Online: https://jurnal.fk.uisu.ac.id/index.php/stm

Jurnal Kedokteran STM (Sains dan Teknologi Medik)

ISSN 2614-610X (Print) | ISSN 2614-8218 (Online)

J. Ked STM
(Sains dan Teknologi Medik)

Sistematik Review

MODULASI NEUROENDOKRIN TERHADAP FREKUENSI EJAKULASI: TINJAUAN SISTEMATIS TENTANG KINETIKA ANDROGEN, SENSITIVITAS RESEPTOR ANDROGEN, DAN IMPLIKASI METABOLIK

NEUROENDOCRINE MODULATIONS OF EJACULATORY FREQUENCY: A SYSTEMATIC REVIEW OF ANDROGEN KINETICS, ANDROGEN RECEPTOR SENSITIVITY, AND METABOLIC IMPLICATIONS

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Histori Artikel

Diterima:
27 Februari 2026

Revisi:
16 April 2026

Terbit:
01 Juli 2026

Kata Kunci

Ejakulasi, Reseptor Androgen, Retensi Semen, Zinc, Aksis HPG

A B S T R A K

Tinjauan sistematis ini bertujuan untuk mengevaluasi secara kritis dampak fisiologis dari pantang ejakulasi (penahanan semen) dibandingkan dengan ejakulasi yang sering terhadap sumbu Hipotalamus-Hipofisis-Gonad (HPG), kadar testosteron serum, dan kepadatan reseptor androgen (AR). Tinjauan sistematis ini dilakukan sesuai dengan pedoman PRISMA 2020 dan terdaftar di PROSPERO (CRD42024336252). Pencarian elektronik dilakukan di tujuh basis data: PubMed/MEDLINE, Scopus, EMBASE, Google Scholar, ScienceDirect, Cochrane Library, dan Web of Science, dari awal hingga Desember 2024. Literatur abu-abu juga dicari melalui OpenGrey dan ProQuest Dissertations. Dua peninjau independen menyaring studi dan mengekstrak data. Risiko bias dievaluasi menggunakan RoB 2 untuk uji klinis terkontrol acak (RCT), Skala Newcastle-Ottawa untuk studi observasional, dan SYRCLE untuk studi pada hewan. Lima belas studi memenuhi kriteria inklusi. Abstinensi jangka pendek (7 hari) menyebabkan lonjakan testosteron di atas fisiologis yang sementara (~145% dari baseline), yang kembali ke homeostasis setelahnya. Kepuasan seksual secara reversibel menurunkan ekspresi reseptor androgen di area preoptik medial hipotalamus (MPOA), dengan pemulihan dalam 72 jam. Ejakulasi yang sering hanya terkait dengan penurunan sintesis testosteron pada defisiensi seng diet. Ejakulasi yang sering (≥21 kali per bulan) dikaitkan dengan penurunan risiko kanker prostat sebesar 20%. Hubungan antara ejakulasi dan status androgen bersifat biphasik dan homeostasis. Pantang seksual jangka pendek secara berkala dapat meningkatkan sensitivitas jalur neuroendokrin, sementara ejakulasi secara teratur mendukung kesehatan prostat. Para tenaga medis sebaiknya mempertimbangkan temuan ini saat memberikan konseling kepada pasien mengenai kesehatan seksual dan hormonal.

Keywords

Ejaculation, Androgen Receptors, Semen Retention, Zinc, HPG Axis

A B S T R A C T

This systematic review aims to critically evaluate the physiological impacts of ejaculatory abstinence (semen retention) versus frequent ejaculation on the Hypothalamic-Pituitary-Gonadal (HPG) axis, serum testosterone levels, and androgen receptor (AR) density. A systematic review was conducted following PRISMA 2020 guidelines and registered in PROSPERO (CRD42024336252). Electronic searches were performed across seven databases: PubMed/MEDLINE, Scopus, EMBASE, Google Scholar, ScienceDirect, Cochrane Library, and Web of Science, from inception to December 2024. Grey literature was also searched via OpenGrey and ProQuest Dissertations. Two independent reviewers screened studies and extracted data. Risk of bias was assessed using RoB 2 for RCTs, Newcastle-Ottawa Scale for observational studies, and SYRCLE for animal studies. Fifteen studies met the inclusion criteria.

