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Cardiovascular Health and Exercise Rehabilitation in Spinal Cord Injury

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Abstract

There appears to be an increased prevalence and earlier onset of cardiovascular disease (CVD) in persons with SCI. Physical inactivity is thought to be a key factor in the increased risk for CVD. Physical inactivity is highly prevalent in persons with SCI and it appears that activities of daily living are not sufficient to maintain cardiovascular fitness and health. This systematic review examines the current literature regarding the risk for CVD and the effectiveness of varied exercise rehabilitation programs in attenuating the risk for CVD in SCI.

Keywords

Cardiovascular disease; spinal cord injury; exercise rehabilitation; glucose homeostasis; lipid lipoproteins; rehabilitation; fitness

INTRODUCTION

Persons with spinal cord injury (SCI) currently have an increased life expectancy owing to improvements in medical treatment [1]. The majority of SCI (80%) occur in individuals who are under 30 years of age [1, 2]. Therefore, persons with SCI are susceptible to the same chronic conditions across the lifespan as able-bodied persons. In fact, cardiovascular disease (CVD) is the leading cause of mortality in both able-bodied individuals and persons with SCI [3]. However, there appears to be an earlier onset of CVD and/or an increased prevalence of CVD in SCI [3–6]. As reviewed by Myers et al. [7] there is consistent information indicating that there is a higher prevalence of CVD in persons with SCI in comparison to ambulatory populations [8]. For instance, the prevalence rates of symptomatic CVD in SCI have approximated 30–50% in comparison to 5–10% in the general able-bodied population [7]. Moreover, Bauman and colleagues revealed that the prevalence of asymptomatic CVD was

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60–70% in persons with SCI [9, 10]. Others have reported prevalence rates of asymptomatic CVD of approximately 25–50% [7]. It also appears that persons with SCI have increased CVD-related mortality rates and experience mortality at earlier ages in comparison to able-bodied individuals [3, 7, 11]. These are alarming statistics, which place a significant burden upon the patient, his/her family and society as a whole.

Physical inactivity is a major independent risk factor for CVD and premature mortality [12]. Unfortunately, physical inactivity and marked deconditioning are highly prevalent amongst persons with SCI [13]. It is likely that low levels of physical activity and fitness (as a result of wheelchair dependency) explain (in part) the increased risk for CVD [7]. For instance, marked inactivity associated with SCI has been associated with lower high-density lipoprotein (HDL) cholesterol [14, 15], elevated low-density lipoprotein (LDL) cholesterol [14], triglycerides [14, 15], and total cholesterol levels [14], abnormal glucose homeostasis [15, 16], increased adiposity [15, 16], and excessive reductions in aerobic fitness [14, 15]. It is important to note, that SCI presents an additional risk for CVD above that seen in able-bodied individuals owing to the marked decrease in physical activity and injury-related changes in metabolic function [17].

METHODOLOGY

The primary data base was obtained by a systematic computerized search of multiple databases (including PubMed/Medline, CINAHL, Embase, PsychInfo) from 1980 to 2006 using the SCIRE methodology as outlined in the companion paper [18]. This database was searched using the keywords of spinal cord injury, tetraplegia, quadriplegia or paraplegia, paired with aerobic fitness, blood pressure, cardiovascular disease, cardiovascular fitness, endurance performance, endothelium, exercise, exercise tolerance, FES, glucose intolerance, glucose sensitivity, health, lipid, maximal aerobic power (VO_2max), oxygen consumption and rehabilitation. This analysis was restricted to English publications and those using human participants. A quality assessment of each investigation was conducted using the Physiotherapy Evidence Database Scale (PEDro) [19] for all randomized controlled trials (RCT) or the Downs and Black tool [20] for all non-RCTs. The PEDro Scale [19] was used to evaluate the methodological quality of randomized controlled trials (RCTs). It evaluates RCT studies using an 11-item scale yielding a maximum score of 10. Higher scores indicate better methodological quality (9–10: excellent; 6–8: good; 4–5: fair; <4: poor) [18]. The D&B Tool [20] which is used to assess the methodological quality of non-RCT studies, uses 27 questions to assess reporting, external validity, and internal validity (bias and confounding). We used a modified version of the D&B Tool[18] to score non-RCT papers out of a maximum of 28, with higher scores indicating better methodological quality.

After each study was rated with the appropriate tool, conclusions about the level of evidence of the accumulated studies were drawn using Sackett's description of levels of evidence [21]. We collapsed Sackett's levels of evidence into 5 categories where Level 1 evidence came from "good" to "excellent" RCTs with a PEDro score ≥6 and Level 2 evidence corresponded to RCTs with PEDro scores ≤5 or non-randomized prospective controlled or cohort studies. Evidence from case control studies were assigned to Level 3, while Levels 4, and 5 corresponded to evidence from pre-post/post-test/case-series and observational/case report studies, respectively [18]. Note that since there were no sample size restrictions, level 1

conclusions could be based on small group sizes, however, these studies were rated highly according to the standardized Pedro Scale.

RESULTS

Exercise rehabilitation has been shown to be an effective means of attenuating or reversing chronic disease in persons with SCI. However, supporting evidence is relatively low in comparison to the general population and other clinical conditions (e.g. chronic heart failure [12]).

The research conducted within the field of SCI has examined predominantly the effects of aerobic exercise and/or functional electrical stimulation (FES) training. In the following sections we will review the literature regarding the effects of varied exercise interventions on the risk for CVD. Particular attention will be given to the changes in cardiovascular fitness, glucose metabolism, and lipid lipoprotein profiles that occur after SCI training interventions.

Our search revealed 42 studies examining cardiovascular fitness before and after an exercise intervention. This included investigations related to treadmill training (4 studies; n=47), arm exercise (20 studies; n=278), and FES (18 studies; n=233) training.

Treadmill Training

Body-weight supported treadmill training (BWSTT) is an exercise protocol that has been used to potentially affect a number of domains, including motor recovery, bone density, cardiovascular fitness, respiratory function as well as quality of life. Traditional BWSTT involves the upright walking on a motor-driven treadmill while a harness (suspended from an overhead pulley system) supports the participant's body weight. Therapists conducting the session determine the magnitude of off-loading of an individual's bodyweight [22]. The treadmill velocity, the amount of body weight supported, and time spent on the treadmill can be individualized [22]. Significant resources are often required as the majority of individuals will require one or two assistants to manually move the limbs forward.

