# Prevalence of secondary erythrocytosis in men receiving testosterone therapy: A matched-cohort analysis of intranasal gel, injections, and pellets

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## ABSTRACT

**Introduction:** Increased hematocrit (HCT) is a common adverse effect in men on testosterone therapy (TTh). We aimed to uncover differences in HCT changes among men receiving different forms of TTh, namely intranasal gels, intramuscular injections, and subcutaneous pellets.
**Methods:** We conducted a single-center, retrospective, matched-cohort study of patients treated for testosterone deficiency (TD) to investigate the effect of three TTh regimens on HCT. We included men who received intranasal testosterone (NT), intramuscular testosterone (TC), or subcutaneous testosterone pellet (TP) regimens between January 2011 and December 2020. We matched treatment cohorts 1:1:1 for age, body mass index (BMI), and history of obstructive sleep apnea. Those taking TTh for less than 16 weeks were excluded. Comparison between groups was performed with U-Mann Whitney test, Student t-test, ANOVA, or Kruskal Wallis test as appropriate.
**Results:** Seventy-eight matched-cohort individuals with testosterone deficiency (TD) received either NT, TC, or TP. The most common TD symptoms prior to initiation of TTh were erectile dysfunction (38%), low libido (22%), and lack of energy (17%). Baseline serum testosterone and

HCT were higher in NT ($p<0.05$) recipients. As expected, all men receiving TTh were found to have increased serum testosterone levels at followup ($p<0.001$). Relative to their respective baselines, men receiving TC experienced the greatest increase in serum testosterone (240.8 ng/dL to 585.5 ng/dL), followed by NT (230.3 ng/dL to 493.5 ng/dL) and TP (210.8 ng/dL to 360.5 ng/dL) (all $p<0.001$). TC and TP were associated with significant increases in HCT (4.4% and 1.7%), while NT was associated with a decrease in HCT (-0.8%) at 16-week followup.
**Conclusions:** When controlled for age, BMI, and OSA, men receiving NT experienced decreased HCT compared to TC or TP at 16-week followup. Intranasal testosterone, while able to increase serum testosterone levels to reference range, does not appear to have a significant impact on HCT compared to the longer-acting forms of TTh.

## INTRODUCTION

Testosterone therapy (TTh) has been regarded as the mainstay of treatment for symptomatic testosterone deficiency (TD) for the last 60 years[1,2]. One of the adverse effects of TTh is increased hematocrit (HCT). Many forms of TTh can lead to increased HCT[3,4]. The underlying mechanism of testosterone-induced rise in HCT is unclear, but it may involve increases in erythropoietin, decreases in hepcidin, or hypoxia from worsening obstructive sleep apnea (OSA). Newer theories have considered estradiol playing a causative role for increased HCT through the stimulation of hematopoietic stem cells[5]. It is also unclear whether route of administration, the peak serum testosterone level, or the area under the therapeutic curve of men receiving TTh contributes to changes in HCT. Regardless of the underlying etiology, it appears that men who develop erythrocytosis (HCT > 54%) within the first year of receiving TTh may have an increased risk of major adverse cardiovascular events[5,6].

To our knowledge, there are no direct studies evaluating differential changes in HCT between intranasal, intramuscular, and subcutaneous testosterone regimens in a matched cohort. We hypothesized that short-acting TTh would more closely resemble physiologic endogenous testosterone release and would have less an effect on HCT relative to longer-acting formulations. This study aimed to quantify the potential differences in HCT change and erythrocytosis prevalence between intramuscular testosterone cypionate (TC), testosterone pellet (TP), and intranasal testosterone (NT). Ultimately, the results from this study may be used to better characterize the adverse effects of TTh regimens and to guide the decision-making process between patients and clinicians.

## METHODS

We conducted a single-center, retrospective, matched cohort analysis of patients treated for TD to investigate the effect of various TTh regimens on HCT. This study was reviewed and approved by our institutional review board.

