

## Erythrocytosis Following Testosterone Therapy

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## ABSTRACT

**Introduction:** A rapid increase in awareness of androgen deficiency has led to substantial increases in prescribing of testosterone therapy (TTh), with benefits of improvements in mood, libido, bone density, muscle mass, body composition, energy, and cognition. However, TTh can be limited by its side effects, particularly erythrocytosis. This review examines the literature on testosterone-induced erythrocytosis and polycythemia.

**Aim:** To review the available literature on testosterone-induced erythrocytosis, discuss possible mechanisms for pathophysiology, determine the significance of formulation, and elucidate potential thromboembolic risk.

**Methods:** A literature review was performed using PubMed for articles addressing TTh, erythrocytosis, and polycythemia.

**Main Outcome Measures:** Mechanism, pharmacologic contribution, and risk of testosterone-induced erythrocytosis.

**Results:** For men undergoing TTh, the risk of developing erythrocytosis compared with controls is well established, with short-acting injectable formulations having the highest associated incidence. Potential mechanisms explaining the relation between TTh and erythrocytosis include the role of hepcidin, iron sequestration and turnover, erythropoietin production, bone marrow stimulation, and genetic factors. High blood viscosity increases the risk for potential vascular complications involving the coronary, cerebrovascular, and peripheral vascular circulations, although there is limited evidence supporting a relation between TTh and vascular complications.

**Conclusion:** Short-acting injectable testosterone is associated with greater risk of erythrocytosis compared with other formulations. The mechanism of the pathophysiology and its role on thromboembolic events remain unclear, although some data support an increased risk of cardiovascular events resulting from testosterone-induced erythrocytosis. **Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis Following Testosterone Therapy. Sex Med Rev 2018;6:77–85.**

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**Key Words:** Hypogonadism; Testosterone; Hormone Replacement; Erythrocytosis; Polycythemia

## INTRODUCTION

With an increasing awareness of men's health issues, including androgen deficiency, the use of testosterone therapy (TTh) is increasing. Testosterone (T) prescription sales for men older than 40 years have tripled during the past decade and quadrupled in men 18 to 45 years old.<sup>1,2</sup> Furthermore, direct to consumer

marketing campaigns by drug manufacturers have introduced the concepts of “andropause” and “low T” to the general population, and physicians have established terminology such as “late-onset hypogonadism” and “androgen deficiency” in the aging man.

Hypogonadism is defined as “biochemically low testosterone levels in the setting of a cluster of clinical symptoms, which may include reduced sexual desire (libido) and activity, decreased spontaneous erections, decreased energy and depressed mood.”<sup>3</sup> Men also can present with decreases in muscle mass and strength, increased fat mass, decreased bone mineral density, and anemia.<sup>3,4</sup> Symptomatic hypogonadism is a pathologic disruption of the hypothalamic-pituitary-testicular axis. There are two widely accepted forms of hypogonadism: primary (testicular failure) and secondary (hypothalamic or pituitary failure). Primary hypogonadism represents failure of T production, characterized by low serum T and increased gonadotropins. Secondary hypogonadism results from a failure of testicular

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stimulation, characterized by low serum gonadotropin and low serum T levels. The Sexual Medicine Society of North America (SMSNA) described the clinical scenario of men presenting with signs and symptoms of low T, distinct from the classic picture of primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism, as adult-onset hypogonadism.<sup>5</sup> The SMSNA suggested that the term *adult-onset hypogonadism* could be applied to most men with hypogonadism, many of whom have concomitant metabolic disease (obesity, type 2 diabetes, metabolic syndrome, etc). In an official statement, the organization proposed an algorithm for TTh in patients with adult-onset hypogonadism.<sup>5</sup>