Two pre-post studies have been conducted by the same research group using BWSTT [23, 24] to determine changes in cardiovascular health. The authors reported that BWSTT did not have substantial group effects on heart rate (HR) and blood pressure in motor complete subjects, but did reveal a significant reduction in resting HR in the study with incomplete tetraplegics. There was also evidence that improvements in HR and blood pressure variability may occur after BWSTT in incomplete SCI and a subset of participants with complete SCI. The authors attributed the change in blood pressure variability to reductions in sympathetic tone to the vasculature. These findings have significant physiological relevance since it indicates that both parasympathetic outflow to the heart (as evaluated by heart rate variability) and sympathetic flow to the vasculature (as evaluated by blood pressure variability) can adapt in response to exercise training. This research group also revealed the potential for improvements in vascular health (e.g. arterial compliance) after BWSTT in individuals with motor-complete SCI. There was no indication of the effects of BWSTT on peak oxygen consumption (VO_2peak).

The mechanisms responsible for the improvement in markers of cardiovascular health and regulation in individuals with incomplete SCI remain to be determined. The authors of the aforementioned studies attributed the training-induced changes in autonomic function to the cardiovascular challenge provided by the upright nature of BSWTT (which potentially could be a sufficient stimulus in individuals with postural hypotension) and the spasticity created during the treadmill training. However, it should also be noted that both weight-bearing and the passive movement of the limbs may contribute to the observed changes in these studies.

Two recent investigations (a pre-post study (Level 4) and a prospective controlled study (Level 2)) from the same research group used partial BWSTT (30–50%) via neuromuscular electrical stimulation assisted by physiotherapists [25, 26]. The first investigation revealed that 3 months of this form of gait training can result in a significant increase in systolic blood pressure at rest and during gait exercise in tetraplegic males [25]. In the latter study [26] the authors revealed that long-term neuromuscular electrical stimulation gait training (6 months) resulted in significant increases in VO_2 (36%), minute ventilation (30.5%), and systolic blood pressure (4.8%) during gait phase. The authors concluded that treadmill gait training combined with neuromuscular electrical stimulation leads to increased metabolic and cardiorespiratory responses in persons with complete tetraplegia.

In a comparison of trials using BWSTT an interesting discrepancy arises. For instance, in the work of Ditor et al. [23, 24] there was no change in resting blood pressure after BWSTT in individuals with complete or incomplete SCI. Whereas, the work by de Carvalho and coworkers [25, 26] revealed an increase in resting blood pressure following partial BWSTT (with neuromuscular electrical stimulation). It is not clear why these discrepancies exist and as such further research is clearly warranted.

In summary, there is level 4 evidence that BWSTT improve cardiac autonomic balance in persons with incomplete tetraplegia. There is also level 4 evidence that BWSTT can lead to improvements in cardiac autonomic balance in a subset of individuals with motor-complete SCI who respond to ambulation with moderate to large increases in heart rate. Moreover, preliminary level 4 evidence indicates that BWSTT can improve arterial compliance in individuals with motor-complete SCI. There is also level 2 evidence that neuromuscular electrical stimulation gait training can increase metabolic and cardiorespirtory responses in persons with complete tetraplegia.

Upper Extremity Exercise

Given the motor loss of the lower limbs, upper extremity exercise is a logical choice. Improving cardiovascular fitness can be challenging using the smaller mass of the arms especially when muscle fatigue can often occur before endurance training targets are met. From our search, we found four RCT (1 high quality [27] and 3 lower quality trials [28–30]), two prospective controlled [31, 32], and fourteen pre-post studies. Given the large number of studies which have looked at upper extremity exercise, we have tabled only those studies which included a SCI control group (Table 1).

The reported improvements in aerobic capacity after aerobic arm training in SCI are approximately 20–30%; however, it is not uncommon for improvements in excess of 50% [33].

The majority of aerobic training investigations have evaluated the effectiveness of moderate (40–59% heart rate reserve (HRR) or 55–69% of maximum HR) to vigorous (60–84% HRR or 70–89% of maximum HR) intensity exercise. These studies have used arm ergometry, wheelchair ergometry, and swimming based interventions. Based on the current level of literature, it appears that moderate intensity exercise performed 20–60 min per day, at least 3 days per week for a minimum of 6 weeks is effective for improving cardiovascular fitness and exercise tolerance in persons with SCI (Level 1 evidence based on 1 high quality RCT [27] and several lower quality RCTs). Therefore, the general recommendations provided by agencies such as the Canadian Society for Exercise Physiology are appropriate for improving the cardiovascular fitness of persons with SCI. It is however important to note that training intensities may need to be established using a rating of perceived exertion (e.g. RPE) (rather than objective measures of heart rate) in individuals with SCI-induced autonomic denervation of the heart.

An exercise intensity threshold of 70% maximal HRR has been advocated for the attainment of training benefits when a minimal training duration (20 min) is the standard [31, 34, 35]. It is also apparent that improvements in exercise capacity and functional status may occur after training without significant changes in VO_2peak, particularly in tetraplegic patients [32].

Questions remain regarding the primary mechanisms of importance for improvements in aerobic fitness after training. It is unclear whether central (heart and lung) or peripheral (skeletal muscle) adaptations are of key importance. Improvements have been observed in peripheral muscle function. For instance, investigators have shown intrinsic cellular adaptations in the paralyzed muscle that facilitate oxidative metabolism following BWSTT [36]. Only limited investigations, however, have shown an improvement in cardiac function after aerobic exercise training [28]. It could therefore be argued that peripheral adaptations are of primary importance to the improvement in aerobic capacity after aerobic exercise. However, this statement is somewhat misleading as the majority of studies have not evaluated directly cardiac output during maximal/peak exercise. This is owing to the fact that the assessment of maximal cardiac output during exercise is one of the most difficult procedures in clinical exercise physiology [37, 38]. When exercise measures of cardiac function have been taken, improvements in central function have been observed [28]. Further research examining the primary mechanism(s) of importance for the improved cardiovascular fitness and exercise capacity seen in SCI after aerobic exercise training is warranted. It is also important to highlight that it is often difficult for patients to attain VO_2 max during exercise conditions. Moreover, the submaximal prediction of VO_2 peak/VO_2 max (based on the heart rate response to exercise) is limited owing to the potential impairment in the sympathetic drive to the heart in many persons with SCI. Furthermore, it is often difficult to determine whether the changes in VO_2peak/VO_2max seen after training are related to changes in musculosketelal fitness (e.g. rather than changes in cardiovascular fitness).

