European Journal of Internal Medicine 109 (2023) 125–127

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

The management of erythrocytosis during testosterone therapy: A practical approach

ARTICLE INFO

Keywords
Hypogonadal men
Transgender care
Testosterone
Erythrocytosis

Dear Editor,

Testosterone is the primary sex hormone and anabolic steroid in men. It is a widely used drug which is used by males as an anabolic–androgenic steroid but it is also the cornerstone in treatment of both hypogonadal men and transgender people. This letter will focus on the use of testosterone as therapy for hypogonadal and transgender men. However clinicians may also encounter males who use testosterone as an anabolic–androgenic steroid. In this group we recommend to strongly advice discontinuation of use; and if hematocrit levels exceed >0.55 perform a phlebotomy.

In hypogonadal men testosterone is prescribed if testosterone is below physiological levels which may cause sexual complaints, fatigue and decline in physical strength [1]. In transgender persons who are assigned female at birth, testosterone is prescribed to induce virilization. This includes deepening of the voice, increase in facial and body hair and changes in body composition.

One of the other effects of testosterone is activation of erythropoiesis. This can lead to red blood cell counts above reference range, also known as erythrocytosis. The physiology of the process is not fully unraveled [2]. However, if hematocrit levels exceed a certain level this can increase the risk of cardiovascular events [3]. In hypogonadal men this is well investigated but in transgender persons this link is less clear [2]. The prevalence of testosterone induced erythrocytosis in hypogonadal men differs greatly between studies depending on study design and cutoff values, with reported prevalence between 6 and 67% [2]. In studies regarding transgender people most studies reporting a prevalence around 11% [4].

In the absence of clear evidence, there are no unambiguous guidelines and cutoff values for the management of testosterone induced erythrocytosis. Therefore we present a practical approach for the management of erythrocytosis during testosterone therapy.

1. Time relation and determinants of erythrocytosis in testosterone users

The largest increase in hematocrit levels is seen in the first year after initiation of testosterone therapy. After this first year, levels still rise slightly but remain quite stable over time [4]. Therefore regular monitoring of hematocrit levels is important in the first years after initiation of testosterone therapy. If levels are stable, monitoring can be performed less frequently. Some testosterone therapy related determinants for erythrocytosis have been identified: the use of intramuscular injections, duration of testosterone therapy and having supraphysiological levels. Besides the use of testosterone, other determinants are established which increase the risk of erythrocytosis. These include: age at initiation of testosterone therapy, smoking, being overweight (BMI> 25 kg/m^2) and a medical history of lung disease (Chronic obstructive pulmonary disorder (COPD), asthma, obstructive sleep apnea(OSAS)) [4].

2. Current guidelines

Current guidelines for hypogonadal men state that hematocrit levels above >0.48 have a moderate to high risk of adverse outcome and that if hematocrit >0.52 discontinuation of testosterone therapy should be considered [5]. The guidelines for transgender care regarding erythrocytosis is based on the previous guideline for hypogonadal men that states that hematocrit levels >0.50 have a moderate to high risk of adverse outcome [6]. In hematology guidelines (for people without polycythemia vera) lebels to suspect erythrocytosis are hematocriet levels of >0.52 in males and >0.48 in females. This is also the cutoff value for phlebotomy in the context of pulmonary diseases. For hypoxic pulmonary disease it is recommended to decrease hematocrit levels to 0.50–0.52 if levels are ≥0.56 [7].

3. Other causes for erythrocytosis

When starting testosterone therapy hematocrit levels should be determined to assess whether there is pre-existing erythrocytosis. When levels are >0.52 in hypogonadal men or >0.48 in transgender people before initiation of testosterone therapy further investigation for other causes of erythrocytosis should be executed. Other causes can be pulmonary (smoking, COPD, asthma, OSAS), hematological (Polycythemia vera (PV), other bone marrow disease) or erythropoietin related [8]. In the assessment of testosterone induced erythrocytosis other causes should also be considered. PV should always be considered if hematocrit

https://doi.org/10.1016/j.ejim.2022.10.018
Received 13 October 2022; Accepted 22 October 2022
Available online 28 October 2022

levels show a sudden increase, as one can acquire a JAK-2 mutation during life. This is a *JAK2V617F* mutation in >95% of cases, and a *JAK2* exon 12 mutation in <5% of cases. When JAK2V617F mutation is negative, but PV is suspected, a low erythropoietin should also lead to referral to a hematologist for bone marrow examination and checking for the rarer JAK2 exon 12 mutation. Also, when interventions to decrease hematocrit levels are not effective PV diagnostics should be considered. This is important as PV requires a lower cutoff value for hematocrit, namely <0.45 for optimal prevention of thrombosis and cardiovascular complications [7].

