SEXUAL MEDICINE REVIEWS

Erythrocytosis Following Testosterone Therapy

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ABSTRACT

Introduction: A rapid increase in awareness of androgen deficiency has led to substantial increases in prescribing of testosterone therapy (TTh), with benefits of improvements in mood, libido, bone density, muscle mass, body composition, energy, and cognition. However, TTh can be limited by its side effects, particularly erythrocytosis. This review examines the literature on testosterone-induced erythrocytosis and polycythemia.

Aim: To review the available literature on testosterone-induced erythrocytosis, discuss possible mechanisms for pathophysiology, determine the significance of formulation, and elucidate potential thromboembolic risk.

Methods: A literature review was performed using PubMed for articles addressing TTh, erythrocytosis, and polycythemia.

Main Outcome Measures: Mechanism, pharmacologic contribution, and risk of testosterone-induced erythrocytosis.

Results: For men undergoing TTh, the risk of developing erythrocytosis compared with controls is well established, with short-acting injectable formulations having the highest associated incidence. Potential mechanisms explaining the relation between TTh and erythrocytosis include the role of hepcidin, iron sequestration and turnover, erythropoietin production, bone marrow stimulation, and genetic factors. High blood viscosity increases the risk for potential vascular complications involving the coronary, cerebrovascular, and peripheral vascular circulations, although there is limited evidence supporting a relation between TTh and vascular complications.

Conclusion: Short-acting injectable testosterone is associated with greater risk of erythrocytosis compared with other formulations. The mechanism of the pathophysiology and its role on thromboembolic events remain unclear, although some data support an increased risk of cardiovascular events resulting from testosterone-induced erythrocytosis. **Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis Following Testosterone Therapy. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Hypogonadism; Testosterone; Hormone Replacement; Erythrocytosis; Polycythemia

INTRODUCTION

With an increasing awareness of men's health issues, including androgen deficiency, the use of testosterone therapy (TTh) is increasing. Testosterone (T) prescription sales for men older than 40 years have tripled during the past decade and quadrupled in men 18 to 45 years old.[1,2] Furthermore, direct to consumer marketing campaigns by drug manufacturers have introduced the concepts of "andropause" and "low T" to the general population, and physicians have established terminology such as "late-onset hypogonadism" and "androgen deficiency" in the aging man.

Hypogonadism is defined 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."[3] Men also can present with decreases in muscle mass and strength, increased fat mass, decreased bone mineral density, and anemia.[3,4] Symptomatic hypogonadism is a pathologic disruption of the hypothalamic-pituitary-testicular axis. There are two widely accepted forms of hypogonadism: primary (testicular failure) and secondary (hypothalamic or pituitary failure). Primary hypogonadism represents failure of T production, characterized by low serum T and increased gonadotropins. Secondary hypogonadism results from a failure of testicular

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stimulation, characterized by low serum gonadotropin and low serum T levels. The Sexual Medicine Society of North America (SMSNA) described the clinical scenario of men presenting with signs and symptoms of low T, distinct from the classic picture of primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism, as adult-onset hypogonadism.[5] The SMSNA suggested that the term *adult-onset hypogonadism* could be applied to most men with hypogonadism, many of whom have concomitant metabolic disease (obesity, type 2 diabetes, metabolic syndrome, etc). In an official statement, the organization proposed an algorithm for TTh in patients with adult-onset hypogonadism.[5]

The Hypogonadism in Males (HIM) study found that the prevalence of hypogonadism in men older than 45 years is higher than 38%, with a 17% increase in risk for every 10-year increase in age; however, the HIM study did not include symptoms in its definition of hypogonadism.[6] In the European Male Aging Study, the overall prevalence of low T (total T $<$ 10.5 nmol/L without symptoms) was somewhat lower at 23.3%.[7] Further assessment of the cohort with an evaluation of nine candidate symptoms in addition to low T levels found a prevalence of 2.1% for symptomatic hypogonadism (low T with at least three symptoms).[8] The investigators acknowledged the lower prevalence of hypogonadism in consideration of serum T levels and symptoms, noting that "this finding underscores the paramount importance of using not only biochemical measures but also stringently defined, symptom-based criteria to prevent over diagnosis…"[8] Although these studies demonstrated that the incidence of hypogonadism differs as a function of patient age and definition of hypogonadism, the Food and Drug Administration has concluded that available evidence does not support an indication for TTh in the setting of "age-related hypogonadism."[9] Given increased testing for low T levels, the large increase in T prescribing, and incompletely defined indications for therapy, it is paramount that we thoroughly understand the risks and benefits of TTh.