Less is known about the effects of resistance training on cardiovascular fitness. However, the incorporation of resistance training into the treatment of SCI appears to be essential. In fact, muscle weakness and dysfunction are key determinants of pain and functional status in SCI.

Previous studies have revealed improvements in VO_2peak/VO_2max [39, 40], exercise tolerance [40], and musculoskeletal fitness [40] after resistance training (such as circuit training).

In summary, there is level 1 evidence that moderate intensity aerobic arm training (performed 20–60 min/day, 3 days/week for at least 2 months) is effective in improving the aerobic capacity and exercise tolerance of persons with SCI. Recent research also indicates level 1 evidence that vigorous intensity (70–80% HRR) leads to greater improvements in aerobic capacity than moderate intensity exercise. It remains to be determined the relative importance of changes in cardiac function and the ability to extract oxygen at the periphery in persons with SCI after aerobic training.

Functional Electrical Stimulation (FES)

Computer-assisted FES during leg cycling has been shown to be an important and practical means of exercising a relatively large muscle mass in persons with SCI [41]. These devices also permit the activation of the skeletal muscle pump during leg cycling. For these reasons, FES training has been advocated widely as an effective SCI treatment strategy.

There is a growing body of literature indicating that FES exercise training is effective in improving cardiovascular health, peak power output, and exercise tolerance/capacity in persons with SCI (Table 2). This research generally employs a cycling motion, although rowing and bipedal ambulation have also been evaluated. It appears that moderate-to-vigorous intensity FES training (relative to baseline capacity) is effective to improve cardiovascular fitness in persons with SCI. The majority of the investigations are pre-post designs (Level 4) with investigators reporting marked changes in VO_2max or VO_2peak after FES training. Similar to aerobic training, 20–40% changes in aerobic capacity are often observed after FES training. However, it is not uncommon for improvements in excess of 70% [42].

Investigations with FES training have also shown an improvement in musculoskeletal fitness. Similar to arm exercise training, limited investigations have shown an improvement in cardiac function after FES training. A recent investigation has also revealed that the degree of muscular adaptation that can be achieved via FES exercise is dependent upon the load that is applied to the paralyzed muscle [43].

Researchers have also shown that hybrid exercise training (FES-leg cycling combined with arm ergometry) may elicit greater changes in peak work rates and VO_2peak/VO_2max than FES-leg cycling exercise alone [44, 45]. Moreover, it appears that the physiological adaptations to combined FES-leg cycling and arm ergometry training are maintained partially following 8 weeks of detraining [46]. Other interventions (Table 3) that make use of hybrid FES training have also been shown to improve the exercise capacity and cardiovascular health status in SCI. It would appear that the potential adaptations with hybrid exercise may be greater than FES alone; however, further research is required to test this hypothesis.

A series of intrinsic muscle adaptations can also occur after FES training that enhance the ability for oxidative metabolism at the cellular level, which in turn facilitate improved endurance, exercise tolerance and functional capacity. Key intrinsic muscle adaptations that

have been observed include an increase in the proportion of type 1 fibres, an enhancement in cross-sectional fibre area, an increase in capillary number, a shift towards more fatigue resistant contractile proteins, and increased citrate synthase and hexokinase activity [43, 47–49]. Given the importance of musculoskeletal fitness for health and functional status [50–52] further research is clearly warranted in persons with SCI. Randomized, controlled exercise interventions (both arm and/or FES training) that evaluate concurrent changes in musculoskeletal fitness and health status are particularly needed.

In summary, there is Level 4 evidence from pre-post studies that FES training performed for a minimum of 3 days per week for 2 months may be effective for improving musculoskeletal fitness, the oxidative potential of muscle, exercise tolerance and cardiovascular fitness.

Glucose Homeostasis

Glucose intolerance and decreased insulin sensitivity are independent risk factors for CVD [53]. Abnormal glucose homeostasis is associated with worsened lipid-lipoprotein profiles and an increased risk for the development of hypertension and type 2 diabetes [50, 51, 53]. It is well-established that habitual physical activity is an effective primary preventative strategy against insulin resistance and Type 2 diabetes in the general population [52]. Although comparatively less information is available for SCI, it appears that exercise training programs are effective in improving glucose homeostasis [22, 27, 54–56].

The majority of the data is from experimental non-RCT trials. A search of the literature revealed 7 investigations (n = 47). This included one RCT [27] and six experimental non-RCT (pre-post) trials [22, 54–58]. The one RCT involved the randomization to two different forms of exercise, and as such an exercise condition served as the control (Table 4). The majority (5) of these trials examined the effectiveness of FES training.

Similar to other studies in the field of SCI research, this area of investigation is limited by the lack of quality RCT. Moreover, the majority of the research relates to the effects of FES training. Limited work has been conducted using aerobic and/or resistance exercise training. As a whole, however, these studies are consistent and reveal several important findings. For instance, the improvements in glucose homeostasis may be the result of increased lean body mass (an associated changes in insulin sensitivity), and increased expression of GLUT4, glycogen synthase, and hexokinase in exercised muscle.

Consistent with findings in able-bodied individuals [50, 51], the improvement in glucose homeostasis after exercise interventions (such as aerobic training or FES) does not appear to be related solely to decreases in body adiposity and/or increases in VO_2max. This is due to the fact that significant improvements in glucose homeostasis can occur with minor changes in body composition and/or aerobic fitness.