4. Recommended approach

In Fig. 1 we propose a flowchart for the management of erythrocytosis during testosterone therapy. We recommend to measure hematocrit levels before initiation of testosterone therapy to identify pre-existing erythrocytosis. Hematocrit should be monitored regularly, yearly the first 3 years, hereafter every 3 years. If levels are >0.55

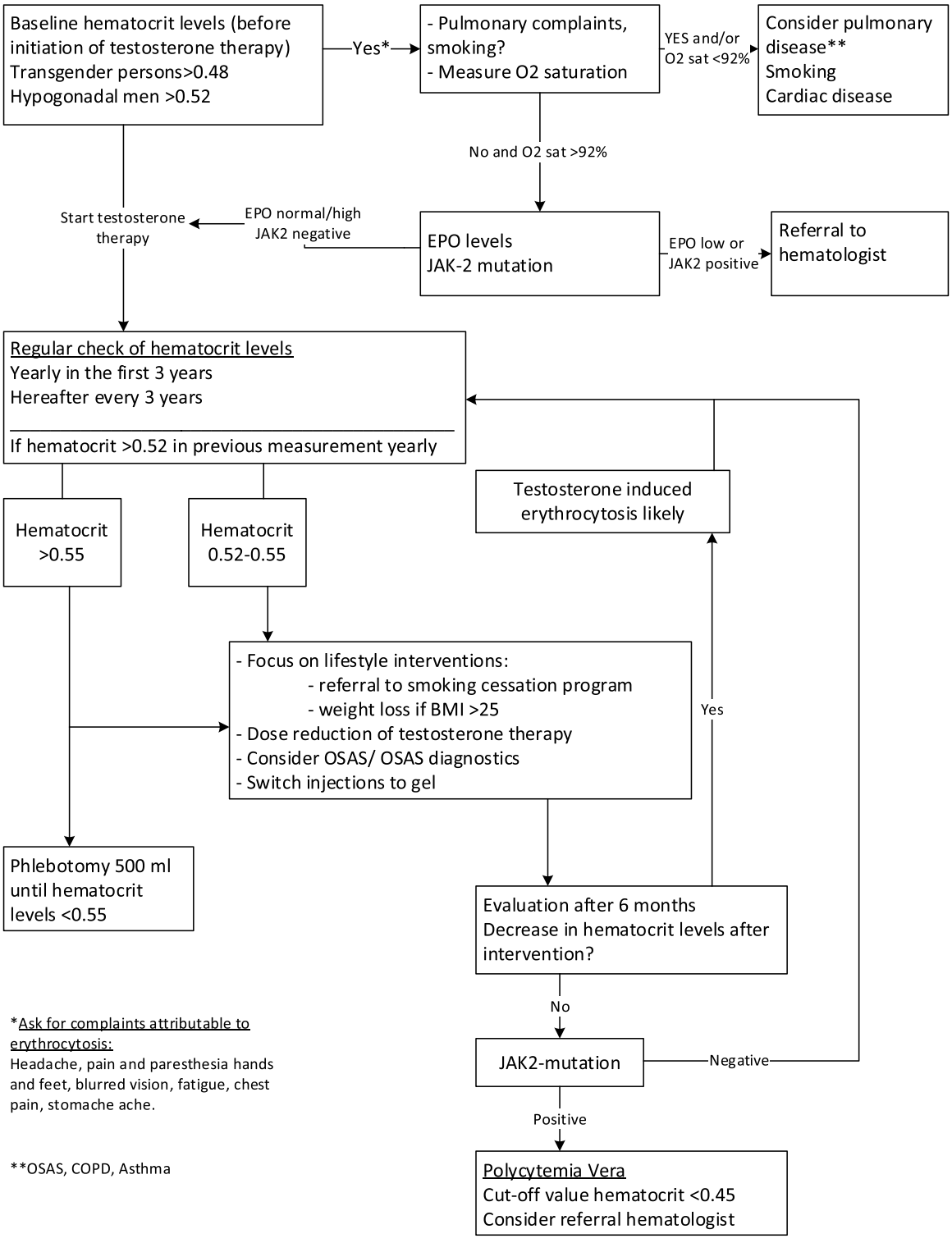

Fig. 1. Flowchart for the management of erythrocytosis during testosterone therapy.

