BIOAVAILABLE

The Modern Clinical Framework for Male Androgen Restorative Therapy

A clinical review for evidence-based preventive practice

Two men can have identical Total Testosterone concentrations but vastly different physiology

High Actual
Tissue Exposure

Low Actual
Tissue Exposure

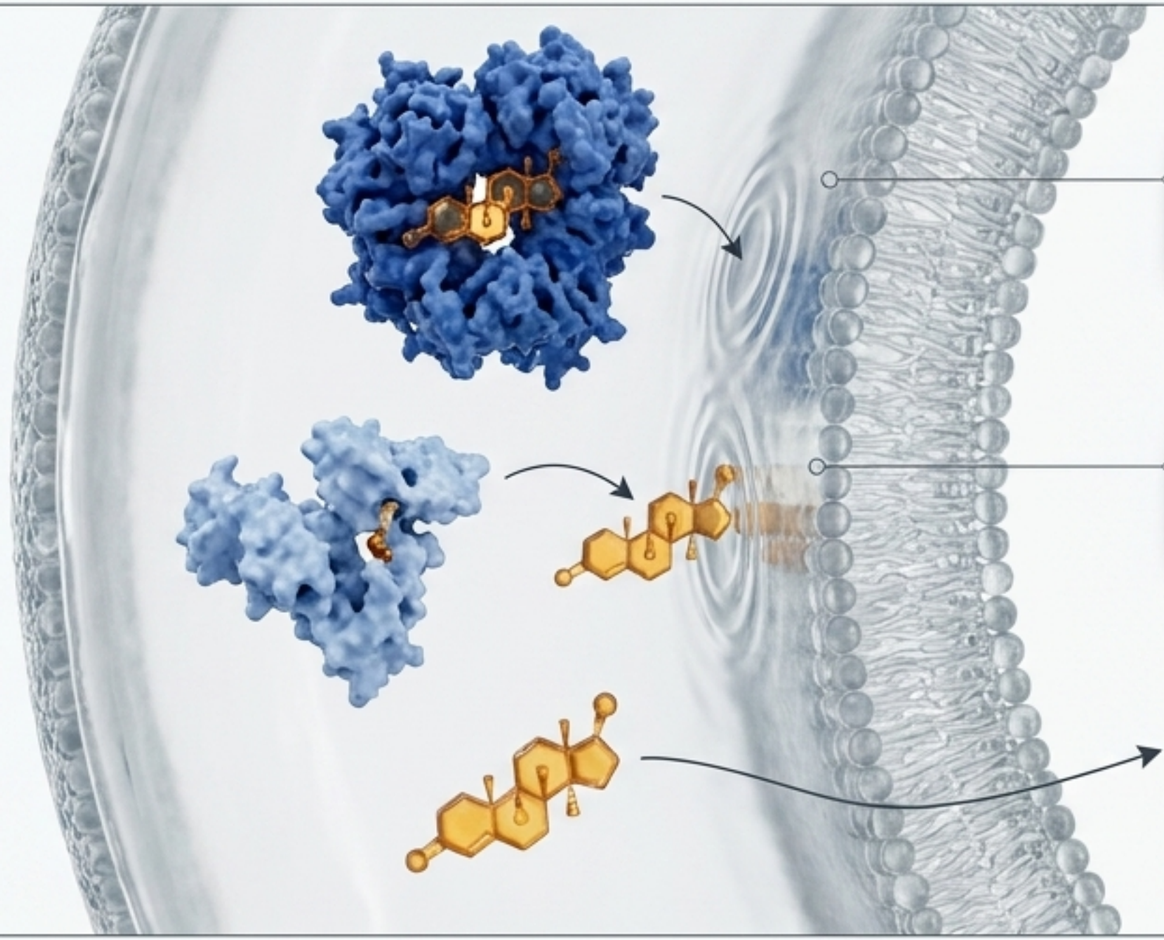
Free binding proteins

SHBG: Sex Hormone-Binding Globulin

Takeaway

Total concentration is biochemical noise. Tissue delivery is the biological truth. The difference between these two identical vials is the presence of binding proteins that trap the hormone before it can be used.

The Compartmentalization Model dictates what actually penetrates the cell membrane



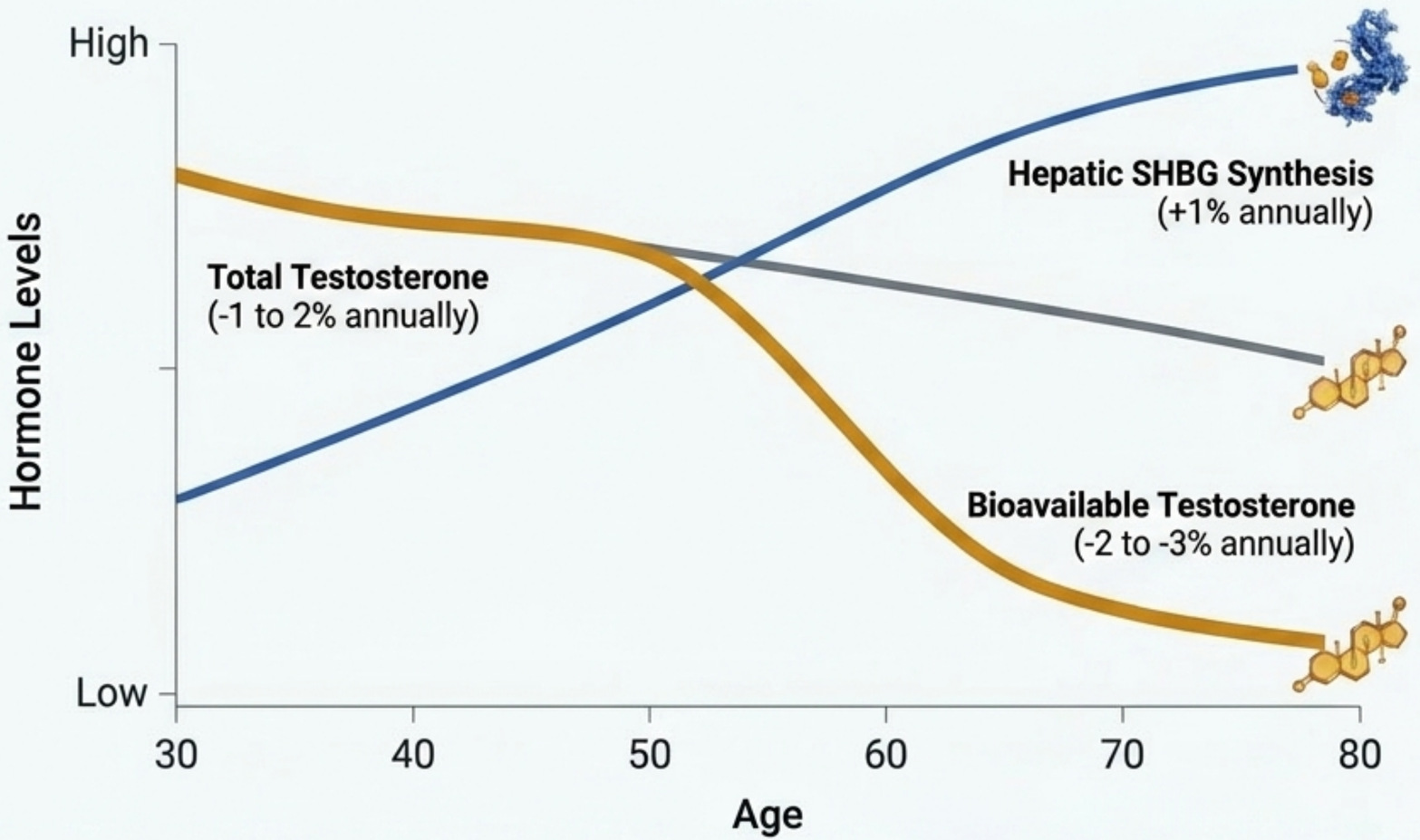
Tightly Bound (44-65%): Locked to Sex Hormone-Binding Globulin (SHBG). Biologically inert during transit.