Despite its positive effects, TTh has several common side effects, including increases in estrogen levels, gynecomastia, and erythrocytosis.[10–15] Much recent attention has been focused on the effects of TTh on the cardiovascular (CV) system. Extensive debate has focused on high-impact publications with questionable methodologies and controversial conclusions that suggested significant CV risk for men on TTh with alternative studies suggesting benefit.[16–20] In light of this controversy, the American Urological Association issued a policy statement stating that, based on current evidence, definitive answers on the CV risks of TTh are not currently available.[3]

T-induced increases in hemoglobin (Hb) and hematocrit (Hct) can lead to erythrocytosis, clinically defined as an Hb level higher than 18.5 g/dL or an Hct higher than 52% in men, although this definition varies.[21] Physiologically, erythrocytosis is defined by an erythrocyte mass that exceeds 125% of that predicted for sex and body mass.[22] This is the most common dose-limiting adverse effect of TTh.[10,12,21,23] Much of the concern on increases in blood viscosity resulting from increased red blood cell mass centers on the potential increased risk for venous thromboembolism, myocardial infarction, and cerebrovascular accidents.[24] However, little evidence supports an increased risk of these negative sequelae in men on TTh.[25] We review the literature examining T-induced erythrocytosis and summarize proposed mechanisms and risks of thromboembolic sequelae.

HYPOGONADISM AND TESTOSTERONE THERAPY

T levels decrease by 1% to 2% per year after 35 years of age, correlating to a decrease of 110 ng/dL per decade of life.[26,27] These age-related decreases in T are often attributed to a combination of decreasing gonadotropin levels and testicular hypofunction. Most professional society guidelines recommend treatment for T levels lower than 300 ng/dL in men with concomitant hypogonadal symptoms.[8,28–30]

The primary treatment for hypogonadism is TTh, which can correct insulin resistance; increase bone and muscle mass; decrease subcutaneous fat; lower low-density lipoprotein cholesterol, triglycerides, blood glucose, HbA_{1c}, and blood pressure; increase high-density lipoprotein cholesterol; and improve erectile function and life parameters (ie, increased energy and friendliness, decreased anger and anxiety, etc).[31,32] Although improvement in physiologic parameters is enough to warrant therapy, it is the improvement in physical and mental symptoms that drives patient satisfaction. Kovac et al[33] longitudinally evaluated patient satisfaction of men treated with different formulations of TTh (52.5% injection, 30.6% gels, and 16.9% pellets), with overall satisfaction rates ranging from 62.8% with less than 6 months of therapy to higher than 79% at 25 to 36 months.

Currently, numerous T formulations are available, including short- and long-acting injections, topical gels and creams, transdermal and buccal patches, and implantable pellets. As early as the 1940s, subcutaneous T pellets were available. Relatively short-acting intramuscular (IM) injections, such as T enanthate (TE), an ester metabolized over 4 to 5 days, and T cypionate (TC), a longer-acting testosterone metabolized over 7 to 8 days, were introduced in the 1950s. Oral T undecanoate (TU) was developed in the 1970s, although this formulation is not currently approved for use in the United States. Transdermal patches were developed in the 1990s, and soon after, topical gels, buccal patches, and extended-release IM formulations (TU) became available.[34,35] Although all T formulations are effective, each formulation's unique adverse effect profile is determined by dosage, pharmacokinetics, and method of administration.[33,36]

TESTOSTERONE-INDUCED ERYTHROCYTOSIS

Polycythemia and *erythrocytosis* are used interchangeably to refer to an abnormal increase of Hb or Hct. Although stimulation of