The Hypogonadism in Males (HIM) study found that the prevalence of hypogonadism in men older than 45 years is higher than 38%, with a 17% increase in risk for every 10-year increase in age; however, the HIM study did not include symptoms in its definition of hypogonadism.<sup>6</sup> In the European Male Aging Study, the overall prevalence of low T (total T < 10.5 nmol/L without symptoms) was somewhat lower at 23.3%.<sup>7</sup> Further assessment of the cohort with an evaluation of nine candidate symptoms in addition to low T levels found a prevalence of 2.1% for symptomatic hypogonadism (low T with at least three symptoms).<sup>8</sup> The investigators acknowledged the lower prevalence of hypogonadism in consideration of serum T levels and symptoms, noting that “this finding underscores the paramount importance of using not only biochemical measures but also stringently defined, symptom-based criteria to prevent over diagnosis...”<sup>8</sup> Although these studies demonstrated that the incidence of hypogonadism differs as a function of patient age and definition of hypogonadism, the Food and Drug Administration has concluded that available evidence does not support an indication for TTh in the setting of “age-related hypogonadism.”<sup>9</sup> Given increased testing for low T levels, the large increase in T prescribing, and incompletely defined indications for therapy, it is paramount that we thoroughly understand the risks and benefits of TTh.

Despite its positive effects, TTh has several common side effects, including increases in estrogen levels, gynecomastia, and erythrocytosis.<sup>10–15</sup> Much recent attention has been focused on the effects of TTh on the cardiovascular (CV) system. Extensive debate has focused on high-impact publications with questionable methodologies and controversial conclusions that suggested significant CV risk for men on TTh with alternative studies suggesting benefit.<sup>16–20</sup> In light of this controversy, the American Urological Association issued a policy statement stating that, based on current evidence, definitive answers on the CV risks of TTh are not currently available.<sup>3</sup>

T-induced increases in hemoglobin (Hb) and hematocrit (Hct) can lead to erythrocytosis, clinically defined as an Hb level higher than 18.5 g/dL or an Hct higher than 52% in men, although this definition varies.<sup>21</sup> Physiologically, erythrocytosis is defined by an erythrocyte mass that exceeds 125% of that predicted for sex and body mass.<sup>22</sup> This is the most common

dose-limiting adverse effect of TTh.<sup>10,12,21,23</sup> Much of the concern on increases in blood viscosity resulting from increased red blood cell mass centers on the potential increased risk for venous thromboembolism, myocardial infarction, and cerebrovascular accidents.<sup>24</sup> However, little evidence supports an increased risk of these negative sequelae in men on TTh.<sup>25</sup> We review the literature examining T-induced erythrocytosis and summarize proposed mechanisms and risks of thromboembolic sequelae.

## HYPOGONADISM AND TESTOSTERONE THERAPY

T levels decrease by 1% to 2% per year after 35 years of age, correlating to a decrease of 110 ng/dL per decade of life.<sup>26,27</sup> These age-related decreases in T are often attributed to a combination of decreasing gonadotropin levels and testicular hypofunction. Most professional society guidelines recommend treatment for T levels lower than 300 ng/dL in men with concomitant hypogonadal symptoms.<sup>8,28–30</sup>

The primary treatment for hypogonadism is TTh, which can correct insulin resistance; increase bone and muscle mass; decrease subcutaneous fat; lower low-density lipoprotein cholesterol, triglycerides, blood glucose, HbA<sub>1c</sub>, and blood pressure; increase high-density lipoprotein cholesterol; and improve erectile function and life parameters (ie, increased energy and friendliness, decreased anger and anxiety, etc).<sup>31,32</sup> Although improvement in physiologic parameters is enough to warrant therapy, it is the improvement in physical and mental symptoms that drives patient satisfaction. Kovac et al<sup>33</sup> longitudinally evaluated patient satisfaction of men treated with different formulations of TTh (52.5% injection, 30.6% gels, and 16.9% pellets), with overall satisfaction rates ranging from 62.8% with less than 6 months of therapy to higher than 79% at 25 to 36 months.

Currently, numerous T formulations are available, including short- and long-acting injections, topical gels and creams, transdermal and buccal patches, and implantable pellets. As early as the 1940s, subcutaneous T pellets were available. Relatively short-acting intramuscular (IM) injections, such as T enanthate (TE), an ester metabolized over 4 to 5 days, and T cypionate (TC), a longer-acting testosterone metabolized over 7 to 8 days, were introduced in the 1950s. Oral T undecanoate (TU) was developed in the 1970s, although this formulation is not currently approved for use in the United States. Transdermal patches were developed in the 1990s, and soon after, topical gels, buccal patches, and extended-release IM formulations (TU) became available.<sup>34,35</sup> Although all T formulations are effective, each formulation's unique adverse effect profile is determined by dosage, pharmacokinetics, and method of administration.<sup>33,36</sup>