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Short-term abstinence (7 days) induces a transient supraphysiological testosterone spike (~145% of baseline), which returns to homeostasis thereafter. Sexual satiety reversibly downregulates androgen receptors in the hypothalamic medial preoptic area (MPOA), with recovery within 72 hours. Frequent ejaculation correlates with reduced testosterone synthesis only in dietary zinc deficiency. Frequent ejaculation (≥21/month) was associated with a 20% reduction in prostate cancer risk. The relationship between ejaculation and androgen status is biphasic and homeostatic. Periodic short-term abstinence may resensitize neuroendocrine pathways, whereas regular ejaculation supports prostate health. Clinicians should consider these findings when counseling patients regarding sexual and hormonal health.

DOI: https://doi.org/10.30743/stm.v9i2.1201

INTRODUCTION

The physiological relationship between the frequency of ejaculation and male endocrine health remains a subject of significant debate within urological medicine and sports physiology. Historically, cultural traditions have posited that semen conservation preserves vital energy — a concept revitalized by online communities advocating for "semen retention" to enhance virility and athletic performance.[1] However, the medical consensus views ejaculation as a benign or beneficial biological function, particularly regarding prostate health. The disparity between anecdotal claims of supernormal physiological states achieved through abstinence and standard clinical advice necessitates a rigorous review of underlying neuroendocrine mechanisms.[2]

Central to this investigation is the homeostatic regulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis. Testosterone synthesis in Leydig cells is regulated by Luteinizing Hormone (LH), subject to negative feedback loops influenced by circulating androgens and estrogens.[3] A critical question is whether abstinence disrupts this feedback loop to create an anabolic environment, or whether the body downregulates production to maintain equilibrium. Furthermore, the metabolic cost of seminal fluid — rich in fructose, prostaglandins, and zinc — suggests that frequent ejaculation could tax nutritional reserves in specific dietary contexts.[4]

This systematic review synthesizes data across three physiological domains: (1) the temporal kinetics of serum testosterone during abstinence; (2) the neuroplasticity of androgen receptors following sexual satiety; and (3) the interplay between ejaculation, zinc status, and anabolic potential.

METHODS

Protocol and Registration

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) prior to commencement of the search (Registration number: CRD42024336252). The full protocol, including predefined eligibility criteria, search strategy, and analysis plan, is publicly available at www.crd.york.ac.uk/prospero. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[5] The AMSTAR 2 compliance summary is presented in Table 4.

Eligibility Criteria

Studies were included based on the following criteria:

1. Original research articles, systematic reviews, and meta-analyses published in peer-reviewed journals;
2. Studies investigating the relationship between ejaculation frequency and hormonal parameters (testosterone, LH, FSH, prolactin);
3. Studies examining androgen receptor expression or sensitivity in relation to sexual activity;
4. Studies evaluating zinc status and reproductive hormone interactions;

5. Human studies or animal models with translational relevance to human physiology; and
6. Articles published in English language.

Exclusion criteria included:

1. Case reports and case series with fewer than 10 participants;
2. Conference abstracts without full-text availability;
3. Studies focusing exclusively on female reproductive physiology;
4. Studies investigating pharmaceutical interventions for sexual dysfunction without relevance to natural ejaculatory frequency; and
5. Articles with insufficient methodological quality as determined by risk of bias assessment.

Information Sources

A comprehensive electronic search was conducted across seven major databases: PubMed/MEDLINE, Scopus, EMBASE, Google Scholar, ScienceDirect, Cochrane Library, and Web of Science. The search covered publications from database inception through December 2024. Grey literature was identified through OpenGrey (www.opengrey.eu), ProQuest Dissertations and Theses, and ClinicalTrials.gov (for registered but unpublished studies). Additionally, reference lists of included articles were manually screened (backward citation searching), and forward citation searching was performed using Google Scholar to identify studies citing key publications.

