Review

The effects of electrical stimulation on body composition and metabolic profile after spinal cord injury – Part II

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Diet and exercise are cornerstones in the management of obesity and associated metabolic complications, including insulin resistance, type 2 diabetes, and disturbances in the lipid profile. However, the role of exercise in managing body composition adaptations and metabolic disorders after spinal cord injury (SCI) is not well established. The current review summarizes evidence about the efficacy of using neuromuscular electrical stimulation or functional electrical stimulation in exercising the paralytic lower extremities to improve body composition and metabolic profile after SCI. There are a number of trials that investigated the effects on muscle cross-sectional area, fat-free mass, and glucose/lipid metabolism. The duration of the intervention in these trials varied from 6 weeks to 24 months. Training frequency ranged from 2 to 5 days/week. Most studies documented significant increases in muscle size but no noticeable changes in adipose tissue. While increases in skeletal muscle size after twice weekly training were greater than those trials that used 3 or 5 days/week, other factors such as differences in the training mode, i.e. resistance versus cycling exercise and pattern of muscle activation may be responsible for this observation. Loading to evoke muscle hypertrophy is a key component in neuromuscular training after SCI. The overall effects on lean mass were modest and did not exceed 10% and the effects of training on trunk or pelvic muscles remain unestablished. Most studies reported improvement in glucose metabolism with the enhancement of insulin sensitivity being the major factor following training. The effect on lipid profile is unclear and warrants further investigation.

Keywords: Spinal cord injury, Electrical stimulation exercise, Body composition, Metabolic profile, Glucose metabolism, Lipid metabolism

Application of electrical stimulation to exercise paralyzed skeletal muscle has been the focus of many research and clinical investigations. The strategy has been implemented to offset several of the significant negative health implications that result from the extensive skeletal muscle atrophy after spinal cord injury (SCI). It is highly recommended that the reader refer to part-I of the current review, which discusses the adaptations in body composition and metabolic profile following SCI. Briefly, persons with SCI experience dramatic loss in muscle mass and fat-free mass (FFM) over the

first few months post-injury. The rapid loss of lean mass (LM) is associated with decline in basal metabolic rate and increased whole body and regional adiposity. Accumulation of ectopic adipose tissue may interfere with insulin signaling and serve as a source of circulating triglycerides (TG) and free-fatty acids (FFA) which are risk factors for cardiovascular disease. These adaptations in body composition provide an environment for the development of several metabolic abnormalities including type 2 diabetes mellitus, dyslipidemia, cardiovascular diseases, and metabolic syndrome (MS).

There are other reviews that focused on muscle plasticity, nutrition, and the evolution of electrical stimulation therapies related to individuals with SCI.^{1–3} Carlson *et al.*⁴ suggested that previous studies had

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small sample sizes and there is insufficient evidence to determine the effects of exercise on carbohydrate and lipid disorders after SCI. However, Carlson *et al.*⁴ summarized evidence from exercise interventions without considering the physiological differences in upper or lower extremity training after SCI. The focus of the current review is to summarize the available evidence about the adaptations in body composition and metabolic profiles following applications of surface neuromuscular electrical stimulation (NMES) or functional electrical stimulation (FES) in humans with SCI. For the purpose of this review, FES is a form of NMES which provides stimulation of selected muscles in a coordinated manner resulting in a functional pattern similar to walking, cycling, rowing, etc. This is contrary to surface NMES which is used for a single or multiple muscle groups, but without the intention of producing a functional or coordinated movement. The theme of the current review is to determine whether NMES or FES training that leads to positive changes in body composition is necessary to achieve metabolic benefits or do metabolic changes primarily happen independent of body composition changes after SCI. Unlike voluntary active upper extremity muscle training after SCI, there are no established guidelines or consensus on the appropriate strategy, frequency, or intensity of FES or NMES to exercise paralytic muscles after SCI.

A key aspect of this review is highlighting the significance of training the paralyzed musculoskeletal system to prevent secondary complications and comorbidities that may result from disuse muscle atrophy after SCI. Maintaining a healthy musculoskeletal system below the level of injury is an essential component in attenuating several of the aforementioned metabolic disorders after SCI. Previous works established important examples of the significance of training the paralyzed muscles after SCI.^{1,4-6}

Effects of activity on body composition and metabolic profile

Increased physical activity is a commonly prescribed therapeutic modality to reduce obesity, abdominal adiposity, and associated metabolic consequences such as cardiovascular diseases, MS, and type 2 diabetes mellitus through the regulation of blood glucose and lipids.⁷⁻¹²

Aerobic exercise has been advocated as the most suitable exercise mode for the management of health-related complications secondary to obesity.^{8,9} The Centers for Disease Control, the American Heart Association, and the American College of Sports Medicine recommend daily exercise for 30 minutes to

prevent the occurrence of health- and obesity-related secondary complications.^{10,11} However, physical and functional limitations in people with SCI interfere with maximizing the benefits of exercise protocols.¹³ Buchholz *et al.*¹³ reported that physical activity is lower in individuals with paraplegia compared to able-bodied (AB) controls. The situation is even worse in those with tetraplegia because of limited upper extremity mobility and function. A person with tetraplegia who relies on sip and puff technique to operate his/her wheelchair has increased risk of developing cardiovascular disorders because of diminished physical activity. These individuals commonly experience muscular, respiratory, cardiovascular, and mobility barriers that limit the ability to perform many exercise protocols which would attenuate deterioration of body composition and metabolic profiles exhibited after injury.¹⁴⁻²⁰

Exercise opportunities are either not possible or limited to the skeletal muscles above the level of SCI.^{21,22} Persons with C5 and higher motor complete SCI are characterized by low exercise tolerance after failing to maintain a cadence of 50 rpm longer than 5 minutes during arm-crank ergometry. During upper extremity exercise in persons with SCI, left ventricular end diastolic volume remains largely constant especially for those with SCI at or above T6. These limitations result from unchanged or decreased venous blood return to the heart which ultimately contributes to limited cardiac stroke volume. Inability to shunt blood from the viscera and non-exercising trunk and lower extremity musculature to the working muscles is due to impaired sympathetic responses including impaired venoconstriction after SCI, resulting in blood remaining pooled in the lower extremities and inferior vena cava.²⁰⁻²⁴ Furthermore, the inability to voluntarily contract lower extremity musculature eliminates the activity of the venous pump system.

