Spinal cord injuries in Sweden
Studies on clinical follow-ups

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Umeå 2016

Responsible publisher under Swedish law: the Dean of the Medical Faculty

ISBN: 978-91-7601-526-1
ISSN: 0346-6612
New series: 1824
Cover picture: Bill Olson
Layout: Mikke Hedberg
E-version avaliable at http://umu.diva-portal.org/
Printed by: UmU-tryckservice, Umeå University, SE-90187 Umeå
Sweden, 2016

“A mind is like a parachute. It doesn´t work if it´s not open. ”

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Frank Zappa

To my family...

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Abstract

A spinal cord injury is a serious medical condition, often caused by a physical trauma. An injury to the spinal cord affects the neurotransmission between the brain and spinal cord segments below the level of injury. The SCI causes a loss of motor function, sensory function and autonomic regulation of the body, temporary or permanent. Significantly improved acute care, primary comprehensive rehabilitation and life-long structured follow-up has led to persons with spinal cord injury (SCI) living longer than ever before. However, increased long-time survival has allowed secondary conditions to emerge, like diabetes mellitus and where cardiovascular disease (CVD) now is the most common cause of death among SCI patients. Other possible CVD-related comorbidities in this patient group have been reported to be pain and mood disturbances. There is still lack of, and need for more knowledge in the field of CVD-related screening and prevention after SCI.

The overall aim of this thesis was to contribute to a scientific ground regarding the need for CVD-related screening and prevention after SCI.

In Paper I and Paper II, patients with wheelchair-dependent post-traumatic SCI (paraplegia) were assessed. The results in paper I showed that 80% of the examined patients had at least one cardiovascular disease risk marker irrespective of body mass index (BMI). Dyslipidemia was common for both men and women at all BMI categories. The study also showed a high prevalence of hypertension, especially in men. Paper II showed a low frequency of self-reported physical activity, where only one out of 5 persons reported undertaking physical activity ≥30 min/day. The physically active had lower diastolic blood pressure but no significant difference in blood lipids.

In paper III and IV, patients with SCI (tetraplegia and paraplegia) participated in the studies. Eighty-one percent of the patients had dyslipidemia, where also a majority of the patients with normal abdominal clinical measures had dyslipidemia. Self-reported physical activity ≥30min/day was reported by one third of the patients. No differences were found between physically active and not physically active patients when it came to blood glucose, serum lipid values and clinical measures (paper III). Pain was common in the patient group, however, most often on a mild to moderate level. Anxiety and depression was less common than reported in other studies (paper IV).

Original Papers

I. Flank P, Wahman K, Levi R, Fahlström M. Prevalence of risk factors for cardiovascular disease stratified by body mass index categories in patients with wheelchair-dependent paraplegia after spinal cord injury. J Rehabil Med. 2012 May; 44(5):440-3. Erratum in: J Rehabil Med. 2012 Jul; 44(8):708.

II. Flank P, Levi R, Boström C, Lewis JE, Fahlström M, Wahman K. Self-reported physical activity and risk markers for cardiovascular disease. J Rehabil Med. 2014 Oct; 46(9):886-90.

III. Flank P, Ramnemark A, Levi R, Wahman K, Fahlström M. Dyslipidemia is common after spinal cord injury – independent of clinical measures. J J Physical Rehab Med. 2015, 1(1): 001.

IV. Flank P, Ramnemark A, Wahman K, Levi R, Fahlström M. Pain, anxiety and depression in spinal cord injured patients. Submitted manuscript.

Abbreviations

ADL	Activities of daily living
AIS	ASIA impairment scale
BMI	Body mass index
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DL	Dyslipidemia
DM	Diabetes mellitus
HADS	Hospital anxiety and depression scale
HDL	High density lipoprotein
HTN	Hypertension
LDL	Low density lipoprotein
NLL	Neurological level of lesion
NTSCI	Non-traumatic spinal cord injury
NWD	Not wheelchair dependent
SAH	Sagittal abdominal height
SBP	Systolic blood pressure
SCI	Spinal cord injury
TG	Triglycerides
VAS	Visual analogue scale
WC	Waist circumference
WD	Wheelchair dependent
WHO	World Health Organization

