optml

FIELD GUIDE NO. 05

FOR MEN · 35 TO 75+ · EDUCATIONAL REFERENCE

Testos-terone.

An evidence-led reference for understanding testosterone biology in men — what the published literature describes about the HPG axis, age-related decline, hypogonadism, lab interpretation, and the therapies that men and their clinicians consider.

FOR	USE	FORMAT	AN OPTML FIELD GUIDE
Men 35–75+	**Lifetime Reference**	**Cited Atlas**	**No. 05**

A NOTE BEFORE YOU BEGIN

Testosterone in men is among the most *over-claimed* and *under-explained* areas of adult medicine.

The published medical literature on testosterone biology, age-related decline, and replacement therapy is large, fast-moving, and frequently summarized in patient-facing materials in ways that don't match the underlying evidence.

This guide is an **educational atlas** — a curated reference of what the peer-reviewed literature reports about the hypothalamic-pituitary-gonadal axis, the biology of testosterone, the definition and diagnosis of hypogonadism, the laboratory markers used to characterize it, the modalities of testosterone therapy that have been studied, and the lifestyle inputs for which the strongest evidence base exists. Every clinical statement is footnoted to its primary source. The intent is comprehension, not prescription.

The contents are organized to mirror how clinicians think about the field: the biology first, then the natural age-related decline, then the symptom and diagnostic frameworks, then the laboratory markers, then the therapeutic categories that have been studied — and finally the lifestyle and adjunct considerations that interact with all of the above.

Nothing in this guide is intended as medical advice or treatment recommendation. Read it as a reference. Bring questions to a licensed clinician.

EDUCATION ONLY · NOT MEDICAL ADVICE

This guide presents published research and clinical guidelines for educational purposes. **It does not diagnose, treat, prescribe, or recommend any therapy.** Testosterone replacement and adjunct therapies are scheduled medications in the United States; decisions involve individual medical history, risk factors, and clinical judgment — those decisions belong with a licensed clinician who has reviewed your personal health record.

CONTENTS

Inside.

What this guide is — *and what it isn't.*

This document is a reference. It collects, organizes, and cites the peer-reviewed literature describing testosterone biology in men, age-related decline, hypogonadism, and the therapies that have been studied. It is written to help a reader understand what is currently published — not to recommend any particular course of action.

The four things this guide does.

01 **Summarizes the published biology.**
Testosterone synthesis, transport, receptor signaling, and metabolic conversion to estradiol and dihydrotestosterone are well-characterized in the literature. This guide presents that biology with citations to the primary references — including the major endocrine society guidelines, longitudinal cohort studies (BLSA, EMAS, MMAS), and the principal physiological reviews. [1]

02 **Maps symptoms to mechanism.**
Symptoms attributed to low testosterone span sexual, physical, and psychological domains. This guide pairs each symptom category with the mechanism described in the literature and the population-level prevalence data from cohort studies that have examined the question. [2]

03 **Reports what studies of therapies have found.**
Where therapies have been studied — testosterone replacement in multiple modalities, fertility-preserving alternatives such as clomiphene and hCG, and lifestyle interventions — this guide summarizes what randomized trials and meta-analyses report. It does not interpret those findings as a recommendation for any individual reader. [3]

04 **Cites every clinical statement.**
Numbered superscript references [4] link each clinical claim to a citation listed in the References chapter at the end. Most citations are peer-reviewed journal articles indexed on PubMed; others are major clinical society position statements from the Endocrine Society, AUA, and EAU.

IMPORTANT — READ BEFORE CONTINUING

Nothing in this guide constitutes medical advice, diagnosis, or treatment. Testosterone-related decisions, medication choices, dosing, monitoring, and the assessment of individual risks and benefits require a licensed clinician who has reviewed your personal medical history.

If a section of this guide raises a question about your own health, write the question down and bring it to a clinician. **Do not start, stop, or modify any medication or supplement based on this guide.** Testosterone is a Schedule III controlled substance in the United States; legal use requires a prescription from a licensed clinician.

References to specific medications, doses, or laboratory ranges describe what has been published in the medical literature. They are not prescriptions and they are not recommendations.

Testosterone production is the *output of a feedback loop* — not a standalone signal.

Endogenous testosterone production in men is controlled by the hypothalamic-pituitary-gonadal (HPG) axis: a three-tier feedback loop in which the hypothalamus secretes gonadotropin-releasing hormone (GnRH), the anterior pituitary responds with luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the testes produce testosterone, dihydrotestosterone, estradiol, and inhibin B. [5] Understanding this loop is foundational to interpreting every laboratory measurement and every therapeutic intervention discussed later in the guide.

The three tiers.

01 **Hypothalamus — GnRH pulse generator.**
Specialized hypothalamic neurons secrete GnRH in pulses approximately every 90–120 minutes. Pulse frequency and amplitude determine the relative LH and FSH output downstream. Continuous (rather than pulsatile) GnRH exposure suppresses gonadotropin secretion — a mechanism exploited pharmacologically by GnRH agonists used in prostate cancer. [5]

02 **Anterior pituitary — LH and FSH.**
GnRH pulses stimulate gonadotrope cells in the anterior pituitary to release LH and FSH into the systemic circulation. LH primarily targets the testicular Leydig cells to drive testosterone synthesis; FSH primarily targets the Sertoli cells to support spermatogenesis. [5]

03 **Testes — Leydig and Sertoli cells.**
Leydig cells in the testicular interstitium synthesize testosterone from cholesterol under LH stimulation; intratesticular testosterone concentrations are typically 50–100× systemic levels and are required for normal spermatogenesis. Sertoli cells, within the seminiferous tubules and under FSH and intratesticular testosterone signaling, support the developing germ cells through spermatogenesis and produce inhibin B. [6]

The two feedback loops.

The HPG axis maintains testosterone within a relatively narrow range via two coupled negative-feedback loops: [5]

- **Testosterone and estradiol** feed back at both the hypothalamus (slowing GnRH pulse frequency) and the pituitary (reducing LH and FSH responsiveness). Much of testosterone's negative feedback is mediated by its aromatization to estradiol, which acts via estrogen receptor α centrally. [7]
- **Inhibin B**, secreted by Sertoli cells, selectively suppresses pituitary FSH secretion. The inhibin B–FSH loop is a sensitive indicator of seminiferous tubule function and is one of the markers used clinically to assess primary versus secondary testicular failure. [8]

Why the loop framing matters. Several patterns of "low testosterone" reflect failures at different levels of the axis. A man with low testosterone and high LH/FSH has primary testicular failure; a man with low testosterone and low or inappropriately normal LH/FSH has secondary (hypothalamic-pituitary) failure. The distinction determines the appropriate diagnostic workup, the choice of therapy, and the fertility implications discussed in Chapters 4 and 13. [3]

Exogenous testosterone *suppresses* the loop. That fact has consequences.

Administration of exogenous testosterone activates the same negative feedback loops that endogenous testosterone normally activates — but at supraphysiologic delivery rates and without the natural pulsatility. The result is suppression of GnRH, LH, and FSH; cessation of Leydig cell testosterone production; and arrest of spermatogenesis. These changes are central to multiple discussions later in this guide. [9]

What happens to each marker.

MARKER	EFFECT OF EXOGENOUS T	MECHANISM / CONTEXT
Serum testosterone	**Rises (depending on dose/route)**	Reflects the exogenous load plus any residual endogenous production. [10]
LH	**Suppressed, often to undetectable**	Negative feedback at hypothalamus + pituitary. [9]
FSH	**Suppressed**	Same loop; with additional suppression as intratesticular T falls and inhibin B drops. [9]
Intratesticular testosterone	**Falls dramatically**	Loss of LH stimulation halts Leydig cell synthesis; intratesticular T falls from ~50× to near systemic levels. [11]
Spermatogenesis	**Suppressed; often azoospermia**	Intratesticular T below threshold for normal sperm production; FSH loss compounds. [12]
Inhibin B	**Falls**	Sertoli cell production declines with loss of intratesticular T signaling. [8]
Testicular volume	**Reduced**	Loss of seminiferous tubule mass. [12]
Estradiol	**Rises (variable)**	Aromatization of the higher serum testosterone load; magnitude depends on dose, body fat, and individual aromatase activity. [13]

Why this matters for several decisions discussed later.

The suppression of the HPG axis by exogenous testosterone has direct implications for several clinical scenarios examined in subsequent chapters:

- **Fertility** — TRT suppresses spermatogenesis; fertility-preserving alternatives are discussed in Chapter 13. [14]
- **Discontinuation** — recovery of endogenous production after stopping TRT requires re-activation of the suppressed axis, which can take months and is not always complete. [15]
- **Testicular volume change** — reflects loss of intratesticular signaling rather than systemic T levels per se. [12]
- **Estradiol management** — the rise in estradiol with TRT is downstream of the elevated serum testosterone and is discussed in detail in Chapter 9. [13]

> **A clarification on terminology.** "Testosterone replacement therapy" implies replacing a deficiency. Pharmacologically, what is administered does both — replaces circulating testosterone and shuts down the endogenous axis. This dual effect is intrinsic to the pharmacology, not an avoidable side effect. [9]

Testosterone synthesis: *cholesterol to androgen, in five enzymatic steps.*

Testosterone is synthesized in Leydig cells of the testes (and in smaller quantities by the adrenal cortex) through a sequence of enzymatic conversions beginning with cholesterol. Approximately 95% of circulating testosterone in adult men is of testicular origin; the remaining ~5% is of adrenal origin. [6]

The synthetic pathway.

Steroidogenesis proceeds via the following principal steps, each catalyzed by a specific enzyme: [16]

01 **Cholesterol → Pregnenolone (CYP11A1, P450scc).**
The rate-limiting step. Occurs in mitochondria after cholesterol is imported by the steroidogenic acute regulatory protein (StAR). LH stimulation acutely increases StAR expression. [16]

02 **Pregnenolone → 17α-Hydroxypregnenolone → DHEA → Androstenedione.**
The Δ^5 pathway: a series of conversions catalyzed by CYP17A1 (17α-hydroxylase/17,20-lyase). The Δ^4 pathway via progesterone is the alternative route. [16]

03 **Androstenedione → Testosterone (17β-HSD).**
17β-hydroxysteroid dehydrogenase catalyzes the final step to testosterone. Once synthesized, testosterone diffuses out of the Leydig cell into circulation. [16]

Daily production and circulating concentrations.

Total daily testosterone production in healthy young adult men is approximately 5–7 mg/day. [6] Serum total testosterone in healthy young adult men ranges approximately 264–916 ng/dL based on the 2017 Harmonized Reference Range derived from four U.S. cohort studies using mass-spectrometry assays in non-obese men 19–39 years old. [17]

Testosterone secretion is pulsatile, following the pulsatile LH pattern from the pituitary. There is also a diurnal rhythm: peak concentrations occur in the early morning (approximately 6–10 AM), with progressive decline through the day to a nadir in the evening. [18] This diurnal pattern is the basis for the standard recommendation that diagnostic testosterone measurements be obtained in the morning. [3]

Two important downstream conversions.

Testosterone serves as both the principal circulating androgen and a precursor for two key downstream conversions: [7]

- **Testosterone → Dihydrotestosterone (5α-reductase).** DHT is a more potent androgen than testosterone (3–10× higher receptor affinity) and mediates many androgenic effects on the prostate, skin, and hair follicles. 5α-reductase inhibitors (finasteride, dutasteride) reduce DHT and are used clinically for benign prostatic hyperplasia and male-pattern hair loss. [19]
- **Testosterone → Estradiol (aromatase, CYP19A1).** Approximately 0.2% of testosterone is aromatized to estradiol in peripheral tissues (adipose, brain, bone, others). Despite the small fraction, the absolute amount is biologically significant; estradiol mediates important effects on bone density, cardiovascular tissue, and central feedback to the HPG axis — discussed in Chapter 9. [13]

Implications throughout the guide. The two downstream conversions explain several clinical observations: why some androgenic side effects (acne, hair loss) are partially attributable to DHT rather than T per se; why aromatase inhibition is sometimes used (or misused) alongside TRT; and why estradiol — often considered a "female hormone" — has well-established roles in male physiology. [20]

Transport: *SHBG, albumin, and the "free" testosterone concept.*

Once testosterone is secreted into circulation, it is largely protein-bound. In healthy young men, approximately 44% is bound to sex hormone-binding globulin (SHBG) with high affinity, ~54% is bound to albumin with lower affinity, and ~2% circulates as "free" testosterone unbound to either protein. [21] The "bioavailable" fraction is sometimes defined as the sum of the albumin-bound and free fractions.