## TESTOSTERONE-INDUCED ERYTHROCYTOSIS

*Polycythemia* and *erythrocytosis* are used interchangeably to refer to an abnormal increase of Hb or Hct. Although stimulation of

erythropoiesis is therapeutic in the treatment of anemias, an unclear understanding of the thromboembolic potential of T-induced increases in Hb and Hct necessitates vigilant screening. In the clinical setting, erythrocytosis generally translates to an Hb level higher than 18.5g/dL or an Hct level higher than 52% in men, although this definition varies. The Endocrine Society uses an Hct level higher than 50% as a relative contraindication to the initiation of TTh and an Hct level higher than 54% as a reason to stop therapy.<sup>4</sup> Other professional societies use Hct levels ranging from 52% to 55% as thresholds to modify or discontinue TTh.<sup>37</sup> When obtaining laboratory studies on patient, we recommend using a single laboratory to longitudinally track results for each patient. Such an approach provides consistency and reproducibility of results. Physiologic erythrocytosis can be subdivided into primary and secondary subtypes, with primary erythrocytosis arising from a bone marrow-mediated proliferation of erythrogenic precursors and secondary erythrocytosis resulting from an external alteration to which erythroid hyperplasia is a compensatory response. This compensatory response could be physiologically appropriate (ie, compensation for hypoxia) or inappropriate (ie, secondary to T replacement therapy).<sup>38</sup>

The erythrogenic effect of T has been well established since before the recent surge in prescribing.<sup>23,39</sup> Increased Hct is associated with increased blood viscosity, decreased venous return, and increased platelet adhesiveness.<sup>40–42</sup> Clinical and academic interest currently concerns persistently increased Hb and Hct and the potential increased risk for thromboembolic events and ischemic sequelae from blood hyperviscosity, particularly in the setting of TTh-induced erythrocytosis.<sup>43–45</sup>

## ERYTHROCYTOSIS AND THROMBOEMBOLIC RISK

Several studies have attempted to evaluate the relation between erythrocytosis and endothelial dysfunction. In 1978, Pearson and Wetherley-Mein<sup>45</sup> observed a positive correlation between packed red cell volume and vascular veno-occlusive episodes. Although not induced by T, an increased thromboembolic risk from increased Hct was demonstrated. In 2010, Braekkan et al,<sup>24</sup> in a large, prospective, population-based study, found that a 5% increase in Hct in men resulted in an increased risk of venous thromboembolism (hazard ratio [HR] = 1.46, 95% CI = 1.15–1.84); this relation remained significant in the multivariable model adjusted for age, smoking, and body mass index (HR = 1.33, 95% CI = 1.05–1.70). Unfortunately, smoking was assessed as a dichotomous variable and the investigators acknowledged this as a limitation, because they could not take into account the potential dose-dependent effect. Also, there were limited data on underlying medical diseases that might have acted as confounding variables. In a 2013 study, Marchioli et al<sup>46</sup> randomized 365 adults (62% men) with polycythemia vera to a more intensive (target Hct < 45%) or less intensive (target Hct 45–50%) treatment group with the primary end point of time until death from CV causes or major thromboembolic event.

After 31 months of follow-up, the less intensive treatment group developed significantly more events (HR = 3.91, 95% CI = 1.45–10.53,  $P = .007$ ) than the more intensive treatment group.

Conversely, numerous studies have reported conflicting results, observing no increased risk of thromboembolism with persistent Hct increases. Tsai et al<sup>47</sup> used prospective data from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study and assessed CV risk factors and venous thromboembolism incidence. Of the variables investigated, an increased Hct did not correlate with increased risk (HR = 1.03, 95% CI = 0.69–1.53). Unfortunately, the upper Hct threshold was higher than 43.5%, which included many subjects with normal Hct levels. It is unclear whether an increased risk would have been observed in subjects with Hct levels above a higher threshold value. Shibata et al<sup>48</sup> investigated the relation between thromboembolic complications and erythrocytosis (Hct > 85%) in a transgenic mouse model and observed no evidence of thromboembolic complications. They hypothesized that decreased clot strength and slowed clot formation kinetics, possibly secondary to a high erythrocyte concentration, resulted in mechanical interference of platelet and fibrin interactions with the endothelium.

