Body Composition changes after Testosterone Replacement Therapy following Spinal Cord Injury and Aging. A Mini Review

Abstract

CONTEXT: Hypogonadism is a male clinical condition in which the body does not produce enough testosterone. Testosterone plays a key role in maintaining body composition, bone mineral density, sexual function, mood, erythropoiesis, cognition and quality of life. Hypogonadism can occur due to several underlying pathologies during aging and in men with physical disabilities, such as spinal cord injury (SCI). This condition is often under diagnosed and as a result, symptoms undertreated.

METHODS: In this mini-review, we propose that testosterone replacement therapy (TRT) might be a viable strategy to improve lean body mass (LBM) and fat mass (FM) in men with SCI.

EVIDENCE SYNTHESIS: Supplementing the limited data from SCI cohorts with consistent findings from studies in non-disabled aging men, we present evidence that, relative to placebo, transdermal TRT can increase LBM and reduce FM over 3 – 36 months. The impact of TRT on bone mineral density and metabolism is also discussed, with particular relevance for persons with SCI. Moreover, the risks of TRT remain controversial and pertinent safety considerations related to transdermal administration are outlined.

CONCLUSION: Further research is necessary to help develop clinical guidelines for the specific dose and duration of TRT in persons with SCI. Therefore, we call for more high-quality randomized controlled trials to examine the efficacy and safety of TRT in this population, who experience an increased risk of cardiometabolic diseases as a result of deleterious body composition changes after injury.

Keywords: Testosterone replacement therapy, body composition, lean body mass, fat mass, spinal cord injury

Introduction:

Sarcopenia refers to the loss of skeletal muscle mass with age and plays an important role in the etiology of functional and mobility impairments in older adults (1). It has been suggested that persons with spinal cord injury (SCI) represent a model of accelerated sarcopenia or premature aging (2). Following SCI, as a result of paralysis and disuse, considerable atrophy of lean mass occurs below the level of injury within the first 6 – 12 months (3, 4). Accelerated loss of lean mass has also been reported above the level of injury (5), which is likely a factor of overall reduced physical activity observed in this population (6). Besides the loss of lean mass, the quality of skeletal muscle that remains below the level of the injury also deteriorates. In persons with SCI, adipose tissue has been shown to accumulate within and between muscle groups (7, 8) and the accumulation of intramuscular fat (IMF) has previously been linked with impaired glucose tolerance (9, 10). While the specific mechanisms regarding the impact of IMF on skeletal muscle metabolism remains to be elucidated, studies have suggested IMF impairs blood flow and releases pro-inflammatory mediators resulting in local inflammation (11, 12). Such changes within the skeletal muscle of persons with SCI have profound implications in the progression of certain chronic diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Collectively, the loss of lean body mass (LBM) is responsible for the decreased resting metabolic rate (RMR) reported in persons with SCI (13). Such reductions in energy expenditure may contribute to an energy surplus, which if sustained, will eventually lead to increased fat mass (FM) accumulation. Consequently, best available estimates suggest that up to two thirds of the

SCI population are overweight or obese (14). Besides an increased prevalence of obesity, the location of adipose tissue accumulation is also different in persons with SCI. Edwards *et al*, (15) found that persons with SCI had 58% more visceral adipose tissue (VAT; quantified by computed tomography) than waist circumference-matched able-bodied controls. The accumulation of VAT is of particular importance as it has been linked with impaired carbohydrate and lipid metabolism in persons with SCI (16) and exhibits a more pro-inflammatory profile (17). Even modest subclinical elevations in inflammatory cytokines (interleukin-6) and acute phase proteins (C-reactive protein) may increase the risk of developing cardiovascular disease (18, 19). Epidemiological evidence suggests that individuals characterized as low muscle/high fat mass have an elevated all-cause mortality risk compared to other body composition subtypes (20). To mitigate such mortality and cardiometabolic disease risks, it is important to identify appropriate strategies that could facilitate the restoration of favorable body composition, particularly in vulnerable populations such as persons with SCI.