It is also important to note that there appears to be a minimal volume of exercise required for improvements in glucose homeostasis. For instance, Mohr et al. [58] revealed that a reduction of FES training was not sufficient to maintain the beneficial changes in insulin sensitivity and GLUT4 protein observed during a 3 days/week FES training program.

In summary, there is level 1 and level 4 evidence that both aerobic and FES training (approximately 20–30 min/day, 3 days/week for 8 weeks or more) are effective in improving glucose homeostasis in SCI.

Lipid Lipoprotein Profiles

Abnormal lipid-lipoprotein profiles have been associated with an increased risk for CVD [12, 50–53]. Several studies have revealed worsened lipid lipoprotein profiles in persons with SCI [59–64]. Routine physical activity has been shown to enhance lipid lipoprotein profiles, e.g., reduced triglycerides (TG), greater levels of HDL and lower LDL/HDL in the general population [12, 50, 51]. Although limited, similar findings have been observed in persons with SCI [27, 31, 36, 65–67] (Table 5).

The information regarding the effects of exercise training on lipid lipoprotein profile is derived from one high quality RCT (level 1) [27], 1 non-randomized prospective controlled trial (level 2) [31] and several level 4 studies[36, 65–67] (N = 110). The majority of the investigations examined a form of aerobic training (either arm ergometry or assisted-treadmill walking). Another investigation examined the effects of reciprocating gait orthosis powered with electrical muscle stimulation.

These findings provide level 1 evidence (based on one high quality RCT and several lower quality studies) for the role of exercise in the reduction of atherogenic lipid lipoprotein profiles and the reduction of the risk for CVD in persons with SCI. It appears that a minimal threshold of training exists for changes in lipoprotein profile. For instance, authors have reported that 70% of maximal HRR (for at least 20 min/day, 3 days/week for 8 weeks) is the threshold necessary to achieve significant improvements in lipid lipoprotein profiles. Future research is warranted, however, to quantify the effects of varying forms of exercise (including aerobic exercise, resistance exercise, and FES) on lipid lipoprotein profiles in persons with SCI.

DISCUSSION

There is a growing body of evidence to suggest that persons with SCI are at an increased risk for CVD. Increasing data indicates that persons with SCI experience an earlier onset and increased prevalence of CVD. Similar to able-bodied individuals, physical inactivity plays a significant role in the risk for CVD in persons with SCI. In fact, the ordinary activities of daily living do not appear to be sufficient to maintain cardiovascular fitness in SCI. Moreover, extremely low levels of physical activity and fitness may lead to a vicious cycle of further decline. Ultimately these changes will have significant implications for the development of CVD (and associated comorbidities) and the ability to live an independent lifestyle. It appears that SCI presents an additional risk for CVD above that observed in able-bodied individuals owing to marked physical deconditioning and injury-related changes in metabolic function (e.g. insulin resistance) [7, 17].

Physical activity interventions have been shown widely to be effective at attenuating the progression of CVD and related comorbidities. The forms of exercise interventions are varied, and the experimental data is limited in comparison to other patient populations (such

as chronic heart failure). However, there is compelling evidence supporting the health benefits of upper extremity aerobic exercise (Level 1 and 4) and FES (Level 4) training (see Tables 6 and 7). For instance, there is research indicating that upper extremity exercise at a moderate to vigorous intensity, 3 days/week for at least 6 weeks improves cardiovascular fitness and exercise tolerance in persons with SCI. It remains to be determined the optimal exercise intervention for improving cardiovascular fitness. There is level 1 evidence [27] that high intensity (70–80% HRR) exercise leads to greater improvements in peak power and VO_2peak than low intensity (50–60% HRR) exercise. Further investigation is required to determine the relative roles cardiac and peripheral muscle function play in the improvement of exercise capacity in SCI. There is level 4 (pre-post) evidence that resistance training at a moderate intensity for at least 2 days/week also appears to be appropriate for the rehabilitation of persons with SCI [39, 40, 54, 67].

There is also growing evidence (predominantly level 4) from several pre-post trials that FES training for a minimum of 3 days per week for 2 months can improve oxidative metabolism [43, 47–49], exercise tolerance [41, 48, 68–71], and cardiovascular fitness [41, 48, 68–72]. There is limited (Level 4) evidence [23, 24] that BWSTT can improve indicators of cardiovascular health in individuals with complete and incomplete SCI.

Preliminary (Level 1 and Level 4) evidence indicates that aerobic and FES exercise training programs (performed 30 min/day, 3 days per week for 8 weeks or more) are effective in improving glucose homeostasis in persons with SCI [27, 57]. The magnitude of change in glucose homeostasis appears to be of clinical significance for the prevention and/or treatment of type 2 diabetes in SCI.

There is level 1 evidence from a 1 high quality RCT [27] and several pre- post studies [31, 36, 65] to suggest that aerobic exercise training programs (performed at a moderate to vigorous intensity 20–30 min/day, 3 days/week for 8 weeks) are effective in improving the lipid lipoprotein profiles of persons with SCI. The optimal training program for changes in lipid lipoprotein profile remains to be determined. However, a minimal aerobic exercise intensity of 70% of HRR on most days of the week appears to be a good general recommendation for improving lipid lipoprotein profile. Preliminary level 4 data also indicates that FES training (3 hr/week for 14 weeks) may improve lipid lipoprotein profiles in SCI [66].

CONCLUSIONS

A growing body of evidence supports the finding of an increased risk for CVD and CVD-related mortality in persons with SCI. Marked physical inactivity appears to play a central role in the increased risk for CVD in SCI. Intuitively, exercise training should lead to significant reductions in the risk for CVD and an improved in overall quality of life in persons with SCI. However, the relationship between increasing physical activity and health status of SCI has not been evaluated adequately to date. Based on preliminary evidence (primarily Level 4) it would appear that various exercise modalities (including arm ergometry, resistance training, BWSTT and FES) may attenuate and/or reverse abnormalities in glucose homeostasis, lipid lipoprotein profiles, and cardiovascular fitness in persons with SCI. As such, exercise training appears to be an important therapeutic intervention for

reducing the risk for CVD and multiple comorbidities (such as type 2 diabetes, hypertension, obesity) in SCI. Future well-designed RCTs are required to establish firmly the primary mechanisms by which exercise interventions elicit these beneficial changes. Similarly, further research is required to evaluate the effects of lesion level and severity on exercise prescription, such that exercise programs can be developed that address the varied needs of persons with SCI. Moreover, long-term follow-up investigations are required to determine whether training-induced changes in risk factors for CVD translate directly into a reduced incidence of CVD and premature mortality in persons with SCI.