Our health system database was searched for men receiving TTh between January 1, 2011, and December 31, 2020. Filtered patients completed a washout period of four weeks for gels and injection-based therapies and 16 weeks for subcutaneous pellets and reported rigorous adherence to their respective treatment schedule. We included men with a morning serum total testosterone (T) under 300 ng/dl; and hypogonadal symptoms, including erectile dysfunction (ED), sleep disturbances, decreased energy, low libido, premature ejaculation (PE), and depressed mood. Included men had a baseline HCT, and were started on either TP, NT, or TC. Furthermore, we included men who stayed on TTh for 16 weeks or more, and had subsequent bloodwork (testosterone and HCT, at a minimum) at that time point. We excluded men if they used more than one type of TTh during the targeted period.
A minimum of 16-week follow-up from treatment initiation was chosen as one cycle of erythropoiesis is approximately 120 days[7]. The dosages and frequency of administration were as follows: for TP, 800 mg every 5 months; for NT, 11 mg three times a day; and for TC, 100 mg every week[8,9].

We performed a retrospective chart review to characterize the distribution of presenting hypogonadal symptoms (listed above) of men diagnosed with TD (Figure 1). Among cohorts, we were able to match for age within three years, established history of OSA, and body mass index (BMI) within 4%.

**Outcomes**

We collected laboratory results including HCT, serum total testosterone (T), estradiol (E), and prostate specific antigen (PSA). The primary outcomes were changes in HCT and T following at least 16 weeks of TTh. We also recorded changes in estradiol and PSA during the same 16-week period. In accordance with American Urological Association guidelines, erythrocytosis was defined as HCT > 54%, and successful treatment of TD was defined as T level of ≥450 ng/dL[10]. All T assays were collected using liquid chromatography–mass spectrometry.

**Power calculation**

The sample size of the study was calculated *a priori* based on previously published data for NT (+1% HCT; SD 4%) as well as the Beggs et al. study that demonstrated a 5% increase in HCT in men using weekly injections of TC[11,12]. We set α to 0.05 and statistical power to 0.8. The two-tailed sample size calculated for an adequate power was 25 patients for each cohort.

**Statistical analysis**

We performed a matched cohort study within the [University of Miami Database]. The exposure was defined as use of TTh. Matched cohorts were constructed with patients placed in a 1:1:1 ratio for age, BMI, and OSA. Patients satisfying the inclusion and exclusion criteria were artificially compared in “triplets” for matching characteristics. Of all eligible patients, cohorts were constructed based on age, BMI, and OSA values or histories. Constraints for age was

within three years, BMI within 4%, and prevalence of OSA was maintained in all three treatment cohorts[13,14].

Data analysis was performed with SPSS version 28, continuous variable was presented as mean ± standard deviation or median [interquartile range 25-75] in accordance with data distribution, and comparison between groups was performed with the U-Mann Whitney test, Student T-test, ANOVA, or Kruskal Wallis test as required. Differential prevalence of OSA among groups was analyzed with the chi-square test. Changes in testosterone, estradiol, and PSA over time within groups were evaluated with the Wilcoxon test. Absolute HCT change (from baseline to follow-up) was also reported. A p-value of <0.05 was considered statistically significant.

## RESULTS

78 men receiving either NT, TC, or TP (26 men in each treatment cohort) within University of Miami Health System were "triplet" grouped into cohorts for appropriate matching of age, BMI, and OSA. The most common hypogonadal symptoms prior to initiation of TTh were ED (38%), low libido (22%), and lack of energy (17%) (Figure 1). Overall, mean age was 44.6 ± 10.6 years and mean BMI was 30.5 ± 5.8 kg/m$^2$, with a baseline T of 223.5 [191.1-260.4] ng/dL, PSA of 0.7 [0.4-1.15] ng/dL, and HCT of 44% [40.8–46.3%]. Age, T, E, and PSA at baseline were similar among groups ($p > 0.05$). At baseline, HCT and BMI were higher in men in the NT group ($p < 0.05$). All three TTh regimen groups had significantly different levels of T, HCT, and E at follow-up ($p < 0.05$) (Table 1).