Testosterone replacement therapy (TRT) has been identified as an effective strategy in restoring LBM and decreasing FM in different clinical population. Testosterone (T) is an important anabolic hormone that influences muscle, bone, adipose tissue, hematopoiesis, sexual function, mood, quality of life and cardiovascular disease risk factors (21). The majority of testosterone production takes place in the Leydig cells of the testes. Each day males produce 3 – 10 mg of endogenous T; approximately 60-70% of which circulates tightly bound to sex hormone binding globulins (SHBG), loosely bound to albumin (30-40%), or free (0.5-2%) (22). The anabolic effects of androgens on skeletal muscle have been a source of controversy for decades.

Increasing serum T can increase LBM via hypertrophy of both type I and II skeletal muscle fibers (23). T acts upon androgen receptors; activating transcription factors in the nucleus of the cell thereby increasing protein synthesis (24), and promoting differentiation of pluripotent mesenchymal cells into the myogenic lineage and inhibiting differentiation into the adipogenic lineage (25). Besides the indirect effect of TRT modulating FM through increased energy expenditure caused by skeletal muscle hypertrophy, TRT may also have a direct effect on adipose tissue metabolism. De Pergola *et al*, (26) demonstrated that T promotes lipolysis and reduces fatty acid synthesis, with these effects being more evident in VAT.

In older men, the gradual decrease of serum T concentrations, known as late onset hypogonadism (levels of total serum T; < 6.9 nmol/L or 200 ng/dl), occurs at the same time in life as sarcopenia and osteoporosis (27-29). About 60% of men over the age of 65 years have low serum T levels (< 10.4 nmol/L or 300 ng/dl) (30). Such hormonal changes may contribute to muscle loss and increased FM with aging (31-33). Similarly, previous research indicates between 46 – 60% of men with SCI have low serum T levels (34, 35). Body composition changes with aging are accelerated in persons with SCI; the etiology of which could be due to the combination of low serum T and reduced physical activity [which also declines with aging (36)]. T levels are also inversely related to time since injury (34, 37) and persons with motor complete SCI have a greater prevalence of low serum T than persons with motor-incomplete SCI (38). Interestingly, reduced physical activity levels have been associated with longer time since injury (39) and motor-complete injuries (6). Although cause and effect may be difficult to define, the combination of reduced physical activity, low serum T, and aging in persons with complete SCI

may further exacerbate adverse body composition changes and associated cardiometabolic parameters.

Current therapeutic methods for TRT are oral formulations, intramuscular injections or transdermal delivery. Oral T has a high first-pass liver metabolism and certain oral formulations therefore have significant liver toxicity (40), a notable limitation of this delivery method. Although intramuscular injections produce a high level of serum T initially, short-acting T esters (i.e. Enanthate, Cypionate and Proprionate) decline rapidly towards the end of the injection cycle. Whereas, injectable T-undecanoate (i.e. Aveed) has been shown to elevate serum T for ≥ 10 weeks following injection (41). However, this mini-review aims to primarily focus on transdermal (i.e. patch or gel) TRT administration for the following reasons; (i) elevated patient compliance compared to other methods of delivery and convenience of administration (42), (ii) effective at sustaining plasma T levels over 24 hours in a way that mimics the human body's natural T production cycle (43) and, (iii) high bioavailability. The aim of this review is to discuss the impact of transdermal TRT on body composition changes, with relevance to persons with SCI. Other potential health benefits derived from TRT; preserved bone mineral density, maintenance of basal metabolic rate, and improved metabolic regulation will also be discussed. Lastly, we aim to discuss the safety of TRT and considerations for its application in persons with SCI.

Methods

Data sources and searches

To examine the effects of transdermal TRT on body composition parameters, a scoping review of the literature was performed using online databases [MEDLINE (PubMed) and Google Scholar] to identify relevant articles. Reference lists from identified studies were also scrutinized to retrieve other appropriate papers.

Study inclusion criteria

Studies included in this scoping review were required to meet the following criteria: (i) study participants [males with SCI and able-bodied elderly men (either hypogonadal or with low serum T concentrations], (ii) sample size ($n \geq 20$ in T treatment group) to ensure a degree of statistical confidence in the findings, (iii) transdermal delivery of T (i.e. patch or gel) and, (iv) LBM or FM measured by dual-energy X-ray absorptiometry (DXA).