Electrical stimulation and body composition

Over the past two decades, surface NMES has been proposed as an effective alternative method to exercise the paralyzed muscles below the level of lesion.^{1,3,5,25} Although regular voluntary physical activity is well established as a primary tool to combat unhealthy glucose and lipid blood levels, there are limited research findings that the use of NMES exercise will do likewise, especially for the amelioration of impaired glucose tolerance and reduced insulin sensitivity in individuals with SCI.³

The use of electrical stimulation has been introduced as an alternative to voluntary muscle exercise in order to increase physical activity levels and reintroduce

paralyzed muscles to exercise.^{1,3,25,26} This is accomplished via activation of the desired muscle groups to achieve a functional task such as knee extension or cycling. Moreover, the extent of muscle activation can be altered by adjusting the stimulation parameters.²⁷ Increasing the amplitude of the current and pulse duration increases the evoked torque as well as skeletal muscle recruitment, whereas increasing the frequency increases the evoked torque without changing the cross-sectional area (CSA) of the activated muscle.²⁷ The ultimate goal is to reverse the process of skeletal muscle atrophy, enhance force output, increase energy expenditure, produce healthy body composition, and promote efficient chemical and hormonal processes resulting in healthy lipid and glucose blood profiles.^{26,28–37} Despite variations in electrical stimulation parameters, exercise protocols, and subject demographics,^{32–37} these studies reported increasing muscle size and mass, muscle force, reduction in spasticity, and improvement in body composition following lower extremity training in persons with SCI.^{30–34}

One electrical stimulation modality that has proven effective at improving body composition in individuals with SCI is FES leg cycle ergometry (FES-LCE),^{31,32,34,37–42} Skold *et al.*³² utilized FES-LCE two to three times per week for 6 months, reported a 10% increase in muscle fiber CSA in persons with motor complete tetraplegia. Similarly, Mohr *et al.*⁴² found a 12% increase in muscle mass after 1 year of FES-LCE at two to three sessions weekly in individuals with both tetraplegia and paraplegia. Cramer *et al.*²⁸ found similar results with significant increases in muscle fiber CSA of the vastus lateralis muscle and total work output after 10 weeks of FES-LCE 3 days/week in individuals with SCI. In addition, further improvements in muscle hypertrophy have been found in studies that utilize FES-LCE in combination with other forms of NMES.³⁴ Scremin *et al.* utilized a three-phase training protocol including quadriceps strengthening, progressive sequential stimulation, and FES-LCE. After 1 year of this mixed NMES protocol held at two to three sessions per week, 13 of the subjects with SCI experienced increases in the CSA of vastus medialis-intermedius, vastus lateralis, adductor magnus-hamstrings, sartorius, and rectus femoris averaging 31, 39, 26, 22, and 31%, respectively.³⁴

The positive effects of FES-LCE therapies are becoming more widely known as home-based FES-LCE therapy options are becoming available.^{43–47} Home-based exercise helps to ameliorate many of the external barriers to exercise adherence for those with SCI. A home-based FES-LEC study for individuals with SCI

demonstrated an exercise rate twice that reported for the AB population.⁴⁶ Other studies using home-based FES-LEC on participants with tetraplegia and paraplegia have resulted in positive alterations in body composition (increased LM and decreased body fat percentage).^{43,44}

In healthy AB persons, resistance training (RT) at least twice per week provides a safe and effective method of improving muscular strength, inducing skeletal muscle hypertrophy by 10% within 8–12 weeks of training, decrease fat mass (FM), and possibly enhancing glucose homeostasis and improving lipid profile.^{48–51} RT has also been shown to increase skeletal muscle CSA, LM, reducing FM, and visceral adiposity in adults with MS.⁵¹ Ibanez *et al.*⁵¹ reported that twice weekly RT increased skeletal muscle CSA and LM and also decreased FM and visceral adiposity in older adults with MS. RT has also been shown to induce the release of insulin-like growth factor-1 (IGF-1) which is reported to play a role in evoking skeletal muscle hypertrophy and increasing LM, suggesting that RT may be an effective method of attenuating body composition deterioration after SCI.^{52,53} The role of IGF-1 in evoking skeletal muscle hypertrophy through its effect on satellite cells has been previously reviewed.⁵² In addition, IGF-1 has been associated with increasing LM in healthy individuals. This renders RT as an effective method that could attenuate body composition deterioration after SCI.

Several studies have tested the effects of RT in conjunction with surface NMES applied to the knee extensor muscles of individuals with SCI via surface electrodes to induce concentric–eccentric actions.^{26,33,38,54–58} Mahoney *et al.* utilized NMES RT with sessions held twice weekly for 12 weeks in five individuals with chronic complete SCI. The study found increased CSA of the quadriceps femoris muscles (35–39%) and a trending towards improvement in blood glucose profile.²⁶ A study by Gerrits *et al.*³⁸ found a 20% increase in evoked quadriceps muscle strength after 12 weeks using both low and high electrical frequencies as well as significant improvement in muscle fatigue with the use of low stimulation frequencies after 2 weeks of NMES.

Surface NMES RT has resulted in increasing knee extensor muscle size by almost 40%.^{26,33,54,55} Training was performed 2 days/week for 12 weeks, with training sessions consisting of four sets of 10 NMES-induced knee extensions lasting for 45 minutes. A 5-second work/rest ratio was used with a 3-minute rest between sets, 30 Hz, 450 μ s pulses and a current sufficient to evoke full knee extension.^{26,33,54–58} In these studies,

RT was applied via progressive increase in ankle weights and knee extension was performed while participants were sitting in their wheelchairs with the weights attached to their shins. Once the participant attains 40 repetitions of full knee extension, the weights were progressed by 2 lbs. The weight was gradually progressed to avoid strenuous bending torque on femoral and tibial condyles. In our experience, the maximum loading after 16 weeks of training was 26 lbs/leg. A previous study recommended that ankle weights should not exceed 33 lbs or 15 kg to protect against condylar fracture during dynamic leg extension.⁵³ The effects of this training protocol on body composition and skeletal muscle adaptation are listed in Table 1. A recent study documented a similar increase in the CSA of the knee extensor muscle group following 16 weeks of RT.⁵⁸ Contrary to previous findings that showed improvement in glucose homeostasis and insulin sensitivity, the study did not document improvement in the glucose or insulin profiles.⁵⁸ However, the study showed 25% improvement in mitochondrial function as measured by the phosphocreatine rate.

