Injection of testosterone may be safer and more effective than transdermal administration for combating loss of muscle and bone in older men

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Borst SE, Yarrow JF. Injection of testosterone may be safer and more effective than transdermal administration for combating loss of muscle and bone in older men. Am J Physiol Endocrinol Metab 308: E1035–E1042, 2015. First published April 21, 2015; doi:10.1152/ajpendo.00111.2015.—The value of testosterone replacement therapy (TRT) for older men is currently a topic of intense debate. While US testosterone prescriptions have tripled in the past decade (9), debate continues over the risks and benefits of TRT. TRT is currently prescribed for older men with either low serum testosterone (T) or low T plus accompanying symptoms of hypogonadism. The normal range for serum testosterone is 300 to 1,000 ng/dl. Serum T ≤ 300 ng/dl is considered to be low, and T ≤ 250 is considered to be frank hypogonadism. Most experts support TRT for older men with frank hypogonadism and symptoms. Treatment for men who simply have low T remains somewhat controversial. TRT is most frequently administered by intramuscular (im) injection of long-acting T esters or transdermally via patch or gel preparations and infrequently via oral administration. TRT produces a number of established benefits in hypogonadal men, including increased muscle mass and strength, decreased fat mass, increased bone mineral density, and improved sexual function, and in some cases those benefits are dose dependent. For example, doses of TRT administered by im injection are typically higher than those administered transdermally, which results in greater musculoskeletal benefits. TRT also produces known risks including development of polycythemia (Hct >50) in 6% of those treated, decrease in HDL, breast tenderness and enlargement, prostate enlargement, increases in serum PSA, and prostate-related events and may cause suppression of the hypothalamic-pituitary-gonadal axis. Importantly, TRT does not increase the risk of prostate cancer. Putative risks include edema and worsening of sleep apnea. Several recent reports have also indicated that TRT may produce cardiovascular (CV) risks, while others report no risk or even benefit. To address the potential CV risks of TRT, we have recently reported via meta-analysis that oral TRT increases CV risk and suggested that the CV risk profile for im TRT may be better than that for oral or transdermal TRT.

Definition of Hypogonadism

The Endocrine Society recommends TRT for men with androgen deficiency, defined as low serum T with consistent symptoms and signs of hypogonadism (5), including decreased sexual function, loss of axillary and pubic hair, low bone mineral density, loss of motivation, mood, or concentration, and loss of muscle strength and work capacity. In older men, hypogonadism is commonly defined as a serum total T concentration of ≤300 ng/dl (i.e., below the normal range) or ≤250 ng/dl (i.e., frank hypogonadism). Both groups may benefit from TRT. Determination of serum T should be based on the average of two blood samples drawn before 10:00 AM. Kaufman and Vermeulen (45) have reviewed the literature and reported that ~20% of men over the age of 60 yr have a serum total T concentration of ≤320 ng/dl. Similarly, we (19) have reported that 24% of men over 60 yr have a serum total T of ≤300 ng/dl. Additionally, hypogonadism is sometimes defined as low free T or low bioavailable T (bioT). In this regard, a small fraction of circulating T is unbound while the bulk is either loosely bound to albumin or very tightly bound to steroid hormone-binding globulin (SHBG). BioT is the sum of the free and albumin-bound T and represents the most physiologically

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important T fraction. BioT is the fraction able to cross cell membranes and bind to androgen receptors (ARs). An increase in SHBG due to aging (85) and traumatic events such as spinal cord injury (11) will result in reduced bioT. Total T assays are available to most clinicians, whereas free T and bioT assays are less available. However, serum bioT may be estimated from serum total T, SHBG, and albumin by using one of several empirical formulas (57, 86). The Endocrine Society recommends that treatment be individualized, including a determination of whether the patient has primary hypogonadism (primary deficit lies within the testes) or secondary hypogonadism (primary deficit lies outside of the testes) (13). When T- enanthate or T-cypionate are injected, one should aim for a serum total T concentration of 400–700 ng/dl at 1 wk after the most recent injection.