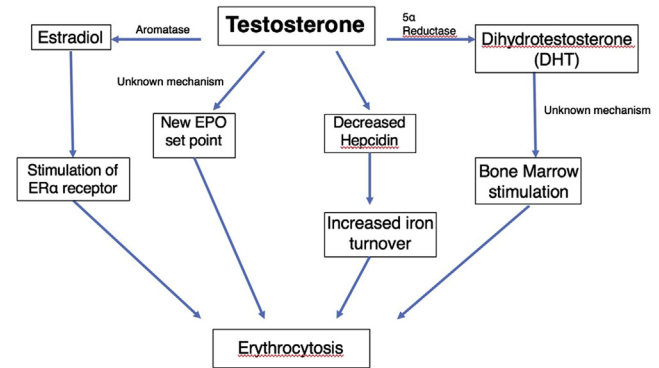
## TESTOSTERONE-INDUCED ERYTHROCYTOSIS RISK

These studies highlight a potential link between blood hyperviscosity and thromboembolic complications. However, to date, no randomized or prospective studies have observed a direct relation between TTh-induced erythrocytosis and thromboembolic events. One small retrospective study by Krauss et al<sup>44</sup> examined a 15-subject cohort of men receiving short-acting IM TE every 3 weeks and observed a correlation between increased Hct and transient ischemic attacks when the men were separated into groups with a mean Hct level higher or lower than 48%. However, the small sample precluded the ability to draw significant conclusions. Other studies that directly assess TTh-induced erythrocytosis and CV risk are not available. Widely debated studies by Basaria et al,<sup>16</sup> Finkle et al,<sup>17</sup> and Vigen et al<sup>19</sup> have reported an increased CV risk related to TTh, but these studies do not specifically correlate CV events to T-induced erythrocytosis, irrespective of their methodologic flaws. More recently, in a meta-analysis of all randomized controlled trials related to TTh and CV risk, Corona et al<sup>49</sup> concluded that the available evidence “does not support a causal role between testosterone supplementation and adverse CV events when hypogonadism is properly diagnosed and replacement therapy correctly performed.” With regard to the risk of CV events, despite the lack of evidence, the Food and Drug Administration has mandated that T manufacturers add a warning to T labels indicating “a possible increased risk of heart attacks and strokes in patients taking testosterone.”<sup>9</sup>

## PATHOPHYSIOLOGY OF TESTOSTERONE-INDUCED ERYTHROCYTOSIS

Multiple explanations for the mechanism of T-induced erythrocytosis have been offered, with the proposed mechanisms outlined in a 2015 review by Jones et al.<sup>50</sup> Initial hypotheses posited increased production of erythropoietin (EPO) by the kidneys, and subsequent studies suggested direct stimulation of erythroid progenitor cells; however, more recent studies in humans have not supported this mechanism.<sup>11,23,51–55</sup> In a study by Maggio et al,<sup>53</sup> 108 men older than 65 years with T levels lower than 475 ng/dL were randomized to 36 months of T patch vs placebo in a double-blinded fashion. Of these, 67 men (43 in treatment group, 24 in placebo group) ultimately had serum available for T, Hb, and EPO assays using samples from before and after treatment. Mean T and Hb levels increased significantly in the treatment group, but no significant changes in EPO were observed between the treatment and placebo groups (treatment-by-time interaction,  $\beta = -0.24$ , standard error = 2.16,  $P = .9$ ).