Loosely Bound (30-50%): Bound to Albumin. Dissociates rapidly enough to release into tissue during transit.

Free (1-4%): Unbound. Readily diffuses across cell membranes.

THE BIOAVAILABLE FRACTION = Free + Albumin-Bound.
This is the only fraction actually delivered to your tissues.

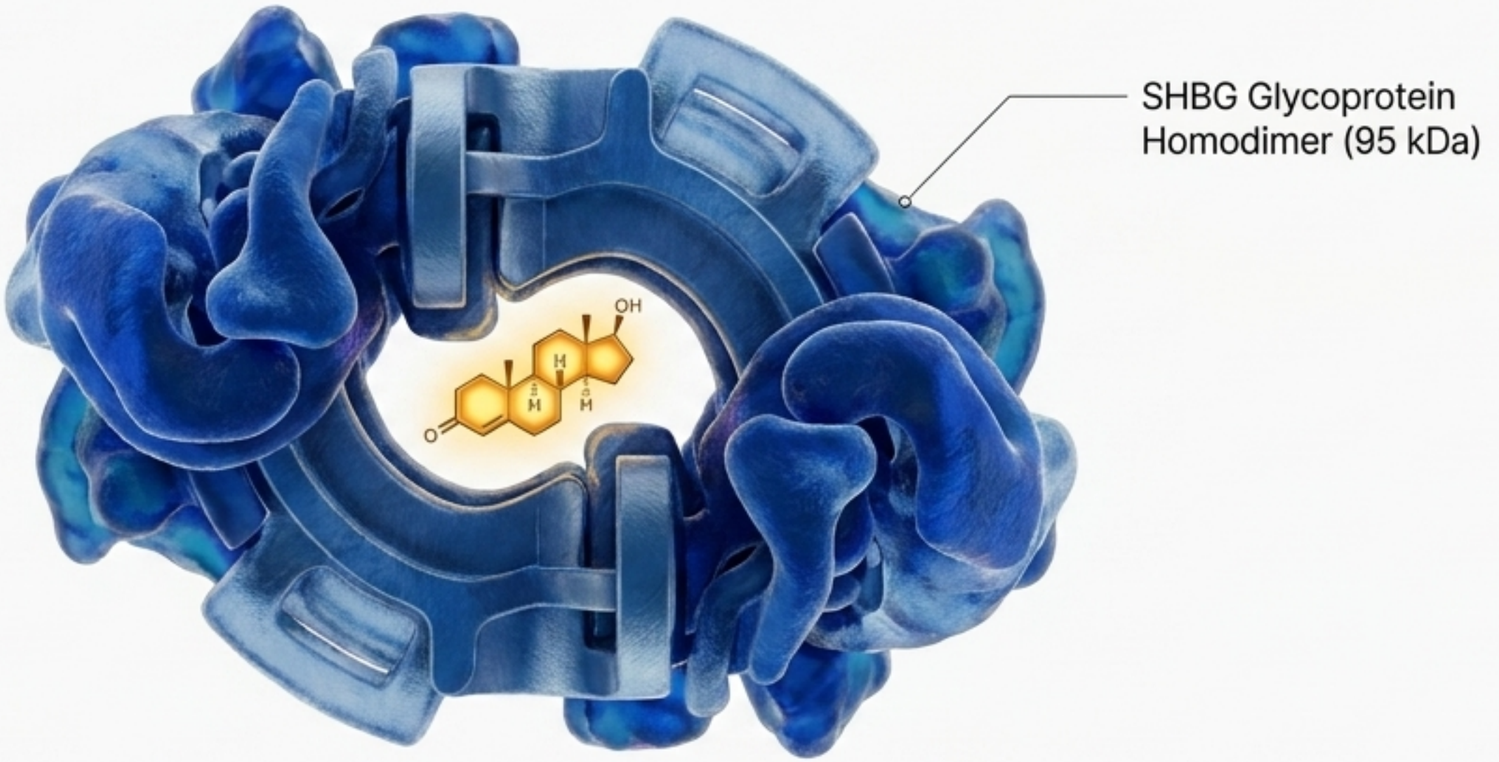
The decline in Total Testosterone hides the true physiological crash



Because **SHBG rises with age**, it aggressively sequesters what little testosterone remains.

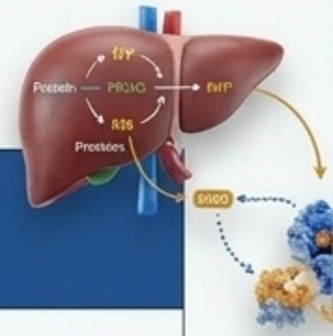
The bioavailable fraction **plummets exponentially faster** than the total concentration suggests, which is why older men with normal Total T frequently present with severe clinical deficiency.

