Research Article

Epidural stimulation with locomotor training improves body composition in individuals with cervical or upper thoracic motor complete spinal cord injury: A series of case studies

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Context: Four individuals with motor complete SCI with an implanted epidural stimulator who were enrolled in another study were assessed for cardiovascular fitness, metabolic function and body composition at four time points before, during, and after task specific training. Following 80 locomotor training sessions, a 16-electrode array was surgically placed on the dura (L1-S1 cord segments) to allow for electrical stimulation. After implantation individuals received 160 sessions of task specific training with epidural stimulation (stand and step).

Outcome measures: Dual-energy X-ray absorptiometry (DXA), resting metabolic rate and peak oxygen consumption (VO_2peak) were measured before locomotor training, after locomotor training but before epidural stimulator implant, at mid-locomotor training with spinal cord epidural stimulation (scES) and after locomotor training with scES.

Findings: Participants showed increases in lean body mass with decreases on percentage of body fat, particularly android body fat, and android/gynoid ratio from baseline to post training; resting metabolic rate and VO_2peak also show increases that are of clinical relevance in this population.

Conclusions: Task specific training combined with epidural stimulation has the potential to show improvements in cardiovascular fitness and body composition in individuals with cervical or upper thoracic motor complete SCI.

Keywords: Cardiovascular fitness, Body composition, Epidural stimulation with locomotor training

Introduction

Spinal cord injury (SCI) disrupts the central nervous system in various ways. As a result, typical secondary problems such as sympathetic impairments[1] and atrophy[2] of the muscles below the injury are common. This, in turn, can result in increases in the percentage of body fat and decreases in lean mass, and cardiovascular fitness.[2–5] Atrophy and fat infiltration in muscles below the level of the injury predispose individuals to metabolic disease. Individuals with motor complete SCI (i.e. AIS A or B) have a higher incidence of metabolic disease than those with a motor incomplete SCI (i.e. AIS C or D).[6,7]

Under normal physiological conditions, human muscles have a mixture of slow and fast twitch fibers, each with unique morphologic, metabolic and enzymatic characteristics.[8] Exercise training can improve the histochemical characteristics to appear either more fatigue resistant (oxidative phenotype)[9] or less fatigue resistant (glycolytic phenotype).[10] These characteristics will affect energy expenditure at rest and during exercise. On the other hand, paralyzed skeletal muscle has a progressive decline in the proportion of slow myosin heavy-chain isoform fibers and an increase in the proportion of fibers that co-express both the fast and slow myosin heavy chain isoforms. As a result, muscle fibers

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become less fatigue resistant and oxidative metabolisms are progressively decreased.[11] In fact, in individuals with chronic SCI, skeletal muscle mitochondrial mass and physical activity are associated with improved metabolic health, independent of percentage of lean body mass.[12]

In addition to the changes in muscle fibers, an increased accumulation of fat below the level of the injury is prevalent.[13–15] Since the majority of the lesions to the spinal cord occur in the cervical or upper thoracic segments,[16] most individuals with SCI accumulate more visceral fat in the abdominal cavity compared to individuals without SCI.[13,17] Distribution of fat is a reliable predictor for risk of cardiovascular disease, hyperlipidemia and insulin resistance, not only for people that are obese or overweight,[18] but also for individuals with normal weight.[19] In fact, the majority of the individuals with SCI exhibit at least one cardiovascular disease risk factor (i.e. hypertension, hyperlipidemia, diabetes) regardless of their body mass index (BMI).[3] Android fat distribution, describes the distribution of human adipose tissue mainly around the abdomen, trunk and upper body; whereas gynoid fat distribution describes the distribution of human adipose tissue mainly in hips and buttocks. Android-gynoid percent fat ratio is expressed as android fat divided by gynoid fat. Android-gynoid ratio of 1.0 or above is associated with an increased risk for metabolic syndrome in healthy adults. Individuals with SCI typically show increased android, gynoid and android/gynoid ratio fat distribution.[19]

Increased visceral adiposity tissue, but not subcutaneous adipose tissue, result in android fat distribution pattern, with the concomitant increase of cardiometabolic risk factors. Non-injured individuals with either low or moderate-to high risk of cardiometabolic complications have higher subcutaneous adipose tissue than their SCI counterparts at any BMI or waist circumferences. However, SCI individuals have around 43% more visceral adipose tissue than non-injured individuals,[20] putting SCI individuals at a disproportionate risk of metabolic syndrome.

