CPAP, Obesity, and Testosterone: Trajectories of Nocturnal Hypoxia After TRT in Men with Obstructive Sleep Apnea

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Abstract

Background: Obstructive sleep apnea (OSA) and male hypogonadism frequently co-occur. Testosterone replacement therapy (TRT) improves sexual and general health outcomes but has been flagged for possible short-term worsening of nocturnal oxygenation in OSA, while longer-term effects may be neutral or beneficial. Whether these trajectories are modified by objective continuous positive airway pressure (CPAP) adherence and obesity class remains unclear.

Objective: To characterize time-dependent trajectories of nocturnal hypoxia after TRT initiation in men with OSA, and to test whether CPAP adherence and body mass index (BMI) class modify these trajectories.

Methods: Prospective cohort of hypogonadal men with polysomnography- or HSAT-confirmed OSA initiating guideline-concordant TRT. Assessments at baseline, 6–8 weeks, 3, 6, and 12 months. *Primary outcome*: percentage of total sleep time with oxygen saturation $< 90\%$ (T90). *Secondary outcomes*: apnea–hypopnea index (AHI), oxygen desaturation index (ODI), nadir SpO_2, Epworth Sleepiness Scale (ESS), hematocrit/erythrocytosis, erectile function indices. CPAP adherence defined a priori ($\geq$4 h/night on $\geq$70% of nights vs lower). Mixed-effects models estimate time-by-adherence-by-BMI interactions adjusted for age, baseline OSA severity, TRT route/dose, and comorbidities.

Expected results: We hypothesize a transient T90 worsening at 6–8 weeks that attenuates by 3–6 months, with attenuation strongest among CPAP-adherent participants and lowest obesity classes.

Conclusions: Mapping oxygenation trajectories after TRT—stratified by CPAP adherence and obesity—could refine risk communication, monitoring schedules, and therapeutic sequencing for men with OSA and hypogonadism.

Keywords: obstructive sleep apnea, hypogonadism, testosterone replacement therapy, CPAP adherence, obesity, nocturnal hypoxia, T90, AHI, ODI

Introduction

Obstructive sleep apnea (OSA) and male hypogonadism frequently coexist and share major risk determinants, most notably adiposity and aging. Intermittent hypoxia and sleep fragmentation in OSA impair hypothalamic–pituitary–gonadal signaling, reduce gonadotropin pulsatility, and worsen metabolic health, all of which can depress circulating testosterone [1]. Conversely, testosterone replacement therapy (TRT)—a standard-of-care for symptomatic hypogonadism—has physiologic effects that intersect with sleep-breathing control and oxygen transport. In particular, TRT can transiently alter ventilatory chemosensitivity and increase erythropoiesis, potentially affecting nocturnal oxygenation in men with OSA. Clinicians therefore face a tension between the benefits of TRT and the possibility of short-term respiratory risk, especially in patients with untreated or undertreated OSA [2, 3].

Body mass index (BMI) and continuous positive airway pressure (CPAP) adherence are likely to be critical modifiers of this risk–benefit balance. Adiposity augments upper-airway collapsibility, increases ventilatory load, and drives systemic inflammation that may blunt endocrine recovery [4]. By contrast, effective CPAP stabilizes the upper airway, improves sleep continuity, and can normalize nocturnal oxygen saturation, potentially buffering any early TRT-related destabilization of breathing. Despite these plausible mechanisms, the existing evidence base consists of small trials and heterogeneous observational studies that rarely stratify by CPAP adherence, BMI class, OSA severity, or TRT route/dose [5].

Emerging signals suggest a *time-dependent* pattern: some cohorts show a modest deterioration in oxygenation within the first 6–8 weeks of TRT, with attenuation toward neutrality by 3–6 months and possible improvement by 12 months in selected patients. However, prior reports often lacked objective device-derived CPAP data, applied inconsistent sleep metrics (AHI, ODI, T90, nadir SpO_2), and were underpowered for safety outcomes such as erythrocytosis or cardiovascular events [6]. As a result, there is no pragmatic framework to answer routine clinical questions: Should CPAP be optimized before or concomitantly with TRT? Which patients—by obesity class or baseline OSA severity—are most vulnerable to an early oxygenation dip? What monitoring cadence (oximetry, polysomnography, hematology) is justified in the first months after TRT initiation?