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Table 1

Effects of Upper Extremity Training on Cardiovascular Fitness and Health

Author Year Country Score Research Design Total Sample Size	Methods	Key Outcomes
Arm Ergometry		
de Groot et al. 2003[27] Netherlands PEDro=7 RCT N=6	Population: 4 male, 2 female, C5-L1, ASIA A (n=1), B (n=1), C (n=4), age 36yr. Treatment: Interval training (3min exercise:2min rest), 1hr/d, 3d/wk, 8 wk. Randomized to low intensity (50–60% HRR) or high intensity (70–80% HRR).	**1** Greater changes in VO_2peak in the high intensity (59%) versus low intensity group (17%).
Davis et al. 1991[29] Canada PEDro=4 RCT N=24	Population: 8 spina bifida, 16 traumatic, age 17–42yr. Treatment: Random assignment to 1) control or 1 of 3 arm ergometry programs 2 d/wk, 24 wk: 1) high-intensity long duration (40 min at 70% VO_2peak), 2) high-intensity short duration (20 min at 70% VO_2peak), and 3) low- intensity short duration (20 min at 50% VO_2peak) training.	**1** Training increased VO_2peak in the 3 arm ergometry groups (~21%). **2** There were increases in submaximal stroke volume and cardiac output in the high intensity long and the low intensity long training groups. **3** The low intensity short duration training and control groups exhibited small non-significant decreases in stroke volume.
Davis et al. 1987[28] Canada PEDro=4 RCT N=14	Population: Sedentary SCI (n=9 exercise group, n=5 control group), age 20–39yr. Treatment: Arm ergometry, 50–70%VO_2peak, 20–40min/d, 3d/wk, 16wk	**1** Significant improvement in VO_2peak (31%) and HR (−9.5%) with training. **2** During isometric handgrip exercise, decreased rate pressure product (20%), and increased stroke volume (12–16%).
Hjeltnes & Wallberg-Henriksson 1998[32] Norway D&B=16 Prospective Controlled Trial N=27	Population: Exercise group: 10 tetraplegia, C6-8, 7 ASIA A & 3 ASIA B, Control: 10 paraplegia, T7-11, all ASIA A. Treatment: Exercise group: standard rehabilitation + Arm ergometry, 30min/d, 3d/wk, 12–16wk; Control: standard rehabilitation.	**1** Tetraplegics increased peak workload (45%) with no change in VO_2peak. **2** Peak workload (45.5%) and VO_2peak (27.7) increased significantly in the paraplegics. **3** No change in peak HR, systolic BP, submaximal exercise stroke volume or cardiac output in either SCI group.
Mixed Arm and Other Exercise		
Hicks et al. 2003[30] Canada PEDro=5 RCT N=23	Population: 18 tetraplegia and 16 paraplegia, ASIA A-D, C4-L1, ages 19–65 yr. Treatment: Exercise: 90–120min/d, 2d/wk, 9mth of arm ergometry (15–30 mins, ~70%VO_2max) and circuit resistance exercise. Control group: bimonthly education session.	**1** Power output increased by 118% and 45% after training in the tetraplegic and paraplegic groups, respectively. **2** There were progressive increases in strength over the 9 months of training (ranging from 19–34%).
Wheelchair Ergometry		

Author Year Country Score Research Design Total Sample Size	Methods	Key Outcomes
Hooker & Wells 1989[31] USA D&B=9 Prospective Controlled Trial N=8	Population: Low-intensity group n=6, C5-T7, moderate- intensity group n=5, C5-T9. Treatment: Wheelchair ergometry 20min/d, 3 d/wk, 8 wk: Low-intensity (50–60% max HRR) and moderate-intensity (70–80% max HRR).	**1** The moderate-intensity group had significantly lower post-training submaximal HR, lactate, and RPE but no changes in oxygen consumption. **2** 70% maximal HRR appears to be the beneficial training threshold.