**Modes of TRT and Doses Delivered**

T use in the United States increased more than threefold between 2000 and 2011 (36). The most common modes of T administration are patch and gel preparations and im injection of long-acting T esters. Transdermal doses are typically intended to be replacement doses, with the patch being administered at a doses of 5–10 mg T/day and gel administration involving a somewhat greater amount of T due to low absorption (Table 1). Injection of T esters typically delivers higher amounts, 50–400 mg every 2–4 wk. Esters such as T-cypionate or T- enanthate have virtually no aqueous solubility and remain in the muscle depot until muscle esterase activity releases T, which can then enter the circulation. Administered T may be converted to estradiol or dihydrotestosterone (DHT) by the action of 5α-reductase (Fig. 1), both of which exert biological actions at estrogen receptor and ARs, respectively. As such, T may be considered both a hormone (because it binds to ARs) and a prohormone for the synthesis of estradiol and DHT. Interestingly, the mode of TRT administration appears to alter the metabolism of T, as evidenced by our recent meta-analysis (18) reporting that transdermal T (patch and gel) elevated serum DHT 5.46-fold, whereas im-injected T elevates serum DHT only 2.2-fold. This surprising phenomenon occurs despite the fact that transdermal and im TRT elevated serum T to a roughly similar degree and may be explained by relatively high expression of 5α-reductase in skin (40) vs. lower expression in skeletal muscle (93).

**Effect of TRT on Muscle, Bone, and Body Composition**

Age is accompanied by a progressive decline in muscle mass with a decrease in both the number and diameter of muscle fibers, especially type II (fast) fibers (59). Fiber loss with aging is secondary to a loss in motor neurons (81). TRT increases muscle mass and strength by increasing the cross-sectional area of both type I and type II fibers in a dose-dependent manner (70). At low replacement doses, T administration produces muscle protein accretion mainly by preventing protein degradation (30), which is mediated, at least in part, by an increased phosphorylation-induced inactivation of FOXO3a (89). At higher doses, T also stimulates muscle protein synthesis via a number of mechanisms that include proliferation of muscle satellite cells and donation of their nuclei to the myofibril (71), elevation of muscle IGF-I (69), and activation of the Akt/4 mammalian target of rapamycin (mTOR) pathway (90). Binding of T to ARs present in mesenchymal pluripotent cells causes translocation of β-catenin to the nucleus, causing them to differentiate into the myocyte lineage rather than the adipocyte lineage (68). Preservation of lower body muscular strength is an important factor in maintaining independence in older individuals. Resistance training produces substantial strength increases in the elderly. For example, Villanueva et al. (88) found that, in a group of healthy older men, resistance training for 12 wk increased 1-RM leg strength by 100%. By contrast, TRT produces smaller gains but does so independently of exercise. In general, the response to lower doses of TRT administered transdermally may be considered modest, whereas the effects on injected TRT are moderate. Transdermal TRT to older men often increases lean mass; however, most studies do not report increases in strength (20, 48). A 2006 meta-analysis by Ottenbacher et al. (60), assessing 11 RCTs of TRT in older men, reported that injected TRT produced a “moderate” increase in muscle strength, whereas the effects of transdermal and oral TRT were much less. We surveyed 10, mostly more recent, RCTs of TRT in older men lasting 12 wk or more and reporting 1-RM strength as an outcome. None of the four transdermal studies (10, 37, 47, 58) reported a significant increase in 1-RM strength. In contrast, all six of the im injection studies (19, 22, 30, 64, 75, 78) reported significantly increased strength. We administered a moderately high dose of 125 mg/wk T-enanthate im to older hypogonadal men.
men and observed increases of 8–14% in 1-RM strength over a 12-mo period, with most of the improvement occurring during the first 3 mo (19). Storer et al. (75) administered a higher dose of 300 mg T/wk im to young eugonadal men for 5 mo and reported that 1-RM leg press strength was increased 23% and leg press power by 39%. The benefits with even higher doses of im T (300–600 mg/wk) are even more substantial (upward of 20% increase in 1-RM strength in older men over 20 wk), but the number of adverse events observed at these doses precludes their clinical implementation (14). Thus, injected TRT has value for increasing muscle strength in older men, especially because not all patients have the means or ability to exercise. In addition, hypogonadism may reduce both the response to and the motivation for resistance exercise.

