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REVIEW

Risk of erythrocytosis in transgender individuals undergoing testosterone therapy: a systematic review

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ABSTRACT

INTRODUCTION: In transgender individuals assigned female at birth, testosterone therapy is employed for body masculinization. Guidelines recommend close monitoring for potential side effects of hormonal therapy, especially during the first year. Erythrocytosis is a common finding during testosterone therapy and has been associated with a potential risk of thrombotic and cardiovascular events. Currently, the hematologic effects of testosterone therapy are understudied, with existing data primarily derived from the cisgender male population. The aim of this study was to comprehensively examine the hematological changes induced by testosterone therapy in the transgender population.
EVIDENCE ACQUISITION: A systematic search was conducted using the electronic database PubMed.
EVIDENCE SYNTHESIS: Thirty-six manuscripts were retrieved. After screening for original studies, 19 articles were included. Selected articles were published between 2005 and 2023.
CONCLUSIONS: In our systematic review, the prevalence of erythrocytosis varied from 0% to 29.3%, with severe erythrocytosis ranging from 0.5% to 2.3%. Testosterone therapy was associated with an increase in hemoglobin and hematocrit, particularly within the first year of therapy. Factors such as serum testosterone levels, along with the duration, doses, and formulation of testosterone therapy, were found to be associated with the development of erythrocytosis. Further research is crucial to provide specific recommendations for clinical practice.

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KEY WORDS: Polycythemia; Hematology; Transgender persons; Gender identity; Gender dysphoria; Testosterone.

Introduction

The transgender and gender-diverse population

Transgender and gender-diverse (TGD) people are individuals who experience a discrepancy between their gender identity and/or expression and the one typically associated with their sex assigned at birth.[1] This condition is referred to as Gender Incongruence (GI), as defined by the World Health Organization.[2] Albeit precise and definitive data concerning the size of the TGD population globally are lacking, population-based surveys suggest that 0.3-0.5% of adults identify as TGD.[1] While not universal, many TGD individuals opt for medical interventions, such as gender-affirming hormone therapy (GAHT) and/or surgery (GAS), to align their physical appearance with their gender identity.[3]

Hormone therapy can induce a wide variety of physical changes in TGD individuals. Testosterone (T), for instance, is used for body masculinization in individuals assigned female at birth (AFAB), manifesting as facial and body hair growth, deepening of the voice, increased muscle mass, clitoral enlargement, menstrual cessation.[4] Various T formulations, including transdermal gel (TD), long-acting injectable T undecanoate (TU), and injectable T esters (TE), are available.[5]

Conversely, in those assigned males at birth (AMAB) GAHT typically involves a combination of estrogen and anti-androgen drugs (*e.g.*, spironolactone, cyproterone acetate).[5] The goal is to maintain hormone levels within the desired male or female ranges to achieve desired physical changes while minimizing complications.[3] Due to the pleiotropic effects of sex hormones, international guidelines[1, 4] underscore the importance of evaluating general health conditions and closely monitoring potential side effects during GAHT.

Initial visits involve comprehensive clinical evaluations, biochemical tests (including complete blood count, renal and hepatic function, metabolic and hormonal profile), and eventually sonographic and densitometric exams.[6] After GAHT initiation, it is important to identify the appearance of possible adverse effects with regular follow-up.

In particular, transgender AFAB (t-AFAB) individuals may be at risk of erythrocytosis (Ery), cardiovascular events, hypertension, dyslipidemia, acne, androgenic alopecia, elevation in liver enzymes, mood swings, infertility.[1, 3, 4]

Ery, also known as polycythemia, is probably the most common adverse event associated with T therapy.[6, 7] Despite this, there is a paucity of studies exploring the hematologic effects of T therapy in the t-AFAB population. To address this gap, we have undertaken a systematic review of the literature to shed light on this specific subject.

Testosterone and hematology

The definition of Ery has changed over the years according to changes in WHO recommendations. The most recent WHO criteria set defined Ery as Hct>49% or Hb>165 g/L in males, and Hct>48% or Hb>160 g/L in females: a lower threshold compared to the previous one.[8] As a consequence, the definition of Ery in studies regarding T therapy, mainly in the context of testosterone replacement therapy (TRT) in hypogonadal cisgender men, is not uniform. Different guidelines and recommendations, as well as original studies, have defined Ery by levels of Hct between >50% and >54% or Hct>185 g/L.[9-11] This discrepancy has to be taken into account when comparing data on T-induced Ery.

As said above, most studies which reported this evidence were performed in cisgender men on TRT. Although similar in pharmacological regimes, T therapy has different goals in GAHT and TRT. In fact, GAHT is used to suppress ovarian function and increase total T levels within the male ranges, in a process of defeminization and masculinization.[4] On the other hand, TRT is employed to restore physiological levels of serum testosterone in hypogonadal cisgender men.[12] Unlike GAHT, TRT is not focused on aligning physical characteristics with gender identity, but rather on addressing androgen deficiency in cis men for overall health and well-being.

