Polycythemia Associated with Testosterone Use in Transgender Men: An Integrative Literature Review.

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Abstract: Transgender people can be defined as people whose gender does not align with the gender assigned at birth based only on their anatomical features**.** They are part of a diverse spectrum and may experience gender dysphoria. However, the extent of gender-affirming care that transgender individuals may require is individualized and encompasses the use of hormones. According to the literature, transgender men under the use of testosterone have an increased risk of developing polycythemia. This integrative literature review aims to synthesize the scientific literature regarding cases of polycythemia in transgender men. The search question was "What does the scientific literature contain about experiences of polycythemia in transgender men who use testosterone?". The descriptors transgender people, polycythemia, and erythrocytosis, as well as their synonyms and translations to Portuguese and Spanish, were connected by Boolean operators. The search occurred through BVS, PubMed, SciELO, and Science Direct. Initially, 74 results were found. After a peer review in three steps, 11 articles were selected. The authors emphasized the potential risk of polycythemia in transgender men using testosterone, particularly with intramuscular administration.Research on the incidence of polycythemia with topical forms is limited, but they may be safer than intramuscular testosterone. Age, formula, and dosage were factors associated with secondary polycythemia development. This field requires further research; articles were primarily found in Europe and the USA. Some authors recalled the importance of periodic health appointments during testosterone use to prevent greater collateral effects. Those studies corroborate the importance of pharmacotherapy follow-up of transgender people to contribute to positive outcomes on hormone use.

Keywords. Transgender men, polycythemia, testosterone, pharmacotherapy.

1. Introduction

Transgender people are defined as individuals whose identity of gender differs from the gender assigned at birth considering only anatomical sexual aspects [1], They are part of a diverse community worldwide influenced by cultural and social factors [2]. Because of that diversity, some people may need different gender-affirming care. The use of hormones is one strategy to attenuate gender incongruence promoting body changes aligned to their gender [3]. Although evidence points to adverse reactions and risks associated with hormone use - cardiovascular conditions, diabetes, dyslipidemias, and metabolic dysfunctions – there is still scarce evidence to fully address and comprehend the risks associated with testosterone use.

The use of testosterone by transgender men has the goal of developing masculine characteristics. However, it is important to note that nonbinary people can also use the hormone during their lifetime. While testosterone use offers significant benefits, it is crucial to acknowledge the potential risks associated with its long-term use. A specific condition with likely increased risk is secondary polycythemia, that can also be named as erythrocytosis [1].

Considering terminologies there are controversies between the use of polycythemia and erythrocytosis. Erythrocytosis can be defined as a disorder associated with increasing red blood cell mass. Primary polycythemia or polycythemia vera is a clonal disorder of hematopoietic cells – red blood cells, granulocytic, monocytic, and platelet cells - caused by inherited mutations and posterior effects on blood cells physiologic regulations. On the other hand, secondary polycythemia also increases hematopoietic cells. However, it's associated with an individual's exposure to stimulatory factors such

as erythropoietin, cobalt, smoking, high altitude, and other chemical agents. Secondary polycythemia is a known potential adverse drug reaction to testosterone use. Testosterone plays a key role in erythrocytosis, a condition in which hematocrit levels reach 50% or higher. This happens because testosterone inhibits the secretion of hepcidin, a hormone that regulates iron absorption. When hepcidin levels are low, ferroportin, a protein responsible for iron transport, is expressed. This allows iron to be released into the bloodstream, leading to increased production of red blood cells [4].

Given the potential impact of hormone therapy on polycythemia in the transgender male community, further research is essential. Promoting the rational use of medications involves evaluating their efficacy, safety, and necessity. Hormone therapy should be closely monitored, particularly when used alone or in conjunction with other medications. A multi-professional approach is crucial to provide comprehensive care [3]. This review aims to gather evidence regarding polycythemia in transgender men using testosterone. The question was: " What does the scientific literature contain about experiences of polycythemia in transgender men who use testosterone?"

2. Research Methods

2.1 Study design and location

The research was an integrative literature review. It was developed during the months of August and September 2024. The following databases were used: PubMed, BVS, SciELO, and Science Direct. The results were accessed and collected by the Café network through Periódicos CAPES.

The Health Sciences Descriptors - DeCS and Medical Subject Headings - MeSH libraries were used to select terms for the search expression. The descriptors or keywords utilized were: transgender persons, transgender, transsexual, polycythemia, erythrocytosis, and their translations into Portuguese and Spanish. They were connected by the Boolean operators AND and OR.