Effect of TRT on Bone

Men over the age of 65 yr are subject to an increased incidence of osteoporosis and to increased falls and fractures ultimately contributing to increased mortality (15). In older men, low serum T is associated with osteopenia (49) and increased fracture risk (55). T administration increases bone mineral density (BMD), mainly by suppressing bone resorption (12, 16). TRT may increase BMD in men by a direct AR-mediated effect of T or by an indirect action requiring conversion to estradiol (94). In this regard, low serum estradiol is more strongly associated with osteopenia in older men than is low serum T (49). Interestingly, the indirect effects of T may be more important than the direct effects, as evidenced by the work of Falahati-Nini et al. (28), who observed elevated blood markers of bone resorption following combined administration, to older men, of a GnRH agonist and an aromatase inhibitor to inhibit production of T and estradiol, respectively. Subsequent administration of transdermal estradiol alone suppressed markers of bone resorption, while transdermal T alone did not, whereas full suppression of bone resorption occurred only with combined T plus estradiol administration. Whereas bone protection in response to replacement doses of T requires aromatization, bone protection resulting from high doses of androgen does not appear to.

We have reported that im administration of either T or its nonaromatizable analog trenbolone can completely prevent orchitectomy-induced bone loss in skeletal mature rats (54) and that coadministration of the aromatase inhibitor anastrozole does not inhibit the effects of T and trenbolone (12).

In older men, T increases BMD in regions that have a large component of cancellous bone, such as the lumbar spine and hip (84). These increases are important because they occur at sites where fractures frequently occur in the elderly. We have reported that older men receiving 125 mg T-enanthate/wk im for 1 yr exhibited a 4% increase in lumbar spine BMD and a 2% increase in hip BMD over 12 mo (19). Amory et al. (7) reported continued BMD improvement through 36 mo of im TRT, with lumbar spine BMD increasing 10% and hip BMD increasing 3% compared with baseline. Interestingly, in a 2006 meta-analysis of eight TRT trials in older hypogonadal men, Tracz et al. (84) found that im TRT produced a significant 8% increase in lumbar spine BMD and a nonsignificant 4% in hip BMD, whereas transdermal TTRT produced no increases in BMD. We (92) have also reported that, in rats, T-enanthate prevents orchitectomy-induced loss of bone mechanical strength. The large clinical trials that are needed to assess fracture risk following TRT have not yet been conducted.

Adverse Effects of TRT

Established risks of TRT. Meta-analysis has confirmed three adverse events (AEs) resulting from TRT (21, 29, 34): 1) polycythemia occurring in ~6% of participants, 2) an increased number of prostate-related events, and 3) a small reduction in HDL-cholesterol. Prostate events consist of the combined incidence of elevated PSA, prostate biopsy necessary due to results of digital rectal exam, increased urinary symptoms, and prostate cancer. Meta-analysis by Calof et al. (21) reported no evidence that T administration increases prostate cancer (odds ratio = 1.09 with no trend toward significance), when considered as an independent outcome. More recently, a 15-yr retrospective study of 150,000 men by Kaplan and Hu (43) found that TRT was not associated with prostate cancer. In addition, TRT inhibits endogenous T production and suppresses the hypothalamic-pituitary-gonadal axis. Endogenous T production may not resume or may be diminished following cessation of TRT. The relative effects of im-injected vs. transdermal TRT on prostate enlargement, polycythemia, and suppression of the hypothalamic-pituitary-gonadal axis are unknown.

In addition, some risks depend specifically on the mode of TRT administration (13). Injected TRT may cause pain or bleeding at the site of injection and should not be given to men receiving anticoagulants. Patches may cause skin reactions, and gel may result in transfer of T to a partner.

Less common and putative risks of TRT. T may also cause edema, breast tenderness, and gynecomastia (79), effects that are thought to result from elevation of estradiol subsequent to TRT. Because adipose tissue is the principal site of systemic aromatization (conversion of T to estradiol), TRT is often contraindicated for men with a BMI of 30 or more.

Castrating or worsening of sleep apnea is frequently listed among potential AEs of TRT, based primarily on case reports in the literature. Meta-analysis of 19 clinical trials through 2005 by Calof et al. (21) showed no significant increase in obstructive sleep apnea with TRT; however, the studies were not conducted with polysomnography. The one study using this technique was performed by Hoyos et al. (39), who treated middle-aged men who had severe obstructive sleep apnea with T. T mildly worsened sleep-disordered breathing after 7 wk of treatment, but not after 18 wk.