Search Strategy

The search strategy was developed in consultation with a medical librarian and used a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The full PubMed search string was:

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("ejaculation"[MeSH] OR "ejaculatory frequency" OR "semen retention" OR "sexual abstinence"[MeSH] OR "coitus"[MeSH] OR "orgasm"[MeSH]) AND ("testosterone"[MeSH] OR "androgen"[MeSH] OR "gonadal hormones"[MeSH] OR "HPG axis" OR "hypothalamic-pituitary-gonadal") AND ("receptors, androgen"[MeSH] OR "AR sensitivity" OR "neuroendocrine" OR "neuroplasticity"[MeSH]) AND ("zinc"[MeSH] OR "micronutrient" OR "trace element"[MeSH])
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Equivalent search strategies were developed for all other databases using database-specific controlled vocabulary. The complete search strategies for all seven databases are provided in Supplementary Material 1. The searches were conducted between January 10 and January 15, 2025.

Selection Process

All retrieved records were imported into Rayyan systematic review software (Ouzzani et al., 2016) for deduplication and blinded screening. Two independent reviewers (MAP and RZD) screened all titles and abstracts against predefined eligibility criteria without being aware of each other's decisions. Full-text articles were retrieved for studies meeting inclusion criteria or where eligibility was uncertain. Both reviewers independently assessed full-text eligibility. Disagreements were resolved through discussion and consensus; a pre-specified third

reviewer (independent biostatistician) was available for arbitration. Inter-rater reliability at title/abstract screening was assessed using Cohen's kappa (κ = 0.83, indicating strong agreement). The screening and selection process is documented in the PRISMA 2020 flow diagram (Figure 1).

Data Collection Process

A standardized data extraction form was developed a priori and piloted on five randomly selected studies; minor revisions were made to improve clarity before full extraction. Two reviewers (MAP and RZD) independently extracted data from all included studies using the finalized form. Extracted items included: study characteristics (author, year, design, country, funding source), participant characteristics (age range, health status, sample size), intervention/exposure details (abstinence duration, ejaculation frequency), outcome measures (testosterone levels, androgen receptor expression, zinc parameters, reproductive outcomes), and key findings with associated statistics. Any discrepancies in data extraction were resolved through discussion; unresolved discrepancies were adjudicated by the third reviewer. Raw data and the completed extraction forms are available upon request from the corresponding author.

Risk of Bias Assessment

The risk of bias in included primary studies was assessed independently by two reviewers using standard, validated tools appropriate to each study design:

- Randomized controlled trials: Cochrane Risk of Bias Tool 2.0 (RoB 2), assessing five domains — randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.
- Observational (cohort and case-control) studies: Newcastle-Ottawa Scale (NOS), evaluating selection, comparability, and outcome/exposure domains (maximum 9 stars); scores of 7–9 = high quality, 5–6 = moderate, <5 = low quality.
- Animal studies: SYRCLE Risk of Bias Tool, assessing domains including sequence generation, baseline characteristics, allocation concealment, random housing, blinding, outcome assessment, incomplete data, and selective reporting.

Studies were categorized as low, moderate (some concerns), or high risk of bias based on overall domain assessment. Results are presented in Table 2. Disagreements between reviewers were resolved by discussion.

Synthesis Methods

A narrative synthesis approach was employed due to the substantial clinical and methodological heterogeneity across included studies (diverse designs, populations, interventions, and outcome measures), which precluded quantitative pooling (meta-analysis). Studies were grouped by thematic areas: (1) hormonal kinetics and testosterone fluctuations; (2) androgen receptor neurobiology; and (3) zinc and metabolic interactions. Key findings were summarized descriptively, with attention to direction, magnitude, and statistical significance

of effects. Where available, quantitative data were reported as mean differences or percentage changes with 95% confidence intervals.

To assess the robustness of findings, a sensitivity analysis was planned a priori, limited to studies rated as low risk of bias (Table 2). Additionally, the potential impact of publication bias on the overall conclusions is discussed qualitatively in the Publication Bias section below.

Heterogeneity Assessment

Given that a formal meta-analysis was not conducted, statistical heterogeneity (I^2 statistic) was not calculable. Instead, clinical heterogeneity was assessed qualitatively by examining variability in study populations (healthy men vs. athletes vs. animal models), intervention definitions (duration of abstinence, frequency of ejaculation), and outcome measurement methods (immunoassay type, timing of blood collection). The primary sources of heterogeneity were identified as: (a) use of animal vs. human models; (b) variable abstinence durations (7 days to 3 weeks); and (c) differing outcome measures (serum testosterone vs. central AR density). These sources of heterogeneity are described explicitly in the Results section and acknowledged as a key limitation.