According to a recent literature review conducted by Jones SD *et al.*,[13] hypogonadal cisgender men undergoing TRT have a 315% greater risk for developing Ery when compared with controls. In addition, all TRT formulations might increase Hb and Hct in hypogonadal cis men, but injectable T formulations tended to produce the greatest effect.[14]

Notwithstanding, hematologists are concerned about Ery as for the lesson learned from myeloproliferative neoplasms, particularly from polycythemia vera (PV).[8] In fact, in PV one-quarter of patients with high Hct will experience major arterial or venous thrombosis.[15] Although the thromboembolic risk of secondary Ery in TRT is less clear,[9, 16] some evidence has found a higher risk of cardiovascular disease and unprovoked venous thromboembolism as well as an increased mortality in hypertensive men with high Hct values.[14, 17, 18]

While it is well-known that T stimulates erythropoiesis, the mechanisms and implications of T-induced Ery remain poorly understood and under-researched.[10] Some evidence suggest that T stimulates the production of red blood cells (RBC) through various mechanisms. Some studies have demonstrated that iron availability can be enhanced by T through the hepcidin pathway: a hepatic protein with a central role in the regulation of iron metabolism.[19] Bachman *et al.*[20] found that T therapy inhibited hepcidin in a dose-dependent manner, suggesting that a decrease in hepcidin may be responsible for the increased iron metabolism, systemic absorption of iron and increased erythropoiesis.

An alternative mechanism triggered by T is the stimulation of erythropoietin (EPO). Authors observed a transient increase in EPO during the first months of T therapy.[20] After 6 months, Hb and Hct values increased, while EPO tended to normalize. The authors interpreted this phenomenon as a new "set-point" of EPO toward higher levels of Hb and Hct. Nonetheless, the relationship between T and EPO has not been uniformly confirmed in the literature.[13, 21-25]

Although based on rather weak evidence, other factors linking T to increase erythropoiesis have been proposed. Stimulation of the proliferation of by estradiol (E2), derived from T aromatization,[26] and conversion of testosterone to dihydrotestosterone (DHT) might directly stimulate hematopoietic and erythroid lineage cell proliferation,[27, 28] although the exact mechanism has not been elucidated, yet.[9, 28]

Furthermore, TRT could stimulate Ery through other indirect mechanisms. In fact, TRT has been associated with obstructive sleep apnea syndrome (OSAS), a condition that exposes individuals to periods of relative hypoxia, a potent inducer of EPO.[29-31]

When encountering high Hct levels, clinicians might either adjust T dosage or temporarily stop T therapy, order a phlebotomy, or recommend a combination of these strategies. Unfortunately, guidelines and recommendations for screening and management strategies remain poorly defined and scarce for T therapy in t-AFAB individuals.[1, 3, 4]

If it is accepted that pre-existing polycythemia is a contraindication for initiating T therapy, the development of Ery during treatment can be alternatively addressed by cessation of therapy, lowering of the dose, or switching to a lower-risk formulation to avoid increased risk of myocardial infarction, stroke, and venous thromboembolism.[12] The Endocrine Society guidelines indicate a value of Hct>50% as a relative contraindication to initiation of TRT, and Hct>54% as a reason to stop therapy, being associated with a moderate-high risk of adverse outcome.[10] The Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE) recommend TRT withdrawal for Hct level higher than 54% and that Hct levels between 48% and 54%, in the presence of specific conditions such as chronic obstructive pulmonary disease (COPD) or OSAS, should be carefully monitored, and handled on an individual basis, before and during TRT.[12] Other scientific societies consider Hct ranging from 52% to 55% as thresholds to modify or discontinue TRT.[11] On the other hand, an alternative clinical prospective proposes that serum T measurement should be taken into account in cisgender men, particularly older individuals, who experience unexplained anemia.[32]

Noteworthy, polycythemia is a particularly hot topic in sports medicine. To enhance aerobic capacity, athletes may increase their RBC through various techniques or substances, including the use of androgens.[33, 34] Studies have shown that during exercise, both Hct and blood viscosity rapidly increase, due to fluid loss with perspiration.[35, 36] In this condition of elevated cardiac output and oxygen request, athletes may be particularly at risk of cardiovascular events.[34, 36]

As mentioned earlier, recommendations for managing Ery in the t-AFAB population are limited, relying heavily on evidence from hypogonadal cisgender men. To detect Ery, guidelines[1, 4] recommend monitoring blood counts every 3 months during the initial year of GAHT and, thereafter, once or twice annually.

It's crucial for physicians to recognize that Ery, if not managed appropriately, can contribute to adverse health outcomes such as hypertension, cardiomegaly, and thromboembolic complications. Currently, no specific thresholds for Ery in the transmasculine population are established.[1, 4]

It could be argued that clinicians should consider the upper limit of Hct or Hb for the female population based on biological sex, for both cisgender and transgender AFAB people. On the other hand, for individuals on T therapy, sex hormone levels are in the male range and therefore, the male laboratory references could be more appropriate. Future research should explore specific thresholds for thromboembolic and cardiovascular risk in the TGD population, considering the diverse definitions of Ery in existing guidelines.