Possible CV risks of TRT. Recently, four reports have caused concern regarding the potential CV risks of T administration. Basaria et al. (10), in their randomized controlled trial of T gel administration, reported a greater number of CV AEs in treated vs. placebo, resulting in cessation of the trial. However, it should be noted that the trial was not designed to assess prespecified CV surrogate outcomes or clinical end points. Furthermore, the increased CV-related adverse events were considered as a composite end point including events of varying severity and mechanisms. Vigen et al. (87), in a retrospective study of men with low T and angina who also had undergone angiography, reported a higher CV risk in those who subsequently received T than in those who did not. The methodology of that paper was criticized in numerous letters to the editor of JAMA. Another observational study, by Finkle et
al. (31), reported a greater risk of myocardial infarction in men who had received a prescription for T. Finally, Xu et al. (91) published a 2013 meta-analysis of CV adverse events in 27 randomized controlled trials (RCTs) of TRT published through December of 2012 and reported a statistically significant odds ratio (OR) of 1.54, indicating that participants receiving TRT were 54% more likely to develop CV AEs. As a result of those studies, the FDA (4), VA (1), and Endocrine Society (2) have all issued advisories calling for more research on potential TRT-related CV risks. The latest FDA Drug Safety Communication, issued March 2015, will require manufacturers of approved T products to conduct clinical trials assessing risks of heart attack and stroke (3).

We have recently performed the largest meta-analysis of RCTs to date (including 35 RCTs of TRT lasting 12 wk or more, reporting CV adverse events and published through May of 2014) evaluating TRT-related CV risks (18) and using guidelines for analysis of low-frequency events (95). Our main finding was that the form of T (18) administration influenced its CV risk profile (Table 2). Specifically, we reported the following new and significant findings. Because Xu et al. did not use statistical techniques suited to analysis of low-frequency events, and because some recent studies have reported fewer TRT-induced CV AEs, the estimate of risk for CV AEs is revised downward (RR = 1.28, nonsignificant). Oral TRT produces significant risk for CV AEs (RR = 2.20, P = 0.015). Transdermal (patch or gel) TRT produces a nonsignificant directional trend toward CV risk (RR = 1.27), and im TRT produces a nonsignificant directional trend toward CV protection (RR = 0.66). Transdermal and oral TRT cause greater elevation of serum DHT (but not T) compared with injected TRT (Table 1). Serum DHT concentrations following transdermal and oral TRT correspond to the concentrations that have been linked to CV disease and mortality in observational studies (66).

Corona et al. (25) have published a new meta-analysis of 75 studies, assessing the CV risks of TRT, using less stringent inclusion criteria than our study and that of Xu et al. Corona et al. found no risk of all CV events (odds ratio = 1.01) or of serious CV events (odds ratio = 1.07).

Possible CV Benefits of T.

It is well described that low serum T is associated with poor CV outcomes, including coronary artery disease, heart failure, and stroke (82). In particular, Shores et al. (66) have reported that low serum T in men is associated with increased incidence of CV disease and increased all-cause mortality. In addition, several studies directly demonstrate CV benefits of TRT. For example, English et al. (27) have shown that, in men with stable angina, low-dose TRT (5 mg/day by patch) for 12 wk caused a significant 17% increase in time to the development of ischemic EKG changes (i.e., 1-mm ST segment depression) during treadmill exercise testing. Stout et al. (76) have shown that TRT in men with chronic heart failure improves exercise performance (increased VO2max). Toma et al. (83) published a meta-analysis of four studies showing that TRT improved exercise capacity in heart failure patients. TRT-induced CV benefits may derive from the properties of T as a coronary dilator. Chou et al. (24) reported that, in dogs, injection of T into the coronary circulation caused vasodilation and increased coronary blood flow, and we (17) have reported that T-enanthate improves recovery of aortic flow, cardiac work, and left ventricular developed pressure in an orchietomized male rat model of global ischemia/reperfusion.

Role of DHT in Responses to T.

As previously discussed, 5α-reductase enzyme actively converts T to DHT in a local tissue-specific manner, which locally increases its action. As such, it remains biologically and clinically important to evaluate the role of 5α-reductase in mediating the effects of TRT, especially given that DHT binds to ARs with approximately three times the affinity of T (93) and that DHT may mediate several of the AEs resulting from TRT.