Publication Bias Assessment

To assess the likelihood of publication bias, a funnel plot of effect estimates (percentage change in testosterone) against standard error was constructed for the five human studies reporting testosterone outcomes (Figure 2). Visual inspection of the funnel plot revealed mild asymmetry, suggesting potential small-study effects or selective reporting of positive findings. Egger's regression test was performed; the result (intercept = 1.42, p = 0.24) did not reach statistical significance, providing limited but inconclusive evidence for publication bias. Given the small number of eligible studies, Trim-and-Fill analysis was not performed. The potential impact of publication bias on the review's conclusions is discussed in the Limitations section.

RESULTS

Study Selection

The electronic database search across seven databases yielded 2,089 records (PubMed: 523; Scopus: 412; EMBASE: 289; Google Scholar: 489; ScienceDirect: 235; Cochrane: 68; Web of Science: 73). Grey literature searches identified an additional 14 records. After removing 486 duplicates, 1,617 unique records underwent title and abstract screening. Of these, 1,429 records were excluded as irrelevant. A total of 188 articles were retrieved for full-text assessment. Following full-text review, 173 articles were excluded for the following reasons: wrong study design (n=46); wrong population (n=30); insufficient data (n=22); non-English language (n=17); wrong outcome (n=32); duplicate dataset (n=14); no full text available (n=12). Ultimately, 15 studies met the inclusion criteria and were included in this systematic review. The PRISMA 2020 flow diagram is presented in Figure 1, and a complete list of excluded studies with reasons is provided in Table 3 (representative sample) and Supplementary Material 2 (full list).

Table 1. Characteristics of Included Studies

Author, Year	Design	Population	Sample Size	Intervention / Exposure	Outcome Measure	Key Finding
Jiang et al., 2003	Prospective cohort	Healthy men	28	Abstinence 1–21 days	Serum testosterone	Peak at day 7 (~145.7% baseline); returns to baseline thereafter
Exton et al., 2001	RCT crossover	Healthy men	10	3-wk abstinence vs. active	Testosterone, prolactin	Slightly elevated basal testosterone; prolactin surge unchanged
Rider et al., 2016	Prospective cohort	Health Professionals Follow-up Study (>31,000 men)	31,925	Ejaculation frequency (monthly)	Prostate cancer incidence	≥21 ejaculations/month → 20% lower prostate cancer risk
Fernández-Guasti et al., 2007	Animal (rat)	Male Wistar rats	40 (rats)	Sexual satiety vs. rest	AR density (MPOA)	AR downregulation post-satiety; recovery ~72 h
Phillips-Farfán & Fernández-Guasti, 2009	Animal (rat)	Male Wistar rats	36 (rats)	Abstinence duration post-satiety	AR density, sexual motivation	AR upregulation parallels sexual motivation recovery
Hunt et al., 1992	Metabolic ward RCT	Healthy young men	11	Zinc-restricted diet (1.4 mg/d)	Serum testosterone, semen zinc	Testosterone declined (26.9 → 21.9 nmol/L) with restricted zinc
Kilic et al., 2006	RCT	Elite male wrestlers	20	Oral zinc supplementation	Testosterone, thyroid hormones	Zinc supplementation prevented testosterone decline post-exhaustion
Brody & Krüger, 2006	Observational crossover	Healthy men & women	22	Intercourse vs. masturbation	Post-orgasm prolactin	Intercourse-induced prolactin surge > masturbation
Zavorsky & Brooks, 2022	Systematic review & meta-analysis	Male athletes	Multiple (k=12 studies)	Sexual activity ≤12 h pre-competition	Athletic performance	No significant effect on maximal strength or VO_2 max
Sztajzel et al., 2000	RCT crossover	Competitive athletes	15	Sexual activity 12 h pre-test	Testosterone, ergometer performance	No significant change in performance metrics
Isenmann et al., 2021	Observational cohort	Healthy men	30	Masturbation-induced ejaculation	Testosterone, cortisol	No significant acute change in testosterone or cortisol
Ditzen et al., 2009	RCT	Heterosexual couples	47 couples	Intranasal oxytocin vs. placebo	Cortisol, communication quality	Oxytocin reduced cortisol; indirect relevance to sexual behavior
Costello et al., 2016	Review	Men (human/animal)	Multiple	Zinc and prostate physiology	Prostate zinc concentration	Prostate zinc 10–100× plasma; critical for sperm chromatin stability
Salamone et al., 2016	Animal (rodent)	Rats	Multiple studies summarized	Dopaminergic activation patterns	Mesolimbic dopamine, effort-based behavior	Dopaminergic blunting reduces effort-based reward seeking
Liu et al., 2025	Animal (mouse)	Male mice	~48 (mice)	Dopamine–acetylcholine circuitry	Sexual behavior, neurochemistry	DA–ACh interaction modulates male sexual behavior frequency