Sammanfattning på svenska

Traumatisk ryggmärgsskada (spinal cord injury – SCI) drabbar cirka 120 personer per år i Sverige. Vanligaste orsaken till SCI är trafikrelaterade olyckor. Andra vanliga orsaker är relaterade till idrott/fritid och fall, och i vissa delar av världen är skadorna ofta orsakade av fysiskt våld, t ex kniv- och skottskador. Cirka 50-70% av patienter med SCI i Sverige är under 30 år men antalet nyskadade över 60 år ökar. 80-85% av patienterna är män. Drygt hälften av alla skador är inkompletta och andelen inkompletta skador ökar successivt. Uppskattningsvis 55% av alla traumatiska skador drabbar halskotpelaren, medan bröstrygg, ländrygg och sacrum drabbas i ca 15% av fallen vardera. Den vanligaste skadenivån för tetraplegiker (neurologisk påverkan i både armar och ben) är C5 (femte halskotan) medan den vanligaste skadenivån för paraplegiker (neurologisk påverkan endast i nedre extremiteterna) är Th12 (tolfte bröstkotan) (1). En skada på ryggmärgen påverkar neurotransmissionen mellan hjärna och ryggmärgssegment nedanför skadenivån. SCI leder till en förlust av motorisk och sensorisk funktion samt en förlust av den autonoma regleringen av kroppen, antingen temporärt eller permanent.

SCI är en livsomvälvande skada för patienten och dennes anhöriga, som fram till mitten av 1900-talet innebar en dyster prognos där många patienter dog inom ett par år efter skadetillfället, främst av medicinska komplikationer i form av trycksår, urinvägs- och luftvägsinfektioner (2, 3). Signifikant förbättrat akut omhändertagande, omfattande rehabilitering och livslång uppföljning har lett till en markant förbättring där mortaliteten under sjukhusvistelsen efter SCI i Sverige idag är ca 3 procent (1), men mortaliteten varierar stort i olika delar i världen. Den ökade långtidsöverlevnaden innebär dock att sekundära tillstånd kan uppstå, som till exempel kardiovaskulär sjukdom (CVD), som nu i dagsläget är den vanligaste dödsorsaken för personer med SCI. Andra troliga komorbiditeter relaterade till CVD har rapporterats vara smärta och depression/ångest.

Det övergripande syftet med avhandlingen var att bidra till en vetenskaplig grund gällande behovet av CVD-relaterad screening och prevention vid klinisk uppföljning efter SCI.

Paper I och II omfattar rullstolsburna patienter med post-traumatisk SCI (paraplegi). Paper I visade att 80% av patienterna hade minst en riskmarkör för CVD, och avvikande blodfetter var vanligt för både män och kvinnor, oavsett BMI. Studien visade på hög förekomst av högt blodtryck, speciellt hos män.

Resultaten i Paper II visade att bara en av fem personer rapporterade fysisk aktivitet ≥30 minuter/dag. De som var fysiskt aktiva ≥30 minuter per dag var signifikant yngre och hade lägre diastoliskt blodtryck än fysiskt inaktiva personer. Ingen skillnad sågs på blodfetter mellan fysiskt aktiva och inaktiva.

I Paper III och IV ingick både patienter med tetraplegi och paraplegi. Paper III visade att 82% av patienterna hade avvikande blodfetter, där majoriteten av patienter med normalt bukfomfång och bukhöjd också hade avvikande blodfetter. Självrapporterad fysisk aktivitet ≥30min/dag rapporterades av en tredjedel av patienterna. Studien visade inte någon skillnad vad gäller blodsocker, blodfetter eller bukomfång/bukhöjd mellan fysiskt aktiva och inaktiva.

Paper IV påvisade att smärta var vanlig i patientgruppen men smärtintensiteten låg oftast på en mild till moderat nivå. Ångest och depression var mindre vanligt förekommande än i andra studier.

Denna avhandling visar på komplexiteten och sårbarheten som följer efter en SCI, likväl som det betonar vikten av regelbunden, livslång uppföljning av patientgruppen. Avhandlingen belyser vikten och behovet av uppföljning av SCI-patienternas på kliniker som är specialiserade inom de områden som den enskilde patienten behöver, samt på behovet av utvecklande av strategier för prevention och intervention av sekundära komplikationer.