On follow-up there was no patient with erythrocytosis, that is, HCT ≥ 52%. The overall absolute median HCT change during the study period was 1.5 [-0.9 – 4.0] (1.5 ± 3.9). The median HCT change for the TP group was 1.7 [-0.05 – 3.7] (1.7 ± 3.2), for the NT group -0.8 [-2.3 – 1.1] (-1.2 ± 2.8), and for the TC group 4.4 [1.6 – 6.9] (4.1 ± 3.8) (Figure 2B). Within each group, all TTh formulations successfully increased T levels to reference range ($p < 0.001$), with TP from 210.8 [145 - 234.4] ng/dL to 360.5 [250.8 - 486]; NT from 230.3 [200.3 - 261.6] ng/dL to 493.5 [391 - 698.3] ng/dL; and TC from 240.8 [193.4 - 288.4] ng/dL to 584.5 [349.5 - 802.3] ng/dL (Figure 2A).

When considering the other serologic markers, there was no significant change in PSA (TP: $p = 0.147$, NT: $p = 0.057$, and TC: $p = 0.336$), and E (TP: $p = 0.909$, NT: $p = 0.915$, and TC: $p = 0.149$) during follow-up.

Overall, 12 (15.4%) men had OSA at baseline, and OSA prevalence was similar among the three groups ($p = 0.7440$). Baseline T, E, PSA, and HCT were similar among men with OSA and those without OSA ($p > 0.05$). On follow-up, patients with and without OSA had similar E, PSA, and HCT levels ($p > 0.05$); however, T levels were lower in patients with OSA (Without OSA: 480 [342 - 675.3] ng/dL vs. with OSA: 338.5 [183 - 527] ng/dL; $p = 0.048$) (Table 2).

## DISCUSSION

Testosterone therapy has remained the mainstay of treatment for men with symptomatic TD; often, patients require lifelong supplementation to abate hypogonadal symptoms[15]. Increased HCT is a common adverse effect of TTh, with the potential to cause serious adverse cardiovascular and thromboembolic effects[15]. Previous studies have demonstrated that TTh formulations such as NT can closely mimic the physiologic release of endogenous testosterone by virtue of short-acting properties and daily dosage requirements[16,17]. Given previous studies demonstrating the capability of short-acting TTh to maintain sex hormones and sperm parameters, we hypothesized that NT would have less an effect on HCT than longer-acting formulations.

To our knowledge, this is the first study to compare the changes in HCT between intranasal, intramuscular, and subcutaneous testosterone regimens in a matched cohort. We found that long-acting TTh is associated with significant increases in HCT compared to short-acting formulations. NT does not appear to have a significant impact on HCT compared to the longer-acting formulations while simultaneously increasing T levels to reference range in most patients.

The role of TTh in erythropoiesis has yet to be fully elucidated. Rather than having an indirect role in increasing erythropoietin, testosterone appears to act directly on hematopoietic stem cells to stimulate red blood cell synthesis[18]. Several key mechanisms have been implicated including iron incorporation into red cells[19]. The effect of TTh on red blood cell production is substantiated by the development of anemia in men undergoing androgen deprivation therapy, which can be corrected with androgen replacement or cessation of androgen deprivation therapy[20,21].

Studies directly comparing different TTh modalities with regards to HCT changes are lacking. From individual trials, rates of erythrocytosis have been reported as 1.3% in men using NT, 10.4% in men using TP, and 11.2% in men using TC[12,22,23]. According to AUA guidelines, men on TTh who develop erythrocytosis may require dose adjustment, temporary discontinuation, or referral to a hematologist for phlebotomy. Unfortunately, while these interventions may help mitigate the adverse effects associated with erythrocytosis, patients may experience recurring hypogonadal symptoms for an indeterminate time. These implications highlight the importance of determining the "erythropoetic profiles" of different TTh delivery methods.