This systematic review aims to collect currently available data from scientific literature, focusing on the association between T therapy and blood changes in the t-AFAB population. The subsequent sections will provide a detailed discussion of the obtained data and existing findings.

Evidence acquisition

In order to gather all data and evidence regarding T therapy in t-AFAB individuals, we performed a search in PubMed using the following query: “Polycythemia” [MeSH Terms] OR “Hematocrit” [MeSH Terms] OR “Erythrocytes” [MeSH Terms] OR “erythrocytosis” [All Fields] OR “Hematology” [Mesh] AND “Transgender Persons” [Mesh] OR “Transsexualism” [Mesh] OR “transgender” [All Fields] OR “Gender Identity” [Mesh] OR “Gender Dysphoria” [Mesh].

Up to November 2023, we collected 36 results. We read and analyzed the 36 identified manuscripts. According to the PRISMA statement 2020 on systematic reviews,[37] after excluding systematic reviews (N.=5) and unrelated results, such as opinion papers and commentaries (N.=12), we identified (N.=19) manuscripts based on original studies addressing our issue of interest. The detailed systematic selection of the manuscripts is presented in Figure 1.

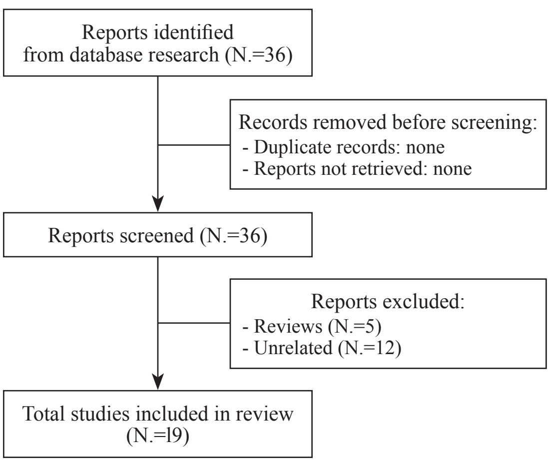

Figure 1.—Systematic selection of the results found on PubMed, according to PRISMA statement, up to November 2023, according to the literature search using search terms (“Polycythemia” [MeSH Terms] OR “Hematocrit” [MeSH Terms] OR “Erythrocytes” [MeSH Terms] OR “erythrocytosis” [All Fields] OR “Hematology” [Mesh] AND “Transgender Persons” [Mesh] OR “Transsexualism” [Mesh] OR “transgender” [All Fields] OR “Gender Identity” [Mesh] OR “Gender Dysphoria” [Mesh].

Evidence synthesis

As detailed above, we identified 19 relevant results. The selected articles were published between 2005 and 2023. The manuscripts of interest are listed in Supplementary Digital Material 1 (Supplementary Table I)[14, 38-55] and thoroughly discussed in the article.

Retrospective studies

A multicentric study[38] from the European Network for Gender Incongruence (ENIGI) presented the data on 53 t-AFAB people receiving injectable TU. The aim of the study was to retrospectively assess the short-term effects of GAHT on clinical changes, hormone levels, and adverse effects. Regarding Ery, during the first year of treatment 20.1% and 3.9% of t-AFAB individuals had Hct>48% and >52%, respectively. No cardiovascular or thromboembolic events, nor any fatalities were recorded over the course of 12 months.

Jarin *et al.*[39] studied 72 t-AFAB adolescents undergoing T therapy. Total T levels rose after the first 6 months of treatment (29.5 ng/dL to 424.8 ng/dL, P<0.05), as well as Hct and Hb (39.4% to 44.5%, P<0.001; 135 g/L to 150 g/L, P<0.05, respectively). Ery occurred in two individuals (27.8%).

In a retrospective analysis conducted in 2018 on 11 t-AFAB adults receiving T enanthate, Vita *et al.*[40] reported a significant increase in total T (1.6±0.5 to 17.0±8.5, P<0.0001), RBC (4.8±0.4 mln/mL to 4.4±0.4 mln/ml, P=0.01), Hb (147±10 g/L to 135±8.0 g/L, P=0.006), and Hct (43.5±3.1% to 40±2.9%, P=0.01). Only one patient experienced Ery.

A retrospective study by Humble *et al.*[41] evaluated 150 t-AFAB undergoing T therapy. Authors observed an increase in levels of serum total T, (33±12 ng/dL to 800±468 ng/dL, P<0.01), Hb (132±13 g/L to 153±12 g/L, P<0.001), and

Hct (39.6±3.4% to 45.6±3.5%, P<0.001) after 12 months of GAHT. Unfortunately, no data on Ery frequency were available.