9–10 jan.

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INTRODUCTION

Introduction

In Sweden, there are approximately 120 new traumatic spinal cord injuries (SCI) per year, mainly caused by traffic accidents. SCI is a condition that affects the patient in multiple ways and involves radical changes and adjustments in lifestyle. It is also a chronic condition that affects not only the individual but also persons in their surroundings. It leads to sensory deficits and paralysis in various extent, due to effected neurotransmission between the brain and the spinal cord segments below the level of injury. Other complications like pain, spasticity, pulmonary problems, pressure ulcers and urinary tract infections are common consequences of the SCI (1).

Up until the mid-20th century, traumatic SCI patients carried a dismal prognosis and patients often died within a few years post-injury. The leading causes of death were infections emanating from pressure ulcers, renal and pulmonary conditions (2, 3).

DeVivo summarized the last decades well in an article regarding the development in SCI care in the USA between 1973 and 2006 (4).

> *"Acute care and rehabilitation lengths of stay has declined dramatically over time where mean functional independence measure motor score at discharge and gain during rehabilitation has decreased, whereas gain per day increased. The probability of neurologic improvement from admission to discharge has increased. Odds of medical complications decreased during in-patient treatment, but increased post-discharge. Re-hospitalizations declined over time. Community integration improved. First year mortality rates improved, but longer term mortality rates showed no improvement since 1982."*

Today, advances in acute care and management, combined with long-time rehabilitation and regular follow-ups at specialist clinics, make the patients with SCI live longer with their disability.

However, the increased long-time survival also allows secondary conditions to emerge, where cardiovascular disease (CVD) now is the leading cause of death. In SCI patients surviving at least 30 years post injury, CVD is the cause of death in 46% of the cases (5, 6). In contrast, the global CVD prevalence in the general population is reported by the World Health Organization (WHO) to be 31% (7). SCI patients also have an 8.5 times higher risk for myocardial infection than the general population (8). In industrialized countries SCI persons have been shown to have a 2.5-5 times higher risk for CVD than the general population (5, 9). Diabetes mellitus (DM) and respiratory disorders also remain major causes of morbidity and mortality (2, 6, 10). In addition, other CVD risk factors like hypertension (HT) (9), dyslipidemia (DL) (11) and overweight/obesity (12) are highly prevalent among the SCI patients.

Due to the high risk profile and lifelong vulnerability to complications that comes with the injury, SCI patients are offered regular follow-ups. Preferably these follow-ups should be performed at least annually and at specialized clinics, with the purpose to prevent, screen and treat medical complication and associated conditions, as described later in this thesis.

Spinal cord injury

A spinal cord injury is a serious medical condition with considerable functional, psychological and socioeconomic consequences. An injury to the spinal cord, including cauda equina and conus medullaris affects the neurotransmission between the brain and spinal cord segments below the level of injury. The SCI causes a loss of motor function, sensory function and autonomic regulation of the body, temporary or permanent.

A SCI is often caused by a physical trauma that involves lateral stress, hyperflexion or extension, compression, rotation or distraction. The injury can cause compression, stretch or contusion of the spinal cord due to fractured vertebrae, dislocation of a vertebrae, bleeding etc.

Figure 1. Example of a fractured vertebral cervical body and spinal cord injury.

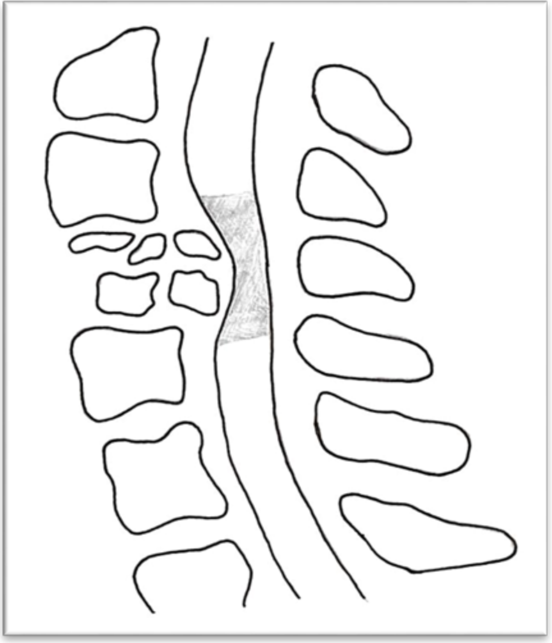
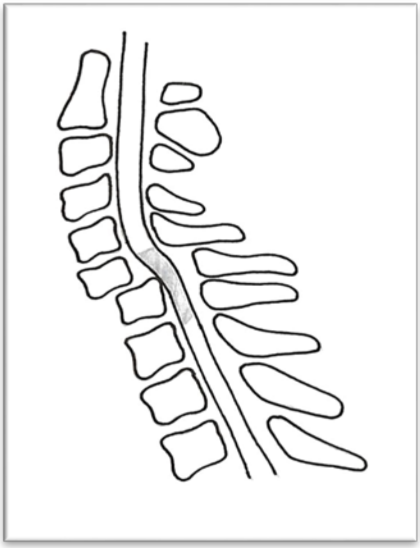