SHBG is not just a carrier; it is the dominant gatekeeper of androgen bioavailability



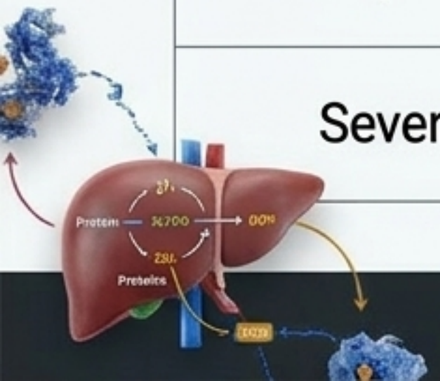
SHBG (Sex Hormone-Binding Globulin) dictates exactly how much hormone your tissues actually receive. Its synthesis is governed by the liver and responds directly to metabolic, nutritional, and age-related inputs.

Hepatic SHBG synthesis is highly reactive to metabolic and clinical states



↑ Factors that Elevate SHBG (Trapping more hormone)	↓ Factors that Suppress SHBG (Releasing more hormone)
Aging (Steady upward drift from 30s)	Hyperinsulinemia
Hyperthyroidism (HNF-4α induction)	Obesity & Visceral Adiposity
Oral Estrogen Exposure	Type 2 Diabetes Mellitus
Hepatic Cirrhosis (Altered clearance)	
Severe Caloric Restriction / Anorexia	

Low SHBG is now recognized as a primary, independent biomarker for insulin resistance and incident Type 2 Diabetes.



Non-pharmacologic clinical levers can effectively lower elevated SHBG

Treat Underlying Thyroid Issues

Address subclinical hyperthyroidism. Normalizing a suppressed TSH often normalizes SHBG within months.

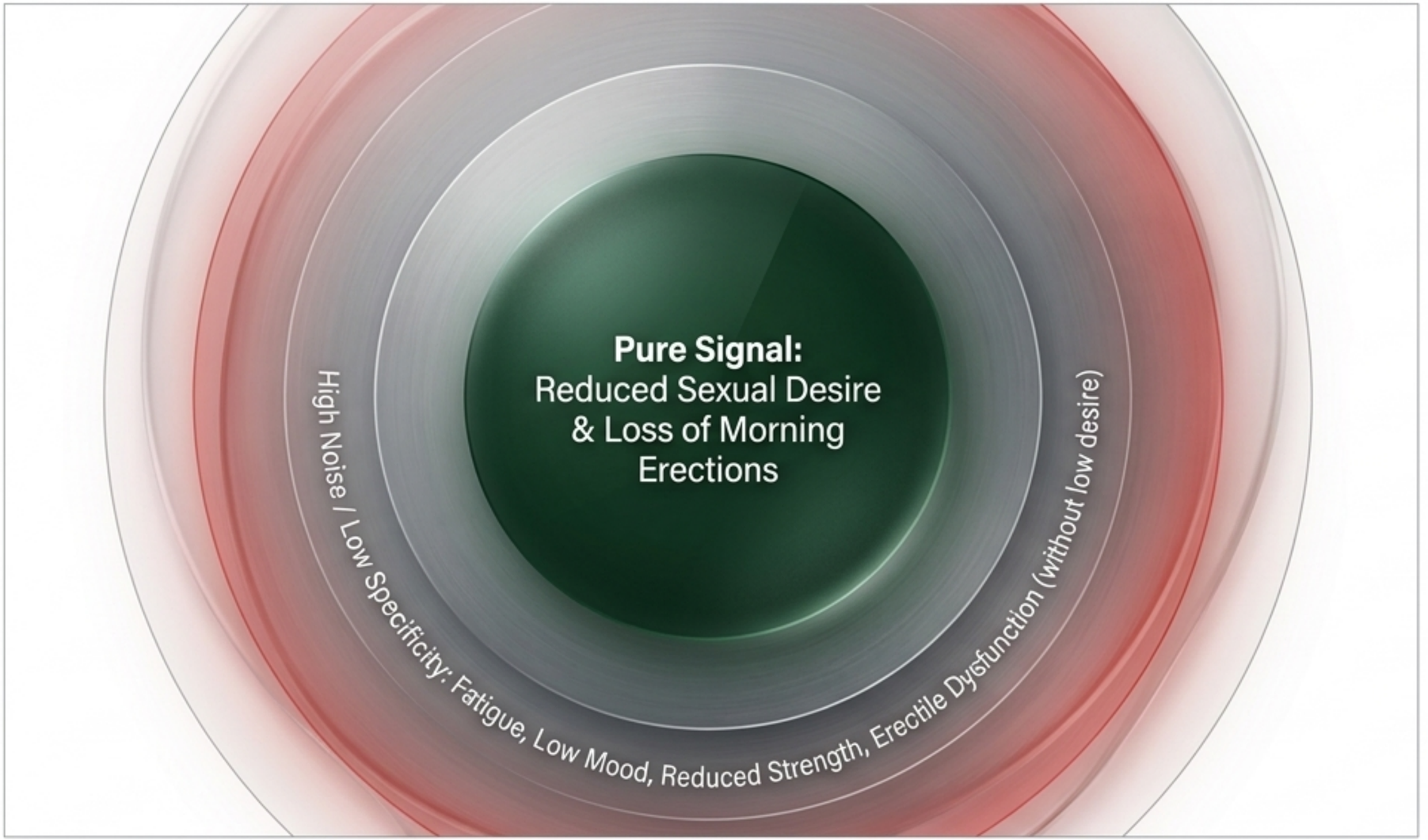
Transition Estrogen Delivery

Switch patients from oral to transdermal estrogens to completely bypass the first-pass hepatic effect on SHBG synthesis.

Optimize Metabolic State

Ensure adequate protein intake (1.2–1.6 g/kg) and prescribe heavy resistance training to optimize insulin sensitivity at the muscle level.