Table 2

Effects of Functional Electrical Stimulation on Cardiovascular Fitness

Author Year; Country Score Research Design Total Sample Size	Methods	Key Outcomes	
Mohr et al. 1997[48] Denmark D&B=14 Pre-post N=10	Population: 6 tetraplegia at C6, 4 paraplegia at T4, all complete, ages 27–45yr, 3–23yr post-injury. Treatment: One-year exercise training using an FES cycle ergometer (30min/d, 3d/wk).	**1**	4-fold increase in work output and 12% increase in thigh muscle mass with FES.
		2	VO_2max increased 17.5% (6mth) and 19.2% (12mth).
		3	Shift towards more fatigue resistant contractile proteins and a doubling of citric synthase activity.
Ragnarsson et al. 1988[73] USA D&B=14 Pre-post N=19	Population: 16 male, 3 females (7 paraplegics T4-T10, 12 tetraplegics C4-C7), ages 19–47yr, 2–17yr post-injury. Treatment: Phase I: quadriceps stimulation with dynamic knee extensions against increasing resistance, 3 d/wk, 4wk. Phase II: leg-cycle FES, 15–30 mins/day, 3 days/week for 12 weeks.	**1**	Most showed an increase in strength and endurance.
		2	VO_2peak increased non-significantly (14.9%) after training.
Hooker et al. 1992[41] USA D&B=13 Pre-post N=18	Population: 17 males, 1 female, 10 tetraplegia (C5-C7), 8 paraplegia (T4-T11), 7 incomplete, age 30.6yr, 6.1yr post-injury. Treatment: FES leg cycle training 10–30min/d, 2–3d/wk, 12–16wk.	**1**	Increase in power output (45%), VO_2peak (23%), cardiac output (13%), HR (11%), and a reduction in total peripheral resistance (−14%) during peak FES leg cycle.
		2	No changes in stroke volume (6%), mean arterial BP (−5%), or arteriovenous oxygen difference (+10%).
		3	No differences during peak arm cranking exercise for any of the cardiovascular variables.
Crameri et al. 2004[43] Denmark D&B=12 Pre-post N=6	Population: Paraplegia, complete, C6-T7, ages 26–54yr, 3–21yr post-injury. Treatment: FES training 45min/d, 3d/wk, 10wk. One leg: dynamic cycle ergometry involved bilateral quadriceps and hamstring stimulation; Contralateral leg: isometric contractions.	**1**	The isometric-trained leg showed larger mean increases in force, increase in type 1 fibres, fibre cross-sectional area, capillary-to-fibre ratio, citrate synthase activity and relative oxygenation after static training in comparison to baseline and the dynamically trained leg.
Hjeltnes et al. 1997[72] Norway D&B=12 Pre-post N=5	Population: 5 males, complete chronic lesions, 2 C5, 2 C6, 1 C7; 4 ASIA A, 1 ASIA A/B, age 35yr, 10.2yr post-injury. Treatment: FES leg cycling, 7 times/wk, 8wk.	**1**	VO_2peak increased (70%) during FES leg cycling, but not during arm exercise.
		2	Increase in lean body mass (3.0%) and muscle cross-sectional area (21.3%).
		3	Decrease in body fat (6.4%).
Barstow et al. 1996[69] USA D&B=12 Pre-post N=9	Population: 9 males, 2 tetraplegia, 7 paraplegia, all ASIA A, age 34.4yr, 10.1yr post-injury. Treatment: FES leg cycle exercise, 30min (minimum of 24 sessions, 3d/wk).	**1**	Training significantly increased VO_2peak (10.9%), peak work rate (46.5%), and peak oxygen pulse (12.6%).

Author Year; Country Score Research Design Total Sample Size	Methods	Key Outcomes
Faghri et al. 1992[42] USA D&B=12 Pre-post N=13	Population: 6 paraplegics (5 complete), 7 tetraplegics (all incomplete), C4-C7 and T4-T10, age 30.5yr, 8yr post-injury. Treatment: FES leg cycle, 3 d/wk, 12wk.	**1** Increased resting HR and systolic blood pressure in the tetraplegics, while decreased systolic, diastolic and mean arterial BP in the paraplegics after training. **2** In both groups, decreased submaximal exercise HR and blood pressure and increased stroke volume after training. **3** After training, submaximal cardiac output increased significantly in the paraplegic group.
Gerrits et al. 2001[74] Netherlands D&B=11 Pre-post N=9	Population: C4-C6 and T4-T8, ASIA A (5), B (3) and C (1), ages 26–61yr, 1–27yr post-injury. Treatment: FES leg cycle, 30min/d, 3d/wk, 6wk.	**1** Increased work output (300%). **2** No change HR and systolic BP. Increased femoral artery diameter (8%), no change carotid artery diameter. Blood flow to the paralyzed limbs was increased.

Table 3

Effects of Hybrid FES Training on Cardiovascular Fitness and Health

Author Year; Country Score Research Design Total Sample Size	Methods	Key Outcomes	
Thijssen et al. 2005[70] Netherlands D&B=14 Pre-post N=10	Population: 9 males, 1 female, T1–T12, 9 complete, age 39.2yr, 1–20yr post-injury. Treatment: simultaneous FES cycle ergometry and arm ergometry, 30min/d, 2–3d/wk, 4wk.	**1**	Training resulted in increased thigh resting (43.5%) and peak blood flow (17.1%), decreased thigh resting vascular resistance (31.8%), and increased femoral artery diameter.
		2	After training, there was an increase in maximal workload (6.8%), VO_2peak (6.1%), and resistance to fatigue.
Thijssen et al. 2006[75] Netherlands D&B=20 Pre-post N=9	Population: 8 males, 1 female, C5-T12, 8 complete ASIA A, 1 incomplete ASIA C, age 39yr, 11yr post-injury. Treatment: simultaneous FES cycle ergometry and arm ergometry, 25min/d, 2d/wk, 6wk followed by 6-wk detraining.	**1**	After 2-wk of training, there was a significant increase in baseline and peak blood flow, an increase in femoral artery diameter, and a decrease in femoral artery FMD.
		2	Detraining lead to a reversal of baseline and peak thigh blood flow, vascular resistance, and femoral diameter.
		3	Detraining did not restore femoral artery FMD.
Gurney et al. 1998[46]; USA D&B=12 Pre-post N=6	Population: all male, C4-T10, 4 paraplegia, 2 tetraplegia, ages 23–41yr, 5–24yr post-injury. Treatment: Phase I: FES leg cycle, 3 d/wk, 6wk. Phase II: FES leg cycle with simultaneous, voluntary arm ergometry, 3 d/wk, 6wk. Phase III: 8-wk detraining.	**1**	Increased VO_2peak (81.7%) and workload with FES leg cycle.
		2	After an 8-wk detraining period peak workload returned to baseline; VO_2peak remained higher.
Mutton et al. 1997[44] USA D&B=12 Pre-post N=11	Population: all male, complete ASIA A, C5-6 to T12-L1, age 35.6yr, 9.7yr post-injury. Treatment: 3 phases of exercise training (FES-Leg cycle ergometry): Phase I progressive FES-Leg Cycle Exercise (FES-LCE) to 30min of exercise; Phase II ~35 sessions of FES-LCE, and Phase III ~41 sessions (30min each) of combined FES-LCE and arm ergometry.	**1**	In response to FES-LCE training both VO_2peak and peak work rate during graded FES leg exercise (but not graded arm ergometry) testing improved.
		2	With hybrid training, VO_2peak (13%) and peak power output (28%) were increased during graded hybrid testing, but not during graded arm or graded FES leg testing alone.
Krauss et al. 1993[45] USA D&B=12 Pre-post N=8	Population: 7male, 1 female, 7 paraplegia, 1 tetraplegia, age 32yr, 13yr post-injury. Treatment: 2 phase program. Phase I: FES leg cycling 3d/wk, 6wk. Phase II: FES leg cycle plus simultaneous arm ergometry for 6wk.	**1**	After Phase I, arm ergometer VO_2peak (21.9%) and FES leg ergometer VO_2peak (62.7%) increased.
		2	After Phase II, the hybrid exercise VO_2peak increased 13.7%.
		3	Peak HR only increased with training during FES leg ergometry.
Pollack et al. 1989[68] USA D&B=11 Pre-post N=11	Population: 7 male and 4 female, C4-C6 and T2-T6, complete motor lesions, ages 18–54yr, 6–132mth post-injury. Treatment: 3 phase program over 13–28wk. Phase I: quadriceps stimulation (knee extension). Phase II: FES leg cycle with 0–1 kp resistance. Phase III: loaded FES leg cycle, 3d/wk, 3wk.	**1**	There were significant increases in endurance time (288%), VO_2peak (95.9%) and HR (16.8%), and decreases in diastolic blood pressure (31.5%) with training.
Other Forms of Electrically Assisted Training			