RT been shown not only to evoke hypertrophy of the trained knee extensors, but also evoke muscle hypertrophy of the surrounding thigh muscles (hamstrings, adductors, gracilis, and sartorius).^{55–57} Gorgey *et al.*⁵⁶ investigated the effects of this training paradigm on surrounding muscle groups as well as proximal trunk muscles. The findings suggested that evoking RT via exercising the knee extensor muscle groups can lead to hypertrophy of the surrounding thigh muscle groups. However, this type of training does not load proximal trunk muscles to evoke muscle hypertrophy.⁵⁶

Table 1 provides a list of the studies that were conducted to examine the effects of FES-LCE and NMES on body composition in a chronological order. In these studies, the purpose of conducting the studies, characteristics of the study population, and body composition assessment methods and primary outcomes were highlighted.

Summary of outcomes of NMES and FES on body composition

Table 1 lists 22 studies focused primarily on studying body composition after SCI. The methods of studying body composition varied widely and included thigh circumference, bioelectrical impedance, dual-energy X-ray absorptiometry (DXA), computerized tomography, and magnetic resonance imaging (MRI). Sixteen studies used FES-LCE (73%) compared to only six studies that used surface NMES training (27%). The duration of the studies ranged from 6 weeks to 2 years. Training

frequency ranged from twice weekly up to 5 days/week. Most of the studies did not provide a clear rationale for the choice of the frequency or the duration of the intervention. The range of effects in twice-weekly exercise overlapped the range of 3–5 days/week, suggesting that twice weekly would be a sufficient training frequency to evoke muscle hypertrophy, and offset several of the body composition and metabolic disorders after SCI. Scremin *et al.*³⁴ found no correlation between the total number of exercise sessions and the magnitude of muscle hypertrophy. A possible explanation is that skeletal muscle in persons with SCI is highly fatigable due to the transformation in fiber types and high susceptibility to muscle damage. This may result in a low frequency fatigue, which may cause decline in evoked torque 48–72 hours following an acute bout of NMES training which in turn may limit the effectiveness of frequent exercise sessions.^{58,63–65} The available evidence does not support that 16 weeks of training are any better than 12 weeks of training as far as the increase in skeletal muscle size.

The effects of training protocols on body composition were modest and likely to be limited by the assessment techniques. LM or FFM is likely to increase by 10%, with or without associated reduction in adipose tissue as measured by DXA. Despite the positive physiological adaptations on body composition and skeletal muscle size following training,^{66,67} none of these studies have investigated possible effects of training on regional or visceral adiposity and the associated metabolic disorders. A possible explanation for the lack of training effects on regional adiposity is the failure of appropriate dietary management throughout the designed interventions. Gorgey *et al.*⁶¹ highlighted the significance of providing dietary control especially during longitudinal intervention with FES-LCE. A recent review of literature also highlighted the role of nutrition and dietary control on body composition and metabolic profile after SCI.² Two studies have noted a reduction in absolute and relative intramuscular fat (IMF) as well as visceral adiposity following RT.^{55,57} There is a noticeable improvement in the absolute IMF, as a reduction in the relative IMF could be a result of increasing muscle size. This supports the hypothesis that NMES training may lead to reduction in ectopic adipose tissue accumulation. However, these findings are not universal as a recent study noted no improvement in absolute or relative IMF following 16 weeks of RT.⁵⁸ It is unclear whether the inclusion of three women in this electrically induced RT study may have masked the effects of training on IMF,⁵⁸ because women are less likely to store ectopic adipose tissue compared to subcutaneous

Table 1 Effects of surface neuromuscular (NMES) and FES on body composition in chronological order

References	Purpose	Protocol	Body composition assessment	Results/conclusion
Ragnarsson <i>et al.</i> ³⁷	To determine the effects of FES training on the paralyzed muscles after SCI	Twenty-three males and seven females; age 19–47 years; 11 paraplegic and 19 tetraplegic	CT scans of the mid-shaft of the femurs	<ul style="list-style-type: none"> Increased strength, endurance, and bulk of the stimulated knee extensor muscles. Mid-thigh circumference showed increase by 2.1 inches A greater amount of work on a lower extremity ergometer, both per unit of time and per length of time Increased aerobic metabolism during the training program
Hjeltnes <i>et al.</i> ³⁰	To investigate body composition adaptations after FES-LCE in persons with tetraplegia	Five individuals with tetraplegia (C5–C7) underwent FES-LC training. After a 2-week adaptation period, the subjects performed seven FES-LC sessions per week for 8 weeks	Whole-body DXA and CT scans for lower extremities	<ul style="list-style-type: none"> Increase in LBM from 2%, with decrease in whole body fat content by 2% after training The CSA of quads, hams, gluteus maximus, and gluteus medius muscles, increased by 21% after training
Mohr <i>et al.</i> ⁴²	To examine the effect of exercise on SCI individuals	Ten individuals with SCI (6 with tetraplegia and 4 paraplegia; age 27–45 years; time since injury 3–23 years) trained for 1 year using an FES-LC ergometer; 3 days/week, 30 minutes duration	Muscle biopsy and MRI of the CSA of thigh muscles	<ul style="list-style-type: none"> Increase in thigh CSA by 12% A shift towards more fatigue resistant contractile proteins was found after 1 year of training The percentage of myosin heavy chain (MHC) isoform IIA increased to 61% of all contractile protein and a corresponding decrease to 32% was seen in the fast fatigable MHC isoform IIB
Baldi <i>et al.</i> ³¹	To determine whether FES-CE (loaded) or non-loaded NMES-induced muscle contractions using portable electrical stimulators are capable of preventing disuse atrophy	Three groups FES-CE, NMES-isometric, and control group. FES-CE group rode an Ergys 1 FES bike for 30 minutes three times per week. Load increased by 6 W at 50 rpm	LBM measured at 0, 3, and 6 months using Lunar DXA scanner	<ul style="list-style-type: none"> FES-CE training prevented atrophy in all regions after 3 and 6 months when compared to the control group FES-CE showed increase in lower legs ($9.3 \pm 3.9\%$) and trunk ($7.7 \pm 2.9\%$) lean body mass (LBM) after 6 months when compared to the NMES isometric group The LBM increased in the FES-CE group at all body composition regions
Scremin <i>et al.</i> ³⁴	To determine the magnitude of changes in muscle mass and lower extremity body composition after regular regimen of FES-induced lower extremity cycling	Thirteen men with neurologically motor and sensory SCI participated in three phases of training – phase 1 quad strengthening, phase 2 cycle progression, phase 3 30 minutes continuous cycling. Average protocol was ~52.8 weeks	CT scans of legs to assess muscle CSA before, 65 and 98 weeks after starting the program	<ul style="list-style-type: none"> Study found a generalized increase in individualized skeletal muscle CSA of thigh The ratio of muscle to adipose tissue increased significantly in thighs and calves