The inclusion criteria were full cross-sectional, case-control, or cohort observational articles published in Portuguese, English, or Spanish. The exclusion criteria were thesis, dissertations, letters, literature reviews, abstracts, conference proceedings, book chapters, and editorials.

2.2 Sample collection and delimitation

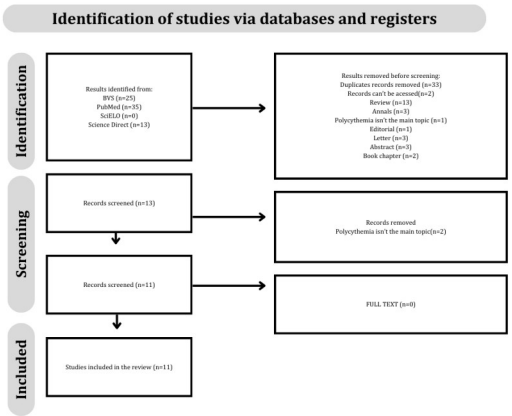
The search expression is applied to the databases considering the search in the titles and abstracts. This strategy was implemented to better capture articles that aligned with the research question. The samples were collected and stored in a local source. References were managed through Mendeley. Data was collected between September 12th and September 17th, 2024.

The analysis consisted of 5 steps: 1) The articles were downloaded and saved with their titles; duplicates were manually removed. 2) The texts that matched the exclusion criteria were removed. 3) The titles and abstracts were evaluated; the evaluation consisted of the identification of the main topic of the review (testosterone use by transgender men and polycythemia). 4) The full texts were evaluated to confirm if they answered the review question. 5) Finally, the variables of the articles were extracted in a spreadsheet. The variables included year of publication, country of study, method, main findings, journal, name of the testosterone used, extension of the sample, sample who developed polycythemia, and outcomes.

Graphs, tables, and flowcharts were formulated to summarize the results. The primary discussion was around polycythemia cases. The search was performed by two researchers and the sample analysis was peer-reviewed. A third member solved any disagreement.

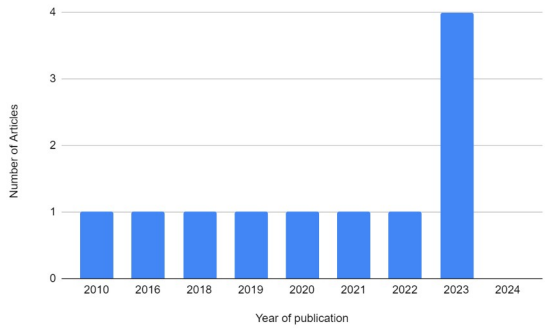
3. Results

Figure 1 – Flowchart of integrative literature review



The flowchart in Figure 1 above summarizes the data selection. Twelve publications were selected in the final sample. The oldest article was published in 2016. The year 2023 had the most recent articles: 3 studies. Figure 2 demonstrates the distribution of articles considering the year of publication. It is possible to note a rising in the interest of the topic.

Figure 2 – Relation of articles published and year of publication



Most studies were published in America with five studies published in the USA. In Europe, four studies were published, two in Germany, The Netherlands, and Belgium had one each. In Australia, two studies were published. Finally, one study was published in Singapore.

Considering the study methodology, nine studies were observational; seven were retrospective, and two were prospective. There were also two case reports and one clinical trial.

The Journal of Sexual Medicine had three publications. The other nine journals had one publication each. One journal was specific about LGBTQIAP+ people (LGBT Health), Three other journals were related to endocrinology studies (The Journal of Clinical Endocrinology and Metabolism, Journal of Endocrine Society, and European Journal of Endocrinology); topics directly related to the main topic of this research.

Table 1 demonstrates the distribution of articles considering the year of publication (Year), the journals' names (Journal), and the study methodology (SM).