Author Year; Country Score Research Design Total Sample Size	Methods	Key Outcomes	
Wheeler et al. 2002[71]; Canada D&B=17 Pre-post N=6	Population: C7-T12, 5 ASIA A, 1 ASIA C, age 42.5yr, 13.8yr post-injury. Treatment: FES (quadriceps) with arm rowing (70–75%VO_2peak) 30min/d, 3d/wk, 12wk.	**1**	Training resulted in significant increases in rowing distance (25%), VO_2peak (11.2%), and peak oxygen pulse (11.4%).
Sabatier et al. 2006[76] USA D&B=15 Pre-post N=5	Population: all male, complete ASIA A, C5-T10, age 35.6yr, 13.4yr post-injury. Treatment: Home-based electrical stimulation 2d/wk, 18wk.	**1**	Training resulted in significant increases in weight lifted and muscle mass, and a decrease in muscle fatigue.
		2	There was no change in femoral artery diameter with training.
		3	Resting, reactive hyperaemia, and exercise blood flow did not change significantly with training.
Solomonow et al. 1997[66] USA D&B=13 Pre-post N=70	Population: all paraplegia, no other details given. Treatment: Reciprocating Gait Orthosis 3hr/wk, 14wk.	**1**	There was a non-significant increase in cardiac output (7.1%) and stroke volume (5.0%) after training.
		2	There was a significant increase in knee extensor torque (78.2%).
de Groot et al. 2005[77] Netherlands D&B=10 Pre-post N=6	Population: SCI: 3 male, 3 female, T4-L2, all complete ASIA A/B, age 43yr, 14.5yr post-injury; Controls: 8 able-bodied individuals (4 male, 4 female), age 41yr. Treatment: Unilateral surface stimulation of the quadricep, tibial anterior and gastrocnemius muscles, 30min/d, daily, 4wk.	**1**	An increase in arterial compliance and a decrease in the flow-mediated dilation in the femoral artery of the trained leg, with no changes in these vascular parameters in the femoral artery of the untrained leg, the carotid artery, and the brachial artery.
		2	There were no significant training-related changes in resting vessel diameter, blood flow or shear rate in the femoral, carotid, and brachial arteries.

Table 4

Effects of Exercise Training on Glucose Metabolism in Persons with SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome	
de Groot et al. 2003[27] Netherlands PEDro=7 RCT N=6	Population: 4 male, 2 female, C5-L1, ASIA A (n=1), B (n=1), and C (n=4), age 36yr, 116d post-injury. Treatment: Randomized to low intensity (50–60% HRR) or high intensity (70–80% HRR) arm ergometry. 20min/d, 3days/wk, 8wk.	**1**	There was a significant difference in insulin sensitivity between groups, with a non-significant decline in the high intensity group and a significant improvement in the low intensity group with training.
		2	A positive correlation between VO_2peak and insulin sensitivity (r=0.68, p=0.02).
Mahoney et al. 2005[54] USA D&B=17 Pre-post N=5	Population: 5 males, complete SCI, C5-T10, ASIA grade A, age 35.6yr, 13.4yr post-injury. Treatment: Home-based neuromuscular electric stimulation-induced resistance exercise training, 2d/wk, 12wk.	**1**	All participants had normal fasting glucose levels before and after training.
		2	There were no significant changes in blood glucose or insulin with training. However, there was a trend towards reduced plasma glucose levels (p=0.074).
Hjeltnes et al. 1998[55] Sweden D&B=13 Pre-post N=5	Population: 5 males, C5-C7, all complete ASIA A, age 35yr, 10yr post-injury. Treatment: Electrically stimulated leg cycling exercise, 7d/wk, 8wk.	**1**	After training, insulin-mediated glucose disposal was increased by 33%. There was a 2.1-fold increase in insulin-stimulated glucose transport.
		2	Training led to marked increases in protein expression of GLUT4 (glucose transporter) (378%), glycogen synthase (526%), and hexokinase II (204%) in the vastus lateralis muscle.
		3	Hexokinase II activity increased 25% after training.
Phillips et al. 2004[22] Canada D&B=12 Pre-post N=9	Population: 8 male, 1 female, incomplete ASIA C, C4-T12, 8.1yr post-injury. Treatment: Body-weight supported treadmill walking, 3d/wk, 6mth.	**1**	Reduction in the area under the curve for glucose (−15%) and insulin (−33%).
		2	The oxidation of exogenous (ingested) glucose and endogenous (liver) glucose increased (68% and 36.8%, respectively) after training.
		3	Training resulted in increased muscle glycogen, GLUT-4 content (glucose transporter) (126%), and hexokinase II enzyme activity (49%).
Jeon et al. 2002[57] Canada D&B=11 Pre-post N=7	Population: 5 male, 2 female, motor complete, C5-T10, ages 30–53yr, 3–40yr post-injury. Treatment: FES leg cycle training, 30min/d, 3d/wk, 8wk.	**1**	There were significantly lower (14.3%) 2h OGTT glucose levels after 8 weeks of training.
		2	Glucose utilization was higher for all 3 participants and insulin sensitivity was higher for 2 of the 3 participants during post-training 2hr clamp test.
Mohr et al. 2001[58] Denmark D&B=10 Pre-post N=10	Population: 8 male, 2 female, 6 tetraplegia, 4 paraplegia, C6-T4, age 35yr, 12yr post-injury. Treatment: FES cycling, 30min/d, 3d/wk, 12mth. 7 participants completed an additional 6mth (1d/wk).	**1**	Insulin-stimulated glucose uptake rates increased after intensive training.
		2	With the reduction in training, insulin sensitivity decreased to a similar level as before training. GLUT 4 increased by 105% after intense training and decreased again with the training reduction. The participants had impaired glucose tolerance before and after training, and neither glucose tolerance nor insulin responses to OGTT were significantly altered by training.
Chilibeck et al. 1999[56] Canada	Population: 4 male, 1 female, motor complete C5-T8, ages 31–50yr, 3–25yr post-injury.	**1**	Training resulted in increases in GLUT-1 (52%) and GLUT-4 (72%).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome	
D&B=10 Pre-post N=5	Treatment: FES leg cycle ergometry training, 30min/d, 3d/wk, 8wk.	**2**	There was a training-induced increase in citrate synthase activity (56%) and an improvement in the insulin sensitivity index as determined from oral glucose tolerance test.