Why SHBG matters for interpretation.

SHBG concentration influences the relationship between total testosterone and biologically active testosterone. Conditions that increase SHBG raise total testosterone without necessarily increasing the free or bioavailable fraction; conditions that decrease SHBG do the opposite. [22] Major influences on SHBG include:

- **SHBG-raising**: aging (modest), hyperthyroidism, hepatitis and other liver disease, anticonvulsants, HIV infection, hypogonadism (paradoxically, mildly), and oral estrogen administration. [22]
- **SHBG-lowering**: obesity and insulin resistance, type 2 diabetes, nephrotic syndrome, hypothyroidism, glucocorticoid excess, androgens, progestins, and growth hormone. [22]

The clinical relevance: a 45-year-old man with elevated SHBG due to thyroid disease may have a "normal" total testosterone but a low free testosterone with corresponding symptoms; conversely, a man with obesity-driven low SHBG may have a low total testosterone but a relatively preserved free testosterone. [22] Major society guidelines recommend measuring SHBG in scenarios where this discordance is suspected. [3]

How "free testosterone" is measured.

The reference method for free testosterone is equilibrium dialysis combined with mass spectrometry; this is performed in specialized laboratories. [23] In routine clinical practice, free testosterone is more often estimated by:

- **Calculated free testosterone** — using the Vermeulen equation or similar, requiring measurement of total T, SHBG, and albumin. Considered an acceptable approach by major guidelines when direct measurement is not available. [24]
- **"Analog" or direct immunoassay free T** — widely available but considered less accurate at the lower concentrations relevant for diagnosis of hypogonadism. Major guidelines have explicitly recommended against analog assays for this purpose. [3]

The Goldman reappraisal of testosterone binding.

The conventional "free hormone hypothesis" — that only the unbound fraction is biologically active — has been revisited in recent literature. The Goldman et al. 2017 reappraisal in Endocrine Reviews argued that SHBG-bound testosterone may have under-appreciated biological roles via SHBG receptor signaling and tissue-specific dissociation, and that the conventional dichotomy between "free" and "bound" may oversimplify the in vivo biology. [21] The full clinical implications of this reappraisal remain under active investigation. [21]

> **Practical reading frame.** Major society guidelines treat total testosterone as the principal screening measurement, with free testosterone reserved for scenarios in which SHBG is suspected to be altered. The Goldman reappraisal does not — at this writing — overturn this clinical framing, but it does temper any view that calculated free T is a universally superior measurement. [21]

The androgen receptor: *one gene, many tissues.*

Testosterone and dihydrotestosterone exert their biological effects primarily by binding to a single intracellular receptor — the androgen receptor (AR), a member of the nuclear hormone receptor superfamily, encoded by the AR gene on the X chromosome. [25] The tissue distribution and downstream gene programs activated by AR signaling explain the wide spectrum of androgen-responsive physiology.

Mechanism of action.

The classical genomic mechanism proceeds as follows: [25]

01 **Ligand binding.**
Testosterone or DHT diffuses into target cells and binds the cytoplasmic AR. DHT binds with 3–10× greater affinity than testosterone. [19]

02 **Receptor activation and nuclear translocation.**
Ligand-bound AR undergoes conformational change, dissociates from heat shock protein chaperones, dimerizes, and translocates to the nucleus. [25]

03 **Transcriptional activation.**
The activated AR binds androgen response elements in target gene promoters and recruits co-regulators to modulate transcription of androgen-responsive genes. [25]

In addition to this classical genomic mechanism, rapid non-genomic AR signaling — via membrane-associated AR and second messenger pathways — has been characterized in some tissues and may contribute to acute androgen effects. [26]

Tissue distribution and effects.

The androgen receptor is expressed in a wide range of tissues; the principal androgen-responsive tissues and the dominant effects mediated through AR include: [7]

- **Skeletal muscle** — AR activation drives muscle protein synthesis, hypertrophy, and satellite cell activity. The mechanism underlying the muscle-anabolic effect of testosterone in clinical trials. [27]
- **Bone** — AR expressed in osteoblasts and osteocytes; effects on bone density partly direct (AR-mediated) and partly indirect (via aromatization to estradiol). [28]
- **Sex accessory organs (prostate, seminal vesicles)** — heavily dependent on DHT signaling for development and maintenance. [19]
- **Skin and hair follicles** — DHT-driven effects on sebaceous gland activity (acne) and on terminal vs. vellus hair patterns (beard, body hair, scalp follicles with genetic susceptibility to androgenic alopecia). [29]
- **Brain** — AR widely expressed in central nervous system; mediates effects on libido, mood, and other cognitive-behavioral domains. [7]
- **Liver** — modulation of hepatic protein synthesis, including effects on lipoprotein metabolism. [7]
- **Erythropoiesis** — testosterone increases erythropoietin and suppresses hepcidin, contributing to the rise in hematocrit discussed in Chapter 10. [30]
- **Adipose tissue** — AR effects on adipocyte biology, with implications for body composition. [27]

The CAG repeat polymorphism. The AR gene contains a polymorphic CAG repeat segment whose length influences receptor transcriptional activity in vitro. Population studies have associated CAG repeat length with various clinical phenotypes (including some androgen-responsive outcomes), though the clinical utility of measuring CAG repeat length in routine practice has not been established. [31]

Testosterone declines with age. *The magnitude and pattern are debated.*

Multiple longitudinal cohort studies have characterized testosterone trajectories across the male adult lifespan. The principal findings — and the principal controversies — concern the magnitude of the age-related decline, the degree to which it is intrinsic to aging versus driven by accumulating comorbidities, and the relationship between population-level trends and individual clinical decisions. [32]

The principal cohort studies.

Four prospective cohort studies are most-cited in this literature:

BLSA · BALTIMORE LONGITUDINAL STUDY OF AGING

Reported a longitudinal decline in total testosterone of approximately **1.0–1.5% per year** from approximately age 30 onward in a community-dwelling male cohort. [33] Free testosterone declined at a faster rate (~2–3% per year), reflecting the concurrent age-related increase in SHBG. [33]

MMAS · MASSACHUSETTS MALE AGING STUDY

Reported similar age-related declines and characterized the symptomatic versus biochemical relationship in detail. Provided some of the earliest population estimates of the prevalence of biochemical hypogonadism among older men. [34]

EMAS · EUROPEAN MALE AGEING STUDY

Examined the relationship between testosterone concentrations and clinical symptoms in 3,219 men aged 40–79 across 8 European centers. Proposed an evidence-based syndromic definition of late-onset hypogonadism requiring concurrent symptoms and biochemical confirmation. [2]

FAMHES + OTHERS

Subsequent cohorts including the Fangchenggang Area Male Health and Examination Survey and others have confirmed the broad pattern of age-related decline in international populations. [35]

Population-level temporal trends.

A widely-cited 2007 analysis (Travison et al.) reported that age-matched testosterone concentrations had declined across successive generations of men in the MMAS cohort — a finding suggesting an additional "secular trend" superimposed on the within-individual age-related decline. [36] The Travison finding has been examined in additional cohorts with mixed results, and the proposed contributors — including changes in body composition, exposure to endocrine-disrupting chemicals, and shifts in lifestyle factors — remain areas of active investigation. [37]

> **The interpretive frame for Chapters 4 and 5.** The population-level age-related decline does not, by itself, define clinical hypogonadism. The major society guidelines explicitly require both biochemical confirmation and a consistent symptom syndrome before applying the diagnosis. This is the subject of Chapter 4. [3] [38]

How much of the decline is *aging itself* — and how much is *everything else?*

One of the more durable findings from the EMAS and related cohorts is that a substantial fraction of the apparent age-related decline in testosterone is associated with accumulating comorbidities — obesity, type 2 diabetes, metabolic syndrome, sleep apnea, and chronic illness — rather than with chronological aging in isolation. [39]

The EMAS analyses on this point.

EMAS analyses examining the determinants of testosterone decline reported that, after adjustment for body mass index, waist circumference, and prevalent chronic disease, the residual chronological-age effect on testosterone was much smaller than the unadjusted trajectory. [39] In men who remained healthy and lean across follow-up, the trajectory was substantially flatter than in men who developed obesity or chronic disease. [39]

Mechanistic pathways from comorbidity to low testosterone.

Several mechanisms link accumulating metabolic disease to lower testosterone: [40]

- **Increased peripheral aromatization.** Adipose tissue is a primary site of testosterone-to-estradiol conversion via aromatase. Increased adiposity raises peripheral aromatization, increases estradiol, and amplifies negative feedback on the HPG axis — lowering LH and downstream testosterone. [41]
- **Insulin resistance and inflammation.** Insulin signaling and pro-inflammatory cytokines influence both hypothalamic GnRH output and Leydig cell function. [40]
- **Sleep disruption and obstructive sleep apnea.** Disordered sleep is associated with reduced morning testosterone and altered LH pulse patterns. [42]
- **Chronic illness and medications.** Many chronic conditions — and a wide range of medications including opioids, glucocorticoids, and some psychiatric drugs — directly suppress the HPG axis. [43]

The clinical concept of "functional" hypogonadism.

The recognition that many cases of biochemical hypogonadism in middle-aged and older men are driven by comorbidities led to the conceptual distinction between **organic hypogonadism** (intrinsic pathology of the testes, pituitary, or hypothalamus) and **functional hypogonadism** (HPG axis suppression secondary to obesity, illness, medications, or other factors). [44] The European Academy of Andrology and other bodies have emphasized the distinction because the implications for clinical management differ: organic hypogonadism is generally a long-term diagnosis requiring management of the underlying pathology, whereas functional hypogonadism may be partly or fully reversible with treatment of the underlying contributors. [44]

What this means for the rest of the guide. Subsequent chapters discuss the laboratory workup that distinguishes the categories (Chapter 6) and the lifestyle interventions with the strongest reported effects on testosterone in functional contexts (Chapter 15). Even where TRT is indicated, addressing modifiable contributors is described in current guidelines as part of management. [3] [38]

Obesity and low testosterone: a *bidirectional loop.*

The relationship between adiposity and testosterone in men is bidirectional: obesity lowers circulating testosterone through several mechanisms, and low testosterone in turn promotes accumulation of fat mass and loss of lean mass. This loop is one of the most-cited modifiable contributors to the population trend in male testosterone concentrations. [41]

How obesity lowers testosterone.

- **Increased aromatization.** Adipose tissue expresses aromatase. Increased adipose mass increases peripheral conversion of testosterone to estradiol, raising estradiol and amplifying central negative feedback on the HPG axis. [41]
- **Reduced SHBG.** Insulin resistance — a hallmark of central obesity — suppresses hepatic SHBG synthesis. This lowers total testosterone (the SHBG-bound fraction declines) even when free testosterone is partially preserved. [22]
- **Hypothalamic inflammation and leptin signaling.** Pro-inflammatory cytokines from adipose tissue and altered leptin signaling have been implicated in disrupted GnRH pulsatility in animal models and in some human studies. [45]
- **Sleep-disordered breathing.** Obesity is a primary risk factor for obstructive sleep apnea, which independently lowers morning testosterone. [42]

How low testosterone promotes weight gain.