Bachman et al<sup>56</sup> proposed a mechanism of T-induced erythrocytosis focused on the suppression of hepcidin, the master iron regulatory peptide, which subsequently results in increased iron absorption, increased systemic iron transport, and erythropoiesis. Graded doses of T were used to assess dose-dependent changes in hepcidin levels during 20 weeks of treatment, with findings that T potently suppressed hepcidin in a dose-dependent manner. This study was followed by further work by Bachman et al<sup>57</sup> that hypothesized a multifactorial model suggesting that “testosterone stimulates EPO transiently, along with suppression of hepcidin, and these two mechanisms result in a new EPO ‘set point’ at a higher physiologic level of hemoglobin.” In this study, 166 subjects from the randomized, double-blinded, placebo-controlled Testosterone in Older Men with Mobility Limitation Trial who had undergone at least 6 months of study intervention were examined. The subjects were older than 65 years and had limited mobility, total T levels of 100 to 350 ng/dL, and no contraindications to therapy. Subjects were randomized to placebo or T gel 10 g. Serum hepcidin and EPO were measured in conjunction with the study design and assessed at baseline and 1, 3, and 6 months after randomization. EPO levels increased 58% from baseline at 1 month of T treatment and remained significantly increased at 3 months. Then, EPO levels trended toward baseline at 6 months. No significant changes in EPO level were observed in the placebo cohort. They further noted that there was a shift in the EPO-Hb relation curve that suggested “testosterone administration had reset the ‘set point’ for EPO in relation to hemoglobin,” with these findings based on EPO levels remaining increased after an increase in Hb, thus suggesting a lack of negative feedback. Furthermore, T was associated with a 49% suppression of hepcidin, supporting the findings of the investigators’ prior study. Suppression persisted at 1 and 3 months but returned to baseline at 6 months. Serum soluble transferrin receptor concentration reflects erythroid



**Figure 1.** Impact of testosterone on erythropoiesis. EPO = erythropoietin; ER $\alpha$  = estrogen receptor- $\alpha$ . Figure 1 is available in color at [www.smr.jsexmed.org](http://www.smr.jsexmed.org).

activation and signifies plasma iron turnover and erythroid transferrin uptake. The investigators further noticed increased soluble transferrin receptor levels in the T treatment group but not in the placebo group. The observed hematologic changes suggest that T increases iron use for erythropoiesis, hypothesizing a mechanism for T-induced increases in hematocrit.

In contrast to the studies that focused on T, Calado et al<sup>58</sup> focused on estradiol as a causative factor for erythrocytosis, basing their hypothesis on the known stimulation of hematopoietic cells by sex hormones. Estradiol is produced by aromatization of T. Calado et al observed that in vitro exposure of peripheral blood lymphocytes and bone marrow to androgens increased the activity of telomerase, an enzyme involved in cell replication. Mutated cells with low telomerase activity exhibited normal telomerase levels at exposure to androgens, and estradiol treatment resulted in similar effects on restoration of telomerase activity. Downregulation of estrogen receptor- $\alpha$ , but not estrogen receptor- $\beta$ , inhibited telomerase function, thus isolating the target for estradiol-mediated telomerase expression, which could lead to increased hematopoietic cell proliferation.

Other studies have correlated dihydrotestosterone with increased Hct, independent of T and free T levels, implicating dihydrotestosterone in T-induced erythrocytosis.<sup>59–61</sup> Several randomized control trials have attempted to further elucidate a relation between dihydrotestosterone and T-induced erythrocytosis by examining whether patients on 5 $\alpha$ -reductase inhibitors and TTh were less likely to develop erythrocytosis.<sup>62</sup> Although one study showed a 4.7% increase in Hct, another showed no difference in post-treatment Hct.<sup>63–65</sup> However, all these studies suggested indirect effects of T levels on bone marrow hyperplasia without describing a clear mechanism. Figure 1 illustrates the proposed direct and indirect effects of T on erythropoiesis.

A proposed genetic correlation between TTh and increases in Hb and Hct was investigated by Zitzmann and Nieschlag<sup>66</sup> who showed that the erythropoietic response to T is inversely related to androgen receptor CAG repeats, which have been associated with androgen receptor activity. They observed that men with

**Table 1.** Testosterone formulations and their impact on erythrocytosis

Testosterone formulation	Dosing regimen	n	Rate of erythrocytosis (>50%)	Mean T level (ng/dL; converted units)	Reference
T enanthate and cypionate (short acting, IM)	100–200 mg IM every week	57	66.7%	306 ± 164	70
T undecanoate (extended release, IM)	1 g every 6 wk × 3, then 1 g every 9 wk	347	7%	467 ± 32	78
Transdermal (Testim gel, AndroGel 1.62%)	T 50–100 mg, 1–2 packets applied to shoulder area daily (Testim gel); T 20.25–80.1 mg, 2–4 pumps applied to skin daily (AndroGel)	47	12.8%	300 ± 89	70
Oral T undecanoate	N/A	1,343	0.003% (Hct > 52%)	N/A	77
T pellets	crystalline T 75 mg/pellet implanted, 10–14 pellets every 3–6 mo	74	35.1%	268 ± 167	70

Hct = hematocrit; IM = intramuscular; N/A = not available; T = testosterone.

fewer than 20 CAG repeats had the highest incidence of blood hyperviscosity.