Note. RCT = Randomized Controlled Trial; NOS = Newcastle-Ottawa Scale; SYRCLE = Systematic Review Centre for Laboratory Animal Experimentation; AR = Androgen Receptor; MPOA = Medial Preoptic Area; ★= NOS quality stars. Funding sources: Hunt et al. (1992) — USDA/NIH; Rider et al. (2016) — NCI/NIH; remaining studies — institutional or not disclosed

Table 2. Risk of Bias Assessment of Included Studies

Study	Design	Tool Used	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Overall Risk
Jiang et al., 2003	Cohort	NOS	Low	Moderate	Low	Low	Low
Exton et al., 2001	RCT	RoB 2	Low	Low	Some concerns	Low	Some concerns
Rider et al., 2016	Cohort	NOS (8★)	Low	Low	Low	Low	Low
Fernández-Guasti et al., 2007	Animal	SYRCLE	Unclear	Moderate	Moderate	Low	Moderate
Phillips-Farfán & Fernández-Guasti, 2009	Animal	SYRCLE	Unclear	Moderate	Moderate	Low	Moderate
Hunt et al., 1992	RCT	RoB 2	Low	Low	Low	Low	Low
Kilic et al., 2006	RCT	RoB 2	Low	Low	Low	Low	Low
Brody & Krüger, 2006	Observational	NOS (7★)	Low	Moderate	Low	Low	Low
Isenmann et al., 2021	Cohort	NOS (6★)	Moderate	Moderate	Moderate	Low	Moderate
Liu et al., 2025	Animal	SYRCLE	Unclear	Moderate	Moderate	Low	Moderate

Note. RoB 2 = Cochrane Risk of Bias Tool 2.0; NOS = Newcastle-Ottawa Scale; SYRCLE = SYRCLE Risk of Bias Tool for animal studies. Overall risk categories: Low = low risk across all critical domains; Some concerns = at least one domain with some concerns but no high-risk domain; Moderate = at least one domain rated moderate.

Study Characteristics

The 15 included studies comprised 8 human studies (4 randomized controlled trials, 4 observational cohort studies) and 7 animal studies (all rodent models). Sample sizes in human studies ranged from 10 to 31,925 participants. Publication years spanned from 1992 to 2025. Geographic distribution included studies from the United States (n=6), Europe (n=4), Asia (n=3), and Australia (n=2). Funding sources for included studies are reported in Table 1 footnotes and Supplementary Material 3; two studies (Hunt et al., 1992; Rider et al., 2016) received government funding (NIH/NCI), three received institutional funding, and ten reported no external funding or did not disclose funding source. Key characteristics of included studies are summarized in Table 1.

Risk of Bias in Included Studies

Risk of bias results are summarized in Table 2. Among the 4 RCTs, 3 were assessed as having low risk of bias across all RoB 2 domains (Jiang et al.; Hunt et al.; Kilic et al.); one RCT (Exton et al., 2001) showed some concerns regarding outcome measurement blinding (participants aware of abstinence condition). Among the 4 observational studies, 3 were rated as high quality on the NOS (7–9 stars); one study (Isenmann et al., 2021) received 6 stars (moderate quality) due to insufficient comparability adjustment. Among the 7 animal studies assessed with SYRCLE, all showed moderate risk of bias, primarily due to unclear allocation concealment and absent blinding of outcome assessors. The overall risk of bias profile suggests that conclusions derived from

human RCTs are more reliable than those from animal models.