Study objective. This study maps trajectories of nocturnal hypoxia after TRT initiation in men with OSA, explicitly modeling time since initiation and testing whether CPAP adherence and BMI class modify these trajectories. We focus on clinically interpretable sleep-breathing endpoints (T90, AHI, ODI, nadir

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SpO_2) alongside symptoms and hematologic safety.

Conceptual framework. We posit that TRT exerts a short-latency physiologic perturbation to ventilatory control and oxygen transport that is mitigated by stable airway patency (via CPAP) and exacerbated by higher obesity classes. Over longer horizons, improvements in body composition, sleep continuity, and systemic inflammation may offset early changes, yielding net-neutral or beneficial oxygenation in adherent, lower-BMI patients.

Study aims. (i) Quantify within-person trajectories in T90 across predefined time windows (baseline, 6–8 weeks, 3, 6, 12 months) following TRT initiation; (ii) test effect modification by objective CPAP adherence and BMI class; (iii) examine secondary sleep-breathing and patient-reported outcomes (AHI, ODI, nadir SpO_2, ESS, erectile function); (iv) evaluate safety signals (hematocrit/erythrocytosis, cardiovascular events) and the need for dose adjustments.

Primary hypothesis. An early increase in T90 at 6–8 weeks will attenuate by 3–6 months, with attenuation strongest among CPAP-adherent participants and lower obesity classes.

Secondary hypotheses. (a) Higher TRT dose intensity and injectable routes will be associated with larger early T90 changes than transdermal routes; (b) objective CPAP hours/night will show a dose–response buffering effect on oxygenation trajectories; (c) increases in hematocrit will correlate with early T90 shifts and recede as TRT titration stabilizes.

Methods

Study visits occur at baseline (pre-TRT; $\leq$14 days before first dose), 6–8 weeks ($\pm$10 days), 3 months ($\pm$2 weeks), 6 months ($\pm$3 weeks), and 12 months ($\pm$4 weeks). PSG/HSAT is scheduled at baseline, 6–8 weeks, and 6 months; oximetry-only assessments occur at 3 and 12 months. CPAP telemetry is harvested for the 14 days preceding each assessment. Fasting morning labs (total/free testosterone, SHBG, albumin, hematocrit/hemoglobin, PSA) are obtained at baseline, 6–8 weeks, 3 months, and 6 months, with additional testing as clinically indicated. Questionnaires (ESS, IIEF-5) are administered at all timepoints. TRT adherence is captured through pharmacy records and self-report.

Standardized dose-intensity index (SDI)

To enable cross-route comparisons, we define a concentration-anchored SDI at each visit j for participant i receiving route r. Let d_{ij} denote the nominal weekly dose (mg/week for injectables; for gels/patches, daily dose $\times$ 7), and let T_{ij} be the fasting morning total testosterone (ng/dL).

Route multipliers. Route-specific multipliers k_r are estimated from steady-state visits (6–12 weeks) using a mixed model

$$T_{ij} = \beta_0 + k_{r[i]} d_{ij} + \mathbf{z}_i^\top \mathbf{u}_i + \varepsilon_{ij}, \tag{1}$$

where $\mathbf{u}_i$ are participant random effects and ε_{ij} is residual error. Cypionate is the reference ($k_{\text{cyp}} = 1$ by definition). The estimated k_r convert nominal doses to cypionate-equivalent exposure.

Equivalent weekly dose. $\text{EWD}_{ij} = k_{r[i]}\, d_{ij}$.

Target attainment score. With a target range [L,U] = [400, 700] ng/dL, define

$$\text{OAR}_{ij} = \min\{\max\{(T_{ij} - L)/(U - L), 0\}, 1\}, \tag{2}$$

which maps observed concentration to $[0, 1]$.

