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Review

Adverse health effects of testosterone deficiency (TD) in men

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ABSTRACT

Testosterone and its metabolite, 5α-dihydrotestosterone are critical metabolic and vascular hormones, which regulate a host of biochemical pathways including carbohydrate, lipid and protein metabolism and modulate vascular function. Testosterone deficiency (TD) is a well-recognized medical condition with important health implications. TD is associated with a number of co-morbidities including increased body weight, adiposity and increased waist circumference, insulin resistance (IR) and type 2 diabetes mellitus (T2DM), hypertension, inflammation, atherosclerosis and cardiovascular disease, erectile dysfunction (ED) and increased incidence of mortality. In this review, we summarize the data in the literature on the prevalence of TD and its association with the various co-morbidities and suggest that T therapy is necessary to improve health outcomes in men with TD.

Contents

1. Testosterone deficiency (TD) (Hypogonadism)

Testosterone (T) is an anabolic hormone that regulates metabolic function and energy utilization and plays a key role in nitrogen retention, carbohydrate and fat metabolism and adipogenesis. Testosterone deficiency (TD), also known as "hypogonadism", is characterized by low circulating levels of plasma T, concomitant with a host of clinical signs and symptoms, attributed to low physiological T levels [1–4]. Clinically, TD is divided into primary hypogonadism (testicular dysfunction), secondary hypogonadism (pituitary or hypothalamic failure) or mixed hypogonadism (a combination of testicular failure and pituitary hypothalamic failure) [1]. There is no universal agreement on the specific signs and symptoms of TD. Reduced sexual desire and nocturnal penile erections are thought to be strong indications of TD. Wu et al., [5] suggested that symptoms of sexual dysfunction such as desire, erection and orgasmic functions are closely associated with low T [5]. Other signs and symptoms include diminished motivation,

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fatigue, decreased energy, reduced muscle mass and strength, depressed mood, irritability and poor concentration [5,6].

2. Prevalence of TD

The overall incidence of TD increases with age and approximately one half a million new cases of TD are expected in the US in men aged 40–69 years old [7]. An independent effects of age on T levels was demonstrated in a study of 890 men by Harman et al., [8]. Also, a significant, independent, age-invariant, longitudinal effect of age on both T and free T index was reported. TD was noted in about 20% of men over 60, 30% over 70 and 50% over 80 years of age [8]. In a study utilizing primary clinical care practice settings in the United States, Mulligan et al., [9] estimated the prevalence of TD in men aged >45 years to be approximately 38.7% based on total T levels and about 36.3% based on bioavailable or free T. The prevalence of major risk factors for presence of TD in the clinical practices was significantly higher in men with obesity, diabetes, hypertension, hyperlipidaemia, prostate disease and asthma or chronic obstructive pulmonary disease when compared with men without such conditions [9].

Wu et al., [10] suggested that age is associated with low free T and with elevated LH, indicating an impaired testicular function. Obesity is associated with lower total and free T and with unchanged/decreased LH, indicating hypothalamus/pituitary dysfunction. Other comorbidities are associated with lower total T but with unchanged LH in younger men but higher LH in older men [10]. These findings suggest that TD may be attributed to a host of abnormalities in hypothalamic–pituitary–testicular axis function in aging men [10]. Men with erectile dysfunction (ED) exhibited higher prevalence of TD due, in part, to a host of chronic illnesses and approximately 6% is due to primary TD and 30% is attributed to secondary TD [11]. Age, waist circumference and health status were found to be associated with symptomatic TD [12]. Since many co-morbidities influence the health status, the findings from this study [12] are congruent with those reported by Mulligan et al., [9] and Wu et al., [10].

The prevalence of TD increases with comorbidities, such as insulin resistance (IR) and type 2 diabetes (T2DM), obesity, hypertension, and cardiovascular disease (CVD) [9]. In a meta-analysis study, in which 20 studies with 3825 T2DM patients were examined T levels were significantly lower in men with T2DM [13]. The prevalence of TD in T2DM ranges from 30–50% [14–16]. T levels are also reduced by increased waist circumference (WC) and obesity [17]. Approximately, 40% of obese non-diabetic men and 50% of obese diabetic men aged >45 years have low free T [18]. The concomitant presence of obesity and diabetes is associated with an additional increase in the prevalence of TD [18]. Similar findings were reported by Corona et al., [19] who demonstrated that TD is more prevalent in men with T2DM and ED and the proportion of patients with TD approaches 34%.