Chan *et al.*[42] found a positive correlation between serum total T and Hct (P<0.05). The average Hct was 45% and no cases of Ery were reported. The sample size was limited to 34 t-AFAB individuals using weekly TE. Authors did not provide a definition of Ery, as the aim of the study was to determine if E2 levels decreased with T therapy.

In their analysis of Kaiser-Permanente Electronic Healthcare Record data, Antun *et al.*[43] examined a substantial cohort of TGD individuals, comprising 559 t-AMAB individuals. Each subject was matched with 10 cisgender men and 10 cisgender women. Among the transmasculine group, baseline Hct levels (42.8±3.9%) fell between the ranges of cisgender males and females. Post-T therapy, Hct levels (44.8±3.6%) rose to match those of cisgender male controls. Notably, 29.3% developed an Hct>48%, and 6.5% had Hct>48%, indicating a 7-fold and 83-fold higher Ery rate than ciswomen, respectively.

In a retrospective study on the safety of GAHT, Meyer G *et al.*[44] evaluated 233 t-AFAB individuals undergoing T therapy. The authors reported an incidence of Ery of 5.6% for Hb>175 g/L and 14.3% for Hct>50%. Only one case of venous thrombosis was recorded, following a surgical procedure.

In a large study, Madsen *et al.*[45] retrospectively assessed 1073 t-AFAB. Patients were treated with various T formulations, including injectable, oral, and transdermal formulations. The study aimed to determine the prevalence of Ery, identify potential risk factors, and evaluate the temporal relationship with T therapy initiation. The prevalence of Ery was calculated using different thresholds: 24% for Hct>50%; 7.6% for Hct>52%; 2.2% for Hct>54%. The largest increase in Hct was recorded during the first year of GAHT (39% at baseline to 45% after one year). The probability of developing an Ery progressively increased during the follow-up (Hct>50%: 8% in the first year, 38% after 10 years, and 50% after 14 years). Patients using long-acting injectable TU had higher odds of Ery (OR 2.9) compared to injectable TE (OR 1.1), oral TU (OR 0.4), and TD (OR 1.0). Individuals with plasmatic T levels above the physiologic male range did not show a higher risk of Ery. Furthermore, tobacco smoke, age, BMI, and a medical history of predisposing pathologies (*i.e.*, chronic obstructive pulmonary disease, OSAS, polycythemia vera) were identified as a risk factors for Ery.

Oakes *et al.*[46] evaluated 519 t-AFAB individuals undergoing T therapy. Authors found a significant increase in Hb (135 g/L to 157 g/L, P<0.0001) and Hct (40.2% to 47.0%, P<0.0001) during the follow-up period. In regard to Ery, 41/519 patients (7.8%) developed Hb levels>175 g/L and 104/519 patients (20%) developed a Hct>50%. The majority of those who developed Ery were receiving injectable formulations of T, while only 21 individuals were using transdermal T. In those who developed Ery, T dose reduction was the most common intervention performed in 42%, 4.8% underwent therapeutic phlebotomy, and watchful observation in the rest of cases. Thromboembolic events developed in 5 cases (0.9%), but none was meeting the criteria for Ery at the moment of the thrombosis.

A retrospective study by Tatarian *et al.*[47] evaluated the contributing factors for Ery in a large cohort of t-AFAB adults undergoing T therapy. Among 511 TGD people, authors found a high prevalence of Ery: 22.1% for Hct>50%, 9.4% for Hct>52%, and 2.1% for Hct>54%. The polycythemic group had a significantly higher age (P≤0.0001), BMI (P=0.002), duration and dose of T therapy (P=0.0027), OSAS (P=0.034), and oophorectomy (P<0.0001). Furthermore, total T concentration was higher (860 ng/dL *vs.* 737 ng/dL, P=0.014). No differences in nicotine abuse, pulmonary disease and route of T administration did were noticed.

In a cross-sectional study by Nolan *et al.*,[14] the risk of Ery with different T formulations (TU, TE, and TD) was analyzed. Data from 180 t-AFAB adults undergoing GAHT for at least 6 months (median duration was 37.7 months) were retrieved. Authors found no significant difference in serum T concentration, Hb or Hct between groups. On the other hand, injectable T formulations had a higher incidence of Ery (Hct>50%: 15% for TU, 23.3% for TE) compared to TD

(0%), although the difference did not reach statistical significance for TU (P=0.066). In their work, researchers excluded differences in age, duration of GAHT, smoking habits, hypertension, or hypercholesterolemia between groups. Unfortunately, due to the cross-sectional nature of the study, it was not possible to assess the time of development of Ery or the pattern of Hb/Hct increase during GAHT. Furthermore, TD (24 people) and TE (31 people) groups were underrepresented compared to TU (125 people).

Recently, Krishnamurthy *et al.*[48] published the largest study on the topic, encompassing data on 6670 t-AFAB individuals. A cross-sectional analysis revealed an incidence of Ery of 8.4% (Hct>50%). Severe Ery was rare, with only 0.9% of participants reaching Hct>54%. Hct values were positively associated with age, serum T levels, and the intramuscular route of administration. Although serum T levels are higher with intramuscular T formulation, a multivariate regression analysis revealed that serum T and formulation were independently associated with a rise in Hct.