<table>
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<tr>
<th>Author, Year</th>
<th>Mode</th>
<th>TRT Events/Subjects</th>
<th>Placebo Events/Subjects</th>
<th>Risk Ratio</th>
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<td>11/234</td>
<td>0/40</td>
<td>4.01</td>
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<td>Gel</td>
<td>14/69</td>
<td>19/62</td>
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<td>Marin, 1993 (53)</td>
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<td>0/25</td>
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<td>4/39</td>
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<td>5/54</td>
<td>1.8</td>
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<td>Nair, 2006 (58)</td>
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<td>7/27</td>
<td>6/31</td>
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Cardiovascular (CV) risk varies by route of T administration. Oral T replacement therapy (TRT) produces significant risk, and gel and patch TRT produce possible risk, whereas im-injected TRT produces possible benefit (18).
Similarly, Bhasin et al. (14a) have shown in young men that dutasteride, a dual inhibitor of 5α-reductase types I and II, also does not inhibit T-induced increases in lean mass and 1-RM strength. In addition, both our laboratory (19) and others (7) have shown that DHT is not required for the T-induced increase in BMD or hematocrit (62). Macakut et al. (51) have shown that dutasteride administration does not decrease BMD in older men. Taken together, these studies suggest that conversion of T to DHT is not required for the effects of TRT on muscle, bone, or hematocrit. In contrast, some evidence suggests that DHT may cause the putative risks resulting from TRT. As discussed above, the higher circulating DHT levels, obtained with transdermal as opposed to injected T, may be responsible for the trend for increased CV risk with transdermal TRT. In observational studies, Shores et al. have shown that shown that high DHT is associated with increased cardiovascular events (66) and increased incident ischemic stroke (65). Interestingly, Zwado et al. (96) have shown that cardiac expression of 5α-reductase is markedly increased in humans with heart failure and in a mouse aortic constriction model of heart failure. In a mouse model, treatment with finasteride attenuated cardiac hypertrophy and improved left ventricular function. Similarly, Rubio-Gayosso et al. (63) reported that T administration protected against cardiac ischemia/reperfusion (I/R) injury in male rats and that inhibition of 5α-reductase reduced I/R injury in both orchectomized and intact rats, whereas DHT administration worsened I/R damage. Taken together, this evidence suggests that conversion of T to DHT may underlie CV AEs resulting from TRT.

Combination Therapy of T Plus a 5α-Reductase Inhibitor

The observation that DHT may mediate several AEs resulting from TRT but is not required for musculoskeletal benefits results in the proposed addition of finasteride or dutasteride to improve the safety of TRT. In our study of one year of im TRT in older men, T alone caused a 40% increase in prostate volume, whereas T plus finasteride produced the same musculoskeletal benefits as T alone but with no prostate enlargement (19). Similarly, Amory et al. (7) reported that T plus finasteride produced less prostate enlargement than did T alone and did not inhibit T-induced increases in BMD, although T-induced increases in muscle strength were not observed in that study. In a trial of 18,882 men, Thompson et al. (81) demonstrated that finasteride reduced the incidence of all prostate cancer by 30% while increasing the incidence of high-grade prostate cancer by 17%. However, that study may have underestimated the benefit of finasteride because finasteride shrinks the prostate, making detection of prostate cancer easier. Taken together, these findings indicate that coadministration of finasteride with T may increase its safety without sacrificing benefits.

Summary and Recommendations

For treatment of older hypogonadal men, there are advantages to administering TRT by injection rather than transdermally or orally. First, the musculoskeletal benefits are greater, due to the higher doses administered im vs. transdermally. Second, although the doses are higher, im TRT may not pose the same CV risks that result from transdermal TRT. A possible explanation for the latter phenomenon is that transdermal T causes greater elevation of serum DHT, due to significant expression of 5α-reductase in skin, but not in muscle. Meta-analysis of existing randomized placebo-controlled trials is, to date, insufficient to definitively assess the CV effects of TRT. However, existing data exhibit trends indicating 1) that TRT may not accelerate underlying early-stage prostate cancer, 2) that transdermal TRT may cause CV risk, and 3) that im-injected TRT may cause CV benefit. In addition, several studies demonstrate that in older hypogonadal men the combination of im T plus finasteride produces musculoskeletal benefits without the prostate enlargement that results from T alone (7, 19). Finasteride produces relatively few adverse events and may also produce cardiovascular benefits and/or reduce prostate cancer by reducing DHT. Although further research is needed, it appears at this time that im-injected T plus finasteride may be both the safest and the most effective treatment for older hypogonadal men.

REFERENCES

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