When examining the secondary outcomes of this study, it is important to note that aside from PSA, many differences were seen among the various TTh delivery methods. No TTh regimen significantly changed PSA at follow-up, reinforcing previous evidence that TTh likely has minimal effect on the prostate[21,22]. Among the three cohorts, the TC group had the highest mean T levels (584.5 ng/dL), followed by the NT group (493.5 ng/dL), and the TP group (360.5 ng/dL). Our results indicate that many patients using TP were unable to reach a T level of 450

ng/dL, the benchmark of therapeutic success[24]. These results directly contrast with those of previous studies demonstrating that TP can sufficiently increase serum testosterone to therapeutic levels[23,25].

Interestingly, despite patients with OSA having similar HCT as those without OSA on follow-up, the former was found to have significantly lower T levels, raising the question of whether patients with concomitant TD and OSA have a blunted response to TTh. Patients with OSA may inherently be subjected to low T levels, potentially due to OSA-induced decreased pituitary gonadal function[26]. Although OSA has been associated with polycythemia in the setting of TTh[27], it remains to be seen whether OSA at varying severities modulates the response to TTh and if so, what the underlying mechanisms are.

In the present study, we were able to create matched cohorts and simultaneously control for age, BMI, and OSA in all three treatment groups. This improves on the existing literature, as most studies fail to adequately account for OSA, a known contributor to increased HCT[28,29]. After matching, we observed an increased BMI among men in the NT arm. As lower HCT was seen in men of this treatment arm, we believe this value is not clinically significant despite statistical significance. Secondly, recruitment took place in a diverse metropolitan area with a unique patient population, many of whom may be traditionally underrepresented in clinical research[30]. All serologic testing was done at outside institutions such as LabCorp or Quest that used liquid chromatography–mass spectrometry, the gold standard for T blood testing.

### Limitations

Limitations of this study include unknown timing of blood tests relative to the TTh dosing schedule. This may have led to unreliable T levels due to the peaks and troughs associated with each TTh modality. Although patients switching TTh modality received routine washout periods, the degree of adherence is not directly observable. Additionally, as NT was not released until 2016, there is a time frame difference for recruitment, which could potentially affect the results. Our timeline to understand HCT changes was within 16 weeks; while this follows the laboratory evaluation guidelines under the American Society of Andrology, it prevents evaluation of HCT changes that may have occurred upon longer term follow-up. Finally, some patients were previously enrolled in ongoing clinical trials and may have possibly benefited from additional visits, closer follow-up, and improved availability of medication, which may have led to enhanced medication adherence relative to the broader population. Further investigation of TTh-induced HCT changes should evaluate genetic and/or environmental dispositions to this phenomenon, how to properly trend individual patient changes in HCT, or even the long-term effect of NT on HCT in larger sample sizes.

## CONCLUSIONS

Short-acting intranasal testosterone appears to adequately treat TD without significantly affecting HCT or risk of erythrocytosis. Men on longer-acting TTh modalities experienced an increase in

HCT. To the best of our knowledge, our study is the first matched cohort analysis to examine the differential HCT changes between intranasal, injectable, and subcutaneous pellet forms of testosterone therapy. Our findings add to the existing evidence on TTh adverse effect profiles and may subsequently influence the shared decision-making process of choosing the optimal TTh regimen.