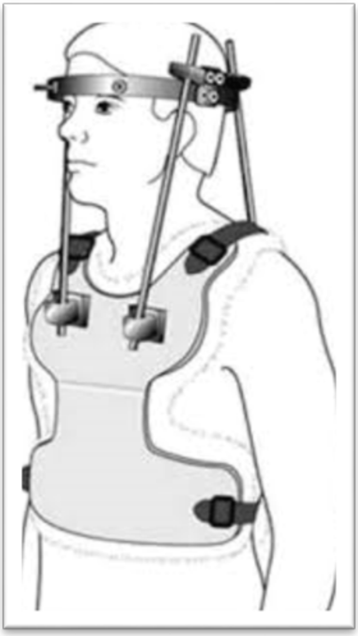
Figure 2. Example of a dislocation of C6/C7 and spinal cord injury.



A clinical decision is made if the traumatic SCI is to be treated non-surgical treatment, i.e. conservative treatment with orthoses or Halo-vest etc., or if the injury needs a surgical intervention with different fusion and internal fixation techniques (1).

A SCI can also be non-traumatic (NTSCI), with consequences similar to traumatic SCI. NTSCI can be caused by degenerative spinal conditions, tumors, vascular disorders, infections and inflammatory disorders etc. (13). In some countries, NTSCI is even more common than traumatic SCI (14, 15). The incidence of NTSCI will increase with an aging population (14, 16). The patients with NTSCI are older and have a more even gender distribution than patients with traumatic SCI (14, 17).

Figure 3. Example of a Halo vest.



The injuries of the SCI patients are classified according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) (18), including the ASIA Impairment scale (AIS) and the neurological level of lesion (NLL). The classification is based on a clinical examination to determine the sensory function, motor function and neurological levels. This examination also generate scores to characterize sensory/motor functioning and to determine the completeness of the injury.

Definitions and key terminology

Tetraplegia: Impairment or loss of motor and/or sensory function in the cervical segments of the spinal cord due to damage of neural elements within the spinal canal. Tetraplegia results in impairment of function in the arms as well as typically in the trunk, legs and pelvic organs, i.e. including the four extremities.

Paraplegia: Impairment or loss of motor and/or sensory function in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord, secondary to damage of neural elements within the spinal canal. With paraplegia, arm functioning is spared, but, depending on the level of injury, the trunk, legs and pelvic organs may be involved. The term is also used in referring to cauda equina and conus medullaris injuries.

Sensory level: The most caudal segment of the spinal cord with normal sensory function bilaterally.

Motor level: The most caudal segment of the spinal cord with normal motor function bilaterally.

Incomplete injury: A lesion with preservation of any sensory and/or motor function below the neurological level that includes the lowest sacral segments S4-S5.

