SEXUAL MEDICINE REVIEWS

Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency

Abdulmaged M. Traish, PhD, MBA

ABSTRACT

Introduction: Testosterone (T) deficiency (TD; hypogonadism) has deleterious effects on men's health; negatively affects glycometabolic and cardiometabolic functions, body composition, and bone mineral density; contributes to anemia and sexual dysfunction; and lowers quality of life. T therapy (TTh) has been used for the past 8 decades to treat TD, with positive effects on signs and symptoms of TD.

Aim: To summarize the health benefits of TTh in men with TD.

Methods: A comprehensive literature search was carried out using PubMed, articles relevant to TTh were accessed and evaluated, and a comprehensive summary was synthesized.

Main Outcome Measures: Improvements in signs and symptoms of TD reported in observational studies, registries, clinical trials, and meta-analyses were reviewed and summarized.

Results: A large body of evidence provides significant valuable information pertaining to the therapeutic value of TTh in men with TD. TTh in men with TD provides real health benefits for bone mineral density, anemia, sexual function, glycometabolic and cardiometabolic function, and improvements in body composition, anthropometric parameters, and quality of life.

Conclusion: TTh in the physiologic range for men with TD is a safe and effective therapeutic modality and imparts great benefits on men's health and quality of life. **Traish AM. Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Testosterone; Testosterone Deficiency; Testosterone Therapy; Sexual Function; Metabolic Syndrome; Diabetes; Bone Mineral Density

INTRODUCTION

Testosterone Is a Metabolic Hormone and Plays a Vital Role in Human Physiology

Testosterone (T) and its metabolite, 5α-dihydrotestosterone, regulate energy metabolism, nitrogen retention, muscle growth and maintenance, inhibit adipogenesis, and modulate male reproductive and sexual function.[1–14] T exerts an important metabolic and functional role in many tissues and organs (Figure 1). Among the well-documented physiologic roles of T is its regulation of muscle growth and function and inhibition of adipogenesis.[15–24] The role of T in the regulation of bone metabolism, erythropoiesis, endothelial and liver functions, and hair growth is well established.[25–55] The wide distribution of androgen receptors in various tissues, including the central nervous system, strongly supports the premise that T plays a key physiologic role in regulating human physiology and that T is an integral hormone in maintaining human health.[1–14]

Hypogonadism (Testosterone Deficiency)

In an effort to use terminology that promotes accuracy and clarity of T deficiency (TD) and T therapy (TTh), this review has adopted the language recommended by an international expert consensus panel.[7] *Testosterone deficiency* is used instead of the older term *hypogonadism*. Also, *testosterone therapy* is used instead of *testosterone replacement therapy*.[7] TD is characterized by low levels of circulating plasma T concomitant with a host of clinical signs and symptoms attributed to decreased physiologic T levels and function.[7,8,56–62] TD is a well-established significant medical condition, which has been recognized since 1940.[6,7,63,64] TD negatively affects men's health and is associated with increased body weight, adiposity, waist circumference (WC), insulin resistance (IR), type 2 diabetes mellitus (T2DM), hypertension, inflammation, atherosclerosis and cardiovascular disease (CVD), infertility, erectile dysfunction, and increased incidence of mortality (for

Received August 17, 2017. Accepted October 6, 2017.