Differentiating diagnostic signal from general physiological noise

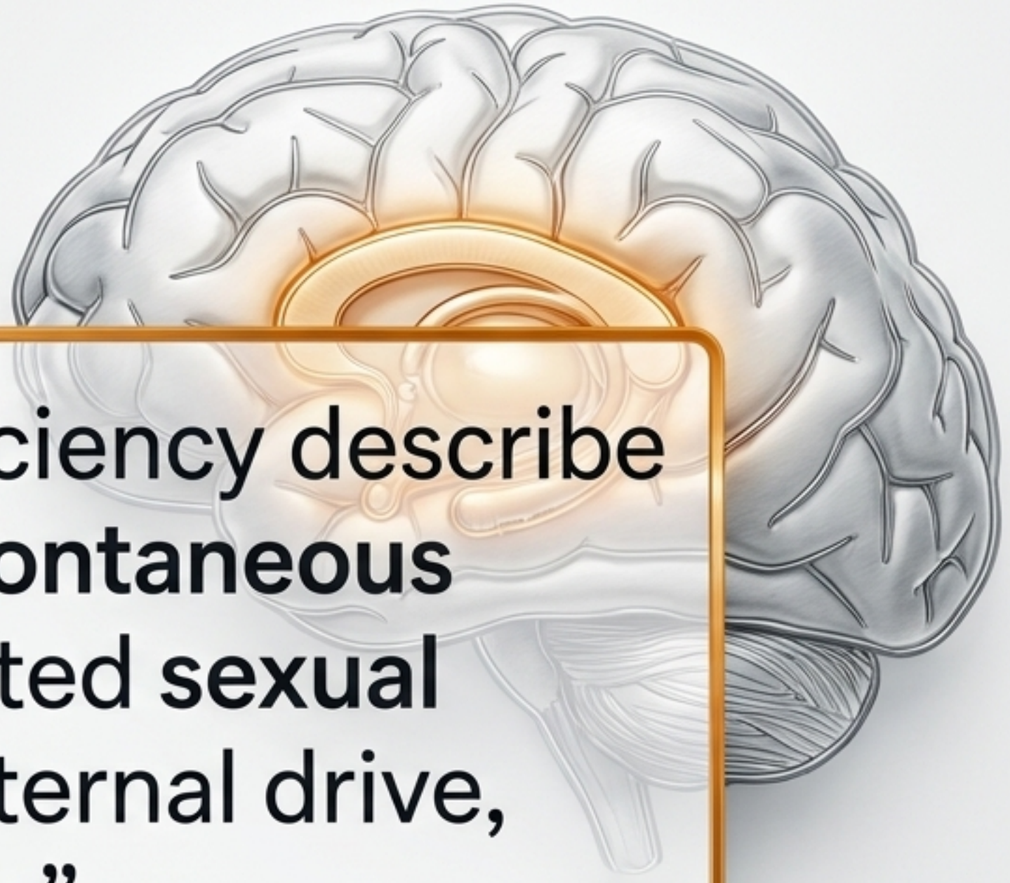


The EMAS Finding

The European Male Ageing Study established that only specific sexual symptoms reliably track androgen status in older men.

Non-specific symptoms are frequently caused by vascular, psychological, or metabolic factors.

Reduced sexual desire is the ultimate diagnostic anchor



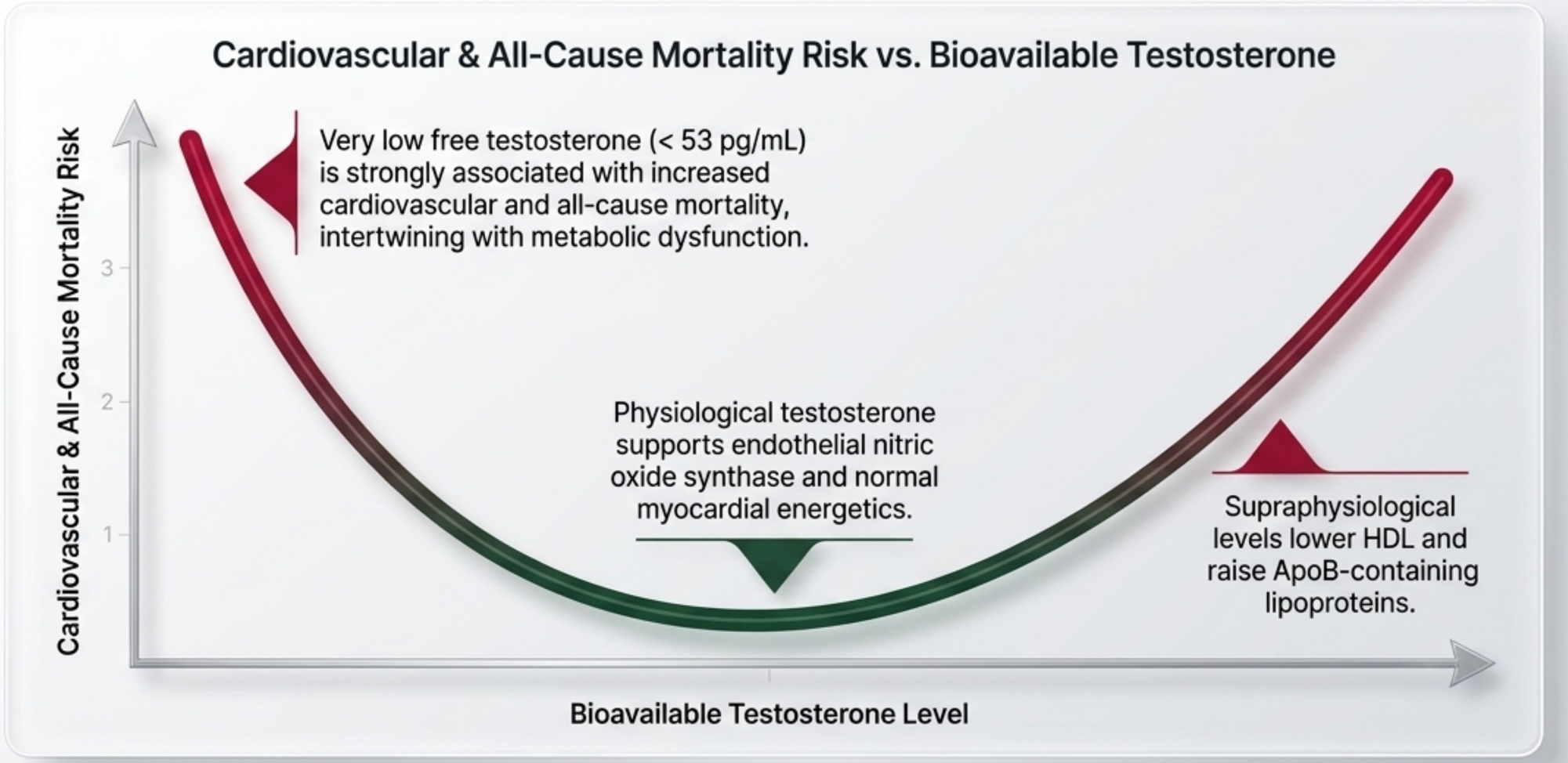
"Men with true androgen deficiency describe a fundamental drop in the **spontaneous interest** that previously initiated **sexual thought.** It is the loss of an internal drive, not merely a loss of capability."