Prospective studies

T'Sjoen *et al.*[49] investigated erythropoietic mechanisms in a cohort of TGD people, both AMAB and AFAB, receiving GAHT for 4 months. Data on 15 t-AFAB individuals using injectable TE, found a significant increase in total T and a decrease in gonadotropins; Hb and Hct levels increased significantly (12.73 g/L to 13.54 g/L, P=0.001; 37% to 40%, P=0.016). At baseline, none presented iron deficiency. Authors investigated the changes in soluble transferrin receptor (sTfR) induced by GAHT, a marker of marrow erythropoietic activity. At baseline, despite differences in total T, Hb and Hct levels, sTfR was similar between groups. After 4 months of T therapy, a significant increase in sTfR and IGF-1 was observed. Authors performed a regression analysis, which found a positive correlation between sTfR and IGF-1 levels at 4 months in the whole sample (r=0.689, P<0.01), but was not significant in the transmasculine group alone.

Jacobeit *et al.*[50] evaluated the effects of TU on a cohort of 17 t-AFAB adults over 36 months. Authors found an increase in Hb (136 g/L to 162 g/L after 24 months, P=0.02) and Hct (40% to 47% after 18 months, P=0.01), which reached a plateau after 18-24 months. As expected, total T levels rose from 0.5 ng/ml to 6.2 ng/mL after 6 months of GAHT. Four individuals (23.5%) developed an Ery (Hct>52%) during the study period. No cardiovascular or thromboembolic complications were recorded.

In another prospective study, conducted in 2010, Mueller *et al.*[51] evaluated the effect of long-acting injectable formulations in t-AFAB individuals. Forty-five subjects received TU for 24 months. Data were collected at baseline, after 12 and 24 months of GAHT. While the effects on erythropoiesis were a secondary outcome, the authors noticed a significant increase in Hb (+12%, P<0.0001) and Hct (+11%, P<0.0001) after 12 months of T therapy, which remained stable after 24 months. No data were available on the incidence of Ery. Furthermore, no thromboembolic events were recorded during the study period.

In their work,[52] Mueller *et al.* reported the effects of long-acting TU on 35 t-AFAB individuals. Data were collected at baseline and after 12 months of treatment. Serum total T and calculated free-T (cfT) increased to typical male levels (total T 1.65 to 27.54 nmol/L, cfT 0.03 nmol/L to 0.80 nmol/L; P<0.0001) and LH levels decreased (9.89 UI/L to 3.90 UI/L, P=0.02) after 12 months of GAHT. At the same time, there was a significant increase in Hb (131.7 to 148.5 g/L, P<0.0001) and Hct (41.5% to 46.3%, P<0.0001). There was a tendency toward the reduction of serum E2 (195.9 pmol/L to 133.1 pmol/L, P=0.06). Only 2 people developed arterial hypertension; no other major adverse effects were reported. No data on Ery were available.

In a multicentric study by the ENIGI, Defreyne *et al.*[53] evaluated 192 t-AFAB individuals on T therapy. There was a progressive increase in Hct levels (41.0 to 46.0%, P<0.001) during the first 12 months of therapy with the most pronounced increase during the first 3 months. Higher total T concentrations were associated with higher Hct levels (P<0.001). In regard to T formulations, TE were associated with the highest Hct increase (+0.8% in Hct compared to TU), while TU was considered the safest for the risk of developing an Ery compared to TE (P<0.0001) and

TD (P=0.033). In total, 22 individuals (11.5%) developed Ery (Hct>50%) during the investigation period; 4 people reached Hct>52%, and one>54%. Ery was associate with higher BMI, but not with tobacco smoke, drinking habits, or recreational drug use. No thromboembolic event was recorded in the transmasculine group. A limitation of the aforementioned study was that blood samples were obtained upon each visit, independently of time of T administration.

Green DN *et al.*[54] tried to determine reference laboratory ranges for TGD people undergoing GAHT. In a sample of 79 t-AFAB, Hb and Hct ranges were within the cisgender male range. Regression analysis revealed a linear relationship between total T and Hb.

In a large longitudinal study, Porat *et al.*[55] found an incidence of Ery (Hct>50.4%) of 12.6%. However, severe Ery was a rare event, occurring in only 0.6% of cases.

