

# Low-dose testosterone replacement therapy and electrically evoked resistance training enhance muscle quality after spinal cord injury

Raymond E. Lai, Ashraf S. Gorgey\*

The current perspective is aimed to highlight the significance of adding low-dose testosterone replacement therapy (TRT) to electrically evoked resistance training (RT). Evoked RT is primarily designed to load the paralyzed lower extremity muscles to elicit muscle hypertrophy in persons with spinal cord injury (SCI) (Ryan et al., 2013; Gorgey et al., 2019). The rationale was based on previous work that indicated that high-dose TRT is likely to enhance muscle quality, increase muscle cross-sectional area, and attenuate trabecular bone loss in a rodent model of SCI (Yarrow et al., 2014). However, high-dose TRT may lead to negative medical consequences including the increased risk for blood clots and enlargement of the prostate gland in humans with SCI (Yarrow et al., 2014). As such a complementary approach of adding low-dose TRT to loading exercise may reciprocate the negative effects of SCI on body composition and cardio-metabolic profiles.

It is well established that 40–60% of men with motor complete SCI (i.e. complete loss in any volitional control below the level of injury accompanied with impaired sensation) have lower circulation levels of basal testosterone (Bauman et al., 2014; Nightingale et al., 2018). Overall, men with low serum levels of testosterone were associated with more unfavorable body composition and cardio-metabolic health outcome measures after SCI (Abilmona et al., 2019). Compared to the normal range serum testosterone group, lower range serum testosterone was shown to have a 9.6% greater total fat mass and 72% greater visceral adipose tissue area (Abilmona et al., 2019). Additionally, %fat-free mass is negatively associated with increase in visceral adiposity and total body fat mass in persons with chronic SCI (Abilmona et al., 2019); providing credence on the significance of restoring lean mass in this population. Previous work revealed the promising utility of TRT (Bauman et al., 2011; Nightingale et al., 2018). Bauman et al. (2011) demonstrated that in hypogonadal men with SCI, 12 months of 5–10 mg daily TRT compared to placebo lead to an increase in lean mass and resting energy expenditure. Furthermore, in a recent systematic review, TRT has been shown to be effective in non-disabled aging men compared to placebo with evidence that demonstrates increases in total body lean body mass by more than 1 kg and reduced fat mass over 3–36

months (Nightingale et al., 2018). Despite the promising findings from investigators exploring the interventions individually, the combined effects of TRT and exercise have not been clearly studied, particularly in the SCI population.

This perspective will summarize the findings and future implications of a recent investigation performed by our group that explores the potential clinical applications of combining electrically evoked neuromuscular electrical stimulation-resistance training (NMES-RT) exercise with low-dose TRT for improving several clinical outcomes of individuals with chronic SCI (Gorgey et al., 2019). Low dose of 2–6 mg/d was prescribed because it was applied in healthy participants with age range of 18–50 years old. A higher dose greater than 5 mg/day may be recommended to reciprocate the loss in lean mass in hypogonadal men with SCI (Bauman et al., 2011; Nightingale et al., 2018).

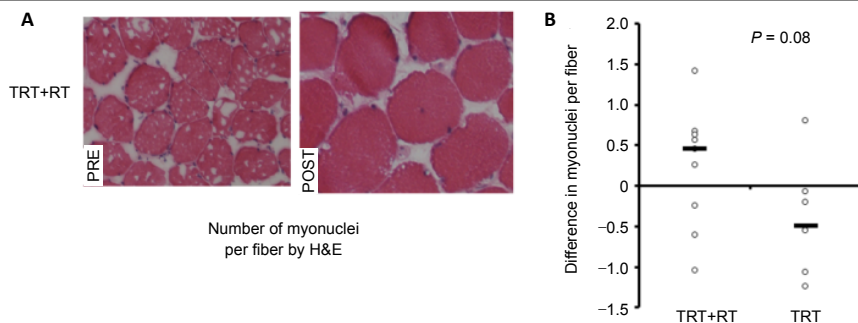
NMES-RT demonstrated robust skeletal muscle hypertrophy of the knee extensor muscle group and reduction of intramuscular fat following 16 weeks of twice-weekly in persons with motor complete SCI (Gorgey et al., 2019). The results attracted attention from the scientific community about the possibility of driving improvement in cardio-metabolic profile in persons with chronic SCI. However, it was not necessarily clear whether the outcomes can be maximized by addition of TRT. It is possible that TRT may provide favorable homeostasis for NMES-RT to possibly increase protein synthesis and attenuate protein degradation after SCI.

A randomized controlled clinical trial was conducted to investigate the effects of daily low-dose TRT (2–6 mg per day) combined with twice-weekly NMES-RT compared to TRT-only for 16 weeks in men with motor complete SCI (Gorgey et al., 2019). The TRT + RT group displayed 30–34% increases in muscle cross sectional area (CSA) of the knee extensors with no significant change observed in the TRT group. Basal metabolic rate increased 14–17% following TRT + RT. Both groups displayed modest reduction in visceral adipose tissue area and drew modest gains in glucose tolerance with glucose effectiveness improving by 28.5–31.5% (Gorgey et al., 2019). Application of TRT+ RT extended to benefit untrained muscle groups and revealed that hip extensors had the highest likelihood to hypertrophy with limited effects on the trunk muscles and no

effect observed in lower leg muscles (Gorgey et al., 2020b). This novel finding suggests that this intervention could be applied to wheelchair and/or bed bound individuals in order to reduce the prevalence and severity of pressure injuries or ulcers. Pressure injuries which are attributed to several factors including friction, shear, and moisture, have a higher likelihood of developing in chronically immobilized individuals impacting up to 85% of the SCI population (Chen et al., 2020). We further derived comparisons between those assigned in the TRT + RT group for 16 weeks (Gorgey et al., 2019) against those in the NMES-RT-only group for 12 weeks in another study (unpublished data). Both groups displayed remarkable muscle hypertrophy of knee extensors that exceeded 30%; however, the findings clearly suggested that those who conducted TRT + RT have greater muscle hypertrophy than those who underwent 12 weeks of NMES-RT-only.