Table 5

Effects of Exercise Training on Lipid Lipoprotein Profiles in Persons with SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome	
de Groot et al. 2003[27] Netherlands PEDro=7 RCT N=6	Population: 4 male, 2 female, C5-L1, ASIA A (n=1), B (n=1), and C (n=4), age 36yr, 116d post-injury. Treatment: Randomized to low intensity (50–60% HRR) or high intensity (70–80% HRR) arm ergometry. 20min/d, 3d/wk, 8wk.	**1**	The TC/HDL and triglycerides decreased significantly more in the high intensity group.
El-Sayed et al. 2005[65] UK D&B=13 Pre-post N=12	Population: 5 SCI: lesion below T10, age 32yr; 7 AB controls: age 31yr. Treatment: Arm ergometry, 30min/d (60–65%VO_2peak), 3d/wk, 12wk.	**1**	Training improved HDL, but did not alter TC or triglycerides.
Solomonow et al. 1997[66] USA D&B=13 Pre-post N=70/33	Population: all paraplegia, no other details given. Treatment: Reciprocating Gait Orthosis 3hr/wk, 14wk.	**1**	There were significant reductions in total cholesterol, LDL, LDL/HDL, and TC/HDL in 8 patients with initially high total cholesterol levels (>200 mg/dL).
Nash et al. 2001[67] USA D&B=11 Pre-post N=5	Population: 5 males, complete lesions T6-L1, age 37.8yr, 4.8yr post-injury. Treatment: Circuit resistance training (50–60%1RM) 3d/wk, 12wk.	**1**	There were significant decreases in LDL, LDL/HDL and TC/HDL after training.
Stewart et al. 2004[36] Canada D&B=10 Pre-post N=9	Population: 8 male, 1 female, incomplete ASIA C, C4-T12, 8.1yr post-injury. Treatment: Body weight-supported treadmill training, 3 d/wk, 6mth.	**1**	There were significant reductions in TC (−11.2%), LDL (−12.9%) and total cholesterol/HDL (−19.8%).
Hooker & Wells 1989[31] USA D&B=9 Prospective Controlled Trial N=8	Population: low-intensity group: n=6, 3 male, 3 female, C5-T10, age 26–36yr, 3mth-19yr post-injury; moderate-intensity group: n=5, 3 male, 2 female, C5-T9, age 23–30yr, 2–19yr post-injury. Treatment: Wheelchair ergometry 20min/d, 3d/wk, 8wk: low-intensity (50–60% max HRR) and moderate intensity (70–80% max HRR).	**1** **2**	No change in lipid levels in low-intensity group. Significant increases in HDL and decreases in triglycerides, LDL, and the TC/HDL ratio in the moderate intensity group.

Table 6

Management of the Risk for Cardiovascular Disease in Persons with SCI through Aerobic Exercise Training Interventions

Risk Factor		Strength of Evidence	Literature Support
Cardiovascular Fitness	• Increased exercise tolerance	Level 1	27, 32, 33, 78–81
	• Increased VO_2max	Level 1	27, 33, 39, 78–82.
	• Increased cardiac output	Level 2	28, 29
	• Reduced submaximal exercise heart rate	Level 4	33
	• Increased maximal heart rate	Level 4	81
	• Increased stroke volume	Level 2	28, 29
	• Decreased total peripheral resistance	Level 2	28, 29
	• Increased power output	Level 1	27, 30, 32, 33, 39, 80, 81
	• Intrinsic cellular adaptations that facilitate oxidative metabolism	Level 4	36
Lipid Lipoprotein Profile	• Increased HDL cholesterol	Level 2	31, 65, 67
	• Reduced LDL cholesterol	Level 1	27, 31, 36, 67
	• Reduced triglycerides	Level 1	27
	• Reduced total cholesterol	Level 1	27, 31, 36
Glucose Homeostasis	• Increased insulin sensitivity, decreased insulin resistance, and/or improved glucose tolerance.	Level 1	27

Table 7

Management of the Risk for Cardiovascular Disease in Persons with SCI through Functional Electrical Stimulation Training Interventions

Risk Factor		Strength of Evidence	Literature Support
Cardiovascular Fitness	• Increased exercise tolerance	Level 4	41, 48, 68–71
	• Increased VO_2 max	Level 4	41, 48, 68–72
	• Increased cardiac output	Level 4	41
	• Reduced submaximal exercise heart rate	Level 4	42
	• Increased stroke volume	Level 4	42
	• Decreased total peripheral/vascular resistance	Level 4	42
	• Increased power output	Level 4	41, 42, 70
	• Intrinsic cellular adaptations that facilitate oxidative metabolism	Level 4	43, 47–49
Lipid Lipoprotein Profile	• Reduced LDL cholesterol	Level 4	66
	• Reduced total cholesterol	Level 4	66
Glucose Homeostasis	• Increased insulin sensitivity, decreased insulin resistance, and/or improved glucose tolerance.	Level 4	57