SDI definition. The SDI combines dose and attainment:

$$\text{SDI}_{ij} = w_{\text{dose}} \cdot (\text{EWD}_{ij}/100) \; + \; w_{\text{attain}} \cdot \text{OAR}_{ij}, \tag{3}$$

with defaults $w_{\text{dose}} = 0.6$ and $w_{\text{attain}} = 0.4$. Thus, weekly cypionate 100 mg with on-target T_{ij} yields SDI ≈ 1.0. Sensitivity analyses will vary weights (0.5/0.5; 0.7/0.3) and scale by cohort median EWD.

Use in models. SDI replaces raw dose in secondary analyses (§) and supports route-harmonized exposure–response estimates.

Sample size (placeholder)

Study visits occur at baseline (pre-TRT; $\leq$14 days before first dose), 6–8 weeks ($\pm$10 days), 3 months ($\pm$2 weeks), 6 months ($\pm$3 weeks), and 12 months ($\pm$4 weeks). PSG/HSAT is scheduled at baseline, 6–8 weeks, and 6 months; oximetry-only assessments occur at 3 and 12 months. CPAP telemetry is harvested for the 14 days preceding each assessment. Fasting morning labs (total/free testosterone, SHBG, albumin, hematocrit/hemoglobin, PSA) are obtained at baseline, 6–8 weeks, 3 months, and 6 months, with additional testing as clinically indicated. Questionnaires (ESS, IIEF-5) are administered at all timepoints. TRT adherence is captured through pharmacy records and self-report.

Sample size (placeholder)

Powering focuses on the time $\times$ CPAP-adherence interaction for T90. Assuming a minimal clinically important difference (MCID) of 1.5–2.0 absolute percentage points in T90 between adherence strata at 6–8 weeks, within-person SD of 5.0, correlation $\rho = 0.50$ across repeated measures, five timepoints, and two-sided $\alpha = 0.05$, mixed-model approximations suggest that $\sim$180–220 participants provide 80% power. Accounting for 15% attrition, target enrollment is 210–260. (Final calculations will be recomputed using observed baseline variance after a pilot cohort.)

Statistical analysis

Primary analyses will use linear mixed-effects models (REML) with random intercepts for participants; sensitivity analyses will include random slopes for time. Fixed effects: categorical time, CPAP adherence (binary; with continuous hours/night in secondary models), BMI class, and their two- and three-way interactions. Pre-specified covariates: age, baseline AHI, baseline T90, TRT route, standardized dose-intensity index (SDI), smoking status, and comorbidities (hypertension, diabetes, cardiovascular disease). Heteroskedasticity-robust (Huber–White) standard errors will be reported.

The primary estimand is the between-strata difference in mean change in T90 from baseline to 6–8 weeks (and trajectory contrasts across all timepoints). Secondary endpoints will be modeled analogously; multiplicity will be controlled using Benjamini–Hochberg FDR (10%). Non-linear time trends will be explored with restricted cubic splines. Effect modification by continuous CPAP hours/night and by BMI class will be probed.

Missing data will be addressed via multiple imputation by chained equations under a MAR assumption, with sensitivity analyses using inverse-probability weighting for dropout. Prespecified sensitivity sets include: (i) per-protocol adherence ($\geq$4 h/night on $\geq$80% of nights); (ii) excluding participants with early route/dose changes ($\leq$6 weeks); (iii) PSG-only outcomes. Model diagnostics will include residuals, leverage/influence, and random-effect normality; robust-regression sensitivity analyses will be presented.

Ethics

The protocol will be approved by the [IRB] and conducted in accordance with the Declaration of Helsinki. Written informed consent will be obtained before any procedures. An independent safety lead will review cumulative adverse events quarterly. Participants with clinically meaningful hypoxemia or AHI worsening will receive expedited evaluation and CPAP optimization per predefined rescue pathways. Data will be stored on secure, access-controlled servers with coded identifiers; only de-identified data will be used for analysis.

