Erythrocytosis and Polycythemia Secondary to Testosterone Replacement Therapy in the Aging Male

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ABSTRACT

Introduction. Testosterone replacement therapy (TRT) is a common treatment for hypogonadism in aging males. Men with low to low-normal levels of testosterone have documented benefit from hormone replacement. Recent meta-analyses have revealed that increases in hemoglobin (Hb) and hematocrit (Hct) are the variants most commonly encountered. Clinically, this response is described as erythrocytosis or polycythemia secondary to TRT. However, the recent Food and Drug Administration warning regarding the risk for venothromboembolism (VTE) has made the increases in Hb and Hct of more pertinent concern. The risks associated with androgen replacement need further examination.

Aim. To review the available literature on erythrocytosis and polycythemia secondary to TRT. To discuss potential etiologies for this response, the role it plays in risk for VTE, and recommendations for considering treatment in at-risk populations.

Methods. A literature review was performed through PubMed regarding TRT and erythrocytosis and polycythemia.

Main Outcome Measures. To assess the mechanisms of TRT-induced erythrocytosis and polycythemia with regard to basic science, pharmacologic preparation, and route of delivery. To review Hct and risk for thrombotic events. To offer clinical suggestions for therapy in patients at risk for veno-thrombotic events.

Results. Men undergoing TRT have a 315% greater risk for developing erythrocytosis (defined as Hct > 0.52) when compared with control. Mechanisms involving iron bioavailability, erythropoietin production, and bone marrow stimulation have been postulated to explain the erythrogenic effect of TRT. The association between TRT-induced erythrocytosis and subsequent risk for VTE remains inconclusive.

Conclusions. All TRT formulations cause increases in Hb and Hct, but injectables tend to produce the greatest effect. The evidence regarding the risk for VTE with increased Hct is inconclusive. For patients with risk factors for veno-thrombotic events, formulations that provide the smallest effect on blood parameters hypothetically provide the safest option. Further trials are needed to fully evaluate the hematological side effects associated with TRT.
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Key Words. Testosterone; Testosterone Deficiency; Late-Onset Hypogonadism; Testosterone Replacement Therapy; Erythrocytosis; Polycythemia; Hematocrit

Introduction

Hypogonadism, or testosterone deficiency (TD), is more common as men age. Recent studies have estimated nearly 5 million new cases of hypogonadism in men between the ages of 49 and 60 years over the last decade [1]. With a concurrent rise in direct marketing by pharmaceutical companies, testosterone replacement therapy (TRT) in the aging male has increased

dramatically. Multiple terms have been used to classify age-related hypogonadism, including andropause, male climacteric syndrome, late-onset hypogonadism, and androgen deficiency of the aging male. The American Urological Association (AUA) defines hypogonadism 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" [2]. Additionally, men afflicted by hypogonadism may experience reduced muscle mass, physical strength, and bone mineral density, as well as anemia and increased body fat [3]. Many men diagnosed with TD do benefit from TRT. However, TRT has come under close scrutiny of late, as there is conflicting evidence regarding the effect of TRT on the cardiovascular system. Some recent studies implicate TRT in increasing cardiovascular events [4], whereas others document TRT as having a protective effect [5,6]. In a policy statement issued in February 2014, the AUA recognized the controversy surrounding TRT, and endorsed its use in the treatment of men suffering with hypogonadism "after a full discussion of potential adverse effects." The AUA went on to state that definitive studies have not been performed, and, consequently, the effects of TRT on cardiovascular disease are not fully elucidated [2].

It is recognized that androgens have an erythrogenic effect on the hematologic system [7]. Elevations in hemoglobin (Hb) and hematocrit (Hct) levels are frequently described consequences of TRT [8] and recent meta-analyses have confirmed that blood profile changes are the most common adverse drug events seen with this therapy [9,10]. It has been proposed that long-term elevation of Hb and Hct may increase the risk of venothromboembolism (VTE), but this hypothesis is not universally agreed upon [11]. The use of exogenous testosterone as treatment for hypogonadism in the aging male is expected to increase as more and more diagnostic testing is conducted. In light of this, patient safety and avoidance of inimical side effects should be a priority for all treatments. Here, we provide an analysis of the proposed mechanisms that may explain the hematological response observed with TRT, a review of the effects this response may have on VTE risk, and recommendations for considering TRT in patients with risk for veno-thrombotic events.

Hypogonadism

The Endocrine Society's clinical practice guidelines define hypogonadism as a "clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis" [3]. The hypothalamic–pituitary–testicular axis is a dynamic physiological system involved with the homeostatic maintenance of testicular activity (Figure 1). Disruption at any level may lead to hypogonadism [12,13]. There are two types of hypogonadism—primary and secondary. If the dysfunction is located at the level of the testes, this is considered primary hypogonadism or *hypergonadotropic* hypogonadism [14]. These individuals will often have markedly decreased serum testosterone levels and compromised fertility due to impaired spermatogenesis. If the dysfunction of the hypogonadal–pituitary–testicular axis is located at the level of the hypothalamus or pituitary gland rather than the testes, this is considered secondary hypogonadism or *hypogonadotropic* hypogonadism [14]. Hypogonadism in the aging male is considered a hybrid of both primary and secondary hypogonadism subtypes. Age-related

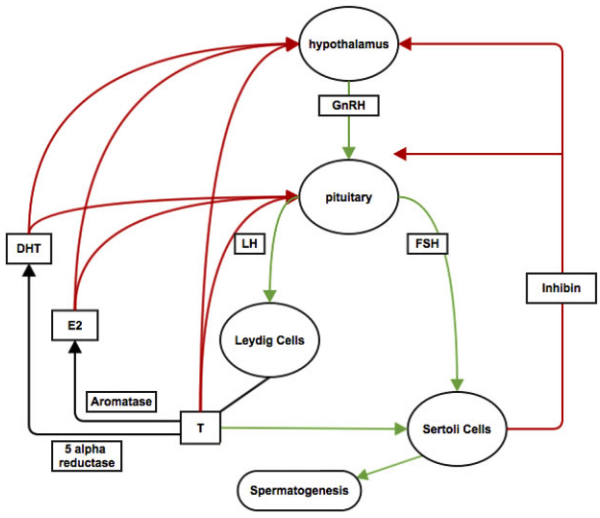

Figure 1 Graphical representation of the hypothalamic–pituitary–testicular axis. Green lines indicate a stimulatory effect; red lines indicate an inhibitory effect. DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T, testosterone; E2, estradiol.
[Correction added on 31 March 2015, after first online publication: arrow running from T to Spermatogenesis was corrected to run from Sertoli Cells to Spermatogenesis.]