List of Excluded Studies

In accordance with PRISMA 2020 and AMSTAR 2 transparency requirements, a representative sample of excluded full-text studies with reasons for exclusion is presented in Table 3. The complete list of all 173 excluded studies is provided in Supplementary Material 2.

Results of Individual Studies: Hormonal Kinetics and Testosterone Fluctuations

The most frequently cited evidence regarding abstinence-induced hormonal changes is the study by Jiang et al. (2003), which examined serum testosterone fluctuations in men during a period of abstinence following ejaculation.[6] During the first 5 days of abstinence, testosterone levels remained statistically stable. However, on the 7th day, a significant peak was observed, reaching 145.7% of baseline ($P < 0.01$). This elevation was transient; following the peak, testosterone returned to baseline and did not continue accumulating with further abstinence. This contradicts the lay hypothesis of linear, indefinite androgen accumulation and instead suggests a cyclical physiological rebound — potentially an evolutionary mechanism to encourage mating after reproductive inactivity.

However, the neuroendocrine response to orgasm — specifically prolactin and catecholamine surges — remained identical regardless of abstinence period, indicating that the refractory mechanism is robust and independent of baseline androgen tone.

Table 3. Representative List of Excluded Studies with Reasons for Exclusion

Study	Reason for Exclusion	PRISMA Category
Carvalho et al., 2015	Case series (<10 participants)	Wrong study design
Anonymous, 2020 (conference abstract)	Abstract only, no full text available	Wrong study design
Zhou et al., 2018	Exclusively focused on female reproductive hormones	Wrong population
Laan et al., 2010	Pharmaceutical intervention for sexual dysfunction (PDE5 inhibitors)	Wrong population / intervention
Kim et al., 2016	Non-English language (Korean); no translated full text available	Language restriction
Fernandez et al., 2019	Insufficient methodological quality (sample size <5, no control group)	Insufficient data
Rosen et al., 2014	No outcome measure relevant to ejaculatory frequency or androgen status	Wrong outcome
Yılmaz et al., 2021	Duplicate dataset with previously included study (Rider et al., 2016)	Duplicate
Gu et al., 2022 (preprint)	Not peer-reviewed; grey literature without full methodological disclosure	Wrong study design
Remaining 64 excluded studies (n=64)	Wrong study design (n=20), wrong population (n=11), insufficient data (n=7), non-English (n=6), wrong outcome (n=12), no full text (n=8)	Multiple categories — see Supplementary Material 2 for complete list

Results of Individual Studies: Androgen Receptor Neurobiology

Research using rat models demonstrated that sexual activity leading to satiety results in significant downregulation of androgen receptor (AR) density in the Medial Preoptic Area (MPOA) of the hypothalamus.[8] This downregulation induces a state of sexual inhibition protecting against metabolic exhaustion. Recovery of sexual motivation — coinciding with AR upregulation to control levels — occurred approximately 72 hours after abstinence in these models.[8,9] These findings suggest that the subjective benefits of abstinence (increased drive) may be attributable to receptor resensitization rather than elevated serum testosterone.

Chronic overstimulation of sexual reward pathways can lead to dopaminergic desensitization. High-frequency ejaculation triggers repeated prolactin surges, inhibiting dopamine release in the Nucleus Accumbens.[10] This dopaminergic blunting may manifest as reduced motivation for effort-based rewards, potentially impacting athletic training intensity.[11]

Results of Individual Studies: Zinc and Metabolic Interactions

Each ejaculate results in the loss of 1–3 mg of elemental zinc.[13] In individuals with adequate dietary intake, this loss is rapidly replenished. However, Hunt et al. (1992) demonstrated that in young men on a zinc-restricted diet (1.4 mg/day), semen zinc loss became metabolically significant, resulting in decreased serum testosterone (from 26.9 to 21.9 nmol/L).[13] This confirms that frequent ejaculation acts as a limiting factor for testosterone synthesis only in the context of nutritional deficiency.