Data synthesis and analysis

The second author extracted descriptive and outcome data from the included studies, which were then fact-checked by the primary author. This scoping review identified 14 and 13 studies that reported the effect of TRT on LBM and FM, respectively. These studies are organized via TRT dosage with: duration of therapy, vehicle of delivery (i.e. gel or patch), participant characteristics and comparative placebo responses (LBM; Table 1, FM: Table 2). The duration of treatment and dosage ranged from 3 – 36 months and 2.5 – 10 mg/day, respectively. Mean ± SD changes (Δ) in

LBM and FM were extracted from the identified studies. These data were pooled to provide a qualitative interpretation of previous findings. Weighted means were calculated in Microsoft Excel to account for differences in sample size between studies using the following formula: $\sum n*\Delta\bar{x}/\sum n$, where $\sum$ = the sum of, n = number of participants in each study and, $\Delta\bar{x}$ = mean change in outcome of each study. Δ in LBM and FM were separated via dose ($\leq$ 5 mg or > 5 mg) and compared to placebo responses, Fig. 1A and 3A, respectively. To better understand the impact of therapy duration and treatment delivery vehicle on Δ in LBM and FM, only studies that used doses $\leq$ 7.5 mg/day were pooled for analysis (Fig. 2A & C; Fig. 4A & C). This is because higher doses (10 mg/day) were only administered for a shorter period of time (3 – 6 months) and predominantly in the gel format (Table 1), which would have impacted the analysis. Scatterplots are also displayed with polynomial lines of best fit to better display the fluctuations in individual study data for the impact of TRT dosage and duration of therapy.

Impact of transdermal testosterone replacement therapy on body composition

While transdermal TRT may offer a logical and effective strategy to counteract deleterious body composition changes post SCI, ambiguity currently remains about the correct dose and duration of treatment. To the best of our knowledge, there is only one small-scale clinical trial that has assessed the safety and efficacy of TRT in men with SCI (44). In light of this we also drew upon randomized controlled trials in able-bodied elderly men (either hypogonadal or with low serum T concentrations) to help inform considerations pertaining to the most appropriate dose and duration of TRT to increase LBM and reduce FM in persons with SCI. The baseline serum T inclusion criterion used in the studies analyzed in the body composition section of this mini-

review (Tables 1 & 2, range < 7.3 – 15.0 nmol/L) is comparable to values (< 11.3 nmol/L) shown in more than 43% of persons with SCI (38). Therefore, in the absence of SCI data, elderly men represent a similar population of interest. Previous reports also suggest that persons with SCI experience a state of pre-mature aging (2). Recent data suggests testicular function was normal in men with SCI compared to able-bodied controls, confirming the absence of primary testicular dysfunction in this population (45). Therefore, hypogonadism in men with SCI is secondary to pituitary-hypothalamic dysfunction. Secondary hypogonadism is associated with obesity (46). However, the etiology of low T in aging men represents a mixture of both primary and secondary hypogonadism components (47). Nevertheless, studying the effects of transdermal applications of TRT in elderly men is likely to reflect clinically on men with SCI.

[PLEASE INSERT TABLE 1 ABOUT HERE]

Hildreth et al, (48)

McNicholas et al, (40)

Wang et al, (49)

Steidle et al, (50)

Frederiksen et al, (51)

Magnussen et al, (52)

Srinivas-Shankar et al, (53)

Behre et al, (54)

Kenny et al, (55)

Bauman et al, (44)

Snyder et al, (56)

Wang et al, (57)

Storer et al, (58)

Wang et al, (49)

McNicholas et al, (40)

Steidle et al, (50)

Bhasin et al, (59)

Lean body mass

Twelve months of TRT (by testosterone patch) restored serum total T to physiological levels in persons with SCI and resulted in concurrent improvements in total LBM (3.5 kg) (44). This considerable increase in LBM was higher than values reported in elderly hypogonadal men. An explanation for this is that persons with SCI have a greater potential to increase LBM due to the extreme loss of LBM post SCI. However all TRT studies, irrespective of dose, improved LBM

(range, 0.7 – 2.7 kg). Participants in the majority of these studies were instructed to continue with their normal lifestyle behaviors rather than perform a concurrent targeted exercise program. Larger doses resulted in greater increases in LBM, with the polynomial line of best fit suggesting the best dose is ~ 8 mg/day (Fig. 1B). However, it is difficult to draw conclusions regarding the most appropriate dose, as numerous studies titrated the dose of TRT over time to maintain measured serum T within a safe physiological range. Therefore, without access to individual data it is not possible to conduct a comprehensive statistical analysis.