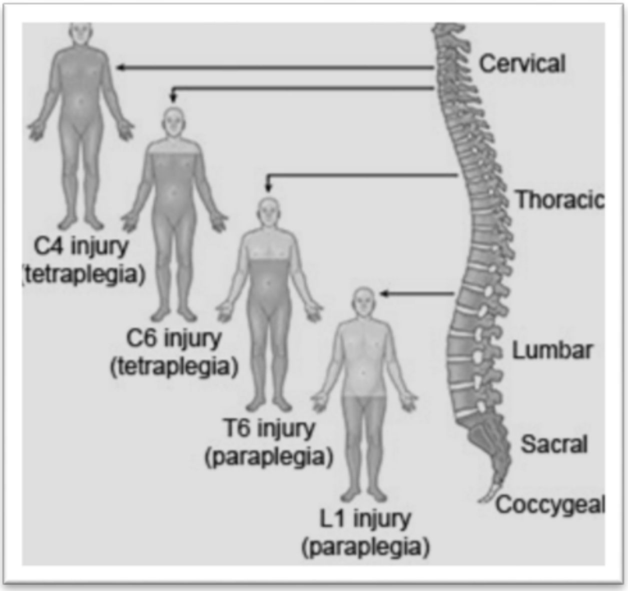
Complete injury: Absence of sensory and motor function in the lowest sacral segments.

Neurological level of lesion: The most caudal segment of the spinal cord with both normal sensory and motor function bilaterally.

Table 1. AIS (ASIA – Impairment Scale).

AIS	
A – Complete	No motor or sensory function is preserved in the sacral segments
B – Sensory incomplete	Sensory but not motor function is preserved below the NLL and includes the sacral segments
C - Motor and sensory incomplete	Motor function is preserved below the NLL, and more than half of the key muscles below the NLL have a muscle grade of less than 3.
D - Motor and sensory incomplete	Motor function is preserved below the NLL, and at least half of the key muscles below the NLL have a muscle grade of 3 or more.
E - Normal	Motor and sensory function are normal

Figure 4. Examples of level of injury and extent of paralysis.



Epidemiology

Cause of injury

In industrialized countries, motor vehicle accidents are the most common cause of SCI, causing four to five out of ten new injuries. Other common causes are falls, acts of violence and sports (19, 20). In a Swedish epidemiologic study, the result showed that 47% of the SCI were caused by falls, 23% by transportation and 17% by sports-related injuries (21). Internationally, transport remains a significant cause of accident in all age groups, while falls is the most common cause of SCI in the patient group over 60 years old (22)

Prevalence and incidence

Prevalence, incidence and causation of traumatic SCI differs between industrialized and developing countries, where especially African and Asian countries lack appropriate epidemiologic data (23, 24). The global incidence of traumatic SCI varies from 8 to 246 cases per million inhabitants and year. The incidence in industrialized countries varies between 10 and 50 cases per million inhabitants. Globally, it means that 250000 to 500000 persons each year get a SCI from all causes (22). The global prevalence varies from 236 to 1298 per million inhabitants. The highest prevalence of SCI in the industrialized countries is in the United States (906 per million) and the lowest prevalence are in areas in France and Finland (250 and 280 respectively per million inhabitants) (25-27). Unfortunately, data on the prevalence of SCI are sparse, especially on NTSCI, so currently there are no reliable global or regional estimates of all-cause SCI prevalence. Thus, the variation in prevalence is more likely due to differences in methodology than to a true fivefold difference in prevalence.

In Sweden, the traumatic SCI incidence is around 10 to 15 cases per million inhabitants, giving approximately 120 persons per year with a traumatic SCI and a prevalence of about 5000 persons in Sweden living with SCI (21).