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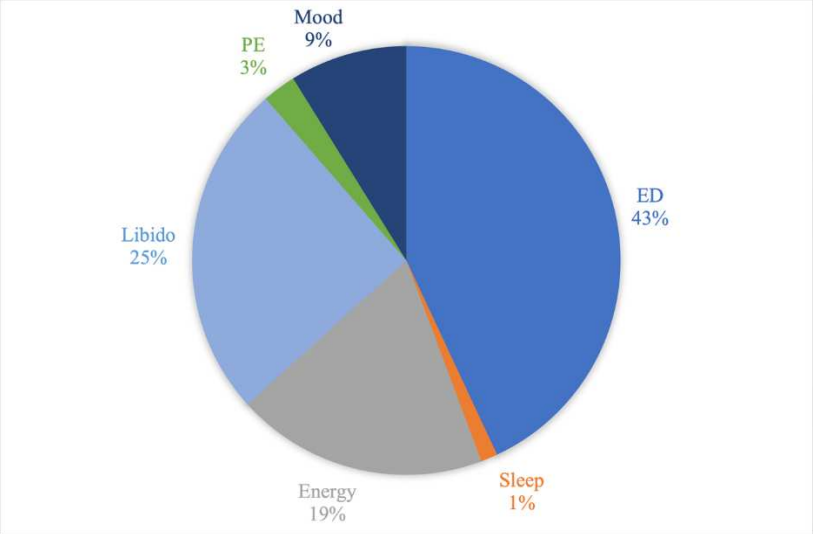
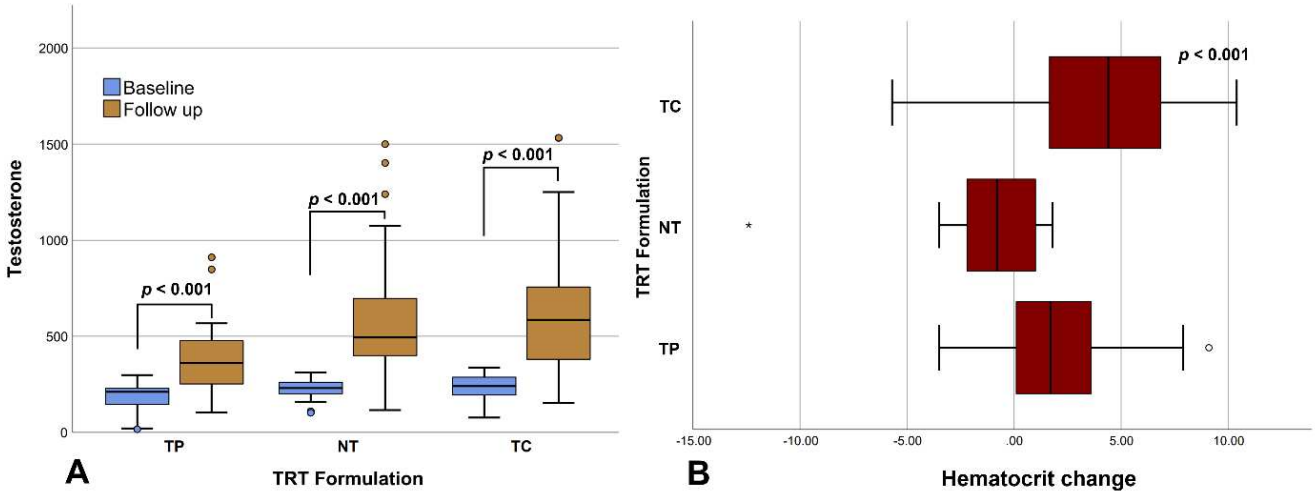
## FIGURES AND TABLES

**Figure 1.** Percent distribution of hypogonadal symptoms prior to initiation of testosterone therapy (TTh) in testosterone deficient (TD) men.




*Estimates are based on retrospective medical chart review of patients.

**Figure 2.** Box plot figure showing the changes within testosterone therapy (TTh) formulation groups of serum (A) testosterone levels and (B) change in hematocrit.