[PLEASE INSERT FIGURE 1 ABOUT HERE]

The weighted means (± SD) show a small increase (0.5 kg) between TRT for ≥12 months as opposed to 3 months. Relatively few studies have administered transdermal TRT for more than a year. One study showed that changes plateaued after 12 months (49). Furthermore, Storer *et al*, (58) reported modest changes in LBM (0.7 kg) after 36 months of treatment with a relatively high dose of T (7.5 mg/day). With regards to treatment delivery vehicle, there were no differences between the weighted means of the two methods (Gel: 1.35 ± 1.16 kg, Patch: 1.25 ± 1.12 kg) (Fig. 2C).

[PLEASE INSERT FIGURE 2 ABOUT HERE]

[PLEASE INSERT TABLE 2 ABOUT HERE]

Fat mass

In hypogonadal elderly men transdermal TRT treatment reduced FM by a range of 0.1 – 3.0 kg (Table 2). In individuals with SCI, TRT treatment had no beneficial impact on FM (0.3 kg) (44). However, relative to the control group, participants on average gained 1.2 kg less FM over the course of 12 months. Analysis of pooled data suggests larger doses of T (> 5mg) resulted in greater reductions in FM (Fig. 3A). Interestingly, data from within studies, showed a minimal impact of increasing dose (5 mg vs. 10 mg); -0.1 ± 1.8 vs. -0.2 ± 1.5 kg (40), -0.90 ± 2.73 vs. -1.05 ± 1.94 kg (49), -0.8 ± 2.4 vs. -0.8 ± 2.0 kg (50). Fig. 3B suggests the weighted mean data could be skewed by one study, where a 6 mg/day dose of TRT over a longer period of time (36 months) significantly reduced (-3.0 ± 3.7 kg) FM (56). Considering these observations, it remains unclear whether manipulating dose *per se* provides additional benefits for reducing FM.

[PLEASE INSERT FIGURE 3 ABOUT HERE]

The duration of TRT affected the reduction of FM (Fig. 4), with longer durations demonstrating greater FM losses. However, within one study, mean changes in FM were greater at 18 than 30 months, -1.57 ± 4.21 kg and -1.30 ± 5.66 kg, respectively (57). Interestingly the method of delivery appeared to have a slight impact on changes in FM (Gel: -1.00 ± 1.00 kg vs. Patch: -0.64 ± 0.80 kg) (Fig. 4C). In one study superior reductions (-0.89 kg) in FM with gel was reported, compared to patch (49). One possible explanation for this difference could be that skin

irritation occurred in 66.0% of the participants using the patch compared to 5.5% of participants using the gel. This consequently altered compliance (65% vs. 93%) and the lower serum T levels in participants using the patch may explain the diminished reduction in FM (49).

[PLEASE INSERT FIGURE 4 ABOUT HERE]

The role of testosterone replacement therapy on bone mineral density and metabolism

In addition to its impact on LBM and FM, TRT has also been shown to improve bone mass and bone mineral density (BMD) (60-63). However, the majority of studies looking at the impact of TRT on BMD used intramuscular injections, which is outside the scope of this mini-review. A recent study of almost 300 able-bodied older men with low serum T levels demonstrated that T gel increased bone density measured by DXA and, volumetric bone density and bone strength by finite element analysis (64). While these findings demonstrate the efficacy of transdermal TRT, a recent review that reported that transdermal TRT had very little effect on BMD (65) and findings from a meta-analysis suggested that TRT administered via intramuscular injections was more effective at improving BMD than transdermal TRT (66). One explanation for this could be that changes in BMD are dose-dependent. In rats, Yarrow *et al*, (67) demonstrated that T dose dependently prevented hindlimb bone loss 21 days post SCI, with high-dose of T fully preserving cancellous bone structural characteristics and volumetric BMD. Clinical practice guidelines recommend a dose of 75 – 100 mg/week for intramuscular TRT and 30 – 70 mg/week for transdermal (patch) TRT (68, 69). Consequently, larger doses are routinely administered via the intramuscular route compared to transdermal application. A clinical case series of two

patients with SCI did not demonstrate any changes in bone cross-sectional area with 16 months of transdermal TRT (70). Currently, no studies of TRT in any population have been big enough to demonstrate reduced fracture risk.