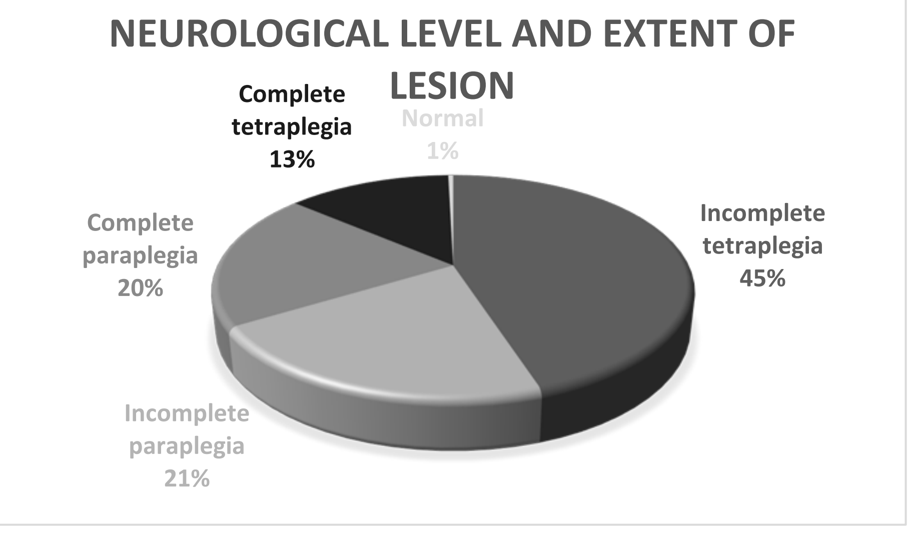
Neurological level and extent of lesion

Injuries that are neurologically incomplete are around 60%, and have increased in the last decades. This trend is likely a result of a combination of improved acute survival among persons with higher level injuries, safer cars, improved transportation from the scene of injury to the hospital, changes in etiology, and increased age at injury where falls among the elderly usually result in incomplete cervical injuries (19, 20).

A diagram of NLL and extent of lesion is shown in Figure 5 (28).

The most common level of neurological injury in the cervical spine is C5 and among paraplegics is Th12 the most common level of neurological injury.

Figure 5. Neurological level and extent of lesion.



Age and gender

In more than 50% of all SCI, the injury occurs between the ages of 15 and 30. The mean age internationally when injured is just over 33 years. In the USA the mean age is 42.2 years (29). The average age is increasing, in accordance with an aging general population at risk and there is a substantial increase in incidence over time among persons over 65 (19, 29, 30).

There is a high male-to-female-ratio where approximately 80% of all traumatic SCI patients worldwide are men (28).

Mortality and life expectancy

Within the SCI population, there is a substantial variation in mortality and life expectancy as well as it is between the SCI population compared to the general population, different WHO regions and country income levels (31). Risk of mortality is higher, and it is between 2 to 5 times more likely to die prematurely with a SCI than without a SCI (22). Survival and life expectancy decreases with increasing severity and increased lesion level. A (32-35).

Overall life expectancy among the SCI population is significantly reduced compared to the general population (33, 36). In addition, the gap in life expectancy widens with increasing lesion severity and age, and tetraplegics die earlier than paraplegics (37-39). Mortality is higher in people with complete lesions as compared to incomplete, with a complete injury nearly doubling the mortality rate of people with paraplegia, and nearly tripling it for those with tetraplegia (32).

Life expectancy in the USA, at different severity grades and age at the time of injury is shown in Table 2 (28).

Table 2. Life expectancy in years for post-injury by severity of injury and age at injury. Persons surviving at least one year post-injury.

Age at injury	No SCI	AIS-D, Motor function at any level	Paraplegia	Low tetraplegia (C5-C8)	High tetraplegia (C1-C4)	Ventilator dependent any level
20	59.5	52.9	45.5	40.7	36.9	25.3
40	40.6	34.5	28.1	24.1	21.0	12.6
60	23.1	18.2	13.4	10.6	8.7	4.0

In a study by Shavelle 2015, there is no evidence for improvement of long-term survival in the SCI population and it has not changed over the past 30 years (4, 40).

In low-income countries on the other hand, people with SCI continue to die from preventable secondary conditions, e.g. urologic complications and pressure sores.

Transportation and time of admission post-injury are important factors affecting survival where the first 24 hours after a SCI are the most critical for survival. Today, the mortality rate during acute, hospital care in parts of the western world is as low as 6-12% (41, 42), while in other parts of the world the mortality can be as high as 29-35% (43, 44). Once again showing the differences between various parts of the world and difference in resources and services, as well as lack in reliable data in many parts of the world.

SCI associated conditions and complications

Cardiovascular disease

CVD morbidity, in particular coronary artery disease is high compared to the general population and tend to occur earlier among SCI persons compared with the ambulatory population (6, 45, 46). A heightened prevalence of virtually all the major risk factors for CVD exists for persons with SCI. Risk factors like obesity, diabetes mellitus (DM), adverse lipid profile changes have all been shown to be more prevalent among SCI than in the general population (9, 10, 47, 48). A SCI often lead to a sedentary lifestyle and reduced physical function associated with loss of motor function (49). In addition, a SCI is also characterized by a disruption of the normal autonomic cardiovascular control mechanisms, which further contributes to CVD risk (50, 51).