Discussion

As discussed above, T is the drug of choice used for body masculinization in t-AFAB individuals. GAHT produces a wide variety of physical changes, including hair growth, muscle mass development, cessation of menses, and deepening of the voice. At the same time, sex hormones influence nearly all bodily systems, and therefore, close medical monitoring is essential to track the onset of potential adverse effects. Among these, Ery is arguably the most common.[6, 7] Hence, guidelines recommend quarterly measurement of the complete blood count in the first year of GAHT.[1, 3, 4]

Nonetheless, most studies addressing T-induced Ery focus on cisgender hypogonadal male. Specific recommendations for the t-AFAB population are limited and primarily derived from evidence based on TRT. Despite the well-established stimulatory effect of T on erythropoiesis, the mechanisms and implications of secondary Ery remain inadequately understood and under-researched.[10] These mechanisms include the stimulation of EPO, an increased iron availability through hepcidin inhibition, direct actions of E2 and DHT on erythropoietic stem cells, and potential contributions from OSAS *via* the hypoxia-inducible factor 1 (HIF-1) pathway.[20, 27] Moreover, other possible mechanisms include the difference in androgen receptor CAG repeat length and the role of DHT.[28]

Only one study evaluating the effects of sex hormones on Hct in TGD individuals also included data on biological markers of erythropoiesis during T therapy.[49] In this study, the increase in Hct upon testosterone administration was associated with an increase in IGF-1, a mediator of GH-anabolic responses in many tissues. The observed increase of IGF-1 in TGD individuals treated with T may correlate with Ery, as it has been previously shown to substantially increase erythroid maturation and proliferation.[56, 57]

The same authors also demonstrated that high Hct levels directly correlate with serum sTfR, a consolidated marker of erythropoietic expansion,[58] suggesting that measurements of sTfR can be used for monitoring the erythropoietic response to T therapy.

Drawing from our understanding of PV, high Hct levels and increased RBC mass can negatively impact Virchow's triad components, increasing the risk of venous thromboembolism, myocardial infarction, and cerebrovascular accidents.[9] However, consequences of high Hct levels in patients on T therapy are difficult to translate into the clinical problem. In fact, if it is true that blood viscosity rises above normal as Hct surpasses 45%, *in vivo* distribution of plasma and RBC in the circulation is not uniform. In fact, Hct is higher in larger vessels than in smaller ones.[59, 60] Estimating RBC mass from peripheral-blood Hct may thus be inaccurate, complicating the evaluation of thrombotic risk in patients with elevated Hct levels.

Frequency of erythrocytosis

As mentioned earlier, the definition of Ery has evolved over time. In each study, the choice of a specific threshold was based on international guidelines, WHO classification, or local laboratory references.[8-11] Consequently, studies analyzing the prevalence of T-induced Ery present different thresholds, and sometimes even more than one. In the articles included in the present review, Hct cutoff ranges from 48% to 54%, and two studies considered an Hb value above 175 g/L as diagnostic for Ery.

Thirteen studies reported the prevalence of Ery, as depicted in Table I.[14, 38-40, 43-48, 50, 53, 55] Data are stratified by Hct or Hb cut-offs. Four studies have a longitudinal cohort study design, while the others are based on retrospective data analysis.

Overall, Ery prevalence ranges from 0%[14] to 29.3%.[43] As expected, Ery prevalence was higher in studies with lower thresholds (Hct>48%: 20.8-29.3%) and tended to decrease for higher cut-offs. Similar prevalence of Ery were found for Hct>50% (0-24%) and Hct>52% (1.0-23.5%). Furthermore, 5.6-7.8% of t-AFAB participants had Hb>175 g/L.

The prevalence of severe polycythemia, defined by Hct>54%, was calculated in six studies (0-10%). When considering only larger studies (with at least 100 participants), the prevalence of severe Ery ranged from 0.5% to 2.3%. In the case of secondary Ery, the Endocrine Society[10] recommends suspending TRT in hypogonadal cisgender men and referring them to a hematologist for therapeutic phlebotomy. In the absence of specific recommendations for the TGD population, adopting the same strategy in t-AFAB individuals undergoing T therapy seems reasonable.

Only a few studies assessed the incidence of Ery. According to Antun *et al.*,[43] the incidence of Ery was 7.5 per 100,000 person-days for Hct>52% and 39.3 per 100,000 person-days for Hct>48%. Furthermore, a retrospective study[45] investigated the cumulative incidence of Ery over time. With a threshold of Hct>50%, 8% of the t-AFAB population experienced Ery during the initial year of GAHT, rising to 38% after 10 years, and reaching 50% after 14 years. In a study by Tatarian *et al.*,[47] participants developed Ery within the first year (46%), 2 years (66%), or 3 years of GAHT (84%), respectively. Notably, the most substantial increase in Hct occurred within the first year of treatment, which corresponds to the period of closer biochemical monitoring. Patients with risk factors for Ery might benefit from more frequent monitoring for an extended duration, such as the initial 3 years of T therapy.