Clinical Warning: Treating isolated erectile dysfunction (with normal libido) via testosterone replacement is rarely effective. The differential diagnosis for isolated ED is dominated by vascular atherosclerosis and neurogenic factors.

The Measurement Truth Table for Androgen Diagnostics

Analyte & Method	Status	Clinical Notes
Total Testosterone (LC-MS/MS)	[Base Requirement]	Must be a fasted morning draw (7-10 AM). Platform immunoassays fail at low levels.
Free T (Direct Analog Immunoassay)	❌ [Explicitly Not Recommended]	Highly unreliable. Produces massive errors in patients with abnormal SHBG.
Free T (Equilibrium Dialysis)	⚠️ [Gold Standard]	Highly accurate but labor-intensive, expensive, and rarely accessible in clinical labs.
Free T (Vermeulen Calculation)	✅ [The Clinical Standard]	Formula using Total T & SHBG inputs. Highly accurate (r ~ 0.99) and practical for routine clinical use.

The Endogenous U-Curve: Low baseline testosterone is an independent mortality predictor



The TRAVERSE Trial (2023) fundamentally reshaped cardiovascular safety guidelines

HR 0.96 (95%CI 0.78-1.17)

Trial Parameters

- N = 5,200 hypogonadal men with high cardiovascular risk.
- Placebo-controlled, mean follow-up 22 months.

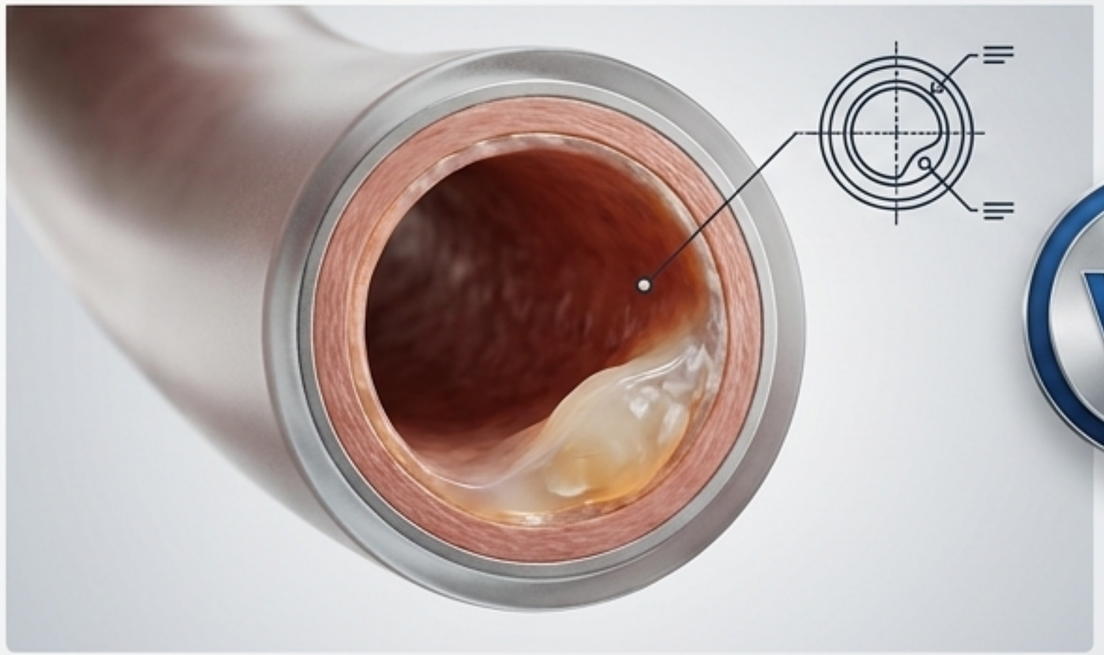
Primary Conclusion

Proved that physiological testosterone replacement in symptomatic men does NOT increase major adverse cardiovascular events (MACE).

CLINICAL IMPACT: Led directly to the 2025 FDA labeling update removing boxed warnings for major adverse cardiovascular outcomes.

Reconciling plaque biology with clinical cardiovascular events

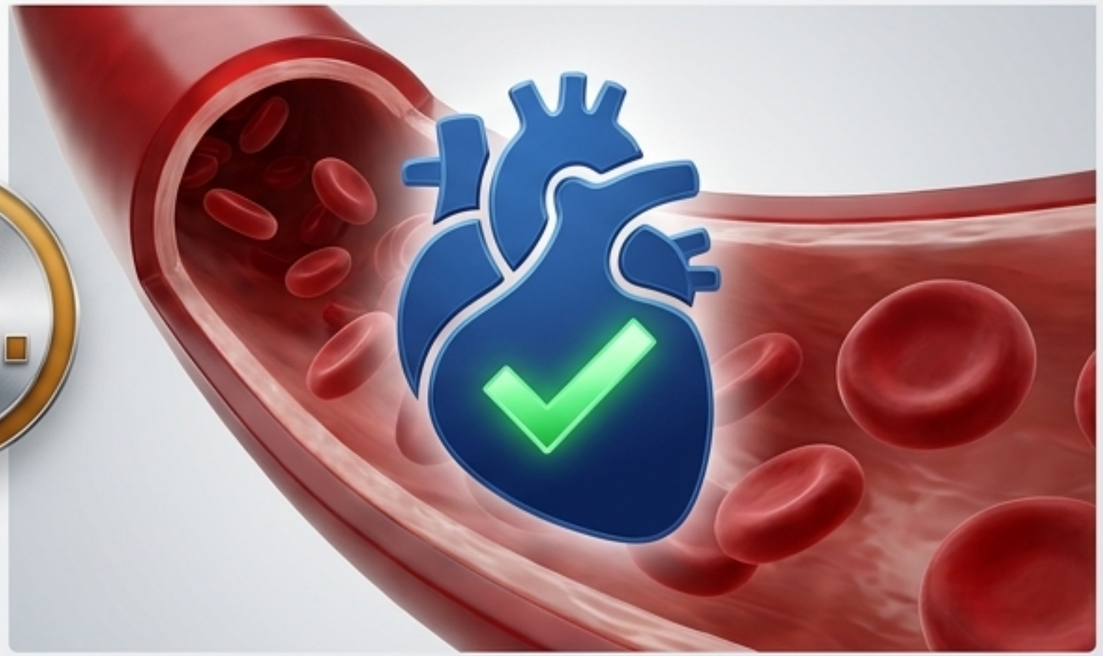
Plaque Biology



Older sub-studies (e.g., the 2017 TRT cardiovascular substudy) noted modest increases in non-calcified coronary plaque volume via CT angiography over over one year.