Metabolic dysfunction and hypertension

Risk factors for CVD are highly prevalent in the SCI population like for instance hypertension (HTN) (6, 9), dyslipidemia (DL) (11) and DM (10, 12).

In a systematic review and meta-analysis (52), significantly lower high-density lipoprotein cholesterol was found in persons with SCI than in the controls. Low high density lipoprotein (HDL) is the most commonly reported serum lipid abnormality reported in the SCI group (53). Low HDL levels have been shown to increase the risk for CVD morbidity and mortality (54).

A recently published article by Adriaansen et al. (55), showed that HTN is common in people with long-term SCI, both in women and men. The recommendation given by the authors is to screen for HTN at regular follow-ups, especially those with NLL below C8, age ≥45 or a time since injury ≥20 years.

Body composition, overweight/obesity

Studies showing prevalence estimates of overweight or obesity is varying between 40-60%, which is in line with the able-bodied population (56-59). A paralysis is accompanied with the loss of lean body mass (i.e. muscle and bone tissue) and, not necessarily simultaneously accompanied with increased body weight and/or body mass index (BMI), there might be an increase in body fat mass (60, 61). As a consequence, a cut-off score of BMI 25 will underestimate the body fat and degree of obesity in persons with SCI (12, 62). BMI cut-off score therefore has been suggested to be lowered for the SCI population as compared to the general population (62, 63).

Psychological complications and life-style habits

Depression is more common in the SCI population than in the general population. During the post-acute phase, the depression prevalence rate is 20-43%. Between 11-60% of the SCI patients develop depression at least once after discharge and anxiety disorders are prevalent at a range between 13-44% (64). Around 20% develops a major depression disorder (65).

Alcohol and substance abuse is reported more common in the SCI population than in the general population (66-68). The suicide mortality is 2 to 6 times more common among those with SCI than the general population (69).

Pain

Pain, neuropathic and/or musculoskeletal pain, is one of the most prevalent health problems among the SCI population. Around two thirds of the population complain of pain of any type (70), and about one third of the patients pain is so severe that it interferes with ADL and reduces quality of life (1). Nociceptive pain is the most common type of pain after SCI (71), where musculoskeletal pain often is developed due to overuse of the upper extremities, poor wheelchair seated posture or muscle weakness (72). Neuropathic pain exists above, at and below level of NLL (73), and it affects 40-60% of the SCI patients and often becomes a chronic condition (74, 75). Typical symptoms and signs of neuropathic pain are burning, pricking, dysesthesia, often described as tingling or itching, electric shock-like or stabbing sensations etc. SCI patients with pain report a lower satisfaction with life and quality of life than SCI patients with no pain (75, 76).

Physical inactivity

Physical activity at a regular basis 30 minutes/day or more at a moderate to vigorous level is recommended by the World Health Organization (WHO) and other studies as a part of increase health in the general population (77-79). Physical activity also has been shown to have a positive effect on CVD risk markers in persons with SCI and there are various guidelines to increase physical fitness in the SCI population (80-83). Increased health by decreasing blood pressure and BMI, as well as reducing waist circumference (WC) and having a healthier body composition (i.e. decreased amount of fat mass and increased fat-free mass) are effects reported as an effect of physical activity after a SCI (84). However, other studies are less conclusive when they analyze the possible beneficial effects on risk markers for CVD or that physical activity only might have a positive effect on CVD blood lipids (85-87). Physical activity also has been shown to have psychological benefits on the general population as it can improve mood and decrease the prevalence of depression (88).

SCI persons experiences many barriers to perform exercise on a regular basis. It might be barriers of structural, architectural, functional or psychological reasons or intrinsic barriers, like lack of motivation or a feeling that it might not give any positive effect. In addition, there is also a socioeconomic factor influencing exercise activity (89, 90).

Musculoskeletal problems

Many SCI persons depend on their arms and shoulders for mobility and activities of daily living (ADL). However, the flexible shoulder joint is not built for repetitive weight-bearing and is therefore at high risk for overuse. Shoulder pain is a very common problem, reported by up to 67% of persons with SCI (91-94), with an increased risk with older age, longer time since injury, higher BMI, tetraplegia, weak muscle strength and shoulder range of motion (95-98). Shoulder pain leads to limited participation in sport and leisure activities (92, 99), lower quality of life, increased use of assistive devices and lower perceived health etc. (98, 100, 101).