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Table 1 Continued

References	Purpose	Protocol	Body composition assessment	Results/conclusion
Dudley <i>et al.</i> ³³	This pilot study was conducted to determine if intermittent, high force actions could increase lower extremity affected muscle size after SCI	Three males about 46 weeks after complete SCI. Conditioning was twice weekly at the subject's home and lasted 8 weeks. Each session and consisted of four sets of 10 repetitions	MRI scans of the thigh was done 6, 11, 24, 46, and 54 weeks post-injury to determine CSA	<ul style="list-style-type: none"> • Training evoked a 20% increase in CSA of the quad • This essentially reversed 48 weeks of atrophy • Muscle CSA of knee extensor muscle group at 54 weeks after SCI was about 75% of AB controls and same as week 6 after SCI
Murphy, <i>et al.</i> ⁶⁸	To investigate possible changes in skeletal muscle morphology and function, as well as hormonal and metabolic effects, after treatment with a selective beta 2-adrenergic receptor agonist	Thirteen individuals with SCI underwent 2-week treatment with salbutamol (2 mg) or placebo (ascorbic acid, 50 mg) twice a day. Program of functional electronic stimulation (FES) cycling for 30 minutes twice a week	Body weight, three measures of leg circumference, muscle fiber area, and total work output per session	<ul style="list-style-type: none"> • Body weight increased by 2.30 kg • The CSA of vastus lateralis muscle increased (1374 ± 493 to $2446 \pm 1177 \mu\text{m}^2$) after salbutamol treatment. • Total work output during FES cycling sessions was increased more during salbutamol treatment (64%) compared with training alone (27%)
Donaldson <i>et al.</i> ⁶⁹	To determine whether strength and endurance for recreational cycling by FES are possible following SCI	Single subject with incomplete SCI performed training for an average of 21 minutes/day for 16 months	Near-isometric or cycling exercise measurements	<ul style="list-style-type: none"> • Training time was 21 minutes/day for 16 months • Subject was able to cycle for 12 km on the level • There was a substantial increase in the measured voluntary strength of the knee extensors
Sköld <i>et al.</i> ³²	To test the hypothesis that FES-CE alter muscle mass, adipose tissue, and spasticity in individuals with motor complete cervical SCI	Fifteen individuals with tetraplegia underwent FES-CE using Ergys 1 bike, cycle 3X weekly for 6 months. Goal was to maintain a total of 30 minutes/session. Load was added each time the subject was able to ride 30 minutes continuously	Twenty-two CT scans of the whole body and whole-body DXA scan were performed	<ul style="list-style-type: none"> • No significant change in body composition during the study. • Muscle tissue was increased by about 10% in the training group • Adipose tissue did not change in the abdomen or in the legs
Mahoney <i>et al.</i> ²⁶	To determine the effects of 12 weeks of evoked RT using surface NMES of the knee extensor muscle groups	Five individuals with complete SCI (C5–T9) participated in the study. Both thighs were trained 2 days/week for four sets of 10 of dynamic knee extensions for 12 weeks.	Serial MRI scans from hip to the knee joint	<ul style="list-style-type: none"> • Skeletal muscle CSA increased by 35 and 39% in the right and the left quadriceps femoris, respectively
Clark <i>et al.</i> ⁷⁰	To determine the effects of discontinuous FES to lower limb muscles (15 minute sessions to each leg twice daily, over a 5-day week, for 5 months) on BMD and FM in individuals with acute SCI (AIS A–D)	Twenty-three individuals underwent FES-CE (13 tetra, 28 ± 9 years, C4–T10) and 10 individuals with SCI were assigned to the control group (CON, 31 ± 11 years, C5–T12, four Tetra)	DXA scans were used to measure bone mineral density (BMD) and FM	<ul style="list-style-type: none"> • FES and CON groups BMD differed significantly at 3 months post-injury. • Regional FM was not different between groups at any time