Department of Urology, Boston University School of Medicine, Boson, MA, USA

https://doi.org/10.1016/j.sxmr.2017.10.001

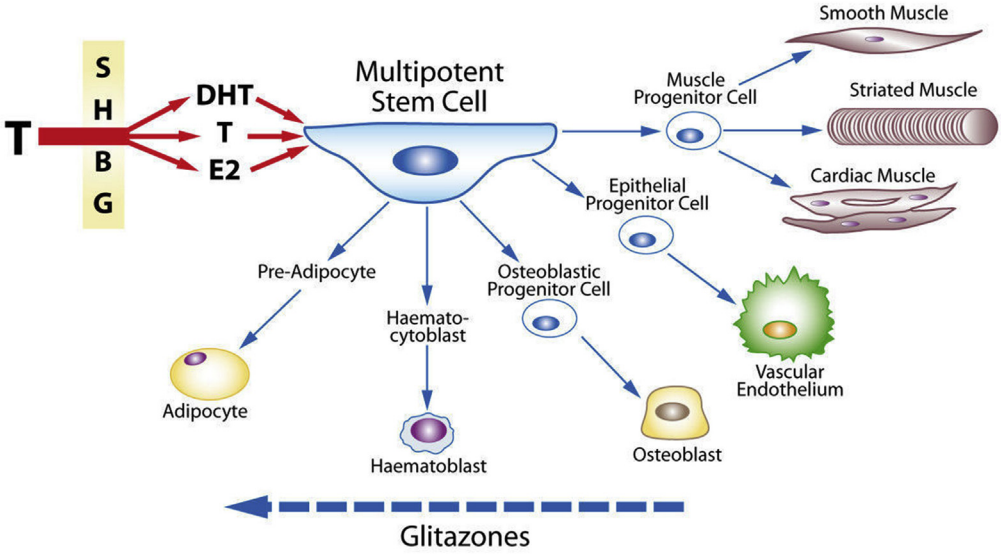

Figure 1. Testosterone, directly or through conversion to 5α-dihydrotestosterone or estradiol, modulates multipotent stem cell metabolism and function to promote differentiation to progenitor cells for muscle, endothelium, bone, and red blood cells. DHT = 5α-dihydrotestosterone; E2 = estradiol; T = testosterone. From Carruthers M, Trinick TR, Jankowska E, et al. Are the adverse effects of glitazones linked to induced testosterone deficiency? Originally published and reprinted from BioMed Central from Carruthers M, Trinick TR, Jankowska E, Traish AM. Are the adverse effects of glitazones linked to induced testosterone deficiency? Cardiovasc Diabetol 2008;7:30.[333]

review see [7–9,65–67]). Clinically, TD is divided into primary (testicular dysfunction), secondary (pituitary or hypothalamic failure), or mixed hypogonadism (a combination of testicular failure and pituitary hypothalamic failure).[60] Signs and symptoms associated with TD include sexual dysfunction, depressed mood, decreased motivation, fatigue, and diminished quality of life.[6,26]

Signs and Symptoms of TD

The signs and symptoms of TD encompass several domains (sexual, physical, psychological, and cognitive). Sexual dysfunctions such as decreased or lost sexual desire, diminished nocturnal and morning erections, and erectile dysfunction are often among the most recognized symptoms of TD.[57] Other recognized symptoms of TD are diminished physical vigor, sarcopenia, energy, and motivation, fatigue, depressive mood, and sleep disturbances. In addition, visceral obesity is often observed, and muscle mass and bone mineral density (BMD) are often reduced. Other signs are the presence of smaller testicles, decreased body hair, and gynecomastia. It must be noted that owing to interindividual variability, not all these manifestations must be present simultaneously to determine the signs and symptoms of TD.[57] Several comorbidities are associated with TD. These include metabolic syndrome (MetS), obesity, diabetes, hypertension, and hyperlipidemia.[68] Thus, it is not surprising that there is an association among obesity, MetS, and TD.[69–72] It is reasonable to suggest that obese men exhibit increased risk of TD and have similar signs and symptoms of TD.

Adverse Effects of TD on Men's Health

TD is associated with decreased lean body mass (LBM), increased fat mass (FM), increased state of inflammation, MetS, dyslipidemia, IR, adiposity, T2DM, bone loss, and anemia.[73–92] TD and T2DM are often diagnosed together in the same patient; TD might be more prevalent in men with T2DM, higher body mass index (BMI), or excessive obesity (BMI > 40 kg/m^2); and men with TD are at a greater risk of developing T2DM.[72,74,75,88–100] Acute T withdrawal markedly decreases insulin sensitivity in young healthy men with idiopathic hypogonadotropic hypogonadism in the absence of changes in BMI or detectable changes in body composition.[101,102] TD has been independently associated with IR in older men without diabetes.[5,103]

An inverse relation between T and IR also has been postulated and higher physiologic T levels appear to be protective against the development of T2DM.[80,87,88,90,104–108] Decreased T levels predict IR and incident T2DM in older adults and increased risk of MetS and T2DM even in initially non-obese men.[71,80,83,85–88,90,93,104–112] TD increases insulin levels and the homeostatic model assessment for IR (HOMA-IR).[107] Men with T2DM are often obese, with significantly lower T levels and higher fasting insulin levels compared with non-obese men.[97–99]

An inverse relation between circulating T levels and inflammatory cytokines has been reported and TTh in men with TD has been shown to rebalance the relation between T and inflammatory cytokines.[70,73–77,79,113] Men with MetS have increased fasting insulin levels and decreased total T compared with men without MetS.[72] TD is a stronger risk factor in the