Camacho et al., [20] investigated the prevalence of TD in a longitudinal survey of 2736 community-dwelling men aged 40–79 years at baseline recruited from eight centers across Europe. The key finding of this study was that weight loss was associated with a proportional increase, and weight gain a proportional decrease, in T and SHBG. More importantly, changes in number of comorbid conditions or physical activity were not associated with significant alterations in hypothalamic–pituitary–testicular (HPT) axis function [20]. These findings led to the conclusion that body weight and lifestyle factors influence HPT axis function in aging and weight loss was associated with a rise, and weight gain a fall, in TT, FT and SHBG. The practical implication of these findings suggests that weight management is important for maintenance of T levels in ageing men, and hormonal imbalances associated with obesity may be reversible following weight loss and adherence to a healthy life style [20].

It has recently been suggested that an age-related decline in T levels is not inevitable but is largely explained by changes in health status, particularly obesity and depression [21]. TD is associated with poorer health outcomes in ageing men, including frailty, reduced sexual activity, IR and CV events and mortality [22]. TD is associated with increased risk of all-cause and CVD death in community-based studies of men, however, this association is not well understood [23].

TD is prevalent in men with obesity, metabolic syndrome (MetS) and T2DM [13,14,16,17,24,25]. TD predicted increased adiposity and overall obesity [26]. Both subcutaneous and visceral fat are increased in TD [24,27,28]. TD was noted in approximately 30% of men with MetS and only about 3.1% in healthy men. A meta-analysis by Corona et al., [29] confirmed that patients with T2DM had higher prevalence of TD compared to non-diabetic group.

3. TD and associated co-morbidities

Considerable evidence exists relating the impact of TD on a host of co-morbidities. As depicted in Fig. 1. TD is associated with increased (i) inflammation, (ii) reduced insulin sensitivity and increased insulin resistance, (iii) increased adiposity and dyslipidemia, (iv) increased vascular stiffness, (v) hypertension, (vi) atherosclerosis and (vii) increased risk of cardiovascular diseases (CVD) and mortality. Below we discuss each of these co-morbidities and its relationship to TD.

3.1. Relationship between TD & inflammation

Laaksonen et al., [30] showed that total T and free T were inversely related with insulin, glucose, triglycerides (TGs), C-reactive protein (CRP) concentrations. An inverse association was demonstrated between CRP and total and free T levels, which remained significant after adjusting for age, BMI, comorbid conditions and lifestyle factors [31]. Similarly, Zhang et al., [32] showed that higher levels of total T, free T were statistically significantly related to lower levels of CRP, even after adjustment for age, WC, TGs, high-density lipoprotein cholesterol (HDL), fasting glucose, insulin, smoking status, hypertension, T2DM and family history of hypertension or diabetes. A significant inverse correlation was reported between baseline IL-6 and total T and bioavailable T levels [33]. In men with hypogonadotrophic hypogonadism (HH) and T2DM an inverse relationship between CRP concentration and T levels was noted [34]. In untreated men, there was a significant increase in IL-6 and CRP levels after coronary stent implantation. T treatment prior to stent implantation significantly attenuated IL-6 and hs-CRP levels, respectively [35]. T treatment in men with MetS and TD reduced fasting blood glucose, WC, and improved surrogate markers of atherosclerosis [36]. T replacement shifts the cytokine balance to a state of reduced inflammation and lowers total cholesterol (TC) [37]. We should point out that other studies have not been able to confirm or demonstrate a relationship between TD and increased inflammation [38–41].

3.2. Relationship between TD & type 2 diabetes (T2DM) and obesity

T2DM and IR are key components of MetS. The prevalence of T2DM is increasing by decade [42] concomitant with increased prevalence of obesity [43]. Men with TD are at a greater risk of developing T2DM [44–50]. Ding et al., [13] suggested that higher plasma T levels were associated with reduced risk of T2DM and vice versa. Low T levels are commonly noted in men with T2DM and IR [51]. Stellato et al., [47] reported that reduced T and SHBG may play a role in