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Table 1 Continued

References	Purpose	Protocol	Body composition assessment	Results/conclusion
Liu <i>et al.</i> ⁷¹	To investigate the change in body composition, leg girths, and muscle strength of patients with incomplete SCI after FES cycling exercises	Eighteen subjects with incomplete SCI were recruited. Each patient received FES three times per week for 30 minutes/session for 8 weeks	Bioelectrical impedance spectroscopy analysis and thigh and calf girth measurements	<ul style="list-style-type: none"> • A significant increase in bilateral thigh girth after 4 weeks of FES-CE and significant increase in muscular peak torque of knee flexion and extension were found after 8 weeks of training • Besides LBM increased significantly after treatment
Shields and Dudley-Javoroski. ⁵	To determine whether long-term electrical stimulation training of the paralyzed soleus could change this muscle's physiological properties (torque, fatigue index, potentiation index, torque–time integral) and increase tibia BMD	Four men with chronic complete SCI underwent training of one soleus muscle for 30 minutes each day, 5 days/week, for a period of 6–11 months.	DXA scans	<ul style="list-style-type: none"> • The findings highlight persistent adaptive capabilities of chronically paralyzed muscle, but suggest that preventing musculoskeletal adaptations after acute SCI may be more effective than reversing changes in the chronic condition
de Abreu <i>et al.</i> ⁷²	To investigate the effect of treadmill gait training with NMES and BWS on the CSA of quadriceps in complete quadriplegics	Two groups ($n = 8$ NMES) and ($n = 7$ control) partial BWS (30 and 50% of BWS) Training was performed during 6 months, twice weekly for 20 minute sessions.	MRI scans	<ul style="list-style-type: none"> • After 6 months of training, a 15% increase in the knee extensor muscle group CSA occurred • Control group showed no change
Griffin <i>et al.</i> ⁵⁹	To conduct a comprehensive analysis of metabolic, body composition, and neurological profiles before and after 10 weeks of FES cycling	FES-CE, Ergys 2 bike, cycling two to three times per week for 10 weeks. Stimulation frequency 50 Hz for all muscle groups. Target 49 rpm. Total time 30 minutes, allowed up to five rides per session to equal 30 minutes total	DXA scans	<ul style="list-style-type: none"> • Total body weight increased from 153.2 ± 9.32 to 157.76 ± 9.11 lb. • LBM (lb) increased from 96.8 ± 5.61 to 100 ± 5.47 (4%) • Did not see a significant decrease in total body adipose tissue after 10 weeks
Janssen and Pringle ⁴¹	To determine whether a modified FES-LCE improved exercise performance and responses compared with the standard FES-LCE	Twelve individuals with motor complete SCI were recruited for 6 weeks training program (age 36 ± 16 years C4–T11, time since injury 11 ± 9 years)	FES-LCE Instrumentation	<ul style="list-style-type: none"> • Power output, metabolic rate, and lower-limb muscle strength increased significantly following training. 18% increase in bone mineral density of the proximal femur after 3 months of cycle training • Muscle performance of all muscle groups studied markedly improved
Gorgey and Shepherd ⁵⁷	To determine the effect of unilateral RT for 12 weeks on knee extensor and surrounding muscle groups, intramuscular and subcutaneous adipose tissue	A C5 motor complete individual with SCI participated in training, twice weekly using surface NMES and progressive ankle weights	Serial MRI scans from hip to the knee joint	<ul style="list-style-type: none"> • The CSA of knee extensor increased by 43% and individual muscle CSAs experience hypertrophy that ranges from 12 to 38% • IMF decreased by 53%

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Table 1 Continued

References	Purpose	Protocol	Body composition assessment	Results/conclusion
Johnston <i>et al.</i> ⁶⁰	To determine the effects of FES cycling and electrical stimulation on muscle volume and stimulated strength	Thirty children with chronic SCI were randomized to FES cycling, passive cycling, or non-cycling NMES Each group exercised for 1 hour, three times per week for 6 months at home	MRI to measure muscle volume, and electrically stimulated isometric muscle strength testing using a computerized dynamometer	<ul style="list-style-type: none"> • Six months post-training, quadriceps muscle volume increased significantly for NMES non-cycling and for FES-LCE compared to passive cycling • The increase in the NMES group was greater compared to FES-LCE • Stimulated muscle strength increased in FES-LCE and NMES stimulation compared to passive cycling. The increase was greater in FES-LCE compared with the other two groups
Gorgey <i>et al.</i> ^{55,61}	To determine the effect of 12 weeks of RT on aspects of body composition and metabolism after providing dietary recommendations (diet)	Nine individuals with motor complete SCI were randomly assigned into two groups: RT + diet ($n = 5$) or diet ($n = 4$)	Serial MRI scans and DXA	<ul style="list-style-type: none"> • The CSA of knee extensor showed hypertrophy close to 35%, whole thigh by 28%, and hamstring muscle groups by 16% in the RT + diet group • Relative IMF showed decrease by 18% and leg LM increased by 10% in the RT + diet group. • Visceral fat decreased by 25% in the region of L5–S2
Fornusek <i>et al.</i> ⁶²	To investigate effects of FES-evoked cycle training cadence on leg muscle hypertrophy and electrically evoked strength	Eight untrained individuals with chronic SCI underwent 6 weeks of training on an FES cycle bike. For each subject, one leg was randomly assigned to cycling at 10 rpm (LOW cadence) for 30 minutes/day, and the other cycling at 50 rpm (HIGH cadence) for 30 minutes/day, 3 days/week	Pre- and post-training measurements of lower limb circumference were performed at the distal and middle position of each thigh	<ul style="list-style-type: none"> • Mid-thigh girth increased in the LOW-cadence ($6.6 \pm 1.2\%$) group was significantly greater than HIGH-cadence ($3.6 \pm 0.8\%$) group after 6 weeks of training

adipose tissue. Finally, one study noted that low cycling cadence during FES-LCE resulted in larger thigh girth compared to the higher cycling cadence.⁶²

Electrical stimulation and metabolic profile

For the purpose of this review, the term “metabolic profile” refers to adaptations in glucose, insulin, or lipid metabolism. It is well recognized that insulin and lipid profiles may play a role in developing cardiovascular diseases and overall mortality after SCI. A few trials presented successful evidence not only on glucose and lipid metabolism but also on the effects of VO₂, inflammatory biomarkers, or protein expressions. We have chosen to list these trials, because they set clear examples that adaptation in response to training with FES-LCE or NMES is multifaceted and leads to improvement in other parameters while improving glucose and lipid metabolism. Moreover, it expands the physiological understanding of why other trials fail to document positive outcomes in response to a similar training paradigm.