Different therapies are used to ameliorate the metabolic and musculoskeletal system deteriorations that occur with chronic SCI. Exercise training has shown to be beneficial in increasing oxygen uptake in individuals with thoracic SCI.[21] Even though voluntary muscle contraction is the preferred means for increasing levels of physical activity, individuals with more severe SCI are unable to perform voluntary muscle contractions in the largest muscle groups. For that reason, several studies have focused on the use of functional electrical stimulation (FES) reporting that FES may result in increased energy expenditure and improved muscle mass.[22,23] Further, FES in combination with activity-based therapy also has been shown to improve cardiometabolic function in SCI individuals.[24] Low frequency, low intensity FES of quadriceps femoris resulted in significant increases in energy expenditure in individuals with cervical and thoracic motor complete SCI.[25] Even though FES seems to be an effective tool to increase energy expenditure,[25–28] most studies show no changes in percentage of body fat,[27,29] and thus, the risk for cardiometabolic disease remains as a major concern.

Recently, a novel intervention, spinal cord epidural stimulation (scES) combined with task specific training, administered in 4 individuals with motor complete SCI showed that the participants regained voluntary movement.[33] The purpose of this study is to investigate if epidural stimulation combined with task-specific training is also a beneficial intervention to improve cardiovascular fitness and body composition in individuals with cervical or upper thoracic motor complete SCI.

Participants

Four males with chronic motor complete SCI average age 27.3 (± 3.7) years old, body weight 69.4 Kg (± 8.4), height 185.3 cm (± 3.8), body mass index (BMI) 20.4 (± 1.9) that were part of an ongoing study participated on this study.

One participant had a cervical AIS B SCI, and three participants had a high thoracic AIS A SCI (Table 1). Time from injury to implantation with an epidural stimulation unit averaged 30.8 (± 3.1) months. Participants volunteered for study participation and signed an informed consent document approved by the University of Louisville Institutional Review Board.

Table 1 Clinical characteristics of the participants at initial baseline.

ID	Sex	Age (Years)	AIS Classification	Time Since Injury (Months)	Body weight (Kg)	Height (cm)	BMI
A53	M	28.4	A – T5	29	64.4	180	20.1
B23	M	31.6	B – C5	35	64.8	188	19.9
A59	M	26.4	A – T4	28	66.6	185	18.5
A60	M	22.7	A – T4	31	81.9	188	23.1

Interventions

Participants received task specific training (stand and step) for approximately 80 sessions prior to implantation (Table 2). Step training with manual assistance occurred on a body weight supported system over a treadmill. Participants stepped for one hour. Stand training with manual assistance occurred overground in a custom made standing device. Participants stood for one hour. Stand and step sessions occurred on the same day, 5 times per week. Following training, participants were implanted with an epidural spinal cord stimulation unit (Medtronic, RestoreADVANCED) and a 16-electrode array as previously described.[34] Post- implant training was performed with scES. Participants received 160 sessions of overground standing with stand-scES and stepping with step-scES on a body weight supported system over a treadmill. For the initial 80 sessions, standing with scES was alternated with stepping with scES. Participants trained one hour a day, 5 days a week. After 80 sessions with scES were completed, intensity was increased to training two times a day (one stand with scES and one step with scES session). The addition of the second training time was added slowly by increasing 1 day of double sessions every 2 weeks. Level of body weight support was lowered with greater independence; speed was not changed in most participants (Table 2). Training was focused on achieving an optimal locomotor pattern with the greatest level of independence. In some cases participants reported fatigue at the end of the sessions (both stand and step), however this was not directly measured. Participant A59, received an additional 60 sessions of stand training with scES prior to the start of stepping with scES due to medical recommendation for an orthopedic condition. One participant (A53), received 80 sessions of standing with stand-scES, followed by 80 sessions of step training with step-scES. Sessions were always one hour long 5-days a week.