VS.

Clinical Events



The TRAVERSE trial confirmed that these isolated imaging signals do NOT translate to an increase in actual clinical cardiovascular events (myocardial infarction or stroke) at moderate follow-up.

Erythrocytosis remains the primary, dose-limiting safety signal

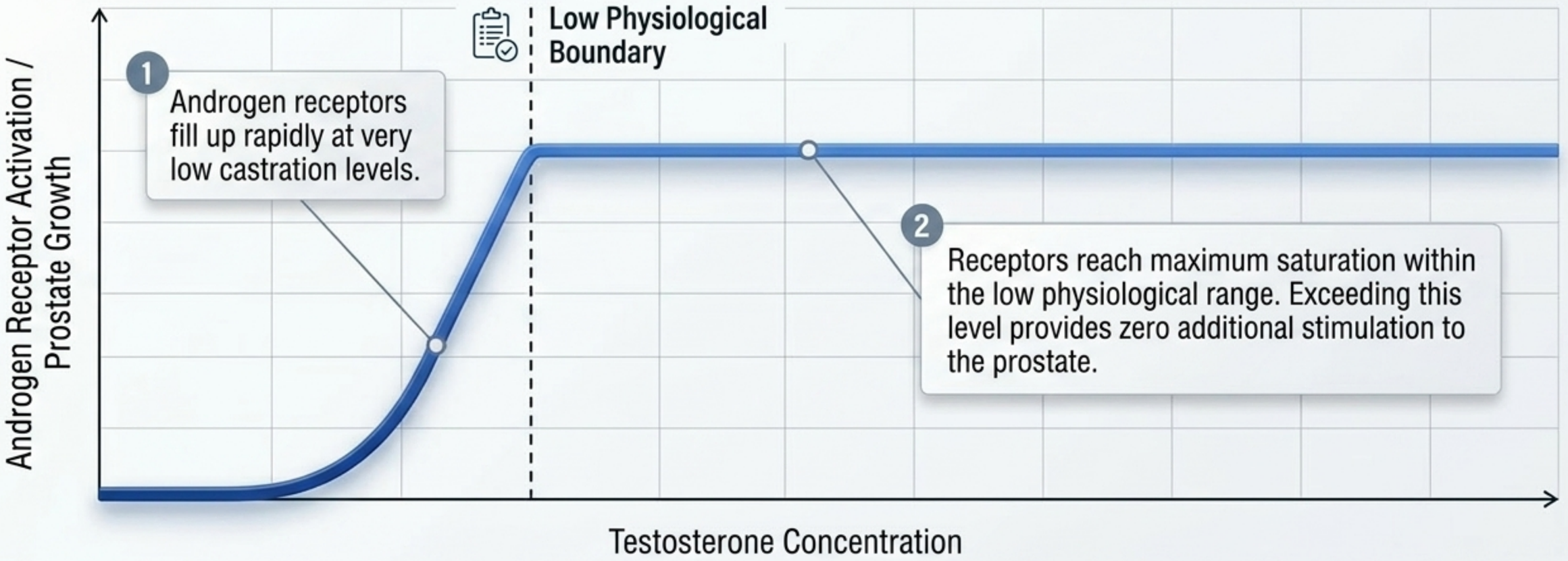
Mechanism: Testosterone stimulates erythropoiesis via direct bone marrow effects and increased erythropoietin production.

Clinical Threshold: A hematocrit excursion above 54% requires immediate clinical intervention.

Mandatory Intervention Steps:

1. Reduce dosage immediately.
2. Change formulation (transition from peaks to steady-state delivery).
3. Assess for undiagnosed obstructive sleep apnea.

The Prostate Saturation Model disproves the linear risk theory



Conclusion: Physiological replacement does not incrementally fuel or cause prostate cancer in men with healthy baseline status.

Therapeutic titration MUST be driven by Bioavailable targets

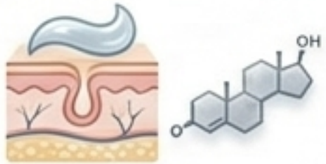
Total T (Secondary Metric)

Bioavailable T (Primary Metric)

Guideline: The aim of replacement is to restore symptoms while keeping biochemistry within the physiologic range for healthy young men.

The SHBG Trap: In men with abnormal **SHBG**, standard doses titrated only to **Total T** will result in massive over-dosing (in low SHBG patients) or under-dosing (in high SHBG patients). Mid-normal Bioavailable T is the ultimate target.

Delivery Modalities: Flattening the pharmacokinetic curve



Topical Gel / Solutions

Delivers steady serum levels approximating the physiologic diurnal rhythm. (Trade-off: potential transfer risk).

Sub-Q / Intramuscular Injectables

The modern shift favors smaller, more frequent micro-dosing (e.g., twice weekly Sub-Q) over massive bi-weekly IM injections to eliminate peaks/troughs and minimize erythrocytosis.