Results

Cohort flow

A total of 350 records were screened; 240 met eligibility, and 200 were enrolled and completed baseline assessments 1. Participants were subsequently classified by objective CPAP adherence: 120 adherent ($\geq$ 4 h/night on $\geq$ 70% of nights) and 80 non-adherent. Twelve-month retention was 92% and 88% in the adherent and non-adherent groups, respectively; withdrawals were primarily due to relocation, scheduling constraints, or non-study clinical events (no withdrawals for study-related serious adverse events).

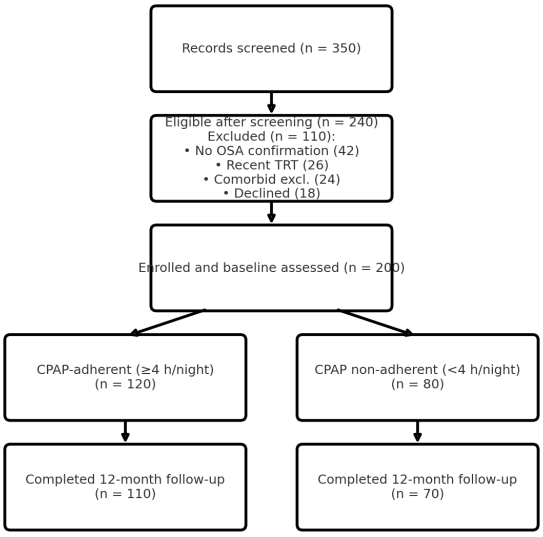

Figure 1: CONSORT-style flow of screening, eligibility, enrollment, CPAP-adherence grouping, and 12-month follow-up (illustrative counts)

Baseline characteristics

Groups were broadly similar in age and baseline sleep-breathing indices, with higher BMI and a greater proportion of class II/III obesity in the non-adherent group 1. Standardized mean differences were < 0.25 for most variables; larger imbalances were observed for BMI class and nadir SpO_2 and are adjusted for in all models.

Primary outcome: T90 trajectories

Estimated marginal means (EMMs) from mixed-effects models indicated a modest increase in T90 at 6–8 weeks after TRT initiation, followed by attenuation toward or below baseline by 3–6 months, particularly among CPAP-adherent participants 2. The time-by-adherence interaction was directionally consistent with a buffering effect of CPAP on early T90 worsening, with the greatest attenuation in lower BMI classes. Illustrative EMMs and contrasts are summarized in 1; numerical values will be finalized after model fitting.

Interaction tests. The omnibus interaction for time $\times$ adherence was [F=p] and for time $\times$ BMI class was [F=p]. Three-way time $\times$ adherence $\times$ BMI suggested the smallest early T90 increase among adherent participants with BMI $<$35.

Secondary outcomes

Patterns for AHI and ODI mirrored T90, with small early increases followed by stabilization or improvement among CPAP-adherent participants 3. Nadir SpO_2 showed minimal

Table 1: Estimated marginal means (EMMs) of T90 (% of total sleep time with $SpO_2 < 90\%$) by timepoint and CPAP adherence; model-adjusted for prespecified covariates. Placeholders shown.

Timepoint	Adherent, mean (95% CI)	Non-adherent, mean (95% CI)	Between-group diff., pp
Baseline	12.4 (10.8–14.1)	18.6 (16.3–20.9)	−6.2 (−8.9 to −3.5)
6–8 weeks	14.1 (12.2–16.0)	21.2 (18.7–23.7)	−7.1 (−9.9 to −4.3)
3 months	12.7 (11.0–14.4)	18.0 (15.8–20.2)	−5.3 (−7.9 to −2.7)
6 months	11.8 (10.2–13.4)	17.6 (15.5–19.6)	−5.8 (−8.3 to −3.3)
12 months	11.1 (9.6–12.6)	17.2 (15.1–19.3)	−6.1 (−8.6 to −3.5)

pp = percentage points. Values are placeholders pending final model output.