Conversely, low testosterone is associated with: [46]

- Reduced muscle protein synthesis and progressive loss of lean mass;
- Reduced resting energy expenditure related to lower lean mass;
- Increased adipose deposition, particularly visceral;
- Reduced insulin sensitivity, which further amplifies the metabolic dysregulation.

What happens when obesity is reversed.

Intentional weight loss — via lifestyle intervention, GLP-1 receptor agonist therapy, or bariatric surgery — is consistently associated with increases in total and free testosterone in men with obesity. [47] The magnitude scales with the degree of weight loss: meta-analyses of bariatric surgery cohorts have reported mean total testosterone increases of ~150–250 ng/dL with substantial weight loss, often returning previously hypogonadal men to the eugonadal range. [48]

GLP-1 receptor agonist trials in men with obesity have reported smaller but still meaningful increases in testosterone proportional to weight loss, with SHBG increases that reflect improved insulin sensitivity. [49]

> **The clinical reading frame.** The reversibility of obesity-associated functional hypogonadism is the basis for the major society guidelines' recommendation that weight loss and metabolic management be considered alongside — or before — TRT in men whose hypogonadism is associated with reversible contributors. This is discussed further in Chapter 4 and Chapter 15. [3] [38]

Hypogonadism is a *two-part diagnosis* — biochemistry and syndrome.

Hypogonadism in men is defined by major clinical society guidelines as the combination of (1) consistent symptoms of testosterone deficiency and (2) laboratory confirmation of low testosterone on at least two separate morning measurements. [3] [38] Both criteria are required for the diagnosis; biochemical low testosterone in the absence of symptoms — or symptoms in the absence of biochemical confirmation — does not meet the diagnostic threshold in current guidelines.

The two anatomical-pathophysiologic categories.

PRIMARY HYPOGONADISM (TESTICULAR)

Pathology of the testes themselves. Low testosterone with elevated LH and FSH (hypergonadotropic). Causes include Klinefelter syndrome, prior chemotherapy or radiation, testicular trauma, mumps orchitis, undescended testes, and various other intrinsic testicular pathologies. [50]

SECONDARY HYPOGONADISM (HYPOTHALAMIC-PITUITARY)

Pathology upstream of the testes. Low testosterone with low or inappropriately normal LH and FSH (hypogonadotropic). Causes include pituitary tumors (prolactinomas most commonly), genetic conditions (Kallmann syndrome and congenital hypogonadotropic hypogonadism), traumatic brain injury, certain medications, and a wide range of acquired causes. [50]

The clinical-context categories.

ORGANIC HYPOGONADISM

Recognized intrinsic pathology of the HPG axis. Includes primary causes (e.g., Klinefelter, post-chemotherapy) and structural secondary causes (e.g., pituitary tumor). Generally requires lifelong management of the underlying condition. [44]

FUNCTIONAL HYPOGONADISM

HPG axis suppression secondary to a reversible contributor. Most commonly obesity, type 2 diabetes, sleep apnea, certain medications, or chronic illness. The European Academy of Andrology and other bodies emphasize the importance of addressing the underlying contributor. [44]

LATE-ONSET HYPOGONADISM (LOH)

Syndromic concept from EMAS. The EMAS criteria require both ≥3 sexual symptoms (reduced libido, erectile dysfunction, less frequent morning erections) AND total testosterone < 320 ng/dL AND free testosterone < 64 pg/mL. [2] Applied this strictly, prevalence in the EMAS population was approximately 2%. [2]

MIXED CATEGORIES

Many older men have features of both functional and (in some cases) age-related changes superimposed. Distinguishing these clinically is part of the standard diagnostic workup discussed in Chapters 5 and 6. [3]

Why these distinctions matter practically. Primary versus secondary distinguishes which workup is needed (testicular ultrasound, karyotype vs. pituitary imaging, prolactin). Organic versus functional distinguishes whether reversible contributors should be addressed first. LOH criteria from EMAS represent one rigorous attempt to define a clinical syndrome from a population perspective — and produce a much smaller prevalence estimate than biochemistry-only approaches. [2]

The workup distinguishes *where in the axis* the problem sits.

Major society guidelines specify a stepwise diagnostic approach: confirm biochemical low testosterone with at least two morning measurements, then distinguish primary from secondary causes via LH/FSH, then evaluate for specific etiologies based on the pattern. [3] [38]

Steps as described in the Endocrine Society and AUA guidelines.

01 **Confirm biochemical low T on two morning specimens.**
Both Endocrine Society 2018 and AUA 2018 guidelines recommend at least two separate morning (7–10 AM) total testosterone measurements, ideally on different days. A single low value is not sufficient for the diagnosis. [3] [38]

02 **Use validated assays.**
Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the reference method. Where unavailable, validated automated immunoassays from accredited laboratories are described as acceptable in guidelines; analog free testosterone assays are explicitly not recommended. [3]

03 **Measure SHBG if total T is borderline or symptoms-discordant.**
Calculated or equilibrium-dialysis free testosterone is recommended in scenarios where SHBG-altering conditions may distort total T interpretation. [3]

04 **Measure LH and FSH to localize the lesion.**
High LH/FSH with low T = primary; low/inappropriately-normal LH/FSH with low T = secondary. The distinction directs subsequent workup. [3]

05 **Secondary hypogonadism → evaluate the hypothalamic-pituitary axis.**
Measure prolactin (to assess for prolactinoma), assess other pituitary hormones if indicated, consider pituitary MRI for severely low T, suspected pituitary disease, or visual symptoms. [3]

06 **Primary hypogonadism → consider karyotype and reproductive workup.**
In men under 50 with primary hypogonadism without obvious cause, karyotyping for Klinefelter syndrome (47,XXY — prevalence ~1:600 male births and commonly under-diagnosed) is recommended. [50]

07 **Assess for reversible contributors.**
Screen for obesity, diabetes, sleep apnea, opioid use, glucocorticoid use, hyperprolactinemia, hypothyroidism, hemochromatosis, and other potentially reversible contributors before or alongside any decision about TRT. [3] [38]

Baseline tests recommended before initiating therapy.

Before any decision about testosterone therapy, current guidelines recommend baseline assessment of: hematocrit, lipid panel, PSA in men ≥40 (per AUA) or ≥50 (per Endocrine Society) or in men with risk factors for prostate cancer, and a baseline cardiovascular risk assessment. [3] [38] These baseline measurements form the comparison set against which on-therapy monitoring will be interpreted.

> **Why the two-morning rule matters.** Testosterone concentrations vary substantially within an individual across days — by as much as 30% in published studies. Single measurements have unacceptably high false-positive (and false-negative) rates for diagnosis. [51]

Symptoms in the literature — and *which are most predictive.*

Symptoms attributed to low testosterone span sexual, physical, and psychological domains. Several are non-specific and overlap substantially with depression, sleep disorders, normal aging, and chronic disease. The EMAS analyses identified a subset of symptoms with substantially higher predictive value than others. [2]

Symptoms with stronger association in EMAS.

The EMAS investigators examined the relationship between specific symptoms and biochemical hypogonadism in 3,219 community-dwelling men aged 40–79. Three sexual symptoms showed the strongest association with measured low testosterone: [2]

- **Reduced morning erections** — strongest individual symptom association in the EMAS analyses. [2]
- **Reduced sexual thoughts (libido)** — second strongest. [2]
- **Erectile dysfunction** — third in the EMAS hierarchy, although ED is multi-causal and the majority of ED is not due to hypogonadism. [2]

The EMAS criteria for late-onset hypogonadism required all three sexual symptoms to be present alongside biochemical confirmation; this combination identified approximately 2% of the EMAS population. [2]

Symptoms with weaker individual association.

Other symptoms commonly attributed to low testosterone — and frequently the basis for clinical evaluation — had weaker individual associations with biochemical hypogonadism in EMAS: [2]

- Fatigue, low energy, reduced exercise capacity;
- Reduced muscle mass and strength;
- Increased body fat;
- Reduced concentration or cognitive performance;
- Depressed mood, irritability;
- Reduced bone mineral density;
- Sleep disturbance;
- Loss of body hair, reduced beard growth (with low specificity).

These symptoms are non-specific and overlap with many other conditions. The literature emphasizes that they do not, by themselves, distinguish hypogonadism from other causes — though they may form part of the clinical syndrome when combined with sexual symptoms and biochemical confirmation. [2] [3]

Symptom screening instruments.

Several questionnaire instruments — including the Androgen Deficiency in the Aging Male (ADAM) questionnaire and the Aging Males' Symptoms (AMS) scale — have been studied as screening tools. Both have high sensitivity but limited specificity in published validation studies, leading to high false-positive rates when used as standalone screens. [52] Major society guidelines do not recommend using these instruments for population-level screening; their role in clinical practice is generally limited to symptom characterization in men already considered for evaluation. [3]

A clinical reading frame. The combination of (1) sexual symptoms — particularly reduced morning erections and reduced libido — and (2) biochemical confirmation on two morning measurements is the most evidence-supported framework for the diagnosis. Non-specific symptoms in isolation are poor diagnostic anchors. [2]

The biochemical threshold: *what the guidelines actually say.*

The numerical threshold below which "low testosterone" is defined varies modestly across society guidelines, and has been the subject of substantial debate. The 2017 Harmonized Reference Range from four U.S. cohorts provided one of the most widely cited statistical anchors. [17]

The Harmonized Reference Range (Travison 2017).

Travison and colleagues, working with data from BLSA, FHS, MrOS, and EMAS, applied LC-MS/MS assay measurements and statistical harmonization to derive reference ranges from non-obese men aged 19–39: [17]

- **Total testosterone 2.5–97.5 percentile range**: 264–916 ng/dL.
- **5th percentile** (used by some guidelines as a threshold for "low"): 264 ng/dL.
- Range estimates apply to morning measurements in healthy, non-obese, non-diabetic young men using mass-spectrometry assays. [17]

Society guideline thresholds.

GUIDELINE	TOTAL T THRESHOLD CITED	NOTES
Endocrine Society 2018	**Lower limit of normal for healthy young men (varies by assay/laboratory)**	Recommends use of LC-MS/MS validated reference ranges; cites Harmonized 264 ng/dL as one reference. [3]
AUA 2018	**< 300 ng/dL**	Threshold for the biochemical component of testosterone deficiency. [38]
European Association of Urology (EAU)	**< 350 ng/dL (12 nmol/L)**	EAU guideline threshold for evaluation; lower threshold considered confirmed deficiency. [53]
EMAS (research definition)	**< 320 ng/dL total AND < 64 pg/mL free**	Late-onset hypogonadism research criterion; both biochemical thresholds required alongside symptoms. [2]

Why the thresholds differ.

The differences across guidelines reflect several methodological and conceptual factors: [54]

- Different reference populations (healthy young men vs. broader adult populations);
- Different assay methodologies underlying the original reference data;
- Different positions on whether the threshold should be set at the lower limit of normal in young men (more conservative for diagnosis) or at a level associated with symptoms (more clinically focused);
- Acknowledgment that single biochemical thresholds inevitably miss the population variability in symptom-concentration relationships.

> **A consistent point across guidelines.** All major guidelines emphasize that the numerical threshold is one component of the diagnosis, not the diagnosis itself. The combination of a confirmed low value (on appropriate testing) with a consistent symptom syndrome is what supports the diagnosis — not the lab number in isolation. [3] [38]

Total testosterone and free testosterone: *what gets measured, and when.*

Total testosterone — the sum of free, albumin-bound, and SHBG-bound fractions — is the principal screening measurement in major guidelines. [3] Free testosterone provides additional information in specific scenarios where SHBG is altered or where total testosterone is borderline relative to the clinical picture. [22]

Total testosterone measurement principles.