| **Table 1. Clinical and biochemical characteristics of the analyzed patients, and comparison between TTh groups** | | | | | |
|---|---|---|---|---|---|
| | **Overall N=78 (100%)** | **TP n=26 (33.3%)** | **NT n=26 (33.3%)** | **TC n=26 (33.3%)** | **p** |
| Age (years) | 44.6±10.6 | 43.7±7.4 | 43.7±10.2 | 46.5±13.5 | 0.550 |
| BMI (kg/m$^2$) | 30.5±5.8 | 29.5±7.2 | 32.7±4.7 | 29.1±4.5 | **0.042** |
| OSA | | | | | |
| No (%) | 66 (84.6%) | 23 (88.5%) | 22 (84.6%) | 21 (80.8%) | |
| Yes (%) | 12 (15.4%) | 3 (11.5%) | 4 (15.4%) | 5 (19.2%) | 0.744 |
| Before treatment | | | | | |
| Testosterone (ng/dL) | 223.5 [191.1 –260.4] | 210.8 [145–234.4] | 230.3 [200.3–261.6] | 240.8 [193.4–288.4] | 0.090 |
| PSA (ng/dL) | 0.70 [0.40–1.15] | 0.60 [0.40–0.82] | 0.84 [0.40–1.53] | 0.70 [0.50–1.30] | 0.450 |
| Hematocrit (%) | 44 [40.8–46.3] | 43.8 [40.7–46.9] | 45.2 [44.3–46.7] | 41.6 [38.9–44.5] | **0.010** |
| Estradiol (pg/mL) | 23 [17.1–29] | 22.2 [13.2–25.3] | 22 [17.3–28.9] | 23.1 [18.5–29.8] | 0.522 |
| After treatment | | | | | |
| Testosterone (ng/dL) | 469 [327–662.5] | 360.5 [250.8–486] | 493.5 [391–698.3] | 584.5 [349.5–802.3] | **0.011** |
| PSA (ng/dL) | 0.70 [0.50–1.20] | 0.65 [0.45–1.03] | 1.05 [0.48–1.50] | 0.68 [0.50–1.10] | 0.402 |
| Hematocrit (%) | 45.5 [43.5–47.4] | 45.5 [43.8–47.2] | 44.3 [42.7–46.5] | 47.1 [44.2–48.7] | **0.033** |
| Estradiol (pg/mL) | 24.6 [18.1–34] | 21.5 [9.1–25.7] | 25.5 [18.3–33.8] | 30 [19.3–54.4] | **0.038** |

Mean ± standard deviation; median [interquartile range 25$^{th}$–75$^{th}$]. BMI: body mass index; PSA: prostate-specific antigen; NT: intranasal testosterone; TC: testosterone cypionate; TP: subcutaneous testosterone pellets.

| **Table 2. Clinical and biochemical characteristics of the analyzed patients, and comparison between men with OSA and those without OSA** | | | |
|---|---|---|---|
| | **No OSA** n=66 (84.6%) | **With OSA** n=12 (15.4%) | **p** |
| Age (years) | 44±10.4 | 48.1±11.6 | 0.221 |
| BMI (Kg/m$^2$) | 29.8±5.1 | 33.9±7.9 | 0.024 |
| TRT | | | |
| TP (%) | 23 (88.5%) | 3 (11.5%) | |
| NT (%) | 22 (84.6%) | 4 (15.4%) | |
| TC (%) | 21 (80.8%) | 5 (19.2%) | 0.744 |
| Before treatment | | | |
| Testosterone (ng/dL) | 226 [193.8–261.6] | 208.9 [190–248.3] | 0.346 |
| PSA (ng/dL) | 0.60 [0.40–1.20] | 0.70 [0.48–1.15] | 0.700 |
| Hematocrit (%) | 44 [40.8–46.3] | 44.1 [39.7–47.7] | 0.938 |
| Estradiol (pg/mL) | 22.5 [16.7–29] | 23 [18–29] | 0.747 |
| After treatment | | | |
| Testosterone (ng/dL) | 480 [342–675.3] | 338.5 [183–527] | **0.048** |
| PSA (ng/dL) | 0.70 [0.50–1.23] | 0.73 [0.50–1.28] | 0.883 |
| Hematocrit (%) | 45.4 [433–47.2] | 46.9 [43.6–47.6] | 0.432 |
| Estradiol (pg/mL) | 24.8 [19–33.2] | 19.5 [15–36] | 0.397 |

Mean ± standard deviation; median [interquartile range 25$^{th}$–75$^{th}$]. BMI: body mass index; OSA: obstructive sleep apnea; PSA: prostate-specific antigen; NT: intranasal testosterone; TC: testosterone cypionate; TP: subcutaneous testosterone pellets.