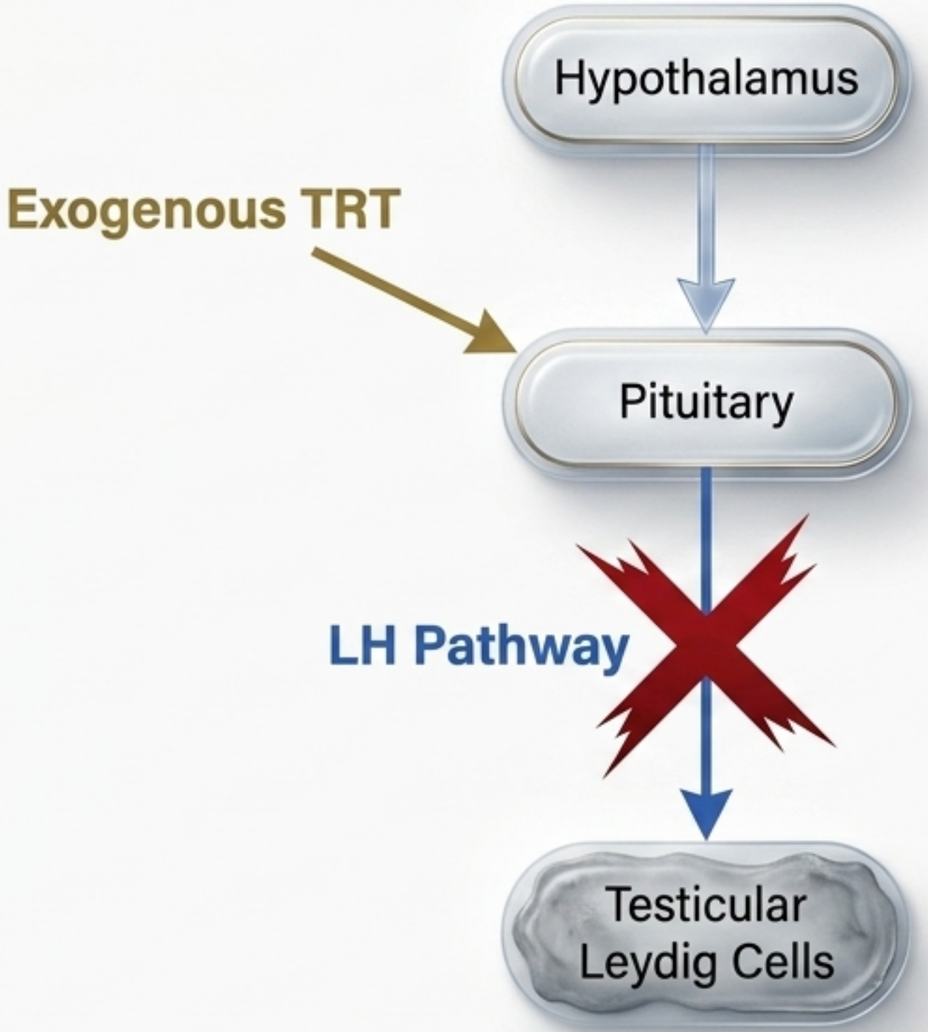
Long-Acting IM (Undecanoate)

Stable levels for 10-14 weeks post-loading phase. Requires in-office observation.

Subcutaneous Pellets

Implanted every 3-6 months for highly stable, infrequent dosing.

The Intratesticular Testosterone Problem



Mechanism

Exogenous TRT signals the hypothalamus to shut down LH production completely.

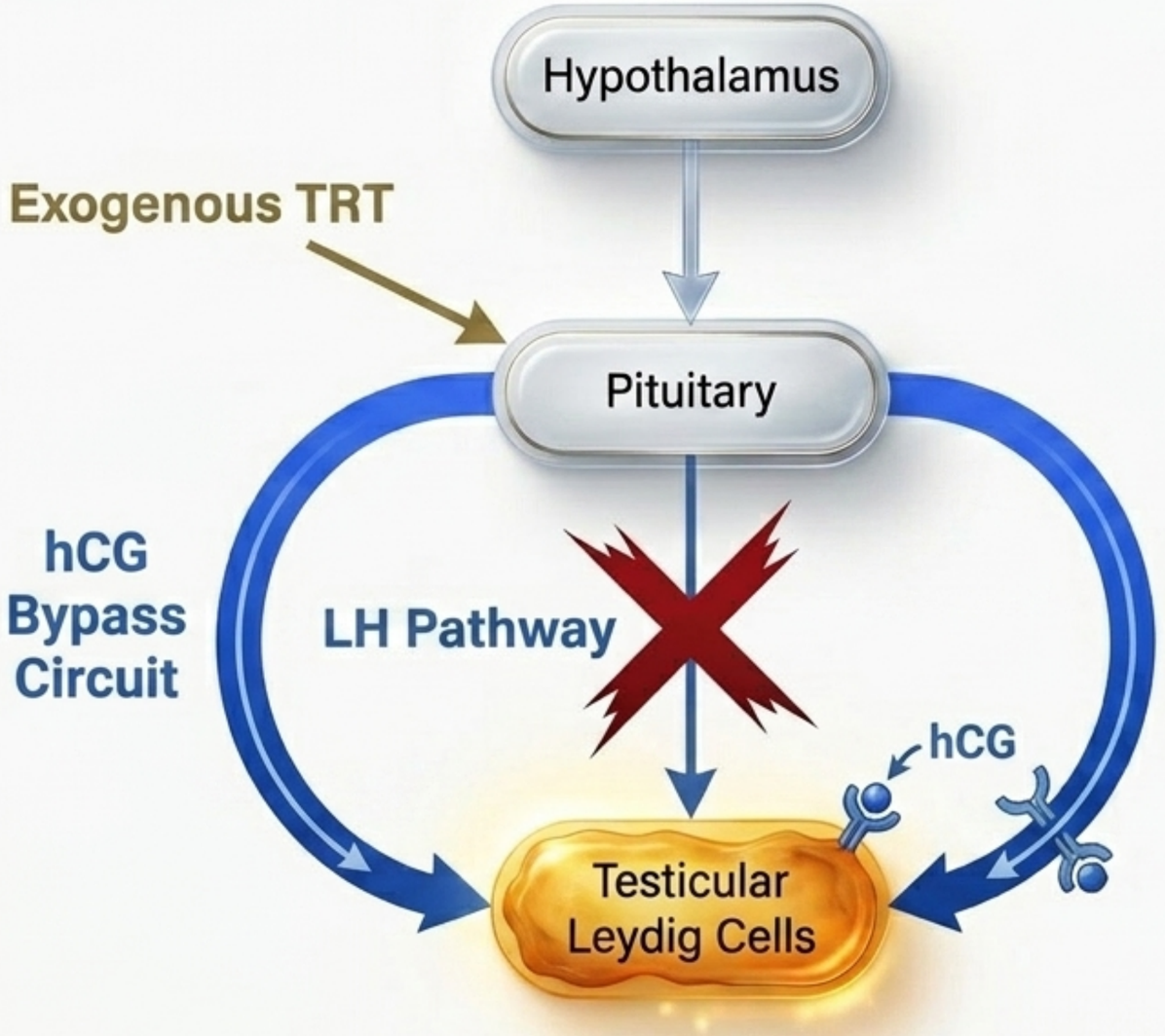
Consequence

Intratesticular testosterone (ITT) collapses by over 90%.

Biological Reality

Spermatogenesis requires ITT levels 50 to 100 times higher than circulating serum levels. Standard TRT physically starves the testes, leading to atrophy and azoospermia.

Human Chorionic Gonadotropin (hCG) is the physiological bypass



Mechanism

hCG acts as a powerful Luteinizing Hormone (LH) analog. It bypasses the suppressed pituitary gland and binds directly to the LH receptors on the Leydig cells.