- **Morning specimens**: testosterone peaks early morning (6–10 AM); afternoon specimens systematically underestimate the diagnostic value. [18]
- **Fasting state preferred but not strictly required**: acute glucose intake can transiently lower testosterone by ~25%, making fasting specimens more standardized for diagnostic purposes. [55]
- **Two separate measurements**: required by both Endocrine Society and AUA guidelines for diagnosis. [3] [38]
- **Assay methodology matters**: LC-MS/MS is the reference method; validated immunoassays from accredited laboratories are acceptable per guidelines. [3]
- **Acute illness**: acute illness or surgical stress transiently lowers testosterone; diagnostic testing should be deferred until recovery. [3]

Free testosterone — when to measure and how.

Major guidelines recommend free testosterone measurement in scenarios including: [3]

- Total testosterone is borderline (close to the diagnostic threshold);
- Conditions that alter SHBG are present (obesity, diabetes, hyperthyroidism, hepatitis, anticonvulsant use, etc.);
- The clinical syndrome and the total testosterone value are discordant.

Free testosterone should be measured by equilibrium dialysis with mass spectrometry (the reference method) or calculated from total T, SHBG, and albumin using the Vermeulen equation. [24] Analog/direct free testosterone immunoassays are explicitly recommended against by major guidelines for diagnostic use. [3]

A note on diurnal variation in older men.

The diurnal variation in testosterone — substantial in healthy young men — is attenuated in older men. [56] This means afternoon measurements in older men, while still less reliable than morning specimens, are less misleading than they would be in younger men. The morning-specimen recommendation remains the standard regardless of age. [3]

A reading frame for the lab chapter. Laboratory measurement of testosterone is one of the most-cited examples in clinical medicine of how methodology affects interpretation. The threshold, the assay, the timing, and the SHBG context all influence what a number means. Apparent discrepancies between symptoms and lab values are frequently methodological rather than clinical. [51]

LH, FSH, SHBG, and prolactin: *localizing the lesion.*

When biochemical low testosterone is confirmed, the next step in the workup is determining whether the lesion is in the testis itself (primary hypogonadism) or upstream in the hypothalamic-pituitary axis (secondary hypogonadism). LH, FSH, and prolactin are the principal markers used for this localization, alongside SHBG to refine interpretation of total testosterone. [3]

LH and FSH — the localizing markers.

PATTERN	LH	FSH	INTERPRETATION
Primary hypogonadism	Elevated	Elevated	Loss of testosterone and inhibin B feedback to pituitary. [3]
Secondary hypogonadism	Low or inappropriately normal	Low or inappropriately normal	Pituitary-hypothalamic dysfunction; failure to mount a compensatory rise. [3]
Isolated FSH elevation	Normal	Elevated	Often reflects impaired spermatogenesis with preserved Leydig cell function. Inhibin B feedback to FSH is selective. [8]

SHBG measurement.

SHBG measurement is straightforward and widely available. Normal reference ranges in adult men are approximately 10–80 nmol/L, with substantial inter-individual variability and age-related drift upward. [22] Major contributors to discordance between total and free testosterone — obesity (low SHBG), thyroid disease (high SHBG), liver disease (high SHBG), and oral medications — should be considered when interpreting total testosterone alongside SHBG. [22]

Prolactin and pituitary workup.

Hyperprolactinemia is a treatable cause of secondary hypogonadism that should be excluded as part of the standard workup. [3] Elevated prolactin suppresses GnRH secretion, lowering LH and FSH and downstream testosterone. Causes include:

- **Prolactinoma** — the most common pituitary tumor; prolactin levels typically scale with tumor size.
- **Medications** — antipsychotics (particularly first-generation), some antiemetics, opioids, and others.
- **Hypothyroidism** — elevated TRH stimulates prolactin secretion.
- **Stress and stalk effect** — non-prolactinoma pituitary lesions can elevate prolactin by disrupting hypothalamic dopaminergic inhibition.

Pituitary MRI is recommended in cases of substantial unexplained secondary hypogonadism, particularly with hyperprolactinemia, headaches, visual symptoms, or other pituitary hormone abnormalities. [3]

Other markers that round out the workup.

- **TSH** — thyroid dysfunction can cause symptom overlap and influences SHBG. [3]
- **Estradiol** — in men with obesity or other contributors, estradiol may be relatively elevated; baseline measurement is part of the workup for some clinicians, though guidelines vary. [13]
- **HbA1c, fasting glucose** — diabetes screening as part of identifying reversible contributors. [3]
- **Iron studies / ferritin** — hemochromatosis can cause both primary and secondary hypogonadism by iron deposition in testes and pituitary; ferritin screening is part of the workup in suggestive cases. [57]
- **Inhibin B** — primarily a research and infertility marker; reflects Sertoli cell function and seminiferous tubule integrity. [8]

Why the workup is structured this way. The pattern of markers — not any single value — distinguishes treatable causes (prolactinoma, thyroid disease) from age-related and functional patterns. Skipping this step risks missing reversible pathology. [3]

Three randomized trials anchor the modern *evidence base.*

The contemporary evidence base on testosterone therapy in older men is anchored by three principal randomized trial programs: The Testosterone Trials (T-Trials, 2016), the earlier TOM trial (2010) that was halted for adverse events, and TRAVERSE (2023) — the cardiovascular safety trial completed nearly a decade after FDA-mandated labeling changes. [58] [59] [60]

The Testosterone Trials — design and population.

The Testosterone Trials (T-Trials) were a coordinated set of seven double-blind, placebo-controlled trials testing 1% testosterone gel versus placebo gel over 12 months in 790 community-dwelling men aged 65 or older with low testosterone (mean total T < 275 ng/dL on two morning measurements) and consistent symptoms. [58] Each of the seven trials evaluated a different primary outcome domain:

- **Sexual Function Trial** — sexual activity, desire, erectile function. [58]
- **Physical Function Trial** — 6-minute walk distance. [58]
- **Vitality Trial** — fatigue measures. [58]
- **Cognitive Function Trial** — memory and executive function measures. [61]
- **Anemia Trial** — hemoglobin in men with anemia. [62]
- **Bone Trial** — bone density and bone strength via QCT. [63]
- **Cardiovascular Trial** — non-calcified coronary plaque volume by CT angiography. [64]

Principal findings as published.

TRIAL	RESULT	EFFECT DIRECTION / DETAIL
Sexual Function	**Positive**	Significant improvement in sexual activity, desire, and erectile function vs placebo. [58]
Physical Function	**Modestly positive**	Small but significant improvement in 6-min walk and self-reported physical function. [58]
Vitality	**Mixed**	No significant change on the primary FACIT-Fatigue scale; significant on a secondary mood/energy measure. [58]
Cognitive Function	**Null**	No significant effect on memory or executive function in men with age-associated memory impairment. [61]
Anemia	**Positive**	Hemoglobin rose significantly in both unexplained anemia and known-cause anemia subgroups. [62]
Bone	**Positive**	Significant increases in vertebral and femoral neck volumetric BMD and estimated bone strength. [63]
Cardiovascular	**Concerning signal**	Greater progression of non-calcified coronary plaque volume in active arm vs placebo over 12 mo. [64]

How the T-Trials are read. The T-Trials demonstrated symptom-level benefit in sexual function, modest benefit in physical function, and end-organ benefit in bone and anemia. The cardiovascular imaging signal — alongside the older TOM data — fueled regulatory and clinical concern that motivated FDA's 2015 labeling change and the subsequent TRAVERSE trial (Chapter 12). [65]

The TOM trial: *halted early for adverse events.*

The Testosterone in Older Men with Mobility Limitations (TOM) trial was a randomized, double-blind, placebo-controlled trial of testosterone gel in 209 men aged 65 or older with low testosterone and mobility limitations. The trial was stopped early by its Data Safety Monitoring Board after 6 months when adverse cardiovascular events occurred at substantially higher rates in the testosterone arm than placebo. [59]

Findings as reported.

- 23 cardiovascular events in the testosterone arm vs 5 in the placebo arm during the trial period. [59]
- Events included myocardial infarction, stroke, syncope, peripheral edema, arrhythmias, and others. [59]
- The testosterone dose used (10g gel/day adjusted upward to target serum T 500–1000 ng/dL) reached higher steady-state levels than typical clinical practice. [59]
- Median age in the cohort was 74 — older than most subsequent TRT trial populations. [59]

How TOM influenced the field.

The TOM trial — combined with two observational analyses published in 2013–2014 (Vigen et al., JAMA 2013; [66] Finkle et al., PLoS One 2014 [67]) reporting increased cardiovascular event rates in TRT-exposed men — triggered:

- A 2014 FDA Drug Safety Communication; [68]
- A 2015 FDA label change adding cardiovascular warning language to all approved testosterone products; [68]
- An FDA requirement that the manufacturer of one product conduct a large randomized cardiovascular outcomes trial — which became the TRAVERSE trial. [60]

Critiques of the TOM evidence.

Subsequent commentary noted several methodological considerations: [69]

- Heterogeneous adverse event categories grouped together;
- Older, mobility-limited population with high baseline cardiovascular risk;
- Aggressive titration to serum T concentrations at the upper end or above the physiologic range;
- Small absolute event numbers leading to wide confidence intervals.

The observational analyses (Vigen 2013, Finkle 2014) were similarly critiqued for selection bias and methodological concerns; counter-analyses with different methodological approaches reported neutral or favorable cardiovascular associations. [70] The mixed signal — randomized data suggesting concern, observational data conflicting — was the principal motivation for the prospectively powered TRAVERSE trial (Chapter 12). [60]

> **The reading frame.** TOM was an important but methodologically limited signal. Whether it represented a true causal cardiovascular harm of testosterone therapy at clinically relevant doses — or an artifact of the specific population, dose, and event capture — was the open question that TRAVERSE was designed to answer. [60]

TRAVERSE: the *FDA-mandated cardiovascular safety trial.*

The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men (TRAVERSE) trial was a multicenter, randomized, double-blind, placebo-controlled non-inferiority trial designed to assess cardiovascular safety of testosterone therapy in men with hypogonadism and elevated cardiovascular risk. Results were published in the New England Journal of Medicine in 2023. [60]

Design.

POPULATION

N = 5,246. Men aged 45–80 with two morning total T < 300 ng/dL, hypogonadal symptoms, and pre-existing or high risk of cardiovascular disease. [60]

INTERVENTION

Transdermal 1.62% testosterone gel vs placebo gel, daily. Dose titrated to maintain serum total T 350–750 ng/dL. [60]

PRIMARY ENDPOINT

First occurrence of major adverse cardiovascular event (MACE): death from cardiovascular causes, nonfatal MI, or nonfatal stroke. Non-inferiority margin 1.5. [60]

DURATION

Mean treatment exposure ~22 months; mean follow-up ~33 months. Conducted at 316 U.S. sites, 2018–2022. [60]

Principal findings.

TRAVERSE met its pre-specified non-inferiority criterion for the primary MACE endpoint: [60]

- **Primary MACE**: 7.0% testosterone vs 7.3% placebo; hazard ratio 0.96 (95% CI 0.78–1.17). Non-inferiority confirmed. [60]
- **Cardiovascular mortality**: similar between groups. [60]
- **Atrial fibrillation**: higher incidence in testosterone arm (3.5% vs 2.4%). [60]
- **Pulmonary embolism**: higher incidence in testosterone arm (0.9% vs 0.5%). [60]
- **Acute kidney injury**: higher incidence in testosterone arm (2.3% vs 1.5%). [60]
- **Prostate cancer incidence**: similar between groups (0.5% vs 0.4%). [60]
- **Fracture incidence**: *higher* in testosterone arm (3.5% vs 2.5%) — a finding that was notable given the prior bone-density benefit reported in the T-Trials. [71]

How TRAVERSE has been interpreted.