Stimulation configurations were specific for each individual. Stand-scES and Step-scES configurations (electrode section, frequency, pulse width and amplitude) were selected to enable the specific motor task (stand or step). The stimulation configuration selection usually took one to two sessions. Stand-scES configurations ranged in frequency from 10–40 Hz. Step-scES configurations ranged in frequency from 25–45 Hz. Voltages varied across research participants.

Outcome measures

Assessments were performed at multiple time points throughout their primary study participation. The initial time point for participants A59, A60 and B23 was prior to any intervention (baseline). This time point was not captured for A53. Assessments were also performed Post LT training to assess the impact of training without scES. Post implant and training assessments were performed following 80 sessions and 160 sessions (Mid Training scES LT and Post Training scES LT respectively).

Dual-energy X-ray absorptiometry (DXA)

DXA was used to measure body composition in the four SCI participants. Weight, height, body composition analysis was performed by the DXA bone densitometer

Table 2 Training interventions and training data per participant.

Baseline				
Subject ID	**A53**	**B23**	**A59**	**A60**
Training	Step Training	Stand and Step Training	Stand and Step Training	Stand and Step Training
weeks	19 (1 x day)	9 (2 x day)	8 (2 x day)	9 (2 x day)
average BWS (SD)	42.3 (2.1)	48.1(2.4)	52.6(3.8)	52.8(2.4)
average speed m/s (SD)	1.03	1.07	0.89	0.98
Post Training LT				
Implantation				
Training	Stand + scES		Stand + scES	
weeks	17 (1 x day)		10 (1 x day)	
Training		Stand + scES / Step + scES	Stand + scES / Step + scES	Stand + scES / Step + scES
weeks		23 (1 x day)	39 (1 x day)	24 (1 x day)
average BWS (SD)		54.7(6.2)	59.1(3.7)	55.5(2.1)
average speed m/s (SD)		0.5(0.1)	0.3(0.1)	0.35 (0.1)
Mid Training scES				
Training	Step + scES	Stand + scES / Step + scES	Stand + scES / Step + scES	Stand + scES / Step + scES
weeks	19 (1 x day)	15 (2 x day)	13 (2 x day)	17 (2 x day)
average BWS (SD)	44.1(2.9)	43.5 (2.7)	56.6 (1.4)	51.5 (4.1)
average speed m/s (SD)	0.89 (0.1)	0.4 (0.1)	0.2 (0.1)	0.35 (0.1)
Post Training scES				

(Model: Prodigy, GE Lunar, Software version 2002 Encore 6.81.003). Regional and total fat mass, fat-free mass, % of android and gynoid fat; lean mass and bone mass, bone mineral content (BMC) and bone density (BMD). The scans were performed at baseline, after LT/before LTscES training; at mid- LTscES training and post LTscES training. Participants were positioned in supine position on the scanner and were not strapped. Every effort was made to consistently place participants in the scanner at the different time points. All the scans were performed by the same trained and certified DXA technician. Total body fat was reported as total body fat in kilograms, and as a percent of total body weight determined by the scan. Height (length) was measured using the electronic ruler function and weight from the DXA scan table scale feature.

Resting metabolic rate (RMR)

RMR is the rate of energy expenditure by humans at rest (reported as kilocalories per day). The release, and use, of energy in this state is sufficient only for the functioning of the vital organs: the heart, lungs, nervous system, kidneys, liver, intestine, sex organs, muscles, brain and skin. RMR was measured first thing in the morning after fasting for 10–12 hours. Participants arrived to the laboratory, and were placed supine in a hospital bed for a minimum of 30 minutes until their resting values for respiratory exchange ratio (RER) were stable. A canopy hood was placed to cover the participant head and shoulders, and expired gases through indirect calorimetry were analyzed with a Parvo Medic TrueOne 2400 (Sandy, UT). Analysis of the oxygen and carbon dioxide composition of the expired air occurred every 10 seconds. The cart was calibrated with a 3-liter syringe for flowmeter calibration and the ambient air for gas calibration at least 30 minutes before testing as recommended by the manufacturer's guidelines. After RER values were stable, participants were instructed to stay awake, without moving or talking while lying down in a bed for about 45 minutes