## EFFECTS OF T FORMULATION

Of the available T formulations, short-acting IM injections (TC and TE) have the highest incidence of erythrocytosis (approaching 40%).<sup>14</sup> Recent studies support a unified hypothesis in which T formulation, dose, and pharmacokinetics collectively determine the risk of erythrocytosis by establishing the duration of supraphysiologic T levels.<sup>52</sup> T formulations that result in stable serum concentrations (pellets, transdermal gels and patches, and extended-release IM TU) result in a low incidence of erythrocytosis that is dependent on dose and serum level and independent of duration of therapy.<sup>11,52,67</sup> The relation of individual T formulations and associated effects on average T levels and incidence of erythrocytosis are presented in Table 1.

In patients treated using subcutaneous T pellets for an average of 8 years, increasing trough T levels linearly correlated with increases in Hb and Hct.<sup>52</sup> Pharmacokinetic studies of patients on transdermal TTh showed that Hb and Hct levels increased for first 5 to 6 months of therapy and then plateaued.<sup>68,69</sup> Discontinuation of TTh resulted in a return to baseline Hb and Hct levels in 3 to 12 months.<sup>57,69</sup> In their comparison of the effects of T on Hct, Pastuszak et al<sup>70</sup> found that Hct levels exceeded the study threshold of higher than 50% significantly sooner with injectable T compared with gels and pellets (10.5 ± 9.1 vs 14.0 ± 12.6 vs 16.4 ± 10.7 months, respectively,  $P = .01$ ). Wang et al<sup>71</sup> found a direct relation between T dose and the rate of erythrocytosis, which increased from 11.3% to 17.9% when increasing the T gel dose from 50 to 100 mg/day.

Short-acting IM T formulations (TC and TE) are associated with the most rapid and significant increases in serum T levels,

with supraphysiologic T levels achieved within days of an injection and a return to baseline by 10 to 14 days, followed by a decrease to sub-physiologic levels within 3 weeks if not redosed.<sup>14,72</sup> In contrast, other T formulations result in more stable serum T levels, with extended-release injectable TU maintaining stable serum levels within the normal range for approximately 12 weeks and transdermal options maintaining stable levels with daily dosing.<sup>32,73,74</sup> For subcutaneous pellets, total T levels peak within 2 to 4 weeks after implantation.<sup>75</sup>

Although initially described by Dobs et al,<sup>76</sup> several subsequent studies have examined the higher incidence of erythrocytosis associated with short-acting injectable T, particularly TC and TE over transdermal formulations.<sup>14</sup> Dobs et al<sup>76</sup> evaluated 58 hypogonadal men randomly assigned to transdermal or IM TTh 4 to 6 weeks after IM TTh was stopped. The two therapies proved effective, although IM administration was associated with 43.8% of patients developing erythrocytosis (Hct > 52%) compared with 15.4% of the transdermal cohort ( $P = .025$ ). Dobs et al's findings were the basis of the 2004 review by Rhoden and Morgentaler,<sup>14</sup> which addressed risks of TTh and recommendations for monitoring. Pastuszak et al<sup>70</sup> expanded the comparison to include subcutaneous T pellets (crystalline T 75 mg per pellet with 10 to 14 pellets implanted to achieve a peak serum T level of 500–800 ng/dL every 3–6 months). They found that erythrocytosis, defined as an Hct level higher than 50%, was more common with injectable (IM TC or TE 100–200 mg weekly) than with transdermal (T 50–100 mg, one to two packets applied to the shoulder area daily; Testim, Endo Pharmaceuticals, Dublin, Ireland; 1.62% T 20.25–80.1 mg, two to four pumps applied to the skin daily; AndroGel, AbbVie, North Chicago, IL, USA) or pellet formulations (66.7% vs 12.8% vs 35.1%, respectively;  $P < .0001$ ).<sup>70</sup> Although not approved for use in the United States, oral TU was compared with short-acting IM TC and TE injections in a

study of 5,813 men included in the polycythemia cohort of United Kingdom General Practice Research Database.<sup>77</sup> The study used an Hct level higher than 52% to define erythrocytosis and found 3.4% of men on IM injections and 0.003% of men on oral TTh developed erythrocytosis. However, they noted inconsistent recording of Hct levels during the study period, likely resulting in an underestimate of the true incidence of erythrocytosis.