The TRAVERSE results have been read across the field as supporting non-inferiority on the primary cardiovascular safety endpoint — relieving the principal concern raised by TOM and the 2013–2014 observational analyses — while identifying secondary signals (atrial fibrillation, PE, acute kidney injury, fracture) that warrant inclusion in monitoring and counseling. [72] Endocrine Society guidance was updated to reflect the TRAVERSE findings, and the FDA's 2015 labeling has been revisited in light of the data. [73]

Important caveats. TRAVERSE was a non-inferiority trial — it did not test whether TRT reduced cardiovascular events. The fracture signal was unexpected and the mechanism is not fully understood. The trial population had elevated CV risk and may not generalize fully to lower-risk men. Subgroup and post-hoc analyses continue to be published. [71]

Same molecule, *different delivery* — different pharmacokinetics.

Testosterone can be administered by intramuscular injection, subcutaneous injection, transdermal application (gel, solution, patch), oral administration (testosterone undecanoate), pellets implanted subcutaneously, nasal gel, and buccal patches. Each modality produces a different pharmacokinetic profile with implications for symptom control, monitoring, and side effects. [74]

The principal categories.

MODALITY	TYPICAL DOSE RANGE STUDIED	PHARMACOKINETIC PROFILE
IM testosterone cypionate or enanthate	50–200 mg q1–2 weeks	Supraphysiologic peak 24–48 hr post-injection; gradual decline to trough by end of interval. [74]
SubQ testosterone cypionate/enanthate	50–100 mg q1 week (or split twice weekly)	Smaller peak/trough swings than IM; comparable bioavailability. [75]
IM testosterone undecanoate (long-acting)	750–1000 mg q10–14 weeks	Slower release; reduced peak/trough variability; product-specific monitoring requirements. [76]
Transdermal gel 1%, 1.62%, 2%	25–100 mg/day applied	Daily dosing; steady-state serum T after 1–2 weeks; risk of transfer to others. [74]
Transdermal patch	2–6 mg/day	Daily application; common skin irritation; less commonly used in current practice. [74]
Oral testosterone undecanoate	158–396 mg twice daily with food	Lymphatic absorption avoids first-pass hepatic toxicity that prevented oral T historically. Approved in U.S. as Jatenzo (2019), Tlando (2022), Kyzatrex (2022). [77]
Subcutaneous pellets	75 mg pellets × 6–12 every 3–6 months	In-office implantation; very stable serum T over months; difficult to adjust mid-cycle. [78]
Nasal gel	11 mg per nostril TID	Multiple-daily intranasal application; less suppression of LH/FSH and spermatogenesis than other routes in some studies. [79]
Buccal patch	30 mg twice daily	Adhesive patch on gum; gum irritation common; less used. [74]

Why the modality choice matters.

The pharmacokinetic differences across modalities have several practical implications: [74]

- **Symptom control** can vary across the dosing interval, particularly for once-weekly or longer-interval IM regimens with greater peak-to-trough swings;
- **Hematocrit rise** is more pronounced with higher peaks; IM regimens that reach supraphysiologic peaks tend to drive larger hematocrit increases than transdermal regimens (Chapter 10);
- **Estradiol** rises with the testosterone load; the magnitude reflects the peak and the individual's aromatase activity (Chapter 9);
- **Transfer risk** is unique to transdermal gels, with FDA boxed warnings about secondary exposure of women and children;
- **Reversibility** differs — short-acting IM and subQ can be stopped abruptly; pellets and long-acting IM undecanoate cannot.

Injection vs. transdermal: *pharmacology and trade-offs.*

The two most-commonly-prescribed categories — injectable testosterone esters and transdermal gel — produce broadly equivalent symptomatic and biochemical efficacy at appropriately titrated doses but differ in side-effect profile and convenience. [74]

Injectable testosterone esters.

The most common injectable testosterone esters in U.S. practice are testosterone cypionate and testosterone enanthate, oil-based intramuscular preparations with similar pharmacokinetics. Both have been used for decades; their long history of use predates modern FDA-style approval processes, contributing to widespread off-label dosing variation in clinical practice. [74]

Subcutaneous administration of testosterone cypionate/enanthate has gained adoption in recent years. Published comparisons report that subQ delivery produces serum testosterone profiles comparable to IM injection with reduced peak-to-trough variability and potentially smaller hematocrit rises. [75] SubQ injection uses smaller-gauge needles and shorter injection times; some patients find it more tolerable. [75]

Transdermal gel.

Transdermal gels (1%, 1.62%, 2% formulations from various manufacturers) produce relatively stable daily serum testosterone profiles. Steady-state is typically achieved within 1–2 weeks of consistent application. [74] Key considerations include:

- **Inter-individual absorption variability**: some men achieve target serum T at standard doses; others require dose escalation or do not achieve target despite higher doses. [74]
- **Transfer risk**: FDA boxed warning describes secondary exposure of women and children from skin contact with the application site. Hand washing, allowing complete drying before contact, and avoiding contact with the application area mitigate but do not eliminate risk. [80]
- **Skin irritation**: minor erythema at the application site is common; severe irritation is uncommon. [74]

Comparative head-to-head data.

Direct head-to-head randomized comparisons of injectable vs transdermal testosterone with hard clinical endpoints are limited; most data come from cross-trial comparisons and pharmacokinetic studies. The Endocrine Society guideline states that the choice between modalities should consider patient preference, cost, side-effect tolerance, and convenience, in the absence of strong outcome-based comparative evidence. [3]

Pellet implants.

Subcutaneous testosterone pellets — fused crystalline testosterone implanted in the subcutaneous tissue of the gluteus or hip every 3–6 months — produce stable serum T over months with low day-to-day variability. [78] Trade-offs include the requirement for an in-office procedure, the difficulty of adjusting dose mid-cycle, occasional pellet extrusion or local infection, and limited reversibility once implanted. [78]

Practical reading frame. No single TRT modality has been demonstrated to be globally superior in randomized comparisons. The choice typically reflects patient preference, cost, monitoring patterns, side-effect profiles, and clinician familiarity. Major society guidelines list all approved modalities as options without preference ordering. [3]

Doses studied and the *standard monitoring panel.*

This page presents dose ranges as studied in published clinical trials and as listed in product labeling, alongside the monitoring panel recommended by major society guidelines. These values are descriptive of published research, not recommendations for any individual reader. [3]

Target serum testosterone range.

Major guidelines describe a target serum total testosterone range during TRT of approximately **400–700 ng/dL** at mid-cycle (for injectable regimens) or steady-state (for transdermal/oral regimens) — corresponding to the mid-normal range for healthy young adult men. [3] [38] Targeting consistently supraphysiologic concentrations is described as inappropriate in published guidelines. [3]

When to draw monitoring labs.

- **IM/subQ regimens**: serum T drawn at mid-cycle (approximately halfway between injections) to characterize the average exposure. Some clinicians also measure trough levels. [3]
- **Transdermal gel**: serum T drawn at any time after steady-state is achieved (typically >2 weeks of consistent use) and at least 2 hours after the most recent application. [74]
- **Oral testosterone undecanoate**: serum T drawn approximately 6 hours after the morning dose (per product labeling), with attention to the specific assay calibration. [77]

The standard on-therapy monitoring panel.

MARKER	FREQUENCY	CONTEXT
Total testosterone	**3 mo after initiation; then q6–12 mo**	Titration and confirmation of target range. [3]
Hematocrit / hemoglobin	**3 mo, 6 mo, then annually**	Monitor for erythrocytosis (Chapter 10). [3]
PSA (men ≥40 or with risk factors)	**3 mo, 12 mo, then per general screening**	Per current prostate cancer screening guidance. [38]
Estradiol	**As clinically indicated**	Routine measurement not universally recommended; some guidelines suggest when symptoms suggest elevated E2 (Chapter 9). [13]
Lipid panel	**As part of standard cardiovascular risk monitoring**	TRT effects on lipids are modest in trials; not a primary monitoring marker. [3]
Symptom response	**3 mo, 6 mo, 12 mo, ongoing**	Symptom improvement is the principal efficacy measure. [3]

When dose adjustment is considered.

Major guidelines describe dose adjustment as appropriate when serum testosterone is outside the target range, when hematocrit rises above safety thresholds (Chapter 10), or when symptoms are not adequately controlled despite biochemical adequacy. [3] Changes in modality or dosing frequency are considered alongside dose changes when peak-trough variability appears to drive symptom fluctuations. [74]

Reading frame. Monitoring frequency, target ranges, and dose-adjustment thresholds are individualized clinical decisions; the table above summarizes the patterns described in major guidelines as defaults. Specific values vary in clinical practice and across guideline versions. [3]

Estradiol in men: *not a side effect — a co-hormone.*

Despite cultural framing as a "female hormone," estradiol has well-characterized and essential roles in male physiology. Major effects mediated at least partly through estradiol — derived from aromatization of testosterone — include bone density maintenance, central regulation of the HPG axis, libido, and vascular function. [20] [81]

The Finkelstein dose-finding study.

Finkelstein and colleagues (NEJM 2013) conducted a controlled study in which young healthy men were pharmacologically induced into a hypogonadal state (via GnRH agonist) and then assigned to testosterone gel at varying doses, with or without an aromatase inhibitor (anastrozole). The design allowed dissociation of testosterone effects from estradiol effects, since aromatase inhibition selectively blocked the latter while testosterone supplementation maintained the former. [81]

Principal findings included: [81]

- **Lean mass, muscle strength, and leg-press performance** were primarily dependent on testosterone exposure, not estradiol.
- **Subcutaneous and intraabdominal fat accumulation** were primarily dependent on testosterone (loss promoted by adequate T).
- **Sexual function** — desire and erectile function — was substantially dependent on estradiol; men with adequate testosterone but suppressed estradiol (from aromatase inhibition) had impaired sexual function. [81]
- The threshold for adverse effects on sexual function from low estradiol was approximately E2 < 10 pg/mL. [81]

Bone density evidence.

Multiple lines of evidence — including case reports of men with aromatase deficiency, estrogen receptor knockout mouse models, and clinical studies — have demonstrated that estradiol is a primary determinant of bone density in men. Estradiol thresholds below approximately 10–20 pg/mL are associated with increased bone resorption and lower BMD. [82]

Reference ranges in men.

Adult male estradiol reference ranges vary by assay methodology. Mass-spectrometry-based reference ranges in healthy adult men generally fall in the approximately **10–40 pg/mL** range. [83] As with testosterone, immunoassay measurements of low estradiol concentrations are less accurate than mass-spectrometry methods, and routine clinical assays are not always calibrated for the male estradiol range. [83]

What the Finkelstein data did not address. The study examined short-term physiologic effects in healthy young men under controlled conditions. Long-term outcomes — including cardiovascular events, cognitive trajectories, and mood — under varying estradiol exposures in men with hypogonadism receiving TRT remain less characterized in randomized data. [81]

Aromatase inhibitors in men: *narrow indications, widespread use.*

Aromatase inhibitors (AIs) — most commonly anastrozole — block the aromatase enzyme that converts testosterone to estradiol. AIs are FDA-approved for use in women with hormone-receptor-positive breast cancer. Their use in men is off-label and concentrated in two settings: as a fertility-preserving alternative to TRT, and as an adjunct to TRT to manage elevated estradiol. [84]

Use as a fertility-preserving alternative.

In men with obesity-associated hypogonadism characterized by elevated estradiol-to-testosterone ratio, aromatase inhibition raises endogenous testosterone (by reducing central estradiol-mediated negative feedback on LH) without suppressing spermatogenesis. [85] This contrasts with exogenous TRT, which suppresses spermatogenesis (Chapter 1.2). Aromatase inhibitor use for this indication is summarized in detail in Chapter 13 (Fertility Preservation). [85]

Use as an adjunct to TRT.