Tab. 2 – Relation of studies and polycythemia

Study	Journal	SM
Mueller et al (2010) [5]	Journal of Sexual Medicine	PO[a]
Wieckx et al (2014) [6]	Journal of Sexual Medicine	PO
Antun et al (2020) [7]	Journal of Endocrine Society	RO[b]
Krishnamurthy et al (2024) [8]	The Journal of Clinical Endocrinology and Metabolism	RO
Meyer et al (2020) [9]	European Journal of Endocrinology	RO
Nolan et al (2023) [10]	JAMA Network Open	RCT[c]
Tatarian et al (2023) [11]	LGBT Health	RO
Nolan et al (2023) [12]	Journal of Sexual Medicine	RO
Porat et al (2023) [13]	Annals of Family Medicine	RO
Oakes et al (2021) [14]	Thrombosis Research	RO
Choy et al (2022) [15]	Retinal Cases & Brief Reports Retinal Cases & Brief Reports	CR
Ederveen et al (2018) [16]	Drug Safety Cases Reports	CR[d]

[a]PO – Progressive observational study; [b]RO – Retrospective observational study; [c]RCT – Randomized clinical trial; [d]CR – Case report

The relation of sample size (SS), patients who developed polycythemia (PP), and polycythemia outcomes (PO) is presented in Table 1 below. In 2 studies, patients did not develop polycythemia.

Tab. 2 – Relation of studies and polycythemia

Study	SS	PP	PO
Mueller et al (2010) [5]	45	0	NA[a]
Wieckx et al (2014) [6]	53	2	NI[b]
Antun et al (2020) [7]	24	NI	NI
Krishnamurthy et al (2024) [8]	6670	560	NI
Meyer et al (2020) [9]	233	13	DR[c]
Nolan et al (2023) [10]	72	5	NI
Tatarian et al (2023) [11]	511	113	DR[d]
Nolan et al (2023) [12]	64[e]	0	NA
Porat et al (2023) [13]	282	36	NI
Oakes et al (2021) [14]	519	125	DR
Choy et al (2022) [15]	1	1	DR
Ederveen et al (2018) [16]	1	1	NI

[a]NA – not applicable; [b]DR – dose reduction; [c]NI – not informed [d]- lifestyle estrategies also were recommended [e]- 32 using testosterone; 32 not using

4. Discussion

There was only one clinical trial, most studies were retrospective reviews (64%), so it is evident from the initial analysis that scientific literature on transgender care is still scarce. Also, most studies were in the USA (45%) followed by Europe (36%) limiting the perspective to some developed countries, also, few studies identified sociodemographic variables and ethnicity. Those variables are important because during transgender care (including testosterone use), following checkups is important to the management of health. However, transgender people are usually disrespected by health professionals [3]. Also, the lack of studies in developing countries demonstrates a huge gap in research on this topic, and little information on no Caucasian transgender people.

We didn't perform a meta-analysis because of the limited published experience and studies available in the field. It is noteworthy that the United States is the main country showing interest in investigating this topic. However, social, and cultural factors continue to limit the number of investigations being conducted on the transgender community.

All studies confirmed the efficacy and safety of testosterone use in trans people, with specific remarks. Monitoring blood pressure and lipid profiles should be performed before and after the onset of testosterone therapy [1], especially because transgender men have a 7-fold higher rate of developing erythrocytosis than cisgender men [4]. However, that could not be the reality of many trans people, as exemplified in the Choy et al case report, where a nonmonitored testosterone user developed polycythemia that developed into a retinal artery occlusion. The patient's testosterone dosage was higher than the physiological ideal levels that happened because the patient acquired testosterone by unofficial methods, and didn't look for health professionals [5]. There weren't other studies in Singapore in this review, so we don't have information on how gender-affirming care is performed in the country or their accessibility.

Considering testosterone formulation, testosterone intramuscular injections were evaluated in 9 studies. The two main formulations cited were testosterone undecanoate 1000mg and testosterone cypionate.

Testosterone cypionate was evaluated in two studies. In Porat et al studies, 279 of 281 patients were administered testosterone cypionate. All the patients that developed erythrocytosis (12,6%) were being administered testosterone cypionate [6]. A similar case occurred in the Oakes et al study, the formulation predominant, with 90% (837 out of 923 patients), was testosterone cypionate. 104 patients developed erythrocytosis because of the injection and 21 because of transdermal testosterone [7].

Testosterone undecanoate 1000mg was evaluated in 4 studies. Two studies observed hematocrit levels gradually increase. In Wierckx et al study, 2 cases of polycythemia were observed, with a sample of 45 [8]. During two years in the Mueller et al study, any case of polycythemia was observed in a sample of 53 [9]. Meyer et al also contribute to this correlation. Their sample was of 233 transgender men, of those, 76,4% used intramuscular testosterone, with 14,3% having hematocrit higher than 50%. And 5,6% of them had erythrocytosis. They also discussed that older technologies of testosterone could have a greater impact on polycythemia. Older studies reported higher erythrocytosis during treatment [10].