Clinical Outcome

Reignites endogenous intratesticular testosterone production, preventing testicular atrophy and preserving the environment necessary for spermatogenesis.

Clinical protocols for hCG administration

hCG as an Adjunct (Combination Therapy)

- **Target:**
  Men on TRT wishing to preserve fertility or prevent atrophy.

- **Dosing:**
  Low-dose (500 IU Sub-Q, 2-3x/week) administered concomitantly with TRT.

- **Result:**
  Preserves intratesticular testosterone and maintains semen parameters across treatment.

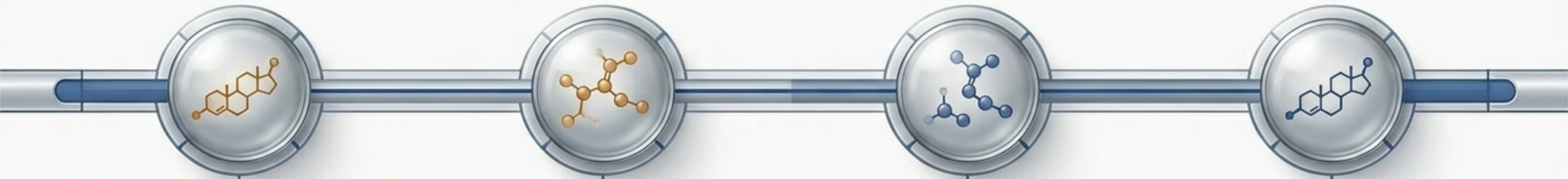
hCG as Monotherapy

- **Target:**
  Younger men with secondary hypogonadism prioritizing fertility over immediate TRT.

- **Dosing:**
  Higher dose (1,000-1,500 IU Sub-Q, 2-3x/week).

- **Result:**
  Stimulates both endogenous T production and spermatogenesis. Requires monitoring for estradiol spikes due to preserved aromatization.

The clinical monitoring protocol for restorative therapy



Baseline

Total T (LC-MS/MS), SHBG, Vermeulen Free T calculation, LH/FSH, CBC (Hematocrit), PSA, and Fasting Lipids/ApoB.

3 Months

Primary symptom review (libido resolution). Repeat Total T (timed to formulation), CBC (trigger intervention if HCT >54%).

6 & 12 Months

Full panel repeat

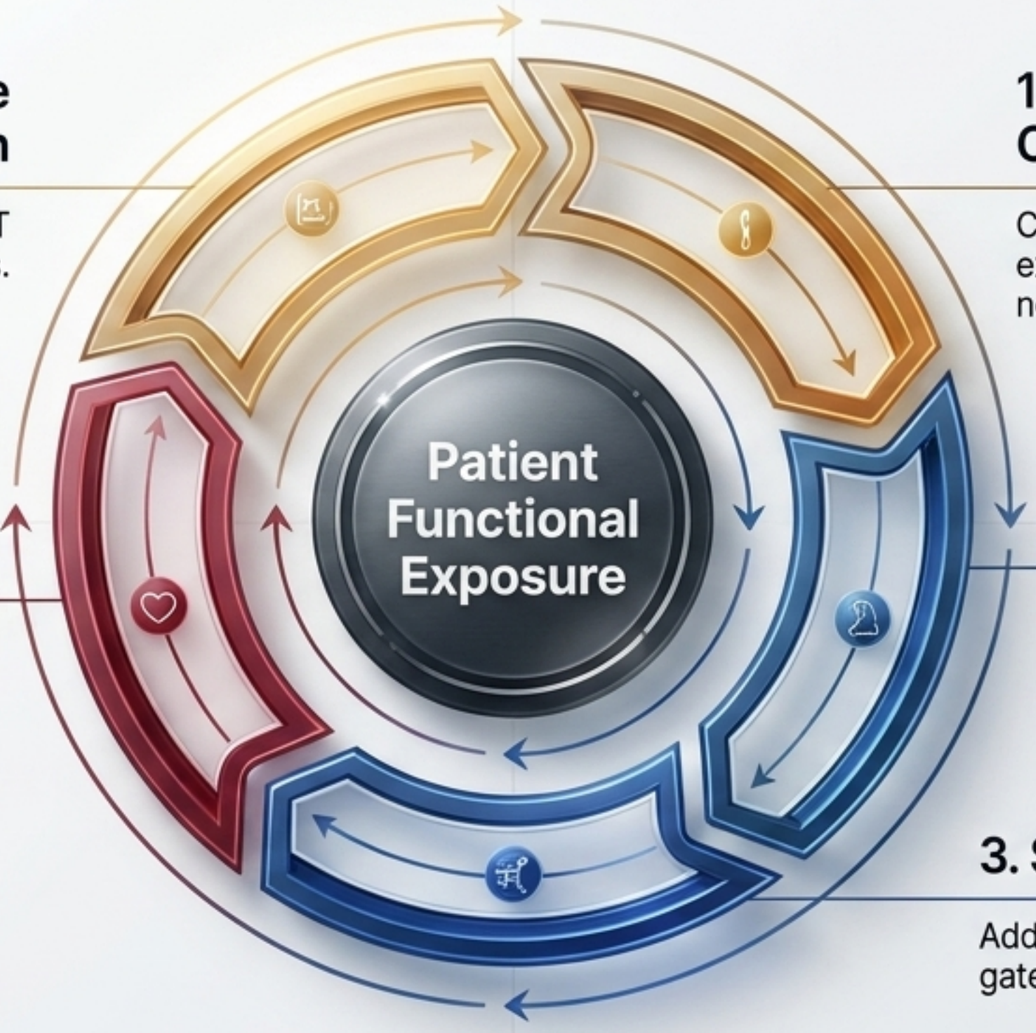
Assess body composition, waist circumference, and glycemic indices in metabolic patients.

Annual

Constant vigilance

TRT is an adjunct to, not a replacement for, aggressive lifestyle and cardiovascular management.

Synthesis: The Modern Androgen Paradigm



1. Bioavailability Confirmation

Calculate functional tissue exposure, ignore biochemical noise.

2. Symptom Match

Anchor diagnosis to reduced sexual desire.

3. SHBG Optimization

Address the metabolic gatekeeper first.

4. Safety Security

Leverage TRAVERSE data, monitor hematocrit strictly.

5. Restorative Execution

Deploy targeted TRT + hCG protocols.

The era of measuring a number on a lab report is over. We now treat the functional exposure.

Treat the Physiology.
Not the Number.