Some men on TRT — particularly those with higher body fat — develop elevated serum estradiol from the increased aromatization substrate provided by exogenous testosterone. Symptoms attributed to elevated E2 in some clinical commentary include gynecomastia, water retention, nipple sensitivity, and mood changes — though the symptom-E2 relationship has not been rigorously characterized in randomized data in this context. [13]

The use of AIs in men on TRT is widespread in clinical practice but is not endorsed as a routine practice by major society guidelines. [3] Major concerns documented in the literature include:

- **Bone density loss** — given estradiol's established role in male bone density, sustained suppression of estradiol is associated with accelerated bone loss in some studies. [82]
- **Impaired sexual function** — Finkelstein demonstrated that E2 below approximately 10 pg/mL impairs libido and erectile function even when testosterone is adequate. [81]
- **Lipid changes** — suppressing estradiol in men can adversely affect lipid profile. [86]
- **Cognitive and mood effects** — less characterized but suggested in some smaller studies. [86]

What the major guidelines say.

The 2018 Endocrine Society guideline does not recommend routine aromatase inhibitor use in men on TRT. [3] The AUA 2018 guideline similarly does not endorse it as routine. [38] Use in clinical practice is generally reserved for specific scenarios — symptomatic elevated estradiol with documented elevated levels — and approached with monitoring of both E2 and the downstream effects on bone, lipids, and sexual function. [3]

> **The reading frame.** "Treating" elevated estradiol with aromatase inhibition is one of the more common areas in TRT practice where the published evidence and the prevailing practice patterns are not aligned. The downstream consequences of estradiol suppression in men — particularly on bone and sexual function — are mechanistically well-characterized and should be considered when AIs are used. [81] [82]

Hematocrit rise: the *most-monitored adverse effect.*

Among the laboratory changes that consistently occur with testosterone therapy, the rise in hematocrit and hemoglobin is the most predictable and the most-monitored. Major society guidelines specify thresholds at which dose reduction, dose modification, or therapy discontinuation should be considered. [3] [87]

The mechanism.

Testosterone increases red blood cell mass through several mechanisms: [30]

- **Suppression of hepcidin** — the master regulator of iron homeostasis; suppressed hepcidin increases iron availability for erythropoiesis.
- **Increased erythropoietin sensitivity** — bone marrow erythroid precursors show enhanced responsiveness to EPO under androgen stimulation.
- **Direct effects on erythroid precursors** — AR-mediated effects on proliferation and differentiation.

The rise in hematocrit is dose-dependent and modality-dependent. IM regimens with high peak concentrations tend to produce larger hematocrit rises than transdermal regimens delivering similar average concentrations. [87] In the T-Trials, hematocrit increased significantly in the testosterone arm vs placebo, with values exceeding 54% in approximately 7% of treated men. [88]

Thresholds and clinical implications.

Endocrine Society and AUA guidelines specify hematocrit thresholds for intervention: [3] [38]

- **> 54%** — discontinue or reduce dose; consider switch to a lower-peak modality; consider therapeutic phlebotomy.
- **50–54%** — closer monitoring; consider dose reduction; address contributors (obesity, sleep apnea).
- **Baseline > 48%** — caution before initiation; some guidelines suggest deferring TRT and addressing reversible contributors first.

The principal concern with elevated hematocrit is increased blood viscosity, with theoretical risk of venous thromboembolism, stroke, and other vascular events. [89] Some — though not all — observational studies have reported associations between elevated hematocrit on TRT and adverse cardiovascular outcomes; the data are less consistent than the mechanistic plausibility might suggest. [89]

Sleep apnea as a contributor.

Obstructive sleep apnea is an independent driver of erythrocytosis (via chronic intermittent hypoxia). The combination of TRT and untreated OSA is particularly likely to produce elevated hematocrit. Screening for and addressing OSA is described in some guidelines as part of the workup for elevated hematocrit on TRT. [3]

Therapeutic phlebotomy.

Therapeutic phlebotomy — periodic removal of one unit (~500 mL) of blood — is used in clinical practice to manage elevated hematocrit while continuing TRT. The approach has not been rigorously studied in randomized trials specifically for TRT-induced erythrocytosis; it is borrowed from the management of polycythemia vera. [90] Blood donation centers often have eligibility restrictions that may apply. [90]

The TRAVERSE context. TRAVERSE reported higher pulmonary embolism incidence in the testosterone arm (0.9% vs 0.5%), consistent with concern about viscosity-related events. The trial's hematocrit monitoring protocol was robust; the residual signal suggests that even with monitoring, some risk persists. [60]

The prostate question: *biology, the older fear, and the current data.*

The relationship between testosterone and the prostate has been one of the most debated topics in TRT for decades. The historical concern — that testosterone "fuels" prostate cancer — was based on observations from the 1940s and shaped clinical practice for over half a century. More recent biology, observational analyses, and randomized trial data have substantially revised this framing while leaving specific clinical questions open. [91]

The androgen-prostate biology.

The prostate is one of the most androgen-dependent tissues. Both growth and function are AR-driven, primarily via DHT after 5α-reductase conversion (Chapter 2). Androgen deprivation — surgical castration or pharmacologic GnRH suppression — produces prostate involution and is the basis for androgen-deprivation therapy in advanced prostate cancer. [19]

The Huggins legacy and the historical fear.

Charles Huggins and colleagues' 1941 demonstrations that androgen deprivation caused prostate cancer regression, and that exogenous testosterone administration to men with advanced prostate cancer (some of whom had been previously castrated) was associated with disease progression, founded the field of androgen-deprivation therapy and earned a 1966 Nobel Prize. [92] This work also generated a durable clinical concern that any testosterone administration would risk causing or accelerating prostate cancer.

The saturation model.

The "saturation model," articulated principally by Morgentaler and colleagues over the past two decades, proposes that androgen-prostate signaling saturates at relatively low testosterone concentrations (approximately 200–250 ng/dL). [93] Above this threshold, additional testosterone does not produce additional prostate AR activation. The model is supported by:

- The lack of dose-response relationship between higher serum testosterone and prostate growth in physiologic-range studies; [93]
- The narrow range of intraprostatic DHT concentrations across a wide range of serum testosterone in human studies; [93]
- The absence of a clear linear relationship between serum testosterone and prostate cancer risk in large epidemiologic studies. [94]

Modern observational and trial evidence.

Contemporary evidence has substantially refined the historical fear: [95]

- Endogenous testosterone levels are **not** associated with prostate cancer risk in large prospective cohort meta-analyses; [94]
- TRT trials including the T-Trials and TRAVERSE have not demonstrated increased prostate cancer incidence in the active arms vs placebo; [60] [88]
- Multiple observational series of TRT in men with treated prostate cancer report no clear increase in recurrence in selected populations. [96]

What this doesn't establish. The data do not establish safety of TRT in men with active or untreated prostate cancer, which remains a contraindication in major guidelines. The data also do not establish that TRT can be initiated in men with prior prostate cancer without specialty input. The revised framing is that low-testosterone status is not protective and high-physiologic testosterone is not a clear-cut risk amplifier within the saturation framework — but individual scenarios require clinical assessment. [3] [38]

BPH, PSA, and the *monitoring framework.*

Beyond cancer concerns, two practical prostate-related issues during TRT are benign prostatic hyperplasia (BPH) and PSA monitoring. The literature has substantially clarified the expected effects on each during TRT. [38]

BPH and lower urinary tract symptoms.

Historical concern that TRT would substantially worsen BPH-related lower urinary tract symptoms (LUTS) has not been borne out in modern data. Pooled analyses of TRT trials report no clinically meaningful increase in International Prostate Symptom Score (IPSS) or in urinary retention events vs placebo at the doses and durations studied. [97] The TRAVERSE trial similarly did not report a meaningful BPH-related signal. [60]

Severe LUTS at baseline is sometimes listed as a relative contraindication for TRT initiation in guidelines, with the recommendation to optimize BPH management before TRT in severely symptomatic men. [38]

PSA changes during TRT.

TRT typically produces a modest, transient rise in PSA — on the order of 0.3–0.5 ng/mL in pooled analyses — reflecting the increased androgen exposure of prostatic epithelium. [98] The rise generally occurs within the first 6 months and then plateaus. Larger or progressive rises warrant additional evaluation. [38]

PSA monitoring thresholds.

Major guidelines specify thresholds at which urologic referral is recommended during TRT: [3] [38]

- **Absolute PSA > 4.0 ng/mL** — urologic evaluation per general PSA screening guidance.
- **PSA rise > 1.4 ng/mL in any 12-month interval** — urologic evaluation.
- **PSA velocity > 0.4 ng/mL/year over a sustained period** — consider urologic evaluation.
- **Abnormal digital rectal examination at any time** — urologic evaluation.

Baseline assessment before initiation.

Major guidelines specify baseline PSA measurement before TRT initiation in men:

- Age ≥ 40 with risk factors for prostate cancer (AUA); [38]
- Age ≥ 40–50 generally (varies by guideline); [3]
- Any man with a family history of prostate cancer or African ancestry, where general screening guidance applies more aggressively. [38]

> **The reading frame.** PSA monitoring during TRT integrates standard prostate cancer screening guidance with the modest expected rise from TRT itself. Patterns that deviate from expected trigger urologic evaluation. Routine PSA monitoring during TRT is one of the standard components of the on-therapy panel discussed in Chapter 8. [3] [38]

The cardiovascular debate: *before and after TRAVERSE.*

The cardiovascular safety of testosterone therapy was the most contentious question in this field for the decade between the TOM trial (2010) and TRAVERSE (2023). The published evidence accumulated in stages — observational signals, mixed meta-analyses, regulatory response, and finally a large dedicated randomized trial. This chapter retraces the evidence and where the field has landed. [65]

The 2013–2014 observational signals.

Two widely cited observational analyses raised cardiovascular concerns: [66] [67]

- **Vigen et al. (JAMA 2013)** — a retrospective analysis of VA records reporting higher rates of adverse cardiovascular events in TRT-exposed men with cardiovascular disease history. [66] The analysis was subsequently critiqued for methodological choices including the definition of TRT exposure and the handling of competing risks. [69]
- **Finkle et al. (PLoS One 2014)** — a cohort analysis reporting increased non-fatal MI risk in the 90 days following TRT initiation, particularly in older men and men with prior cardiac disease. [67]

Counter-analyses with different methodological approaches reported neutral or favorable findings. A consistent take across critiques was that the observational data could not resolve the question due to the inherent confounding by indication. [70]

FDA regulatory response.

The FDA convened an advisory committee in 2014 and issued a Drug Safety Communication acknowledging the conflicting data and announcing a label change. The 2015 label change included: [68]

- A warning about possible increased risk of MI and stroke;
- Clarification that TRT was approved for hypogonadism due to identified medical conditions, not for age-related testosterone decline alone;
- A requirement that one manufacturer conduct a large randomized cardiovascular outcomes trial — TRAVERSE.

Meta-analyses pre-TRAVERSE.

Multiple meta-analyses synthesized the pre-TRAVERSE randomized data with varying conclusions, reflecting differences in inclusion criteria, definition of MACE, and statistical methods. [99] The Endocrine Society 2018 guideline characterized the cardiovascular evidence base as "inconclusive" and noted the pending TRAVERSE results as the principal anticipated resolution. [3]

> **The reading frame.** Between 2013 and 2023, clinical practice on TRT in men with cardiovascular disease was constrained by an evidence base that mixed concerning observational signals with reassuring randomized data — neither resolving the question definitively. TRAVERSE was specifically designed to resolve the major adverse cardiovascular events question. [60]

After TRAVERSE: *where the cardiovascular evidence stands.*

TRAVERSE's primary endpoint result — non-inferiority for the composite of CV death, nonfatal MI, and nonfatal stroke — substantially resolved the central cardiovascular safety question that had dominated the field for a decade. [60] The trial also raised several secondary considerations that have entered ongoing clinical discussion.

What TRAVERSE supports.

- Non-inferiority of testosterone therapy vs placebo for the composite primary MACE endpoint in men with hypogonadism and elevated cardiovascular risk; [60]
- Acceptable primary safety profile sufficient for the trial to confirm non-inferiority; [60]
- Subgroup analyses generally consistent with the primary finding. [60]

What TRAVERSE did not establish.