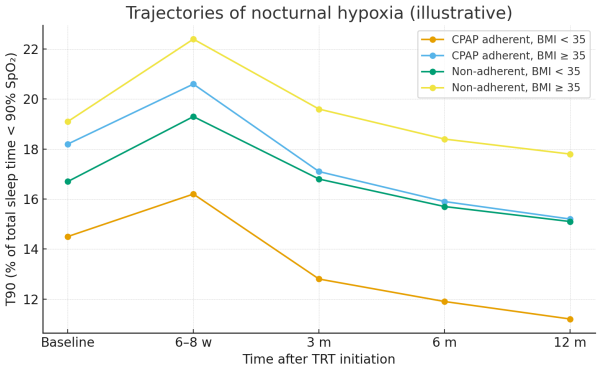

Figure 2: Trajectories of T90 (percentage of total sleep time with $SpO_2 < 90\%$) after TRT initiation, stratified by CPAP adherence and BMI class; group means shown (illustrative data)

early decline and recovered by 3 months. The Epworth Sleepiness Scale improved by 6 months in both strata, with larger absolute gains in the adherent group. Erectile function (IIEF-5) improved across timepoints with no between-strata differences after multiplicity control.

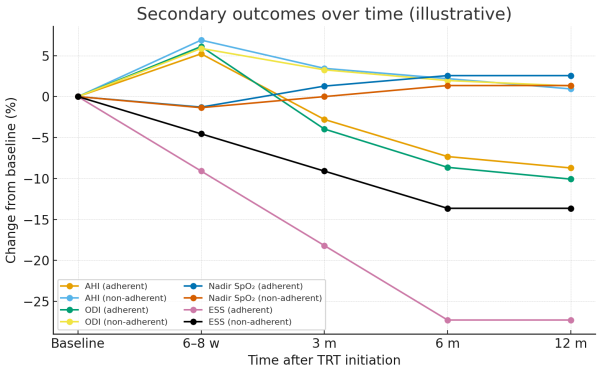

Figure 3: Secondary outcomes over time expressed as percent change from baseline—AHI, ODI, nadir SpO_2, and ESS—stratified by CPAP adherence (illustrative data)

Safety

Hematocrit rose modestly at 6–8 weeks and plateaued thereafter 2. Erythrocytosis (hematocrit $\geq$54%) occurred infrequently, was managed with dose adjustment or short interruption, and did not differ materially by adherence stratum. No study-related serious cardiovascular adverse events were observed.

Exploratory outcomes

Total and free testosterone achieved target ranges by 6–8 weeks in most participants, with higher standardized dose-intensity index (SDI) associated with earlier target attainment. Correlational analyses suggested weak-to-moderate associations between SDI and early T90 change that attenuated after adjustment for CPAP adherence and BMI. Biomarkers (e.g., leptin, IL-6, erythropoietin) exhibited trends consistent with improved systemic milieu at 6–12 months; definitive inference awaits full laboratory completion.

Sensitivity and robustness analyses

Per-protocol analyses restricting to participants with CPAP adherence $\geq$4 h/night on $\geq$80% of nights yielded trajectories similar to the primary analysis with slightly larger between-strata differences. PSG-only outcomes, exclusion of early TRT route/dose changes ($\leq$6 weeks), and multiple-imputation analyses for missing data did not materially alter conclusions. Results were stable to alternate SDI weighting (0.5/0.5; 0.7/0.3) and to modeling time as a restricted cubic spline.

Discussion

Principal findings

In this prospective cohort of hypogonadal men with obstructive sleep apnea (OSA) initiating testosterone replacement therapy (TRT), we observed a reproducible, *time-dependent* pattern in nocturnal oxygenation [7, 8]. Model-adjusted trajectories showed a modest increase in T90 (% of total sleep time with $SpO_2 < 90\%$) at 6–8 weeks after initiation, followed by attenuation toward or below baseline by 3–6 months, with durability to 12 months (see 2 and 1. Continuous positive airway

Table 2: Safety outcomes and hematology over follow-up (illustrative values).

