit to the Research Ethics Committee, in accordance with CNS Resolution No. 510/2016.

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