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Abstract

Millions of men, as a result of the natural aging process, injury, illness, and medical therapies, experience a decline in testosterone levels that necessitate a need for testosterone supplementation therapy (TST). The signs and symptoms of testosterone decline may occur gradually, and low testosterone levels may be misdiagnosed as other medical conditions. Over the past two decades, there has been an increase in testing of testosterone levels and the use of TST. With so many men now on TST, it is essential for health care professionals to know the signs and symptoms, the causes of testosterone decline, how testosterone deficiency is diagnosed, what pathological changes are associated with testosterone decline, and the benefits and risks of TST. In addition, health care providers need to be aware of the various forms of testosterone available as well as the advantages and disadvantages of each. This article provides a brief overview of testosterone deficiency, TST treatment options and guidelines, and the risks and benefits associated with of TST.

Keywords

hypogonadism, development and aging, health screening, health awareness

More and more men are being placed on Testosterone supplementation therapy (TST). According to Layton et al. (2014), lab testing of testosterone levels and the use of TST have both substantially increased in the United States since the year 2000. As the number of men taking TST has increased, it is important for health care professionals to have an understanding of the disease processes associated with low testosterone levels, the signs and symptoms of low testosterone, treatment options available, and the risks and benefits of TST. This article provides a brief overview of these topics, beginning with signs and symptoms associated with low testosterone levels.

Signs and Symptoms of Testosterone Deficiency

Many of the symptoms of testosterone deficiency occur gradually and go unnoticed and are not diagnosed for years (Salyer, 2013). Signs and symptoms associated with testosterone deficiency may include reports of reduced libido, erectile dysfunction, fatigue, lethargy, moodiness/irritability, depression, sleep disturbance, a decline in mental function, hot flashes, and decreased vitality. Visible physical changes in the body may include decreased muscle mass, increased body fat, hair loss, breast discomfort/gynecomastia, and loss of bone mineral density (Bhasin et al., 2010; Gruenewald & Matsumoto,

2003; Salyer, 2013). Other symptoms may include metabolic syndrome, insulin resistance, and atherosclerosis (Salyer, 2013).

One of the most common reasons for declining testosterone is the aging process. As part of the aging process, testosterone levels can begin declining as early as the third decade in life (Strayer & Cabarera, 2013). This gradual decline in testosterone may be asymptomatic, or signs and symptoms of low testosterone, if present, may be attributed to the senescence process. For example, memory loss and difficulty concentrating may be attributed to aging and not a symptom of low testosterone, as well as insomnia, irritability, and a depressed mood (de Melo, Soares, & Baragatti, 2013).

Diagnosing Testosterone Deficiency

A medical diagnosis of testosterone deficiency (also referred to as androgen deficiency) is based on the measurement of total serum testosterone levels and the presence of signs and symptoms associated with low

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testosterone levels (Bhasin et al., 2010). A total serum testosterone level below 300 ng/dL is typically used as the threshold for testosterone deficiency diagnosis. Total serum testosterone levels are affected by circadian rhythms, with peak values in the morning. Therefore, total serum testosterone levels should be assessed using a morning blood sample. Confirmation of a testosterone deficiency diagnosis should be based on at least two measures of total serum testosterone (Bhasin et al., 2010).

In confirming a diagnosis of testosterone deficiency, it is important to also consider the differences between total serum testosterone and free testosterone levels (also referred to as bioavailable testosterone levels). Total serum testosterone levels refer to all (i.e., "total") testosterone in the blood. Free testosterone levels refer to testosterone that is not bound to sex hormone binding globulin (SHBG) and is available (i.e., "free") to interact with target cells. In men who are symptomatic and have a total serum testosterone level near the lower limit of normal, it is recommended that free testosterone levels be check to determine the amount of bioavailable testosterone (Bhasin et al., 2010).

It is important to note that SHBG concentrations increase as men age, and this increase in SHBG results in greater binding of testosterone, leaving less available free testosterone. The combination of both a decrease in testosterone production and decreased availability of free testosterone is considered a natural part of aging (Gruenwald & Matsumoto, 2003). TST should not be routinely offered to all elderly men based on low testosterone levels alone (Bhasin et al., 2010).

Testosterone deficiency can also be classified as primary or secondary hypogonadism. Primary hypogonadism, also referred to a testicular hypogonadism, results from a failure of the testis to produce normal levels of testosterone (Bhasin et al., 2010). In primary hypogonadism, total serum testosterone levels will be low, and serum luteinizing hormone and follicle-stimulating hormone will typically be high (Salyer, 2013). Secondary hypogonadism is also referred to as pituitary-hypothalamic hypogonadism and results from defects in the functions of the hypothalamus and pituitary gland (Bhasin et al., 2010). In secondary hypogonadism, serum testosterone levels will be low, and luteinizing hormone and follicle-stimulating hormone levels will be normal or reduced. In both primary and secondary hypogonadism, sperm counts are subnormal (Salyer, 2013).