Findings from a 24-month study demonstrated the return and maintenance of T levels within the normal range for young adults in men with late-onset hypogonadism resulted in a remarkable reduction of cardiovascular disease risk factors, which cluster together in patients with metabolic syndrome (71). The metabolic syndrome is a constellation of component risks which occur at a heightened frequency in persons with SCI: increased (abdominal) obesity, hypertriglyceridemia, hyperglycemia and reduced HDL-cholesterol (72-74). In aging hypogonadal men, transdermal TRT resulted in increased lipid oxidation, whereas no effect was apparent on whole-body insulin sensitivity (51). In one study transdermal TRT in aging men with T2DM did not change glycemic control, peripheral insulin sensitivity or endogenous glucose production (52). However, T2DM was pharmaceutically controlled (metformin) in these participants, which would have minimized the opportunity to see an effect with TRT on these outcomes. Results from a recent meta-analysis of observational studies (75) suggested TRTs positive effect on body composition is what drives observed improvements in glucose and lipid metabolism.

In persons with SCI, Bauman *et al*, (76) observed a significant increase in resting energy expenditure (pre: 1283 ± 246 kcal/day, 12 months: 1410 ± 250 kcal/day) via favorable changes in LBM with TRT. This increase (**Δ** 127 kcal/day) has profound implications for persons with

SCI. Six months after discontinuing TRT, improvements in LBM and RMR (1393 ± 220) kcal/day persisted along with elevated high-density lipoprotein cholesterol (HDL-C). However, these findings need to be replicated in a larger placebo-controlled, double blind trial in men with SCI. In persons with SCI, independent associations between low T and non-alcoholic fatty liver disease (NAFLD) have been reported; with a 1% and 3% increased risk of NAFLD for each decrement of total T (1 ng/dL) and free T (1 pg/mL), respectively (77). Patients in this sample diagnosed with NAFLD exhibited significantly higher circulating triglyceride concentrations and homeostatic model assessment of insulin resistance (which reflects hepatic insulin resistance). Such findings are in keeping with associations between NAFLD and metabolic syndrome components commonly observed in the able-bodied individuals (78). Steatosis, the first stage of NAFLD, is the abnormal retention of lipids and represents the liver phenotype of metabolic syndrome. These findings therefore present another plausible mechanism whereby TRT could improve specific metabolic syndrome risk factors, although such conclusions remain to be confirmed by longitudinal TRT trials.

Safety of testosterone replacement therapy

Despite positive effects of TRT on body composition characteristics, BMD and metabolism; all trials were underpowered to evaluate safety. Early evidence for the potential of adverse cardiovascular risk with TRT was provided by the Testosterone in Older Men with Mobility Limitations (TOM) trial (79), which terminated prematurely. While data from participants with mobility impairments might seem relevant to persons with SCI, participants were considerably older (mean age ± SD; 74 ± 6 years) and the transdermal dose administered was large (10

mg/day). Since this study, the use of TRT has been further scrutinized, with conflicting messages regarding its safety. In 2014, a US Food and Drug Administration (FDA) advisory committee noted insufficient evidence existed to confirm a link between T and cardiovascular events (80). Yet a year later the same regulatory authority issued a Drug Safety Communication stating that TRT should only be prescribed to men with low T caused by certain medical conditions due to the potentially heightened risk/benefit ratio (81). A subsequent review has since challenged this, stating that TRT is effective and safe when restoring T to within physiological levels in men with testosterone deficiency, irrespective of its etiology (82). Nevertheless, the FDA has insisted on a labeling change to inform patients about a possible increased risk of cardiovascular risk (81).