TABLE I.—*Prevalence of Ery based on specific threshold of Hct or Hb from 13 studies.*

Definition of Ery	Prevalence	Population (t-AFAB people on T)	Study design
Hct>48%	20.8%	53	Retrospective[38]
	29.3%	424	Longitudinal[43]
Hct>50%	0%	24	Cross-sectional[14]
	2.8%	72	Retrospective[39]
	8.4%	6670	Cross-sectional[48]
	9%	11	Retrospective[40]
	11.5%	192	Longitudinal[53]
	12.6%	282	Longitudinal[55]
	14.3%	233	Retrospective[44]
	15%	125	Cross-sectional[14]
	20%	519	Retrospective[46]
	22.1%	511	Retrospective[47]
	23.3%	31	Cross-sectional[14]
	24%	1073	Retrospective[45]
Hct>52%	1%	282	Longitudinal[55]
	2.1%	192	Longitudinal[53]
	2.7%	6670	Cross-sectional[48]
	3.9%	53	Retrospective[38]
	6.5%	424	Longitudinal[43]
	7.6%	1073	Retrospective[45]
	9.4%	511	Retrospective[47]
	23.5%	17	Longitudinal[50]
Hct>54%	0%	24	Cross-sectional[14]
	0.5%	192	Longitudinal[43]
	0.6%	282	Longitudinal[55]
	0.9%	6670	Cross-sectional[48]
	1.6%	125	Retrospective[14]
	2.2%	1073	Retrospective[45]
	2.3%	511	Retrospective[47]
	10%	31	Cross-sectional[14]
Hb>175 g/L	5.6%	233	Retrospective[44]
	7.8%	519	Retrospective[46]

Ery: erythrocytosis.

Changes in blood composition induced by gender-affirming hormone therapy

All of the studies included in the review reported an elevation in Hb and Hct levels following T therapy. In t-AFAB individuals, Hb values significantly increased from 127-136 g/L at baseline[39-41, 46, 49-52] to 135-150 g/L at 4-6 months[39, 49] and 148-153 g/L after 12 months of GAHT[39, 41, 46, 49, 51, 52] Similarly, Hct levels increased from 37-42.3% at baseline[38-41, 43, 45, 46, 49-53] to 40-44.5% after 4-6 months[39, 49, 52] and 44.8-46% after 12 months[38, 39, 41, 43, 45, 51, 53] In particular, Mueller *et al.*[51] estimated an increase in Hb of 12% and Hct of 11% after 12 months of T therapy. The greatest increase in Hb and Hct was during the first year of GAHT.[45] Afterwards, Hb and Hct levels remained stable (146-162 g/L and 43.5-47%, respectively).[39, 46, 50, 51] Greene *et al.*[54] compared laboratory test results of TGD individuals on GAHT with the cisgender population.

Authors found that transmasculine individuals had Hb (128-174 g/L) and Hct (39-51%) levels within the cisgender male ranges, as well as t-AMAB people had similar levels of Hb and Hct to cisgender women. A similar result was confirmed by Antun *et al.*[43]

As previously mentioned, GAHT aims to achieve and maintain sex hormone levels within the normal male range, facilitating desired physical changes while minimizing side effects. Consistent with expectations, studies demonstrate a significant increase in serum T levels during T therapy, accompanied by a decrease in E2 and luteinizing hormone (LH) levels. The elevation in Hb and Hct values is concurrent with hormonal profile changes.[39-42, 47-50, 52-54] Specifically, research indicates a positive association between serum T and Hct levels.[42, 47, 48, 53] In the largest study of our review, Krishnamurthy *et al.*[48] found a linear relation between serum T levels and Hct. Furthermore, both Jarin and Tatarian[39, 47] observed higher Hct levels in t-AFAB individuals using higher T doses, supporting the idea that total T levels, along with the duration and dosage of T therapy, can influence the risk of Ery. However, findings vary across studies, with Greene *et al.*[54] reporting no association between serum T and Hct levels, and Madsen *et al.*[45] noting that above-the-range serum T levels were not linked to higher rates of Ery.

Interestingly, GAHT produces opposite effects in the transfeminine population. Studies involving t-AMAB individuals have shown a significant decrease in Hb (from 93-150 g/L at baseline to 136-140 g/L after 12 months) and Hct (from 42.8-45.2% at baseline to 40.1-42% after 12 months), falling within the typical female range.[38-41, 43, 49, 53] In particular, Defreyne *et al.*[53] observed a linear relationship, noting that a decrease of 3.47 nmol/L in serum T correlated with a 2 g/L rise in Hb (P=0.04).

Risk of erythrocytosis based on testosterone formulations

T therapy is available in a variety of formulations for t-AFAB individuals. In particular, TD is applied daily, offering precise dosage manageability and a more physiological profile of serum T levels. Long-acting TU involves an intramuscular injection every 10 to 14 weeks and therefore is appreciated for its convenience of administration. TE, including T enanthate and cypionate, are injectable formulations administered every 2-4 weeks, with TE exhibiting a steeper kinetic profile compared to long-acting TU.[4, 10]

According to our results, only four studies have compared different T formulations. In a large cross-sectional study, Krishnamurthy *et al.*[48] demonstrated that intramuscular TE was independently associated with higher Hct values compared to TD. Similarly, Defreyne *et al.*[53] found that users of TU exhibited lower rates of Ery (9.2%) compared to TE (15.9%) and TD (12.8%). Furthermore, TE caused the largest increase in Hct levels. A possible explanation for this phenomenon is the higher peak of serum T reached with TE therapy between injections.[61]