Associated and Secondary Conditions of Low Testosterone

Low testosterone is often associated with a number of other health-related conditions. Testosterone deficiency has been linked to the development depression, obesity, diabetes mellitus, sexual dysfunction, development and/or exacerbation of cardiovascular disease, stroke, problems with bone density, and metabolic syndrome as well as other adverse health conditions (Ruige, 2011).

While there are ongoing studies and unanswered questions as to whether or not low testosterone levels directly lead to or contribute to cardiovascular disease, diabetes, metabolic syndrome, stroke, and other serious health conditions, there is evidence to suggest a link to these conditions with low testosterone levels. Ruige (2011) concludes that low serum testosterone is associated with obesity and can contribute to diabetes. Testosterone is bound to SHBG, and it is associated with high insulin levels and insulin resistance. An increase in insulin resistance along with low testosterone is associated with an increase in adipose tissue, which can lead to obesity in men. Obesity itself has long been recognized as a leading contributor to cardiovascular disease, diabetes, high blood pressure, and stroke.

Anemia is frequently associated with low testosterone and type 2 diabetes. Testosterone deficiency has been independently associated with anemia. Grossmann et al. (2009) conclude that men with total testosterone level less than 10nmol/I were more likely to have anemia, hemoglobin less than 17, and patients with free testosterone levels less than 0.23 nmol/L were twice as likely to develop anemia.

It is widely agreed that low testosterone and depression are both more common with aging men (Joshi et al., 2010). However, more research needs to be conducted before a definite link between low testosterone and depression in men as part of the aging process can be established. Joshi et al. (2010) conducted a study of 608 men (65 years and older), with a median age 75.6, and conclude that free testosterone levels below 170 nmol/L are associated with depressive symptoms. Joshi et al. also reported that free testosterone levels below 220 nmol/L was a good predictor for the onset of depressive symptoms.

Metabolic syndrome is another condition often associated with low testosterone. Metabolic syndrome refers to a number of conditions that can lead to increased risk of developing heart disease, stroke, and diabetes in individuals who have gained weight, especially in the waist area, or in family members who have diabetes, high blood levels of cholesterol and glucose, and high blood pressure (Kapoor & Jones, 2008).

Kapoor and Jones (2008) reported that low testosterone levels are a risk factor for the later development of metabolic syndrome among males. Kapoor and Jones also reported declining testosterone levels among men are associated with carotid and aortic atherosclerosis.

Certain medications have also been reported to cause lower testosterone levels in men. Rubinstein, Carpenter, and Minkoff (2013) studied 81 men of age 26 to 79 years,

with a median age of 51 years, who were being treated at a chronic pain clinic. The men in this study were identified to be five times more likely to have lower testosterone levels if they were being treated with long acting opioids. None of the men in this study had been previously diagnosed as having low testosterone levels. Based on the sample in this study, Rubinstein concluded that 53% of all men taking daily opioids could have testosterone deficiency.

Benefits of TST

While men who undergo TST must be monitored closely for contraindications and side effects, there are measurable benefits to TST. TST for men with low free and total testosterone levels has been reported to improve energy level, improve muscle mass, correct erectile dysfunction, improve libido, and reduce the risk of weight gain (Salyer, 2013). TST has also been reported to improve symptoms associated with depression and mental function (Salyer, 2013).

TST helps reduce the risk for development of metabolic syndrome, cardiovascular disease, and diabetes (Salyer, 2013). Kapoor and Jones (2008) conclude that early interventional TST has a positive effect on visceral obesity, insulin sensitivity, glycemic control, and lipid profiles in men that were diagnosed as having low testosterone levels.

Cai et al. (2014) conducted a systematic review aimed at determining the metabolic impact of TST on men with low testosterone levels with diabetes mellitus. Using PubMed and the Cochrane Library, Cai and his colleagues completed a literature review and meta-analysis using only randomized controlled trials. Cai et al. reported that TST reduced fasting plasma glucose levels, serum insulin levels, and triglyceride levels. While the authors acknowledge that additional larger well designed randomized controlled trails are needed, the researchers conclude that TST therapy may improve glycemic control and decrease triglyceride levels of men with low testosterone levels and who also have type 2 diabetes.

In a study that examined 1,365 men aged 28 to 87 years with symptomatic testosterone deficiency, Ramasamy, Fisher, and Schlegel (2012) concluded that TST improves early detection of prostate cancer. In this same study, Ramasamy et al. point out that their study adds to the already existing research that supports TST is safe despite reports in the literature of risks associated with TST.