In a prospective observational study by Middleton et al,<sup>78</sup> the adverse effects of extended-release TU, including secondary polycythemia, were examined. Three hundred forty-seven patients received a total of 3,022 TU injections over 3.5 years, with 25 patients (7%) developing an Hct level higher than 50% and 14 patients (4%) developing an Hct level higher than 52%. The study showed a contrast in rates of erythrocytosis between short-acting IM formulations, such as TC and TE (up to 40%), and extended-release IM T formulations, such as TU (up to 7%).<sup>78</sup> Previous pharmacokinetic studies comparing TU (1,000 mg every 6 weeks, followed by 1,000 mg every 9 weeks) and TE (250 mg every 3 weeks) also showed higher, stable trough T concentrations for TU at the time of injections compared with TE ( $14.9 \pm 5.2$  to  $16.5 \pm 8.0$  nmol/L for TU vs  $<10$  nmol/L for TE).<sup>73</sup>

## CLINICAL RECOMMENDATIONS

T dosing should generally follow manufacturer recommendations. For at-risk populations (those with type 2 diabetes, those who smoke, and those with obesity), injectable T formulations should be considered only after potential adverse hematologic responses are discussed with the patient. Additional factors for selecting T formulations in consideration of hematologic effects include age, which is an independent risk factor for erythrocytosis in the setting of TTh.<sup>11</sup> Additional risk factors to consider before initiation of TTh include thrombophilia conditions such as factor V Leiden, antiphospholipid antibody syndrome, and prothrombin gene mutations, high factor VIII levels, and high homocysteine levels. Transdermal or subcutaneous formulations should be strongly considered in at-risk populations to minimize significant alterations in Hb and Hct.

For patients who meet criteria for and desire TTh, baseline Hb and Hct levels should be assessed. After initiation of therapy, the SMSNA advises that men should be “monitored regularly” for erythrocytosis.<sup>5</sup> In our practice, that consists of laboratory evaluation of Hb and Hct levels every 3 to 6 months. Consensus International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, and American Society of Andrology guidelines advise that Hb and Hct should be checked after 3 to 4 months, after 1 year, and annually thereafter.<sup>37</sup> Based on Endocrine Society clinical practice guidelines, once an Hct level higher than 54% is reached, TTh should be discontinued or therapeutic phlebotomy should be offered to lower the risk of

potential future thromboembolic events.<sup>4</sup> In our practice, therapeutic phlebotomy is recommended at an Hct level of at least 50%. In the event of a thromboembolic episode for patients on TTh, we recommend discontinuing TTh and beginning anti-coagulation according to recommended guidelines.

## CONSIDERATIONS FOR FUTURE RESEARCH

A complete understanding of the molecular mechanisms of T-induced erythrocytosis is essential to the prevention and treatment of this common and significant adverse effect of TTh. Furthermore, the clinical implications of T-induced erythrocytosis must be elucidated further to identify any actual risks associated with this condition. Alternative options for management of hypogonadal men, such as clomiphene citrate, human chorionic gonadotropin, or aromatase inhibitors, could represent treatment options that can provide symptomatic benefit, with rare supraphysiologic T levels and low rates of erythrocytosis, although these therapies need further study in this context. Randomized controlled trials are still needed to rigorously determine the effects of TTh on erythrocytosis and the potential thromboembolic sequela that can result.

## CONCLUSIONS

Erythrocytosis is often a limiting variable in patients on TTh. Direct and indirect effects related to supraphysiologic T levels are believed to mediate the effects on erythrocytosis. The true mechanism of erythrocytosis and its role in thromboembolic events remain unclear, although some data support an increased risk of CV events resulting from T-induced erythrocytosis. Large multicenter randomized controlled trials are required to study TTh, its effects on Hb and Hct, and the clinical significance of treatment-induced increases in red blood cell mass.

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