Several trials have shown that NMES or FES-LCE can attenuate the deterioration in metabolic profile following SCI (Table 2). The physiological effects of FES-LCE on improving glucose tolerance, insulin sensitivity, and lipid profile are documented to reduce the associated risks of developing cardiovascular diseases after SCI.^{60–62,73–78}

Hjeltnes *et al.* studied the effects of FES-LCE when performed 7 days/week for 8 weeks in individuals with SCI. They found a 33% increase in insulin-mediated disposal, a greater than two-fold increase in insulin-stimulated glucose transport and a large increase in protein expression of GLUT-4.⁷⁵ Similarly, Chillibeck *et al.*⁷⁶ and Jeon *et al.*⁷⁷ completed studies on adults with motor complete tetraplegia and paraplegia utilizing FES-LCE three times per week for 8 weeks. Chillibeck *et al.*⁷⁶ found increases in GLUT-1 and GLUT-4 of 52 and 72%, respectively; whereas Jeon *et al.*⁷⁷ found reduced blood glucose levels by 12.5% following 8 weeks of FES-LCE, this was accompanied with improvement in glucose utilization and insulin sensitivity as determined by hyperglycemic clamp tests. Ten weeks of FES-LCE (30 minutes for 3 days/week) showed an increase in muscle fiber CSA and total work output.²⁸ Training thrice weekly has shown to be effective in improving VO₂ peak (8%), glucose homeostasis, and insulin resistance after SCI.^{23,24} These data confirm that training results in insulin-independent-mediated glucose disposal via stimulation of GLUT-4. Reversing the process of skeletal muscle atrophy is a desirable outcome in persons with SCI, because skeletal

muscle is the largest anatomical site of glucose disposal ~70%.

One year of FES performed 3 days/week for 30 minute sessions resulted in a 25% increase in insulin sensitivity, as assessed by a hyperinsulinemic, euglycemic clamp, in 10 subjects with a SCI in the cervical or thoracic region.⁷⁸ Similarly, 8 weeks of daily lower extremity FES resulted in a 33% improvement in insulin sensitivity for five men with cervical SCI. Euglycemic, hyperinsulinemic clamps were performed 48 hours after a single exercise bout to determine if a single bout of moderate intensity exercise would alter tissue sensitivity to insulin in SCI. Kjaer *et al.*⁷⁹ found that training three times weekly with NMES increased VO₂ peak by 8% and improved glucose homeostasis and insulin resistance after SCI. Mohr *et al.*⁷⁸ completed a study utilizing FES-LCE three times weekly for 12 months and found an increased insulin-stimulated glucose uptake and an 105% increase in GLUT-4 during intense exercise. When exercise intensity was reduced the insulin sensitivity and GLUT-4 levels returned to pre-training levels. Griffin *et al.*⁵⁹ found improvements in blood glucose levels and insulin sensitivity with FES-LCE sessions held two to three times per week for 10 weeks.

In a case report on a young adult male with motor complete SCI, Gorgey *et al.*⁶¹ documented that 21 weeks of FES-LCE resulted in improvement in fasting insulin and insulin sensitivity as determined by a standard 3-hour intravenous glucose tolerance tests (IVGTTs) in a person with SCI. The IVGTT was used to determine insulin sensitivity and glucose effectiveness. All tests were conducted prior to 21 weeks of training and 72 hours following the final exercise bout. Fasting insulin decreased by 24% and peak insulin decreased by 30%. The improvement in insulin sensitivity occurred despite the unanticipated adaptation in body composition that was characterized by a 29% increase in FM.⁶¹

The aforementioned trials on carbohydrate metabolism vary in the length of the FES intervention from 8 weeks up to 1 year. It appears that improvement in glucose tolerance and insulin sensitivity has been attained following short duration of FES training; this could be partially explained by the ability of FES to condition and regain the size of the trained muscles.

RT was associated by improvement in glucose tolerance and enhanced insulin sensitivity. The development of metabolically active lean muscle mass could enhance glucose homeostasis and improve lipid profile.^{47–51} The physiological adaptations to skeletal muscle hypertrophy after a period of resistance exercise and the

Table 2 Effects of surface neuromuscular (NMES) and FES on metabolic profile in a chronological order

References	Purpose	Protocol	Method of assessment	Results/conclusion
Chilibeck <i>et al.</i> ⁶³	The study purpose was to determine the effect of FES-LCE on the GLUT-1 and GLUT-4 content of paralyzed skeletal muscle	Five individuals with motor complete (C5–T8) used ERGYS II FES bike 3 days/week for 8 weeks for 30 minutes/session	Muscle biopsies taken pre- and post-8-week training session to look at GLUT-1 and -4 receptors Oral glucose tolerance test (OGTT) was conducted to look at plasma glucose and insulin response to oral glucose load was conducted	<ul style="list-style-type: none"> FES endurance training is effective to increase glucose transport protein levels in paralyzed skeletal muscle of individuals with SCI
Kjaer <i>et al.</i> ⁷⁹	It was hypothesized that FFA mobilization will be reduced in the absence of somatic neural mechanisms. The study allowed evaluation of the interplay among FFA delivery, FFA uptake, and carbohydrate metabolism in the muscle	Ten SCI (C5–T7) exercised for 30 minutes using the ERGYS system at ~1 l/minute O ₂ uptake and [1-14C] palmitate was infused continuously to estimate FFA turnover	Femoral AV-O ₂ difference, blood flow, muscle biopsies, and indirect calorimetry, leg substrate balances as well as concentrations of intramuscular substrates were determined	<ul style="list-style-type: none"> Blood borne mechanisms are not sufficient to elicit a normal increase in fatty acid mobilization during exercise Furthermore, in exercising muscle, FFA delivery enhances FFA uptake and inhibits CHO metabolism
Mohr <i>et al.</i> ⁷⁸	The study examined whether regular FES-LCE increases insulin sensitivity, oral glucose tolerance, and the GLUT-4 content in the stimulated muscles in individuals with SCI	Ten subjects with SCI (C6–T4) performed 1 year of FES cycling (3 days/week for 30 minutes/session). Seven subjects continued another 6 months 1 day/week	Muscle biopsies – GLUT-4 receptors, euglycemic clamp, OGTT	<ul style="list-style-type: none"> FES cycling performed three times per week increases insulin sensitivity and GLUT-4 content in skeletal muscle in subjects with SCI A reduction to 1 day/week was not sufficient to maintain the training effects. FES training may have a role in the prevention of the insulin resistance syndrome in persons with SCI
Crameri <i>et al.</i> ²⁸	To determine the functional and intramuscular adaptations which occur after electrical stimulation training	Six individuals with SCI were recruited for 10 weeks of electrical stimulation leg cycle training (30 minutes/day, 3 days/week)	Muscle biopsies of vastus lateralis muscle	<ul style="list-style-type: none"> Ten weeks of electrical stimulation training of human paralyzed muscle induces concurrent improvements in functional capacity and oxidative metabolism Reduction in the percentage of type IIX fibers (75% to 12%; $P < 0.05$), a decrease in myosin heavy chain IIX (68% to 44%) Increase in capillary density (2–3.5 capillaries around fiber) and increases in activity levels of citrate synthase (7–16 mU/mg protein) and hexokinase (1.2–2.4 mU/mg protein)
Jeon <i>et al.</i> ⁷⁷	The study determined the effect of electrical stimulation (ES)-assisted cycling (3 days/week for 8 weeks for 30 minutes/day) on glucose tolerance and insulin sensitivity in people with SCI	Seven subjects with motor complete (C5–T10) underwent 2 hour OGTT ($n = 7$) and hyperglycemic clamp tests ($n = 3$) before and after 8 weeks of training with ES-assisted cycling 3 days/week for 8 weeks for 30 minutes/day	Two-hour OGTT ($n = 7$) and hyperglycemic clamp tests ($n = 3$) before and after 8 weeks of training	<ul style="list-style-type: none"> Exercise with ES-assisted cycling is beneficial for the prevention and treatment for type 2 diabetes mellitus in people with SCI