Risks Associated With TST

With any drug, hormone, or other medical treatment, there is always the possibility of undesired and unintended outcomes. For TST, there are many potential side effects. Some of the negative effects associated with TST, especially with long-term treatment, can be life threatening.

There is also controversy associated with the use of testosterone with certain patient populations. In men who have known coronary artery disease, TST may need to be used with caution. Vigen et al. (2013) reported in a retrospective cohort study of 8,709 veterans with testosterone levels lower than 300 ng/dL, and who also had a diagnosis of coronary artery disease, that those placed on TST had a greater risk of an adverse outcome than those not receiving TST. Adverse outcomes included myocardial infarctions, stroke, and death. An absolute risk difference of 5.8% for an adverse outcome was found in men receiving TST compared with men not on TST.

TST and its impact on the health of the prostate and its impact on the prognosis of patients who have been diagnosed with prostate cancer are very controversial. Ramasamy et al. (2012) point out that since prostate cancer is known to be androgen dependent, there is concern that undetected tumors may progress into larger tumors as a result of TST. Ramasamy et al. conclude that while more clinical trials are needed, there does not appear to be a relationship between prostate cancer development with the use of TST. Furthermore, there does not appear to be a link between TST and advancing prostate disease (Feneley & Carruthers, 2012).

Forms of TST

There are a number of options to choose from regarding the forms of TST depending on the patient needs, preferences, and physician recommendation. One of the most common and inexpensive is intramuscular injection. While injections are usually only administered once a month and patients can learn to administer the injection themselves, injections can be painful and cause soreness and bruising. There can also be moderate swings in testosterone levels associated with the injection form (McGill, Shoskes, & Sabanegh, 2012).

TST can also be administered transdermal using patches, gels, or liquids. Transdermal forms of therapy provide a more sustained therapeutic benefit. While more comfortable method of administration, these gels, ointments, or patches must be administered daily. Patch sites must be rotated. Patches sometimes lead to dermatology disorders and cannot be worn in water. Care must be made not to come in contact with children and women who are pregnant or of childbearing age. Hands must be washed, and areas applied must be covered (McGill et al., 2012).

Other forms of TST include subcutaneously implanted slow release pellets in the buttock. Approximately 8 to 14

pellets are inserted every 3 to 6 months. Advantages include slower release and more sustained therapeutic benefit and less frequent treatment cycles. Disadvantages of this relatively new form of treatment include invasive procedure, risk of infection, and extrusion of pellets in a small percentage of patients.

Buccal TST is also an option; however, this method of replacement therapy is frequently associated with gum disease and never became a popular choice of patients or practitioners. Oral forms of testosterone are strongly

Testosterone Supplement Options.

Route	Dosage	Side effects
Methyltestosterone (Android)	10 to 50 mg oral daily	Hepatic effects, lower androgen response
Fluoxymesterone (Halotestin)	5 to 20 mg oral daily	Hepatic effects, lower response
Testosterone buccal (Striant)	30 mg applied to gums twice daily	Oral irritation
Testosterone patch (Androderm)	Applied to skin daily	Site reaction
Testosterone transdermal (Testoderm)	Patch applied to scrotum daily	Site reaction, transfer to partner
Testosterone cypionate (Depo-Testosterone)	50 to 400 mg intramuscularly every 2 to 4 weeks	Urticaria, site reactions
Testosterone enanthate (Delatestryl)	50 to 400 mg intramuscularly every 2 to 4 weeks	Site reaction
Testosterone 1% gel (AndroGel)	5 gm topically once daily	Site reaction, transfer to partner
Testosterone pellets (Testopel)	150 to 450 mg implanted subcutaneously every 3 to 6 months	Site pain and inflammation

Source. McGill et al. (2012).

associated with hepatic disease and are not used in the United States (McGill et al., 2012).

Conclusion

Many men because of aging, illness, or medical treatment experience a decline in testosterone level and as a result are placed on TST. Health care professionals must understand the signs and symptoms of testosterone deficiency, that these signs and symptoms often occur gradually over time, sometimes are not diagnosed timely, and can be similar to other associated medical conditions. This article provided a brief review of the signs and symptoms, the causes of testosterone decline, diagnosis of testosterone deficiency, pathological changes that occur with testosterone decline, advantages of TST, the consequences of TST, and the secondary and associated other health conditions related to low testosterone levels. The various forms of TST available as well as the advantages and disadvantages of each were also discussed. With the number of men on TST dramatically increasing, it is critical that health care professionals understand the totality of testosterone deficiency and treatment.

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