Peak oxygen consumption (VO_2peak)

Oxygen consumption was analyzed with a Parvo Medic TrueOne 2400 (Sandy, UT) following the same calibration and acquisition techniques as described above. Heart rate was recorded using a Polar heart rate monitor as well as by 3-lead EKG. Rating of perceived exertion was recorded using the Borg 6-20 scale, which was explained to each participant using standardized instructions.[35] Any questions the participant had, were answered to ensure full understanding. All variables such as gas consumption, respiratory exchange ratio, heart rate, VE, power output, and time were not visible to the participant during the test.

VO_2peak test protocol: Participants performed a graded exercise test to exhaustion (VO2 peak) on a total body recumbent stepper (Nustep T4 ergometer, Ann Arbor, MI). Each test was conducted on the same total body recumbent stepper. The seat position was set so the participant had a slight bend in their knee at full extension. Arm handles were positioned to allow full extension without leaning forward in the seat. Participants warmed up for two minutes at a resistance of 1 and at 80 steps per minute, following a previously developed exercise test protocol.[36] After the two-minute warm up, participants immediately began the test at a resistance of 4. Every two minutes, the resistance was increased until exhaustion. 20 seconds before the end of each stage, participants were asked to report their RPE. Blood pressure and heart rate were measured before warm up, immediately after the test, and 5 minutes posttest. The test was terminated when 1) the subject reports subjective fatigue and stops the test despite verbal encouragement and 2) the subject is no longer able to keep the step per minute at or above 80.

Results

Participant A53 had a considerable increase in body weight from baseline to post step-scES training (from 64.8 Kg to 66.9 Kg), this increase in body weight was primarily due to increases in fat free mass (from 51.5 Kg to 53.4Kg) with minimal changes in total fat percent (20.9% to 21.1%). Android/gynoid ratio at baseline was 1.17 indicating a risk of cardio-metabolic disease. Android fat distribution in this participant consistently decreased in each time point (Figure 1) with an overall decrease from 24% to 21.8%. As a result, the android/gynoid ratio decreased to 1.04 post LTscES.

Participant B23: had a considerable increase in body weight from baseline to post LTscES training (from 64.8 Kg to 69.2 Kg). He was the only participant that experienced a body weight increase from baseline to post LT, with a slightly lower increase from post LT to post LTscES. The increase in body weight was due to increases in fat free mass, as it increased from 52.4 Kg to 57.4Kg with a decrease in the percentage of body fat from 15.2% to 13.8%, respectively. A large increase in fat free mass was seen between baseline and post LT (52.7 kg to 58.0 kg). Android/gynoid ratio was always below 1.0, but steady increases were observed throughout the training as gynoid fat distribution decreased with no changes in android fat (Figure 1).