Continued

Table 2 Continued

References	Purpose	Protocol	Method of assessment	Results/conclusion
Mahoney <i>et al.</i> ²⁶	To determine the effect of residence-based, RT on affected skeletal muscle size and glucose tolerance after long-standing, complete SCI	Five men with chronic, complete SCI (C5-T9). Subjects performed RT with both thighs, 2 days/week for four sets of 10 unilateral, dynamic knee extensions for 12 weeks. Neuromuscular electric stimulation induced RT by activating the knee extensors	Two-hour OGTT test was performed to assess blood glucose level	<ul style="list-style-type: none"> RT may enhance glucose disposal
Griffin <i>et al.</i> ⁵⁹	To conduct a comprehensive analysis of metabolic, profile before and after 10 weeks of FES cycling with paralysis from SCI	FES cycling two to three times per week for 10 weeks. Stimulation frequency 50 Hz for all muscle groups. Used Ergys 2 bike Target 49 rpm. Total time 30 minutes, allowed up to five rides per session to equal 30 minutes total	OGTT and insulin-response test was performed to assess blood glucose level. Metabolic variables including plasma cholesterol (total-C, HDL-C, LDL-C), TG, and inflammatory markers (IL-6, TNF-alpha, and CRP)	<ul style="list-style-type: none"> Blood glucose and insulin levels were lower following the OGTT after 110 weeks of training TG levels did not change following training Levels of IL-6, TNF-alpha, and CRP were all significantly reduced The NMES group showed declines ($P = 0.032$) in cholesterol levels ($-17.1 \pm 8.5\%$) as compared with the FES-LCE group ($4.4 \pm 20.4\%$)
Johnston <i>et al.</i> ⁸⁰	To examine the effects of FES-LCE on cardiovascular health risks in children with SCI	Thirty children with chronic SCI were randomized to FES-cycling, passive cycling, or non-cycling NMES	Fasting lipid profile was measured before and after intervention	
Gorgey <i>et al.</i> ^{55,61}	The effect of 12 weeks of RT on aspects of metabolism after providing dietary recommendations (diet)	Each group exercised for 1 hour, three times per week for 6 months at home Nine individuals with motor complete SCI were randomly assigned into two groups RT + diet ($n = 5$) or diet ($n = 4$)	Two-hour OGTT and insulin-response test was performed to assess blood glucose level. Additional metabolic variables including plasma cholesterol (total-C, HDL-C, LDL-C), TG	<ul style="list-style-type: none"> Glucose area under the curve (AUC) adjusted to muscle mass was higher before intervention and showed a significant reduction in the RT + diet group with no changes in the diet group Plasma insulin AUC was higher before intervention and non-significantly decreased in the RT + diet group, but not in the diet group The ratio of plasma insulin to plasma glucose concentrations decreased in the RT + diet group compared with the diet group A significant reduction in TG ($P = 0.028$) and cholesterol/HDL-C ($P = 0.017$) in the RT + diet group but not in the diet group A trend towards improvement (10%) in HDL-C was noted in the RT + diet group compared with the diet group. The plasma FFA concentration showed a trend of significant reduction in both groups

associated effects on glucose metabolism and lipid profile have been documented. It is well known that skeletal muscle hypertrophy positively enhances glucose clearance, increases insulin sensitivity and decreases TG level, and enhance high-density lipoprotein cholesterol (HDL-C) levels. Regular voluntary aerobic exercise has been shown to lower high blood TG levels, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and increase levels of the cardioprotective HDL-C.^{81,82} Compared to AB controls, high TC, LDL-C, and HDL-C abnormalities are statistically more frequent in individuals with SCI.^{83,84} Although studies have been more conflicting concerning RT among AB individuals, the incorporation of larger muscle groups of the lower extremities with a high total volume of repetitions and sets is considered most likely to show lipid profile improvement.

Applying RT after SCI is limited to the small muscle groups above the level of injury.⁸⁵ This has limited the associated benefits from exercising large skeletal muscles such as the knee extensor muscle groups.⁸⁵ Applying surface NMES could offer an inexpensive modality to exercise large muscle groups below the level of injury as well as the possibility of applying stimulation for a long duration while sitting in the wheelchair or sleeping in bed. Another option for conditioning paralyzed limbs is home-based FES-LCE. This activity may include distant monitoring through use of the internet.^{43–45} A home-based study examined the effects of training on lipid profile in children with SCI ages 5–13 years and with injury levels from C4 to T11.⁸⁰ The children were randomly assigned to FES-LCE using the RT300, passive leg cycling using the RT100 motorized cycling, and NMES (non-FES-control group). Thirty children exercised 1 hour three times per week for 6 months at home with parental supervision. There were no differences between groups over time in any of the lipid variables. The electrical stimulation group showed declines in cholesterol levels by 17% as compared with the FES-LCE group by 4.4%, despite improvement in oxygen uptake by 16% following FES-LCE compared to the other two strategies.⁸⁰ The findings may suggest that FES-LCE is not necessary to achieve desirable metabolic adaptations.