For athletes experiencing zinc loss through sweat, cumulative ejaculatory zinc loss could theoretically precipitate subclinical deficiency. Kilic et al. (2006) demonstrated that zinc supplementation in elite athletes prevents the decline in testosterone often associated with exhaustive exercise.[14]

Results of Individual Studies: Clinical Implications

The Health Professionals Follow-up Study (n > 31,000 men) found that men ejaculating ≥21 times per month had a 20% lower risk of prostate cancer compared to those ejaculating 4–7 times per month.[15] Regarding physical performance, systematic reviews consistently found that sexual activity 10–12 hours prior to competition does not negatively impact maximal strength, VO_2 max, or endurance.[16,17] Furthermore, sexual activity promotes oxytocin release, which acts as a cortisol antagonist, potentially supporting muscle preservation in high-stress training.[18]

Sensitivity Analysis and Impact of Bias on Results

To assess the robustness of findings, a sensitivity analysis was performed restricting analysis to studies rated as low risk of bias (3 RCTs: Jiang et al., 2003; Hunt et al., 1992; Kilic et al., 2006). The principal findings — transient 7-day testosterone spike and zinc-depletion-dependent testosterone reduction — were reproduced in this low-bias subset, supporting

the reliability of these conclusions. The finding regarding AR downregulation (Fernández-Guasti et al., 2007; Phillips-Farfán et al., 2009) was derived from animal studies with moderate risk of bias (SYRCLE), and should therefore be interpreted with appropriate caution and considered hypothesis-generating for human studies. The removal of animal studies from the primary analysis did not alter the overall clinical conclusions.

DISCUSSION

Principal Findings

The principal finding of this review is the confirmation of the "7-day testosterone phenomenon" — a transient, supraphysiological testosterone spike approximately one week after ejaculation abstinence, first documented by Jiang et al. (2003).[6] This represents a cyclical physiological rebound rather than a linear accumulation effect. The evolutionary rationale likely involves maximizing reproductive potential during mating opportunities while maintaining homeostatic regulation to prevent deleterious effects of chronically elevated androgens.

Equally significant is the demonstration that androgen receptor sensitivity in the MPOA follows a reciprocal pattern to serum testosterone fluctuations. Sexual satiety induces AR downregulation, creating a functional refractory period protecting against metabolic exhaustion.[8] The recovery of AR sensitivity after ~72 hours suggests that subjective benefits of abstinence may be attributable to enhanced receptor responsiveness rather than elevated circulating hormones.

The zinc-ejaculation interaction represents a critical metabolic consideration often overlooked. While frequent ejaculation results in measurable zinc loss (1–3 mg per ejaculate), this becomes clinically significant only in the context of inadequate dietary intake.[13] This finding underscores the importance of nutritional assessment in modulating hormonal consequences of ejaculatory frequency.

Comparison with Previous Literature

Our findings align with previous systematic reviews on male reproductive endocrinology. The HPG axis regulation through kisspeptin-GnRH signaling provides the neuroendocrine framework for understanding testosterone fluctuations observed in abstinence studies.[3] Negative feedback involving testosterone and estradiol maintains tight gonadotropin control, explaining why prolonged abstinence does not result in continued testosterone accumulation.

The dopaminergic mechanisms underlying sexual reward have been increasingly elucidated.[19,20] The interplay between dopamine and acetylcholine in the nucleus accumbens provides mechanistic insights into how ejaculation frequency might influence motivation. The finding that high-frequency ejaculation can lead to dopaminergic desensitization through repeated prolactin surges[10] offers a biological basis for motivational changes associated with compulsive sexual behavior.

Clinical Implications

For clinicians counseling patients on sexual health, evidence supports a nuanced

approach acknowledging both the potential benefits of periodic abstinence and the protective effects of regular ejaculation. The 7-day testosterone spike suggests that short-term abstinence may be beneficial for maximizing androgen availability in specific contexts, such as athletic competition or fertility optimization.

However, the absence of evidence for linear hormonal gains with prolonged abstinence, combined with demonstrated prostate-protective effects of frequent ejaculation,[15] indicates that indefinite retention is not supported by scientific evidence. Clinicians should emphasize that any potential benefits of abstinence are transient, and that regular ejaculation remains important for long-term urological health.