phlebotomy is indicated. If levels are 0.52–0.54 measures could be taken to prevent a further rise. These can be testosterone related: switch from injections to gel, avoiding supraphysiological levels or even aim for lower target levels. Or related to other determinants: cessation of smoking, lose weight if BMI >25 kg/m^2, and optimizing therapy for pulmonary disease in the medical history. If hematocrit levels do not decrease due to these measures, we recommend PV diagnostics. If levels have a rising trend and exceed the level of 0.55 one measurement to decide to perform a phlebotomy is reasonable. If levels show a big, unexpected increase, a second measurement could be considered.

5. Remarks

This letter describes a practical approach to the management of testosterone induced erythrocytosis considering hematocrit levels before initiation of testosterone therapy and different cutoff values during testosterone therapy. In the first three years hematocrit levels should be monitored yearly, after this it is justified to check levels every three years. However if levels were >0.52 in the last measurement yearly check of hematocrit levels is necessary to monitor a potential increase. If levels are >0.55 a phlebotomy is indicated from a rheological perspective. If levels are between 0.52–0.55 action should be taken to prevent further increase. These include a focus on lifestyle interventions (stop smoking, lose weight if BMI >25 kg/m^2), consider diagnostics for pulmonary diseases and OSAS, a dose reduction of testosterone therapy and considering switching injections to a transdermal administration type.

It has to be noted that the largest increase in hematocrit levels is seen in the first year after initiation of testosterone therapy. On the other hand it is expected that a decrease can take a similar amount of time. Especially when taking into account that the lifespan of a erythrocyte is 120 days. Hence, interventions to lower hematocrit levels should be evaluated after 6 months and a decrease can be expected until 1 year after the intervention.

Hypogonadal men and transgender people seeking masculinization both use testosterone but are not comparable in all aspects. Hypogonadal men are generally older and exposed to testosterone since puberty, transgender people are testosterone naïve when starting testosterone therapy and much younger. Therefor cardiovascular risk profile can differ. Another difference is that transgender people seeking masculinization are birth-assigned female. As mentioned before, hematology guidelines state different cutoff values for men and women. In testosterone treated transgender people male reference values for hematocrit are used. This has been a topic of debate. However, because testosterone is the biggest driver of the difference in reference values and there are no studies on clinical end points in transgender people using testosterone it is justified to use male reference values [9].

This flowchart can be used for the management of erythrocytosis during testosterone therapy. However, for certain patient groups other cutoff values may be applicable. As erythrocytosis is known to increase cardiovascular risk it is important to take other cardiovascular risk factors into account and to treat these risk factors when applicable [3]. For patients with hypercholesterolemia, hypertension, a medical history of a cardiovascular event, obesity or diabetes a lower cutoff value to prevent further increases might be reasonable. Furthermore, this flowchart does not include all possible causes for erythrocytosis, such as erythropoietin producing tumors, central and local hypoxemia, changes in O2 affinity, toxicity for cobalt and manganese, and external erythropoietin administration [7]. As these causes are all rare the likelihood of this existing alongside testosterone use is small.

Further research should focus on the incidence of testosterone induced erythrocytosis related complications, such as venous thromboembolism (VTE). In cisgender men there is some evidence that there is an increased risk of VTE due to testosterone therapy, but this is not directly linked to hematocrit levels [10]. In transgender people using testosterone the direct influence of testosterone and erythrocytosis on VTE risk is not researched yet but in general the VTE risk is low.

In conclusion, based on our own experience and the available scarce literature, we present a flowchart for the handling of testosterone induced erythrocytosis with recommendations for cutoff values on which there should be taken action.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Financial support

No funding was received for this study.

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