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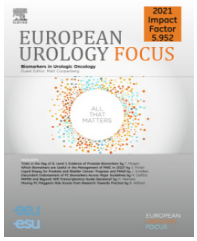

Clinical Consultation Guide

Management of Erythrocytosis in Men Receiving Testosterone Therapy: Clinical Consultation Guide

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1. Introduction

Testosterone deficiency, previously known as male hypogonadism, affects approximately 25% of all men, with prevalence that increases with age [1]. Risk factors for developing adult-onset testosterone deficiency include obesity, chronic disease, and poor general health [2]. Individuals with clinical hypogonadal symptoms and two morning samples demonstrating low testosterone levels often benefit from testosterone therapy (TT).

The European Association of Urology (EAU) lists the following as primary indications for TT: delayed puberty; Klinefelter's syndrome with hypogonadism; sexual dysfunction, including erectile dysfunction not responding to phosphodiesterase-5 inhibitors (PDE5i); osteoporosis due to hypogonadism; hypopituitarism; and adult men with testosterone levels lower than an age-specific physiological range exhibiting hypogonadal symptoms [3,4]. The primary aim of TT is to reduce clinical symptoms of testosterone deficiency by restoring serum testosterone levels to an age-dependent mid-normal range [3,4].

However, TT can lead to adverse effects, including, most commonly, erythrocytosis or an increase in hemoglobin (Hb) and hematocrit (Hct) levels [3,4]. A recent study demonstrated that erythrocytosis in men on TT is an independent risk factor for major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) within the first year of treatment onset [5]. In fact, the EAU lists Hct >54% as a contraindication for TT [3,4]. Low testosterone levels have been associated with unfavorable prognosis for prostate cancer, although this association is still a matter of debate [6]. Therefore, the benefits of TT must be weighed against the higher cardiovascular risk associated with initiation of therapy. Furthermore, any development of erythrocytosis while on TT must be promptly identified and managed.

2. Does the TT route, duration, or dosage matter?

It is hypothesized that the mechanism by which testosterone leads to erythrocyte proliferation is a combination of a decrease in hepcidin production leading to greater iron availability and utilization, an increase in the production and set point of erythropoietin, and peripheral conversion of testosterone to estradiol, which subsequently activates bone marrow estrogen receptor alpha and leads to greater telomere stability [7].

Of the many TT modalities available, it was once thought that injectable formulations caused the most significant increases in Hb and Hct [7]. While that is true, a recent systematic review and network meta-analysis by Nackeeran et al. [1] confirmed that all TT modalities, including gels, oral formulations, patches, intramuscular (IM) testosterone enanthate, and IM testosterone undecanoate, are associated with increases in Hct. The authors demonstrated that IM testosterone enanthate significantly increases Hct com-

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pared to patches, but they did not identify any other significant differences in mean Hct increases between modalities. Furthermore, no modality had a pooled mean Hct increase of more than 4.3%, suggesting that close monitoring and careful patient selection may mitigate the risk of TT-induced erythrocytosis, especially for patients with low to normal Hct at baseline [1]. The risk of developing erythrocytosis has not been correlated with treatment duration, and it is generally thought that the greatest risk occurs during initiation of therapy because of an acute change in hormonal homeostasis [7]. Hb and Hct levels usually continue to rise over the first 6 mo of therapy, before plateauing, with detectable erythropoietic effects at 3 mo after TT initiation [4,7,8]. Typically, Hb and Hct levels gradually return to baseline within 1 yr after TT discontinuation [4,7,8]. However, the risk of erythrocytosis depends on the testosterone dose [8,9]. Although the optimum therapeutic serum testosterone level while on TT has not yet been determined, it is postulated that serum levels higher than the age-specific normal range may increase the risk of erythrocytosis [4]. Consideration of patient-specific factors and selection of the appropriate therapeutic modality are therefore important when choosing an individual's testosterone dosage. For example, a reduction in body mass index or use of PDE5i may increase serum testosterone levels, while older age and other comorbidities such as diabetes may decrease levels [3–5]. Furthermore, transgender males may have a lower threshold for erythrocytosis development, while men living at higher altitudes may have higher baseline Hct levels [2,10]. In addition, while some modalities such as transdermal patches induce a uniform serum testosterone level over time, other formulations such as IM testosterone enanthate lead to fluctuating levels. Thus, deciding on the appropriate timing for serum level measurement is also crucial [4,9].

3. Management of erythrocytosis

Providers must engage patients in shared decision-making regarding the benefits and risks of TT before treatment initiation. Furthermore, providers should perform an initial assessment that includes measurement of baseline Hb and Hct levels, as well as evaluating the patient's cardiovascular risk factors, including any history of VTE. An individual's clinical response to TT and their Hct level should be monitored at 3, 6, and 12 mo after treatment initiation, and annually thereafter [3,4]. If a patient's Hct rises above the Endocrine Society guideline of 54% [2], providers should investigate other possible contributory causes while simultaneously decreasing the testosterone dosage or discontinuing therapy altogether [2–4]. It is worth noting that the EAU and American Urological Association recommend 54% as the upper Hct limit, while the Canadian guidelines recommend 55% [10]. Patients with erythrocytosis on TT may be offered therapeutic phlebotomy of 500 ml; however, it is unknown if phlebotomies result in long-term reductions in Hct while continuing on TT [3,4,7,10]. If Hct remains elevated after a decrease in dosage and/or therapeutic phlebotomy, providers should discontinue TT until the Hct level has normalized, at which point TT may be reinitiated at a lower dose if clinically indicated [3,4].

4. Conclusions

Erythrocytosis is the most common side effect of all TT modalities. Patient-specific factors should be considered when choosing an appropriate TT dosage and modality. Owing to the risk of MACE and VTE, Hct >54% should prompt providers to consider decreasing and discontinuing TT until normalization of Hct.

***Conflicts of interest*:** The authors have nothing to disclose.

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