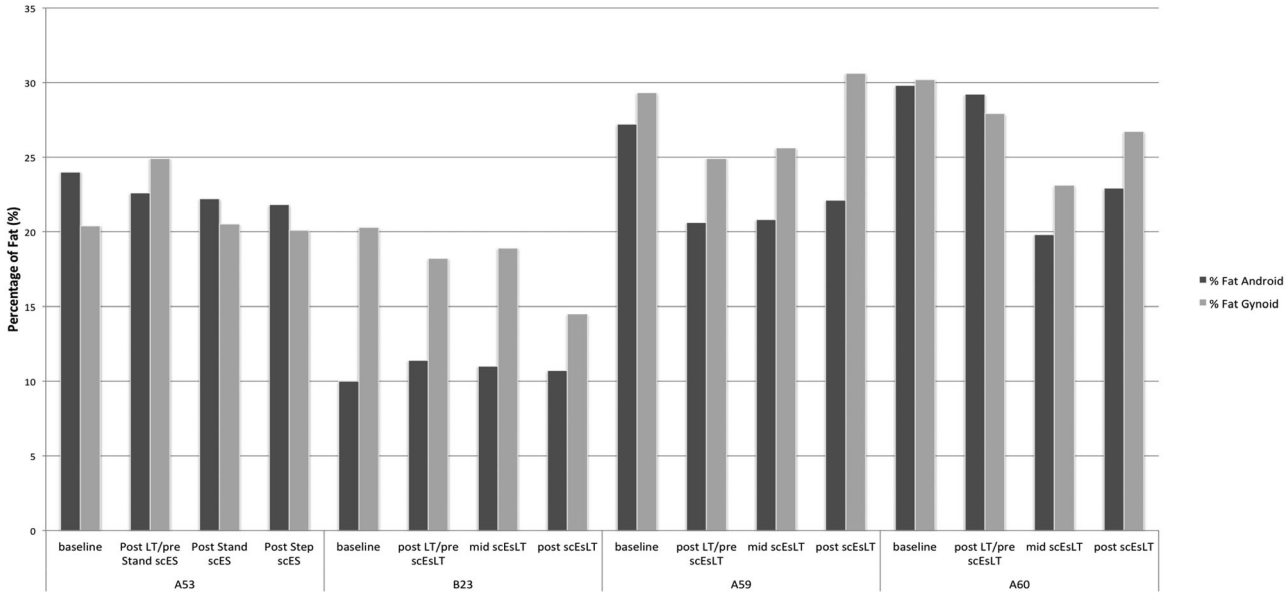

Figure 1 Changes in percentage of android and gynoid fat of subjects at baseline, post locomotor training, mid-locomotor training with epidural stimulation and post locomotor training with epidural stimulation.

Participant A59 had a considerable increase in body weight from baseline to post LTscES training (from 66.6Kg to 72.7 Kg), this increase in body weight was primarily due to increases in fat free mass (50.8 Kg to 54.7Kg). Changes in percent of total fat were minimal (24.7% to 25.7%). Android/gynoid ratio in this participant was 0.93 at baseline. Android fat distribution consistently decreased at each time point (Figure 1) with an overall decrease from 27.2% to 22.1% resulting in a decrease in android/gynoid ratio of 0.72 post LTscES.

Participant A60 had an increase in body weight from baseline to post LTscES training (from 81.9 Kg to 83.9 Kg), this increase in body weight was due to increases in fat free mass (61.5 Kg to 66.5 Kg) with considerable decreases in total fat % (26.1% to 22.2%). Android/gynoid ratio at baseline was 0.99 indicating risk of cardiometabolic disease. Android fat distribution in this participant show robust decreases from 29.8% to 22.9% (Figure 1) with the concomitant decrease in android/gynoid ratio of 0.86 post LTscES.

Changes in RMR and VO2peak are presented in Table 3. Only two participants (B23 and A59) have baseline and post LT data. Both participants showed an increase in RMR from baseline to post LT. A

Table 3 Body weight, percentage of body fat, android/gynoid ratio, peak Oxygen consumption (VO2peak) and resting metabolic rate (RMR) of subjects at baseline, post locomotor training, mid-locomotor training with epidural stimulation and post locomotor training with epidural stimulation.

Subject ID		Body weight (Kg)	Total Fat (%)	Android/gynoid ratio	Fat free (Kg)	RMR (Kcal/day)	VO2 peak (ml/Kg/min)
A53	Baseline	64.4	20.9	1.17	51.5	—	—
	Post LT/pre Stand scES	62.4	21.9	0.91	49.4	1375	23.5
	Post Stand scES	64.4	20.3	1.08	51.9	1530	24.7
	Post Step scES	66.9	21.1	1.04	53.4	1445	26.9
B23	Baseline	64.8	15.2	0.49	52.7	1369	11.0
	Post LT/pre scEsLT	67.5	14.6	0.63	58.0	1417	14.5
	Mid scEsLT	67.9	14.4	0.58	55.9	1377	12.5
	Post scEsLT	69.2	13.8	0.74	57.4	1597	14.5
A59	Baseline	66.6	24.7	0.93	50.8	1315	21.6
	Post LT/pre scEsLT	65.0	22.1	0.49	51.2	1639	21.7
	Mid scEsLT	66.3	23.1	0.81	51.6	1653	—
	Post scEsLT	72.7	25.7	0.72	54.7	1535	
A60	Baseline	81.9	26.1	0.99	61.5	1725	19.5
	Post LT/pre scEsLT	80.3	24.6	1.05	61.5	—	—
	Mid scEsLT	85.2	20.2	0.86	68. 6	2072	21.2
	Post scEsLT	83.9	22.2	0.86	66.1	1782	18.2