- TRAVERSE was a non-inferiority trial. It did not establish that TRT *reduces* cardiovascular events. [60]
- The trial population had elevated baseline CV risk; findings may not generalize fully to lower-risk men or to non-clinical-trial dosing patterns. [60]
- The trial used transdermal gel; findings may not directly translate to other modalities — although mechanistic plausibility supports class-wide read-across for the principal primary outcome. [60]
- The trial duration (mean ~22 months exposure, ~33 months follow-up) is not informative about decade-long outcomes. [60]

Secondary signals to consider.

TRAVERSE identified secondary findings that have entered clinical counseling: [60] [71]

- **Atrial fibrillation**: 3.5% vs 2.4%. Mechanism uncertain; may relate to direct androgen effects or to weight/hematocrit changes.
- **Pulmonary embolism**: 0.9% vs 0.5%. Consistent with viscosity-related concerns.
- **Acute kidney injury**: 2.3% vs 1.5%. Mechanism uncertain.
- **Fracture incidence**: 3.5% vs 2.5%. Unexpected given the T-Trials bone density benefit; mechanism actively investigated. [71]

Mortality and other observational data.

Multiple large observational cohort studies — including analyses from the Mayo Clinic, the Veterans Affairs system, and several international cohorts — have reported associations between treated low testosterone and improved survival vs untreated low testosterone in men with multiple comorbidities. [100] These observational findings are subject to the confounding-by-indication concerns discussed earlier in the chapter and should not be over-read as causal. [100]

The current synthesis. Major society guidance updated post-TRAVERSE is broadly that TRT at appropriately monitored doses in men with confirmed hypogonadism does not appear to increase major cardiovascular events on the timescale studied. Secondary signals warrant inclusion in counseling and monitoring. Indication selectivity, monitoring, and addressing reversible contributors remain the core of safe practice as described in current guidelines. [73]

TRT suppresses fertility. *Alternatives preserve it.*

As characterized in Chapter 1.2, exogenous testosterone suppresses the HPG axis and arrests spermatogenesis through the loss of intratesticular testosterone signaling. Men who desire current or future fertility are therefore generally not candidates for conventional TRT. [14] Several alternative approaches preserve or restore fertility while addressing hypogonadism through different mechanisms. [14]

The four principal alternatives.

CLOMIPHENE CITRATE

Selective estrogen receptor modulator. Blocks estrogen feedback at the hypothalamus/pituitary, increasing GnRH and downstream LH/FSH. Stimulates endogenous testosterone production. Available as a mixture of two isomers (zuclomiphene and enclomiphene). [101]

ENCLOMIPHENE

Pure trans-isomer of clomiphene. Believed to provide the estrogen-receptor-blocking effects responsible for raising testosterone, while excluding the longer-acting zuclomiphene isomer thought to drive some side effects. Has been studied in phase 3 trials for secondary hypogonadism. [102]

HUMAN CHORIONIC GONADOTROPIN (HCG)

LH-mimetic. Binds LH receptor on Leydig cells, stimulating endogenous testosterone production directly. Subcutaneous administration; preserves intratesticular testosterone and spermatogenesis. [103]

AROMATASE INHIBITORS

Most commonly anastrozole. Reduces estradiol-mediated central feedback, raising endogenous LH and downstream testosterone. Most useful in men with elevated estradiol-to-testosterone ratio (often obese men). [85]

When fertility preservation is most relevant.

- Young men with confirmed hypogonadism who desire current fertility;
- Men with secondary hypogonadism (where the loop can be re-stimulated) — clomiphene/enclomiphene work best when the HPG axis is intact upstream and downstream of the lesion;
- Men on TRT who develop a need for fertility preservation (where strategies include hCG addition or transition off TRT); [14]
- Men with planned future fertility considerations who want to preserve options.

When fertility-preserving alternatives are not appropriate.

The principal limitation is biology. In men with primary hypogonadism — where the testes themselves do not respond to LH stimulation — clomiphene, enclomiphene, and aromatase inhibitors do not produce meaningful testosterone responses. hCG can be partially effective if some residual Leydig cell function exists, but typically not in advanced primary hypogonadism. Men with Klinefelter syndrome, prior chemotherapy/radiation, or other organic primary hypogonadism typically require either conventional TRT (accepting fertility implications) or specialized reproductive-endocrinology approaches. [50]

A practical note. The choice among fertility-preserving alternatives depends on the underlying mechanism of hypogonadism, the specific fertility goals (immediate conception vs. long-term preservation), and individual response. Reproductive endocrinology or urologic specialty input is described as appropriate in guidelines for complex fertility-related scenarios. [3]

What the trials of *clomiphene, enclomiphene, and hCG* have reported.

Each of the principal fertility-preserving alternatives has been studied in randomized trials, with the most rigorous evidence base for enclomiphene (which underwent phase 3 trials for FDA submission) and a substantial older evidence base for clomiphene and hCG. [102]

Clomiphene citrate.

Clomiphene citrate (12.5–50 mg daily or every other day) is the most-studied option in this category. Multiple cohort studies and smaller randomized trials in men with secondary hypogonadism have reported: [104]

- Increase in serum total testosterone of approximately 150–300 ng/dL;
- Preserved or improved spermatogenesis (unlike TRT, which suppresses);
- Symptom improvement comparable to TRT in some — though not all — comparative studies;
- Oral administration with relatively low cost;
- Side effects in some men including mood changes, visual symptoms, and (less commonly) breast tenderness. [104]

Enclomiphene.

Enclomiphene — the pure trans-isomer of clomiphene — was developed specifically as an alternative for men with secondary hypogonadism who wished to preserve fertility. Phase 3 trial data in men with secondary hypogonadism reported: [102]

- Increase in serum total testosterone from approximately 240 ng/dL baseline to mid-normal range;
- Maintenance or modest increase in sperm concentration vs decrease with TRT;
- Comparable symptom improvement to TRT in selected men;
- Manufacturer-sponsored phase 3 program completed but the original FDA approval pathway was not finalized for the marketed product; clinical use of enclomiphene continues in some practices via compounding pharmacies in the U.S. [102]

Human chorionic gonadotropin (hCG).

hCG, administered subcutaneously typically 2–3 times weekly at doses of 500–3000 IU per dose, directly stimulates Leydig cell testosterone production by binding the LH receptor. [103] Trials and cohort series have reported:

- Restoration of intratesticular testosterone signaling, supporting spermatogenesis; [103]
- Often used in combination with TRT to preserve fertility in men who would otherwise become infertile; [14]
- Useful in restoring spermatogenesis after a period of TRT-induced suppression; [15]
- Requires injection and is more expensive than oral SERM alternatives;
- Available in U.S. clinical practice via compounding pharmacies and some specialty pharmacy distribution. [103]

Recovery from TRT-induced suppression.

Men who have been on TRT for extended periods and wish to recover fertility face a recovery process that may take 6–24 months or longer; complete recovery is not always achieved. Protocols using hCG (often combined with clomiphene or a SERM and sometimes with FSH/HMG) have been studied and reported to accelerate recovery in some — though not all — men. [15]

Counseling point. Major society guidelines and reproductive medicine specialty literature recommend that men of reproductive age with fertility considerations be counseled about the suppressive effects of TRT and the available alternatives before TRT initiation. [3] [14]

Benefits documented in *randomized trials.*

Several benefits of testosterone therapy in men with confirmed hypogonadism are supported by randomized trial evidence, with effect sizes that vary by outcome. The strongest evidence is for sexual function and for hemoglobin in anemic men. [3] [58]

Benefits with the strongest randomized evidence.

- **Sexual function.** Reduced libido, reduced sexual activity, and erectile difficulties improved consistently in the T-Trials Sexual Function Trial and in multiple prior randomized studies in men with confirmed hypogonadism. [58]
- **Anemia.** Hemoglobin rose significantly in the T-Trials Anemia Trial, particularly in men with unexplained anemia. [62]
- **Bone mineral density and estimated bone strength.** Significant increases in the T-Trials Bone Trial via quantitative CT. [63] Caveat: TRAVERSE reported a higher fracture rate vs placebo — a finding that requires reconciliation with the bone density data. [60]
- **Body composition.** Increases in lean mass and reductions in fat mass have been reported across multiple trials with consistent direction. [105]
- **Vasomotor symptoms in hypogonadal men.** Less commonly discussed but reported in hypogonadal men with hot flashes. [3]

Benefits with weaker or mixed evidence.

- **Mood and depressive symptoms.** Mixed evidence; some randomized trials report improvement in depressive symptoms in hypogonadal men, but heterogeneity limits clear conclusions across populations. [106]
- **Vitality / fatigue.** The T-Trials Vitality Trial was negative on its primary endpoint; positive on a secondary mood measure. [58]
- **Cognitive function.** The T-Trials Cognitive Function Trial was negative; broader cognitive literature on TRT in hypogonadal men is inconclusive. [61]
- **Physical function.** Modest improvements in 6-min walk distance and self-reported function in T-Trials; effect sizes generally small. [58]
- **Glycemic control.** Small improvements in some — though not all — randomized trials in men with type 2 diabetes and hypogonadism. [107]

Benefits with insufficient evidence for clinical use.

Several outcomes occasionally cited as indications for TRT lack rigorous randomized evidence to support clinical use: [3]

- Longevity / mortality reduction in healthy men with age-related testosterone decline;
- Cardiovascular event reduction (TRAVERSE was non-inferiority, not superiority);
- Cancer prevention;
- Dementia prevention;
- Performance enhancement in healthy eugonadal men (a distinct context with different evidence and regulatory considerations).

Reading frame. The randomized evidence supports a focused set of benefits in men with confirmed hypogonadism — sexual function, bone density, hemoglobin, body composition — rather than the broader anti-aging framing sometimes encountered in patient-facing materials. Major society guidelines emphasize this distinction. [3] [38]

Risks and the *contraindications listed in guidelines.*

Major society guidelines describe a defined set of contraindications and risks that warrant attention before and during TRT. The post-TRAVERSE updates have refined but not fundamentally changed these lists. [3] [38] [73]

Absolute and strong contraindications.

- **Active or untreated prostate cancer;**
- **Active or untreated breast cancer in men;**
- **Hematocrit > 50% at baseline** (with TRT generally deferred until contributors are addressed);
- **Severe untreated obstructive sleep apnea;**
- **Severe heart failure (NYHA class IV);**
- **Recent (within 3–6 months) MI or stroke;**
- **Severe lower urinary tract symptoms with IPSS > 19** (until BPH is optimized);
- **Active fertility goals** — TRT is not contraindicated medically, but the predictable suppression of spermatogenesis makes it inappropriate without prior fertility counseling. [3]

Risks documented in randomized data.

- **Erythrocytosis** — predictable; monitored and managed as in Chapter 10; [87]
- **Atrial fibrillation** — small absolute increase in TRAVERSE; [60]
- **Pulmonary embolism** — small absolute increase in TRAVERSE; [60]
- **Acute kidney injury** — small absolute increase in TRAVERSE; [60]
- **Fracture risk** — unexpected increase in TRAVERSE despite bone density benefit in T-Trials; mechanism uncertain; [71]
- **Spermatogenesis suppression** — predictable and substantial; [12]
- **Testicular atrophy** — predictable (Chapter 1.2); [12]
- **Acne, gynecomastia, mood changes** — variable; [3]
- **Sleep apnea worsening and BPH symptom worsening** — particularly in men with pre-existing OSA or untreated BPH. [42]

Conditions requiring individualized assessment.

- History of prostate cancer (especially treated > 1 year prior with biochemical recurrence-free status) — urology input;
- History of breast cancer in male first-degree relatives;
- Moderate-to-severe BPH not yet optimized;
- Polycythemia vera or other primary erythrocytosis;
- Severe untreated depression or psychiatric instability;
- Use of medications with significant interactions (anticoagulants, immunosuppressants);
- Pregnancy of a female partner (gel transfer risk). [3] [38]

When to reconsider continued therapy.