From a research perspective, clinical trial data and meta-analyses suggest decreased (83-85), no effect (80, 86, 87) and increased (88-90) risk of cardiovascular events with TRT. However, the most recent meta-analysis (80) suggested current evidence for cardiovascular risk is of very low quality due to the high risk of bias, imprecision, and inconsistency between studies. Numerous studies have also identified age and pre-existing heart disease as factors that increase the risk of cardiovascular events with TRT (90, 91). With regards to vehicle of administration, studies have linked an increase in cardiovascular events with oral compared to transdermal TRT (87, 92). Furthermore, a recent study of a large administrative database revealed that men receiving testosterone injections had greater cardiovascular risks than those receiving topical testosterone preparations (93). However, this evidence contrasts with findings from two meta-analyses, which suggest a reduction (94) and no difference (92) in the risk of cardiovascular events with intramuscular injections vs. transdermal TRT. Potential mechanisms for an increased risk of

cardiovascular events could be down to increased hemoglobin and hematocrit levels with TRT (49, 95). Although a retrospective study demonstrated no link between deep vein thrombosis and pulmonary embolism with TRT (96), a recent study from Australia reported that soon after starting TRT, the incidence of deep venous thrombosis increased but later returned to close to background levels (97). Furthermore, hemoglobin and hematocrit values have been reported to be on the lower end of the normal range in persons with SCI, 1.39 g/L and 40%, respectively (44). TRT has been shown to significantly increase hemoglobin in men > 65 years with anemia (98), which may have beneficial implications for symptoms of fatigue and wellbeing. Regular health screening is advised to test the stability of hematocrit and hemoglobin over time and check whether values these remain within acceptable limits (hematocrit: < 50%).

Another safety concern raised regarding TRT is its potential link with prostate cancer. A 2005 meta-analysis of pooled studies (99) suggested significantly higher risks of prostate events, specifically elevated prostate-specific antigen (PSA) concentrations in men with TRT than the placebo group. It has been suggested that while TRT may increase PSA, it often remains within clinically acceptable limits (100) and has not been shown to increase the risk of prostrate cancer (101, 102). Nevertheless, PSA concentrations should be regularly checked during TRT treatment and remain under 1.4 ng/ml (67). Logically the use of TRT is contraindicated for men with prostate cancer or significant benign prostate hyperplasia. Benign and malignant hepatic tumors, intrahepatic cholestasis, hepatotoxicity, and liver failure have also been reported with TRT (21, 103). However, it appears these unfavorable hepatic effects appear to be associated with oral forms of T(21). One of the major considerations for using patches as the vehicle of delivery for

transdermal T is that they can cause significant skin irritation with prolonged use (42, 43). Therefore, in men with SCI if patches are worn below the level of injury, we advise regular skin checks from caregivers as a loss of sensation in the patient might prevent the early detection of soreness or skin irritation.

Relevance for persons with spinal cord injury

Hypogonadism in men with SCI has been associated with elevated QT interval variability index (QTVI) (104) and appears to adversely affect temporal ventricular repolarization (VR) (105). Elevated QTVI and changes in the synergy of VR can contribute to an increase risk of fatal arrhythmias (106, 107). Persons with SCI less than 45 years old have approximately a 4-fold higher rate of cardiac mortality compared to the general population (108). Although the etiology of increased cardiovascular related mortality is multifactorial in persons with SCI (109-111), low serum T may be a contributing factor. Indeed, raising T levels into the normal physiological range with transdermal TRT improved QTVI (104) and normalized ventricular repolarization dynamics (105), thereby reducing the risk of arrhythmias in men with SCI. However, Budoff *et al,* (112) recently demonstrated that transdermal TRT in men with hypogonadism, significantly increased coronary artery noncalcified plaque volume (measured by coronary computed tomographic angiography). An increase in noncalcified and total plaque volumes is of clinical concern because any impairment of the vascular lumen can be considered deleterious (113).