similar increase was also seen in their VO2peak values. Only one participant (B23) showed a further increase in RMR following scES training.

Discussion

Results from previous studies[33,34] suggest that epidural stimulation in combination with locomotor training has potential as a clinical intervention for the recovery of function after SCI. Participants who underwent this novel intervention were able to regain significant motor control caudal to the level of the injury. It is postulated that this recovery of motor function could be due to the stimulation of sensory fibers on the dorsal root, resulting in interneuronal plasticity leading to coordinated motor pool activity modulated by proprioception. These motor pools regained the ability to innervate muscles that were previously silent. Motor output was increased significantly when comparing standing with and without scES[37] and stepping with and without scES. As a result, muscle fibers may synthesize contractile proteins, signal for mitochondria and capillary proliferation with higher density, increasing skeletal muscle oxidative metabolism and muscle mass. Participants show an interesting trend of improved metabolic and body composition variables. The most clinically relevant finding of this study is the shift of body composition that occurred in all the participants.

A devastating comorbidity after SCI is the shift on body fat, favoring the accumulation of subcutaneous and abdominal adiposities. It is well known that increases in android body fat and immobility increase several folds the risk of cardiovascular disease, hyperlipidemia, and diabetes.[18,19] The effects of exercise[29,38] and LT[39,40] on body composition following SCI have not shown consistent results. However, it is widely accepted that voluntary exercise may help to improve, maintain and attenuate muscle mass loss.[41] However, none of the currently available therapies for individuals with SCI seem to be effective in reducing fat accumulation below the level of the injury.[26,32,40] In the current study we present evidence that indeed fat free tissue can show some improvements after LTscES training. Even though from baseline to post LT there were changes in percentage of body fat and increases in fat free tissue; more pronounced changes in percentage of body fat, fat free tissue (Table 3) and android fat (Figure 1) were observed after scES LT.

Additionally, RMR and VO2peak, although highly variable among participants, showed positive changes that may provide evidence for future investigations to determine weather this trend is of clinical relevance in preventing and reversing the risks of obesity and cardiovascular disease in this population. The combined preliminary results presented in this study support the idea that scES activates the muscles below the level of the injury to a much greater degree than other therapeutic and rehabilitative strategies. Most importantly the decreases in android, gynoid and android/gynoid fat ratio have important implications for reducing cardiovascular risk factors and other comorbidities.

There are some limitations to the present study. Assessments for this study were performed on a group of individuals participating in a separate training intervention study. Therefore, the study did not control for prior-to-injury fitness status and dietary restrictions. These factors contribute to the heterogeneity of the sample. Another limitation is the fact that one of the four individuals (A53) received a slightly different training paradigm when compared to the others. All individuals received 160 session of Stand/Step with scES following implantation, while A53 received 80 of stand with stand-scES followed by step with step-scES. Although the total number of session was the same, performing only standing and only stepping adds variability to the sample. A53 shows a greater improvement in cardiovascular fitness following the second half of the scES intervention, which in his case would be step with step-scES. All other measures follow a similar trend when compared to the other individuals. Although this is a case series from only four participants, it shows the potential of this intervention in improving key factors associated with cardiovascular fitness and it warrants further investigation in a larger study.

Findings of this study suggest that epidural stimulation with locomotor training may be an effective clinical approach with multidimensional benefits that result in better quality of life among individuals with SCI.

Statement of Ethics

The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Disclaimer statements

Contributors None.

Declaration of interest The authors report no declarations of interest.

Conflicts of interest None.

Ethics approval None.