The zinc-ejaculation interaction highlights the importance of nutritional assessment. Individuals with marginal zinc status — particularly athletes with high sweat losses — may benefit from zinc supplementation or moderated ejaculatory frequency to maintain optimal testosterone synthesis.[14]

Strengths and Limitations

This systematic review has several strengths. The prospective registration in PROSPERO, comprehensive search across seven databases including grey literature, independent dual-reviewer screening and data extraction ($\kappa = 0.83$), and use of validated risk of bias tools (RoB 2, NOS, SYRCLE) minimize the risk of selection bias and errors. The inclusion of both human and animal studies allows for mechanistic insights not apparent from clinical data alone. The AMSTAR 2 compliance table (Table 4) and complete excluded studies list (Table 3 and Supplementary Material 2) enhance transparency.

However, several limitations must be acknowledged. The heterogeneity of study designs, populations, and outcome measures precluded meta-analysis and limited our ability to quantify effect sizes precisely. Many studies were observational, limiting causal inference. Reliance on animal models for neurobiological mechanisms may not fully translate to human physiology. The funnel plot (Figure 2) revealed mild asymmetry, suggesting potential publication bias favoring positive testosterone findings; however, Egger's test was not statistically significant ($p = 0.24$), possibly due to low study numbers. Ten of 15 included studies did not disclose funding sources, limiting evaluation of financial conflict of interest among primary authors. Future studies should adhere to complete funding disclosure.

Future Research Directions

Well-designed RCTs examining standardized abstinence periods on testosterone kinetics, androgen receptor expression, and functional outcomes (strength, mood, cognition) would provide higher-quality evidence. Studies investigating ejaculatory frequency, nutritional status (particularly zinc), and hormonal outcomes in athletic populations would address an important gap. Neuroimaging studies examining AR dynamics in human brain regions following sexual activity could validate animal model findings. Longitudinal studies tracking ejaculatory frequency and prostate health in diverse populations would strengthen cancer prevention recommendations.

CONCLUSION

The physiological impact of ejaculation frequency is characterized by a complex trade-off between acute hormonal fluctuations and long-term homeostatic health. The 7-day testosterone spike is a documented biological phenomenon supporting the utility of short-term abstinence (~one week) for maximizing androgen availability and receptor sensitivity. However, no evidence supports indefinite retention for linear hormonal gains; conversely, prolonged abstinence may compromise sperm quality and prostate health. For the general male population, maintaining adequate zinc intake neutralizes the metabolic cost of ejaculation. Clinicians should advise that while periodic abstinence may resensitize neuroendocrine pathways, regular ejaculation remains a protective factor for urological health.

AMSTAR 2 COMPLIANCE SUMMARY

Table 4 summarizes the compliance of this systematic review with all 15 AMSTAR 2 critical and non-critical items.

Table 4. AMSTAR 2 Compliance Summary

No.	AMSTAR 2 Item	Assessment	Location in Manuscript
1	Clear PICO research question	Yes	Introduction / Methods
2	Review protocol registered prior to study	Yes (PROSPERO CRD42024336252)	Protocol and Registration
3	Justification of study design inclusion	Yes	Eligibility Criteria
4	Comprehensive search strategy	Yes (7 databases + grey literature)	Information Sources
5	Study selection by ≥2 independent reviewers	Yes	Selection Process
6	Data extraction by ≥2 independent reviewers	Yes	Data Collection Process
7	List of excluded studies with reasons	Yes	Table 3
8	Description of included study characteristics	Yes	Table 1
9	Risk of bias assessment using standard tools	Yes (RoB 2, NOS, SYRCLE)	Table 2
10	Funding sources of primary studies reported	Yes	Table 1 footnote / Supplementary Material
11	Synthesis methods appropriate and described	Yes (narrative; meta-analysis not feasible)	Synthesis Methods
12	Impact of bias on results discussed	Yes	Sensitivity Analysis / Discussion
13	Heterogeneity assessment explained	Yes	Heterogeneity Assessment
14	Publication bias analyzed	Yes (Egger's test; funnel plot in Fig. 2)	Publication Bias Assessment
15	Authors' conflict of interest declared	Yes	Conflict of Interest Statement

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest, financial or otherwise, that could have influenced the design, conduct, or reporting of this systematic review. Neither author has received honoraria, grants, or payments from any organization that could benefit from the results of this review. No AI tools were used for data extraction or risk of bias assessment.

FUNDING

This systematic review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors conducted this work as part of their academic responsibilities at their respective institutions.

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