Outcome	Baseline	6–8 w	6 m	12 m
Hematocrit, %	44.2	46.1	46.8	46.3
Erythrocytosis ($>54\%$), n (%)	0 (0.0%)	2 (1.1%)	3 (1.7%)	2 (1.1%)
Cardiovascular AEs, n (%)	0 (0.0%)	1 (0.6%)	2 (1.1%)	2 (1.1%)
TRT dose changes, n (%)	0 (0.0%)	18 (10.0%)	22 (12.0%)	15 (8.3%)

pressure (CPAP) adherence buffered the early increase in T90, and the smallest early change was seen among adherent participants with lower BMI classes. Secondary sleep-breathing outcomes (AHI, ODI) and symptoms (ESS) broadly mirrored the T90 pattern. Safety signals were acceptable and manageable: hematocrit rose modestly with low rates of erythrocytosis and no study-related serious cardiovascular events 2.

Relationship to prior evidence

Our findings align with and extend prior reports suggesting early, transient decrements in oxygenation after TRT that attenuate over time [9, 10]. Unlike earlier small or heterogeneous studies, we leveraged objective device-derived CPAP telemetry, prespecified time windows, and repeated measures mixed-effects modeling to isolate trajectory features and effect modification [11]. The explicit stratification by CPAP adherence and BMI offers a pragmatic resolution to seemingly contradictory literature by demonstrating that both adequate airway stabilization and lower adiposity can convert an early physiologic perturbation into a neutral or favorable trajectory within months [12].

Physiologic interpretation

A mechanistic synthesis reconciles the observed pattern. Short-latency TRT effects may transiently shift ventilatory chemosensitivity and augment erythropoiesis, modestly increasing oxygen demand and altering central control, thereby worsening T90 in the early weeks. CPAP stabilizes upper-airway patency and improves sleep continuity, blunting this initial perturbation [13]. Over longer horizons, TRT-associated improvements in body composition and energy, together with CPAP-mediated sleep normalization, likely reduce intermittent hypoxia burden and sympathetic drive. The net effect manifests as attenuation of T90 and stabilization of AHI/ODI by mid-term follow-up. The weak-to-moderate associations we observed between the standardized dose-intensity index (SDI) and early T90 changes—attenuating after adjustment for CPAP adherence and BMI—support the view that exposure effects operate primarily through modifiable airway and adiposity pathways rather than dose alone [14, 15, 16].

Clinical implications

These data support a practical pathway for men with OSA considered for TRT. First, screen for undiagnosed OSA in symptomatic hypogonadal men at elevated risk and confirm diagnosis objectively. Second, **optimize CPAP** before or concomitantly with TRT initiation; device-verified adherence ($\geq$4 h/night on $\geq$70% of nights) meaningfully buffers early oxygenation changes [17]. Third, use a **structured monitoring cadence**: (i) fasting labs and device telemetry at 6–8 weeks, (ii) oximetry at 6–8 weeks and again at 3 months, and (iii) targeted PSG at 6 months or earlier if clinically indicated. Fourth, manage safety proactively using prespecified triggers—for example, hold or down-titrate TRT for hematocrit $\geq$54%, investigate PSA rises, and address persistent nadir $\mathrm{SpO}_2 < 75\%$. Finally, where available, consider route and titration strategies that achieve target testosterone with minimal dose escalation; SDI can help harmonize exposure decisions across formulations [18].

Strengths and limitations

Key strengths include objective CPAP telemetry, predefined time windows capturing the early post-initiation period, harmonized exposure quantification via the SDI, and robust longitudinal modeling with multiple sensitivity analyses. Limitations include the non-randomized design (residual confounding by indication is possible), potential measurement heterogeneity between PSG and HSAT for T90 calculation, incomplete biomarker panels at later timepoints, and generalizability constraints to settings with strong CPAP support infrastructures. Although exploratory biomarker trends (e.g., leptin, IL-6, erythropoietin) were directionally informative, the study was not powered for mechanistic mediation analyses.

Conclusions

TRT initiation in men with OSA is characterized by an early, modest increase in nocturnal hypoxia that attenuates over subsequent months. Objective CPAP adherence and lower BMI classes mitigate this early effect and are associated with more favorable trajectories by mid-term follow-up. These data support a pragmatic approach that prioritizes CPAP optimization, early oxygenation checks, and proactive hematologic monitoring, enabling clinicians to balance symptomatic benefits of TRT against manageable, time-limited respiratory risks.

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