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References

1 Garstang SV, Miller-Smith SA. Autonomic nervous system dysfunction after spinal cord injury. Phys Med Rehabil Clin N Am 2007;18(2):275-96, vi-vii.
2 Castro M, Apple DJ, Hillegass E, Dudley G. Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. Eur J Appl Physiol 1999;80(4):373-8.
3 Flank P, Wahman K, Levi R, Fahlstrom M. Prevalence of risk factors for cardiovascular disease stratified by body mass index categories in patients with wheelchair-dependent paraplegia after spinal cord injury. Journal of rehabilitation medicine 2012;44(5):440-3.
4 Sisto SA, Lorenz DJ, Hutchinson K, Wenzel L, Harkema SJ, Krassioukov A. Cardiovascular Status of Individuals With Incomplete Spinal Cord Injury From 7 NeuroRecovery Network Rehabilitation Centers. Arch Phy Med Rehabil 2012;93(9):1578-87.
5 Theisen D. Cardiovascular determinants of exercise capacity in the Paralympic athlete with spinal cord injury. Exp Physiol 2012;97(3):319-24.
6 Moore C, Craven B, Thabane L, *et al.* Lower-extremity muscle atrophy and fat infiltration after chronic spinal cord injury. J Musculoskelet Neural Interact 2015;15(1):32-41.
7 Sopher R, Nixon J, Gorecki C, Gefen A. Effects of intramuscular fat infiltration, scarring, and spasticity on the risk for sitting-acquired deep tissue injury in spinal cord injury patients. J Biomech Eng 2011;133(2):021011.
8 Ogata T. Structure of motor endplates in the different fiber types of vertebrate skeletal muscles. Arch Histol Cytol 1988;51(5):385-424.
9 Heden T, Ryan T, Ferrara P, *et al.* Greater Oxidative Capacity in Primary Myotubes from Endurance-trained Women. Med Sci Sports Exerc 2017;[Epub ahead of print].
10 Friedmann-Bette B, Bauer T, Kinscherf R, *et al.* Effects of strength training with eccentric overload on muscle adaptation in male athletes. Eur J Appl Physiol 2010;100(4):821-36.
11 Biering-Sørensen BK, IB; Kjaer, M; Biering-Sørensen, F. Muscle after spinal cord injury. Muscle Nerve 2009;40(4):499-519.
12 O'Brien L, Chen Q, Savas J, Lesnefsky E, Gorgey A. Skeletal muscle mitochondrial mass is linked to lipid and metabolic profile in individuals with spinal cord injury. Eur J Appl Physiol 2017;117:2137-47.
13 Edwards LA, Bugaresti JM, Buchholz AC. Visceral adipose tissue and the ratio of visceral to subcutaneous adipose tissue are greater in adults with than in those without spinal cord injury, despite matching waist circumferences. Am J Clin Nutr 2008;87(3):600-7.
14 Spungen A, Wang J, Pierson R, Bauman W. Soft tissue body composition differences in monozygotic twins discordant for spinal cord injury. J Appl Physiol 2000;88(4):1310-15.
15 Gorgey A, Dolbow D, Dolbow J, Khalil R, Castillo C, Gater D. Effects of spinal cord injury on body composition and metabolic profile - part I. J Spinal Cord Med 2014;37(6):693-702.
16 National Spinal Cord Injury Statistic Center. Spinal cord injury facts and figures at a glance. J Spinal Cord Med 2012;35(1):68-9.
17 Spungen A, Adkins R, Stewart C, *et al.* Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. J Appl Physiol 2003;95(6):2398-407.
18 Aucouturier J, Meyer M, Thivel D, Taillardat M, Duché P. Effect of android to gynoid fat ratio on insulin resistance in obese youth. Arch Pediatr Adolesc Med 2009;163(9):826-31.
19 Okosun I, Seale J, Lyn R. Commingling effect of gynoid and android fat patterns on cardiometabolic dysregulation in normal weight American adults. Nutr Diabetes 2015;5(e155;):1-8.
20 Cirnigliaro C, LaFountaine M, Dengel D, *et al.* Visceral adiposity in persons with chronic spinal cord injury determined by dual energy X-ray absorptiometry. Obesity (Silver Spring) 2015;23(9):1811-7.