In contrast to studies in elderly men, it is interesting that no measurable effect was detected on FM in persons with SCI (44). This may be due to a reduction in whole-body energy expenditure, caused by paralysis of lower extremity skeletal muscles and mobility being restricted primarily to wheelchair use. Bauman *et al*, (44) speculated that reductions in FM with TRT in persons with SCI might not occur without a parallel exercise and/or dietary intervention. Although not a significant increase (P = 0.11), a 1.3 kg increase in leg LBM was observed following 12 months of TRT in persons with SCI without a concurrent exercise intervention or innervation of paralyzed muscles. In individuals with SCI it is plausible that TRT effects on LBM in the legs might be further enhanced with neuromuscular electrical stimulation-induced resistance training (NMES-RT), a hypothesis that is currently being tested in the Testosterone and Evoked Resistance Exercise after Spinal Cord Injury (TEREX-SCI) study (114). Improvement in whole body LMB in persons with SCI equated to 3.5 kg, which is not too dissimilar from the rate of LBM lost every five years (4 kg) post injury in persons with SCI (115). Skeletal muscle hypertrophy is a desirable outcome in persons with SCI as skeletal muscle accounts for ~ 70% of glucose disposal (116). Even increasing LBM by 1.5 kg, which is akin to those reported in elderly men with TRT (Fig. 1), was associated with improvements in glucose and insulin concentrations at the end of an oral glucose tolerance test (117). Therefore, increases in LBM similar to those reported in this review could have dramatic clinical implications for metabolic regulation in persons with SCI who experience a heightened risk of developing insulin resistance and T2DM (118, 119).

Conclusion

This mini-review presents evidence for TRT as a potential strategy to aid in the management of body composition changes and to improve metabolism in persons with SCI. In the absence of adequate studies conducted in patients with SCI, findings from research conducted using aging hypogonadal or low serum T men were incorporated to inform the effectiveness of transdermal TRT for improving body composition parameters. Persons with SCI and aging men exhibit similar reduced serum T levels and elements of restricted mobility. Relative to placebo responses, higher doses of T resulted in larger increases in LBM. Importantly, these findings can be supported by plausible physiological mechanisms. The benefits of TRT must be weighed against potential risks, and continuous vigilance is required from researchers and clinicians when administering T. The clinical relevance of a 0.74 kg increase in LBM and 0.33 kg decrease in FM has with higher (> 5mg/day) vs. lower (≤ 5 mg/day) doses of TRT remains to be established, along with whether these improvements are worth the potential risks associated with higher doses. Future research is necessary to develop clinical guidelines pertaining to the specific dose and duration of TRT treatment and its safety in persons with SCI.

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Figure Legends

Fig 1. Weighted mean ± SD changes (**Δ)** in LBM with different TRT dosages **(A)**. Data was presented as PLACEBO (n = 730), ≤ 5 mg/day (n = 793) and > 5 mg/day (n = 632). Panel **B** is a scatterplot of dose (x-axis) vs. **Δ** in LBM (y-axis) with a polynomial line of best fit. Fig. 1 was devised using data from all studies included in Table 1. Weighted means were calculated for studies where dose of TRT was titrated, providing sufficient information was given within the study to permit this (44, 51, 52).

Fig 2. Weighted mean ± SD changes (**Δ)** in LBM with different TRT durations **(A)** and vehicle of delivery **(C)**. Data was presented as 3 months (n = 506), 6 months (n = 496) and ≥ 12 months (n = 406) and Gel (n = 938) and Patch (n = 307) for panel A and C, respectively. Panel **B** is a scatterplot of duration (x-axis) vs. **Δ** in LBM (y-axis) with a polynomial line of best fit. Fig. 2 was devised using data from studies with TRT dosages ≤ 7.5 mg/day as shorter studies tended to user higher doses, which would have confounded the analyses.

Fig. 3. Weighted mean ± SD changes (**Δ)** in FM with different TRT dosage **(A)**. Data was presented as PLACEBO (n = 608), ≤ 5 mg/day (n = 915) and > 5 mg/day (n = 526). Panel **B** is a scatterplot of dose (x-axis) vs. **Δ** in FM (y-axis) with a polynomial line of best fit. Fig. 3 was devised using data from all studies included in Table 2. Weighted means were calculated for studies where dose of TRT was titrated, providing sufficient information was given within the study to permit this (44, 51, 52).

Fig 4. Weighted mean ± SD changes (**Δ)** in FM with different TRT durations **(A)** and vehicle of delivery **(C)**. Data was presented as 3 months (n = 506), 6 months (n = 496) and ≥ 12 months (n = 300) and Gel (n = 832) and Patch (n = 307) for panel A and C, respectively. Panel **B** is a scatterplot of duration (x-axis) vs. **Δ** in FM (y-axis) with a polynomial line of best fit. Fig. 4 was devised using data from studies with TRT dosages ≤ 7.5 mg/day as shorter studies tended to use higher doses, which would have confounded the analyses.