On the other hand, other studies reached different conclusions. Madsen *et al.*[45] found that TU had a higher odds ratio (2.9) of developing Ery compared to TE (1.1) and TD (1.0). Nolan *et al.*[14] found a higher rate of Ery for injectable T formulations (23.3% with TE, 15% with TU) compared to TD (0%). Overall, all formulations were able to achieve similar serum T levels.[14, 53]

In the case of elevated Hct levels, clinicians may consider switching from an injectable to a TD formulation. Data from TRT in hypogonadal men show that TD formulations are associated with a lower incidence of Ery and smaller increases in Hb and Hct.[9, 13, 62] Surely, TD is more manageable when a dose adjustment is advisable, as in the case of Ery. Nonetheless, data are scarce and partially contradictory, and therefore, more studies are necessary to make appropriate recommendations.

Management of testosterone-induced erythrocytosis

Management strategies proposed by Oakes *et al.*[46] to mitigate the incidence and severity of Ery in TGD individuals undergoing T therapy mirror those employed in cisgender individuals during TRT. These strategies encompass adjusting the dosage of T therapy, undergoing multidisciplinary evaluation with a hematologist, and adopting lifestyle modifications, such as smoking cessation. It's noteworthy that these recommendations align with established practices in the general population. Additionally, identifying risk factors associated with Ery becomes crucial in the management process. Notable risk factors include smoking, OSAS, higher body mass index (BMI), the use of sodium-glucose cotransporter-2 inhibitors (conditions leading to hypoxia), as well as various hematologic diseases.[14, 45-47]

Cardiovascular complications

Several studies have investigated thromboembolic events with varying outcomes. For instance, Oakes *et al.*[46] reported thromboembolic events in 0.9% of 519 t-AFAB individuals, and notably, none of these cases had Ery at the time of thrombosis. Meyer *et al.*[44] documented a single case of post-surgical thrombosis among 233 t-AFAB individuals, while other studies[48, 51, 53, 55] recorded no thromboembolic events. These findings underscore the urgent need for large population studies to draw more definitive conclusions on this topic. Furthermore, conducting additional group stratification to compare the incidence of cardiovascular complications based on types and administration routes of T therapy could help establish whether certain approaches are associated with a higher risk than others.

Limitations of the study

Finally, our literature review highlights certain limitations in the available studies. These include variations in study design, sample size, cutoffs used to define Ery, and incomplete data on testosterone concentrations, hormonal parameters, and relevant comorbidities. These limitations underscore the need for future research to establish specific Hb and Hct thresholds that correlate with the risk of thromboembolic and cardiovascular complications in t-AFAB individuals.

Conclusions

In conclusion, our systematic review underscores the intricate nature of T therapy in the TGD population, shedding light on its diverse effects on Ery. T-induced Ery emerges as arguably the most common adverse effect of GAHT in t-AFAB individuals. The prevalence of Ery fluctuates across studies, with a range from 0% to 29.3%, influenced by Hct and Hb cut-offs. Notably, severe Ery ranged from 0.5% to 2.3%. All studies recorded an increase in Hct and Hb levels during T therapy, particularly in the first 12 months of GAHT. In line with the Standards of Care,[1] regular blood tests are warranted to monitor the development of Ery. Studies comparing different T formulations reveal nuanced outcomes, with TD offering potential advantages in mitigating Ery compared to injectable forms. Some data indicate that TE are associated with the largest Hct increase, although results are partially contradictory. Our findings stress the importance of tailored approaches in managing Ery, emphasizing regular monitoring and dose adjustments. Notably, estrogen and anti-androgen therapy produce opposite effects in t-AMAB individuals. The decrease in Hb and Hct may expose transfeminine people to a higher risk of anemia, although research in this field is lacking. The identified limitations in existing studies, including small sample numerosity, variations in the definition of Ery, and the retrospective nature of most studies, underscore the necessity for further research to establish specific thresholds correlating with thromboembolic and cardiovascular risks in the TGD population. In light of the evolving landscape of GAHT, our review provides valuable insights into the complexities surrounding Ery. Clinicians are encouraged to consider the diverse factors influencing erythropoiesis and individual patient characteristics when crafting personalized hormone therapy regimens. Future investigations should aim to fill existing knowledge gaps, refining guidelines and optimizing the safety and efficacy of T therapy in t-AFAB individuals.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Alberto Scala and Andrea Graziani equally contributed to the manuscript, Alberto Scala and Andrea Graziani have given substantial contributions to study design, data acquisition, analysis and interpretation, Alberto Scala, Andrea Graziani, Fabrizio Vianello, Alberto Ferlin and Andrea Garolla to manuscript writing, Fabrizio Vianello, Alberto Ferlin and Andrea Garolla to manuscript critical revision. All authors read and approved the final version of the manuscript.

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