To further elucidate the mechanisms behind muscle hypertrophy following TRT + RT compared to TRT-only, we examined the signaling properties and protein expression in muscle biopsy samples in men with SCI (Gorgey et al., 2020a). The findings suggested increased phosphorylated AKT expression, a marker of muscle hypertrophy following TRT + RT. Furthermore, TRT + RT resulted in a trend towards increasing the number of stained myonuclei compared to TRT only (**Figure 1**). The increase in myonuclei number may provide future insights on the mechanisms of muscle hypertrophy following training in persons with SCI. Additionally, there was a significant increase in GLUT4 expression, a marker for glucose translocation, highlighting the important role of exercise on insulin independent improvement in glucose disposal considering the prevalence of insulin resistance and type 2 diabetes in this population (Gorgey et al., 2020a). The findings suggest that exercise and TRT are associated with improvements in insulin sensitivity and carbohydrate metabolism, which is vitally important considering that 80% of insulin-dependent glucose uptake occurs in skeletal muscle.

Following SCI, the maintenance and function of the mitochondria is reduced by up to 50–60% (Erickson et al., 2013). TRT + RT demonstrated significant elevation in mitochondrial activity of succinate dehydrogenase, a marker for complex II, as well as of citrate synthase, a validated marker for mitochondrial density. We further investigated the effects of TRT-RT on muscle quality in chronic SCI (Holman and Gorgey, 2019). Due to the low-quality tissue fiber found in individuals with prolonged SCI, the traditional method for measuring fiber type quality with immunohistochemical assays was replaced with the measurement of peak torque and contractile rise time. Following 16 weeks, peak torque increased significantly in relation to knee extensor muscle cross section area for subjects in the TRT + RT



**Figure 1 | Effects of TRT + RT versus TRT on the number of myonuclei.**

(A) Representative images of the myonuclei both at pre- and post-intervention following 16 weeks in the TRT + RT group. (B) Differences in the number of myonuclei between pre- and post-intervention following 16 weeks of TRT + RT and TRT. H&E: Hematoxylin and eosin; RT: resistance training; TRT: testosterone replacement therapy. Figures reproduced from our previous work, which has never been published before.

group suggesting a fiber type shift from fast glycolytic to fast oxidative fibers (Holman and Gorgey, 2019). This fiber type transformation appears to occur in parallel to the increases in citrate synthase activity (Gorgey et al., 2020a).

Future directions should consider a higher dose of TRT in conjunction with exercise or applications of TRT in conjunction with dietary interventions. Low-dose TRT may be safely used in conjunction with caloric deficit for in persons with SCI. This is highly significant because caloric deficit is likely to be associated with loss in both fat mass and lean mass. Additional loss in lean mass in persons with chronic SCI may exacerbate their cardio-metabolic status. In a case report, after 25% caloric deficit, the case managed to maintain lean mass and basal metabolic rate while successfully lose body weight, intramuscular fat, and visceral adipose tissue. Considering the remarkable muscle hypertrophy, this application should be considered for SCI persons with lower motor neuron injury. We are currently exploring the applications of higher dose of TRT with long pulse width stimulation current on denervated muscles after SCI.

The current work is only limited to men with SCI, women with SCI (20–25% of the SCI population) cannot be enrolled in TRT trials because of ethical considerations as imposed by local and national regulatory authorities. Furthermore, considering their underrepresentation, recruitment of women of SCI is rather challenging to examine gender-based differences on muscle quality in response to exercise. However, Ryan et al. (2013) showed that women with SCI are likely to demonstrate muscle hypertrophy following 16 weeks of NMES-RT. The combination of TRT and electrically evoked resistance training intervention in the SCI population appears to be safe as well as effective in promoting muscular hypertrophy and provide beneficial changes in metabolic health, mitochondrial health and function. Furthermore, the intervention appears to be safe and feasible even in those with heterotrophic ossifications, a medical condition that is likely to be excluded from

exercise trials (Moore et al., 2016).

These findings suggest several long-term health benefits from the utilization of TRT and exercise for the SCI community and expand the opportunity for additional interventions that could be explored in future work. Options that include the implementation of dietary supplements, increased daily caloric intake, and additional dosage forms of testosterone administration may be offered to further enhance the clinical outcomes for individuals with chronic SCI.

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### Raymond E. Lai, Ashraf S. Gorgey\*

Spinal Cord Injury and Disorders, Hunter Holmes McGuire VA Medical Center; Physical Medicine and Rehabilitation, Virginia Commonwealth University, Richmond, VA, USA

\*Correspondence to: Ashraf S. Gorgey, MPT, PhD, FACSM, FACRM, ashraf.gorgey@va.gov. <https://orcid.org/0000-0002-9157-6034> (Ashraf S. Gorgey)

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