In 3 studies the type of testosterone injection wasn't specified. In the Ederveen et al case report it wasn't possible to associate with formulation affected the most in his prognostic because they used different formulations (testosterone injections with different posology and testosterone gel) and weren't properly monitored [11]. In the Choy et al case report the patient developed polycythemia and other consequences, but his hormone use wasn't properly monitored and we can't stabilize higher or lower frequency with one patient [5]. Krishnamurthy et al's study had the largest sample in this review and the authors considered their study as the largest sample in this research field. Out of 6670 patients, 560 (8.4%) developed erythrocytosis. Although the authors didn't specify the number of patients being administrated in each formulation, they observed that patients using intramuscular testosterone had higher mean levels of testosterone (590.85 vs 460.95 ng/dL, $P<0.001$). They also observed that serum testosterone level ($P<0.001$) and testosterone formulation route ($P<0.001$) play a significant role in explaining higher levels of hematocrit [12].

Transdermal testosterone is associated with a lower risk of erythrocytosis. In Nolan et al's study, the use of testosterone cream in 71 people caused polycythemia in 5 of them (7%). The authors concluded that testosterone cream had a smaller risk of polycythemia compared to intramuscular testosterone [13]. Tatarian et al study's observed that the higher incidence of testosterone can be associated with the pharmaceutical formulation. In this study, 69% of the sample received subcutaneous testosterone injections and 31% received intramuscular injections Finally, patients with oophorectomy developed polycythemia in the Taratian et al study, but there is low evidence of its relation yet [14].

Even though intramuscular testosterone has a higher incidence of erythrocytosis, other pharmaceutical formulations are associated with erythrocytosis. Topical forms of testosterone seem

to have a lower risk associated with testosterone, but there's a lack of evidence.
Then, pharmacotherapy needs to be properly monitored in transgender people using testosterone, especially because polycythemia has a higher incidence in transgender people than cisgender[4]. And, because in a multivariate analysis age, body mass index, and testosterone dose were factors related to polycythemia development [14], values that can be monitored during pharmacotherapy.

The only randomized clinical trial evaluated two groups. Considering testosterone use for 3 months, 19 people received intramuscular testosterone undecanoate and 12 received transdermal testosterone. No individual developed polycythemia [15]. That could be explained because polycythemia is a long-term adverse reaction as observed in Tatarian et al study using multivariate analysis, considering patients with polycythemia, 46% developed it within 1 year of treatment, 66% within 2 years, and 84% within 3 years. Then, polycythemia is a long-term possible adverse reaction due to testosterone use [14].
Choy et al's study warned against the nonmonitored use of testosterone as a potential cause of retinal artery occlusion. In this case, the testosterone level was supraphysiologic compared to cisgender men and caused a hypercoagulable state. He never had any monitoring of his hematocrit levels especially because he acquired testosterone from unregulated sources. Then, polycythemia was associated with the patient branch retinal artery occlusion [5]. An inconstancy monitoring of testosterone use affected another patient's prognostic, a 55-year-old transgender man who experienced secondary polycythemia while using lifelong testosterone. Since the patient used different pharmaceutical forms of testosterone and did not have a proper accompaniment of his hematocrit levels, they couldn't conclude how much each dosage was related to polycythemia [11]. All this information strengthened the importance of pharmacotherapy monitoring for transgender people under hormone use.
According to this review, hormone therapy can be safe if properly monitored. It is recommended to regularly check hematocrit levels before starting therapy and periodically during and after treatment. Topical forms of hormone therapy have the lowest risk of causing secondary polycythemia but, there is limited research on this phenomenon. As hormones are crucial for promoting body changes and improving gender congruence, it is important to evaluate the potential risks and clinical considerations before starting therapy, especially because the most common response to erythrocytosis is dosage reduction, which can negatively impact trans people's mental health, because some of the effects of testosterone use are remissible [17].

5. Conclusions

It is strongly recommended to monitor the efficacy and safety of hormone therapy. An interdisciplinary approach to care may be beneficial for the transgender community. Overall, it is possible to develop strategies and best practices to ensure holistic care and promote the safety and effectiveness of hormone therapy.

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