21 Ordonez F, Rosety M, Camacho A, *et al.* Arm-cranking exercise reduced oxidative damage in adults with chronic spinal cord injury. Arch Phy Med Rehabil 2013;94(12):2336-41.
22 Griffin L, Decker M, Hwang J, *et al.* Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury J Electromyogr Kinesiol 2009;19(4):614-22.
23 Dudley-Javoroski S, Shields R. Muscle and bone plasticity after spinal cord injury: review of adaptations to disuse and to electrical muscle stimulation. J Rehabil Res Dev 2008;45(2):283-96.
24 Carvalho D, de Cassia Zanchetta M, Sereni J, Cliquet A. Metabolic and cardiorespiratory responses of tetraplegic subjects during treadmill walking using neuromuscular electrical stimulation and partial body weight support. Spinal cord 2005;43(7):400-5.
25 Woelfel J, Kimball A, Yen C, Shields R. Low-Force Muscle Activity Regulates Energy Expenditure after Spinal Cord Injury. Med Sci Sports Exerc 2017;49(5):870-8.
26 Gorgey A, Dolbow D, Dolbow J, Khalil R, Gater D. The effects of electrical stimulation on body composition and metabolic profile after spinal cord injury--Part II. J Spinal Cord Med 2015;38(1):23-37.
27 Dolbow D, Gorgey A, Khalil R, Gater D. Effects of a fifty-six month electrical stimulation cycling program after tetraplegia: case report. J Spinal Cord Med 2016;3(1-4).
28 Coupaud S, Gollee H, Hunt KJ, Fraser MH, Allan DB, McLean AN. Arm-cranking exercise assisted by Functional Electrical Stimulation in C6 tetraplegia: a pilot study. Technol Health Care 2008;16(6):415-27.
29 Panisset M, Galea M, El-Ansary D. Does early exercise attenuate muscle atrophy or bone loss after spinal cord injury? Spinal Cord 2016;54(2):84-92.
30 Dudley-Javoroski SS, RK. Muscle and bone plasticity after spinal cord injury: Review of adaptations to disuse and to electrical muscle stimulation. J Rehabil Res Devt 2008;45(2):283-96.
31 Clark J, Jelbart M, Rischbieth H, *et al.* Physiological effects of lower extremity functional electrical stimulation in early spinal cord injury: lack of efficacy to prevent bone loss. Spinal Cord 2007;45(1):78-85.
32 Gorgey AS, Harnish CR, Daniels JA, *et al.* A report of anticipated benefits of functional electrical stimulation after spinal cord injury. J Spinal Cord Med 2012;35(2):107-12.
33 Angeli C, Edgerton V, Gerasimenko Y, Harkema S. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain 2014;137(Pt 5):1394-409.
34 Harkema S, Gerasimenko Y, Hodes J, *et al.* Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet 2011;4 (377):1938-47.
35 Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-381.
36 McCulloch JL, D; Kloby, M; Love, M; Terson de Paleville, D. Prediction of Maximal Oxygen Consumption from Rating of Perceived Exertion (RPE) using a Modified Total-body Recumbent Stepper. In J Exerc Sci 2015;8(4):414-24.
37 Rejc E, Angeli C, Harkema S. Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. PLoS One 2015;10(7).
38 Hicks A, Martin Ginis K, Pelletier C, Ditor D, Foulon B, Wolfe D. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. Spinal Cord 2011;49(11):1103-27.
39 Giangregorio L, Hicks A, Webber C, *et al.* Body weight supported treadmill training in acute spinal cord injury: impact on muscle and bone. Spinal Cord 2005;43(11):649-57.
40 Astorino T, Harness E, Witzke K. Chronic activity-based therapy does not improve body composition, insulin-like growth factor-I, adiponectin, or myostatin in persons with spinal cord injury. J Spinal Cord Med 2014;38(5):615-5.
41 Burton L, Sumukadas D. Optimal management of sarcopenia. Clin Interv Aging 2010;7(5):217-28.