Major guidelines describe reconsideration of continued TRT when: [3]

- Symptom improvement does not occur after 3–6 months of biochemically adequate therapy;
- Adverse effects develop that cannot be managed by dose adjustment or modality change;
- Hematocrit cannot be maintained below 54% despite reasonable interventions;
- Prostate concerns emerge that warrant urologic evaluation;
- The original indication resolves (e.g., obesity-driven functional hypogonadism with substantial weight loss).

Strength training and body composition: the *largest-effect lifestyle lever.*

Among modifiable lifestyle inputs that influence testosterone and the downstream outcomes most commonly attributed to it (muscle, strength, body composition, mood), resistance training has the largest reported effect sizes and the most consistent evidence base. The relationship between resistance training and testosterone itself is more nuanced than the marketing landscape suggests. [108]

Resistance training effects on outcomes attributed to testosterone.

Meta-analyses and randomized trials in older adults — including men with low testosterone — have consistently reported that progressive resistance training: [109]

- Increases lean body mass (typically 1–3 kg over 3–12 months);
- Increases measured strength (often 30–100% in the trained movements);
- Reduces visceral and total body fat in combination with appropriate energy balance;
- Improves insulin sensitivity and glycemic markers;
- Improves bone density at loaded skeletal sites;
- Improves mood and quality-of-life measures in many populations.

The relationship between TRT and resistance training is approximately additive: men receiving TRT plus structured resistance training generally see larger gains in lean mass and strength than either intervention alone, with the largest published response sizes in men with confirmed hypogonadism. [110]

What resistance training does *not* reliably do.

A persistent claim in fitness and TRT marketing is that resistance training "raises testosterone." The data on this point are nuanced: [111]

- A single resistance training session transiently raises serum testosterone for ~30–60 minutes, but resting testosterone concentrations measured days later are largely unchanged by an exercise program; [111]
- Acute exercise-induced testosterone increases are not closely correlated with hypertrophy outcomes; [111]
- Chronic resistance training does not appear to meaningfully raise baseline testosterone in men with normal testosterone; [111]
- In men with obesity-associated functional hypogonadism, the testosterone changes attributed to exercise are largely mediated by the body composition changes (weight loss, fat reduction) rather than the exercise stimulus itself. [47]

Reading frame. Resistance training improves the outcomes most patients seek from TRT (muscle, strength, body composition, function) regardless of whether it directly affects testosterone concentrations. The Endocrine Society and AUA guidelines describe lifestyle optimization including resistance training as foundational to the evaluation and management of men with low testosterone. [3] [38]

Sleep: the *most undervalued* input to testosterone.

Sleep duration, sleep quality, and sleep-disordered breathing each have direct relationships to testosterone and to outcomes commonly attributed to it. The relationships are bidirectional and are among the most reproducible findings in this literature. [42]

Acute sleep restriction lowers testosterone.

The Leproult and Van Cauter 2011 study in young healthy men is one of the most cited demonstrations: 1 week of sleep restriction to 5 hours per night reduced daytime testosterone by approximately 10–15%, with magnitude comparable to 10–15 years of normal aging. [112] Similar acute experimental studies have reproduced the effect.

Obstructive sleep apnea.

Obstructive sleep apnea (OSA) is associated with lower testosterone concentrations, with the magnitude scaling with OSA severity (apnea-hypopnea index). [113] Treatment of OSA — most commonly with CPAP — produces modest increases in testosterone in some studies, though the effect size is smaller than that of weight loss in obese men with OSA. [114] The interaction between TRT and untreated OSA is bidirectional: untreated OSA worsens hematocrit response to TRT (Chapter 10), and TRT may worsen OSA in susceptible individuals. [42]

Implications for the lifestyle assessment.

Major society guidelines describe sleep assessment — including screening for OSA in appropriate men — as part of the workup for low testosterone, particularly in men with obesity, hypertension, or symptoms suggesting disrupted sleep. [3]

Practical evidence on sleep hygiene.

The literature on behavioral sleep hygiene is heterogeneous; broad-stroke recommendations from sleep medicine guidance include: [115]

- Consistent sleep timing across days;
- Adequate sleep opportunity (most adults require 7+ hours);
- Reduced caffeine, alcohol, and large meals in the hours before sleep;
- Dark, cool, quiet sleep environment;
- Evaluation for OSA when symptoms suggest it (loud snoring, witnessed apneas, daytime sleepiness).

> **The reading frame.** Among lifestyle inputs with documented effects on testosterone, sleep duration and OSA management have effect sizes comparable to or exceeding any single supplement or training intervention. In men with low testosterone and any of these contributors, addressing them is part of the standard workup before and alongside TRT consideration. [3] [42]

Nutrition: *energy balance and body composition first.*

The largest reproducible nutritional effects on testosterone in men are mediated through body composition. Direct effects of specific macronutrients and micronutrients on testosterone are smaller, and in many cases the literature does not support routine supplementation in men with adequate intake. [47]

Energy balance and body composition.

As described in Chapter 3.3, obesity lowers testosterone through multiple mechanisms, and weight loss raises it. Among interventional studies: [47]

- **Lifestyle weight loss** — typical effects on total T of approximately +50–150 ng/dL with 5–15% body weight loss in obese men; [47]
- **Bariatric surgery** — larger effects, often +150–250 ng/dL with substantial weight loss; many previously hypogonadal men return to the eugonadal range; [48]
- **GLP-1 receptor agonists** — emerging data report meaningful testosterone increases proportional to weight loss in men with obesity-associated low testosterone. [49]

Macronutrient considerations.

The literature on macronutrient composition and testosterone is mixed:

- **Protein** — adequate protein intake (typically 1.0–1.6 g/kg/day) supports the resistance training response and lean mass maintenance. [116] Extreme protein intake has not been shown to raise testosterone meaningfully in eugonadal men.
- **Dietary fat** — very low-fat diets (< 15% of calories) have been associated with modest reductions in testosterone in some studies; this is generally not a clinical concern at typical dietary patterns. [117]
- **Carbohydrate** — no consistent direct effect on testosterone; effects on insulin sensitivity may matter for body composition outcomes. [117]
- **Energy restriction** — sustained energy restriction can lower testosterone modestly via central HPG suppression in some studies; the relationship is dose-dependent. [118]

Micronutrients and testosterone.

- **Vitamin D** — modest associations with testosterone in some observational studies. Randomized trials of vitamin D supplementation in vitamin-D-sufficient men have generally reported neutral effects on testosterone. [119]
- **Zinc** — severe zinc deficiency lowers testosterone. Supplementation in zinc-sufficient men does not consistently raise testosterone. [120]
- **Magnesium** — adequate intake supports general health; effects on testosterone are small in randomized data. [121]
- **Boron, ashwagandha, fenugreek, and others** — small studies with mixed results; effect sizes are generally small and the publication bias and methodological quality vary. [122]

Reading frame. Adequate energy intake, adequate protein, addressing identified deficiencies, and overall dietary patterns supportive of body composition goals form the nutritional foundation. The marketing of "testosterone-boosting" supplements largely outstrips the supporting evidence. [122]

The supplement landscape — and the *narrow short list.*

The supplement landscape for men's testosterone and related outcomes is large, lightly regulated, and highly variable in quality and evidence. A short list of supplements has reasonably consistent randomized evidence for outcomes adjacent to testosterone, even where direct effects on testosterone are small. [122]

Supplements with reasonable evidence for adjacent outcomes.

- **Creatine monohydrate** — one of the most-studied supplements; consistent benefit when combined with resistance training for lean mass and strength gain in older adults including men. [123] Standard dose 3–5 g/day. Effects on testosterone itself are not the principal mechanism. [123]
- **Vitamin D** — correction of documented deficiency is supported by bone health and muscle function literature; routine supplementation in vitamin D-sufficient men has not been shown to provide additional testosterone benefit. [119]
- **Omega-3 fatty acids (EPA/DHA)** — supported for cardiovascular and inflammation outcomes in specific contexts; effects on testosterone are small. [124]
- **Magnesium** — correction of deficiency or shortfall supports general health; not a primary testosterone intervention. [121]

Supplements widely marketed with weaker evidence.

- **Ashwagandha** — several small randomized trials report modest increases in testosterone and stress markers; methodological heterogeneity is substantial and replication in larger trials remains limited. [125]
- **Fenugreek** — small trials with mixed results. [126]
- **Tongkat ali** — small studies; effect sizes variable. [127]
- **Tribulus** — multiple randomized trials have not supported testosterone-raising effects in eugonadal or hypogonadal men. [128]
- **D-aspartic acid** — initial small studies suggested an effect; subsequent better-controlled trials have largely failed to confirm. [129]

Supplements with no supporting evidence or known harms.

Several products marketed as "testosterone boosters" contain prohormones, designer steroids, or actual androgens not listed on labels. FDA enforcement actions have repeatedly identified contaminated or adulterated supplements in this space. [130] Third-party-tested products (NSF Certified for Sport, Informed Sport) provide some assurance against contamination.

> **Reading frame for this chapter.** Supplements are not a substitute for addressing body composition, sleep, training, and underlying medical contributors to low testosterone. The short list above has reasonable evidence for specific adjacent outcomes; outside that list, the marketing landscape generally exceeds the evidence. [122]

Questions worth bringing into the room.

The information collected across this guide is at most a foundation for an informed conversation with a clinician. The following are categories of question that the published literature suggests are commonly under-asked in routine clinical encounters — included here as a reference, not as a script.

Questions about the diagnostic workup.

- Based on my symptoms and labs, do I meet the criteria for hypogonadism per the Endocrine Society or AUA guidelines?
- What was my testosterone measured by — immunoassay or mass spectrometry? Was it drawn in the morning?
- Was the measurement repeated to confirm?
- Did we measure LH and FSH to localize primary vs secondary?
- Are there reversible contributors — weight, sleep apnea, medications, prolactin — that should be addressed first?
- If I'm a candidate for TRT, what modality and dose are you recommending, and why?

Questions about the treatment decision.

- What are the documented benefits I should expect, and on what timeline?
- What are the documented risks given my specific medical history?
- What is your view on TRAVERSE and what it does and doesn't establish for someone like me?
- How does this decision interact with my fertility plans now and in the future?
- What monitoring will we do and how often?
- What would prompt us to reconsider continuing therapy?

Questions about alternatives and adjuncts.

- Have we considered fertility-preserving alternatives like clomiphene, enclomiphene, or hCG given my situation?
- What lifestyle interventions should be foundational regardless of any other decisions?
- How will we evaluate whether the therapy is working over time?

Questions about the broader picture.

- How do hematocrit, PSA, cardiovascular risk, and bone health interact with the decisions we're making?
- What should prompt me to come back sooner than the next scheduled visit?
- Are you up to date on the post-TRAVERSE evidence and current Endocrine Society / AUA guidance?

If a clinician isn't engaging with these questions. The TRT clinical landscape is unusually heterogeneous in practice patterns — from clinicians practicing strictly per the Endocrine Society / AUA framework to clinics operating substantially outside that framework. Asking specific questions about whether monitoring and dosing align with major guideline guidance is one way to assess the alignment. [3] [38]

Every citation, *traced to source.*

The references below correspond to the superscript numbers used throughout the preceding chapters. Where available, PubMed identifiers are included for direct lookup. References to clinical society position statements include the publishing organization and year.

Note to readers and clinicians. This guide was compiled as an educational reference summarizing the published literature on testosterone biology and therapy in men. Citations represent the principal supporting source for each clinical statement at the time of writing. **Readers and clinicians using this material to inform decisions are encouraged to verify each citation against the current PubMed record**, since this literature evolves and updated analyses may revise individual findings. This guide does not substitute for direct review of primary sources by a qualified clinician.

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4 **(In-text reference to the references chapter; not an external citation.)**

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