Solomonow *et al.*⁸⁶ studied eight adults with paraplegia who were diagnosed with high TC levels utilizing a combination of a reciprocating gait orthosis powered by FES three times per week for 14 weeks. The study investigated the effect on the lipid panel. The result was a significant reduction in TC, LDL-C, LDL-C/HDL-C ratio, and TC/HDL-C ratio. Ward *et al.*⁸² found a significant decrease in TC/HDL and non-

significant decreases in TC, and LDL along with a non-significant increase in HDL for four adults with motor complete tetraplegia by using a combination of FES-LCE for 1 hour three times per week and NMES with a portable unit for 1 hour three times per week for 12 months. Twelve weeks of evoked RT in adults with chronic motor complete SCI showed improvement in lipid profile. There were significant declines in TG (38%) and TC/HDL-C (14%) in the training group. A trend towards improvement (10%) in HDL-C was also noted in the RT group.⁵⁵

Summary of the outcomes of NMES and FES on metabolic profile

The number of trials that were conducted to study the effects on body composition outweighs the number of trials investigating the metabolic profile (Table 2).

A training frequency of two to three times weekly of NMES or FES resulted in increasing glucose disposal via increasing GLUT-4 expression, insulin sensitivity, and a shift in the histochemical properties of the trained muscle by transformation from fast twitch to oxidative glycolytic fibers. This may lead to reduction in IMF deposition and reduction in inflammatory biomarkers that leads to improvement in insulin sensitivity. Limited evidence exists on the effects of training on lipid profile in persons with SCI; it appears from two separate studies that NMES showed declines in cholesterol and TG levels.^{55,86} Improvement in insulin sensitivity may be accomplished despite without changes in body composition,⁶¹ which may suggest that increased muscle mass is more important than decreased FM to the metabolic parameters studied. The effect of training on lipid profile remains debatable as a handful of trials have shown modest improvement in lipid panels while others documented no changes. The explanation for such discrepancy is not clear and more studies are needed to investigate the effects of training on lipid profiles in persons with SCI.

Barriers to applications of NMES or FES

A common barrier to applications of NMES or FES training is the lack of facilities that contain these specialized modalities. Other facilities may not be accessible to individuals with SCI or may lack space to house FES bikes and other adaptive equipment. Typically, facilities need to be equipped with ceiling lifts or portable mechanical lifts to transfer individuals with SCI. Several trials have encouraged home-based applications of NMES and FES to overcome the barriers that may result from traveling to specialized facilities.^{43–47} However, the cost of acquiring FES for home use is prohibitive

to individuals with SCI as the support from health insurance companies is limited. Therefore, the lack of accessible facilities or equipment may compromise the overall health of persons with SCI. It is also worth noting that training with NMES or FES may not be possible for a large segment of individuals with SCI, for instance, those with SCI below T10 who commonly experience peripheral denervation or those with severe lower extremity osteoporosis and previous history of low trauma or fragility fractures. Although rare, fractures can occur during electrical stimulation activity when severely low bone mineral density is combined with a very strong muscle spasm.⁸⁷ Strong muscle spasms or co-contraction between the agonists and the antagonist muscles may lead to bony fracture. Due to this risk, it is advisable to utilize an FES cycle that offers a spasm control safety mechanism which stops the activity when resistance due to spasm is detected. Therefore, it is advisable to provide alternative approaches for individuals with SCI who cannot benefit from FES-LCE training.

Another aspect that it is worth highlighting is the lack of consensus about the stimulation parameters including the amplitude of current, frequency, and pulse durations used in training persons with SCI. For example, thigh composition may impact the amplitude of the current needed to evoke dynamic leg extension via NMES. A person with SCI that has a high degree of FM or IMF may impede the propagation of the current compared to leaner individuals with SCI.⁸⁸ Several authors have utilized low frequency stimulation (20–30 Hz) to attenuate the process of rapid muscle fatigue during stimulation. Pulse durations of 300 μ s or more are recommended to ensure greater muscle activation, with the consideration not to deliver noxious stimuli that can cause autonomic dysreflexia. Studies vary greatly concerning the frequency of applications from twice to seven times weekly which leads to speculation about the optimal number of sessions per week.^{31,42,46,55,59,61,75–79} Supporting evidence indicate that skeletal muscles of untrained individuals with SCI are highly fatigable and may be susceptible to exercise-induced muscle damage up to 72 hours post-stimulation.^{64,65} This may suggest that a frequency of twice to thrice weekly may be appropriate for untrained individuals with SCI.

Conclusion

The current review summarizes evidence demonstrating the efficacy of NMES or FES training in increasing skeletal muscle size and soft tissue LM. Augmenting skeletal muscle hypertrophy and increasing LM could have significant health-related benefits after SCI and may help

in reducing several of the associated metabolic disorders. There is a lack of knowledge about the effects of training on adipose tissue or regional adiposity especially on visceral adiposity or ectopic adipose tissue and also concerning metabolic changes due to weight loss through diet alone. The evidence on carbohydrate metabolism is well established; however, the effects on lipid metabolism are modest and debatable. There remains no consensus on the optimal duration, frequency, and length of training in persons with SCI. Based on current literature, it appears that training frequency of three or more days per week is not superior to 2 days/week. FES-LCE exercise and RT activities have been shown to produce improvements in muscle mass, glucose metabolism, and insulin sensitivity while NMES has been shown to increase muscle mass. Additional metabolic studies are needed before declarative statements can be made about the importance of electrical stimulation activities on human metabolic profiles after SCI.

Acknowledgments

The authors apologize that all the outstanding work in this area could not be cited because of the space limitations. We would like to thank Dr Lance Goetz for his time and effort to proof read and edits our revised manuscript. Ashraf S. Gorgey is supported by the Department of Veteran Affairs (VA) RR&D.

Disclaimer statements

Contributors All authors contributed to literature search and writing.

Funding None.

Conflicts of interest None.

Ethics approval None.

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