Osteoporosis appears early, within the first year, after a complete SCI and the bone mineral density decreases as much as 50–70% in the lower extremities (102, 103). This loss of bone density is paralleled by an overall increased fracture rate after SCI, which is twice the fracture rate in the able-bodied population (104). Around 30-40% of the SCI patients will have at least one fracture during their lives post-injury (105). Most commonly, the fractures involves the tibia or fibula but upper extremity fractures are also common, especially among patients with higher cord lesions (106-108). The extensive loss of bone mass in the paralyzed extremities is a main factor contributing to the increased fracture risk after SCI (104, 108, 109).

Reported incidence of heterotopic ossification in muscles varies greatly in the SCI population, ranging from 10–53%. Heterotopic ossification begins to develop most frequently within the first 2–3 weeks after SCI and occurs below the NLL. Most common areas are at the hip (in 70–97% of all cases), followed by the knee (110, 111). In patients with SCI with clinically significant heterotopic ossification, 20–30% are affected with a reduction in joint range of motion (111).

Spasticity

Spasticity is a very common complication after SCI and is present in about 60-70% of all SCI patients one year post injury (112, 113). Spasticity is a term expressed by a velocity-dependent increased muscle tone, clonus, enhanced tendon reflexes, extended reflex zones and muscle spasms (114, 115). A mild spasticity can be beneficial, as it might be assistive in transfers, standing up or walking. Severe spasticity on the other hand can be the cause of functional impairment (116) and also decrease the SCI patients quality of life (117-120).

Pressure ulcers

Pressure ulcers have been reported to be the most frequent secondary complication after a SCI, occurring in approximately 21-37% of the individuals during the acute care (121, 122). The prevalence rates in the chronic SCI stage varies from 14-46% in the industrialized countries (123-126). In developing nations, the pressure ulcer prevalence has been reported to be between 27-46% (127). 85% of the individuals with a SCI develop a pressure ulcer at least once during their lifetime (128, 129) - a high prevalence despite numbers of recommendations available and existing prevention strategies (130-132).

Pressure ulcer is associated with longer length of hospital stay. It is the second most common cause of rehospitalization after a SCI (133-135), and has also been shown to affect quality of life (125) as well as it can be the cause of death due to sepsis associated with pressure ulcers (136). The most common areas for pressure ulcers are ischium, coccyx/sacrum and heel (129, 137-139).

Circulatory system

Orthostatic hypotension is a drop in blood pressure when a SCI person changes position, for example from lying to sitting. Both tetraplegic and paraplegic persons are affected, most commonly a problem during the acute and sub-acute phase but for some SCI it might be a problem also later on in life (140, 141). Typical symptoms are dizziness, light-headedness, blurred vision, fatigue and even a temporary loss of consciousness (142).

Autonomic dysreflexia is a sudden increase in blood pressure that occurs in SCI above Th6 level and is potentially life-threatening (143, 144). Usually it is caused by a nociceptive stimuli, such as wounds, pressure ulcers or by bladder or bowel problems, leading to sympathetic activation. Commonly, typical symptoms of autonomic dysreflexia are attacks of blood pressure elevation with severe headache, nausea and bradycardia (143, 145). However, it is not always severe and may then be characterized by facial flushing and sweating above NLL and piloerection (goose bumps) or might even be asymptomatic (146).

Deep vein thrombosis is a risk for SCI, particularly during the acute and post-acute phases of injury. Changes in the normal neurological control of the blood vessels and immobility can result in stasis with obesity, age or lower limb fractures are additional risk factors. Deep vein thrombosis might lead to pulmonary embolism, which is potentially lethal (147).

Pulmonary dysfunction

The respiratory function in a SCI patient is affected by the injury level, if the injury is complete or incomplete and if there is spasticity affecting the inspiratory and expiratory muscles and thereby affecting respiratory function. The diaphragm is the key muscle for breathing, innervated from the C2-C4 segments. An injury with a complete C1-C3 lesion will need ventilator support due to diaphragmatic paralysis and therefore will not be able to maintain effective spontaneous ventilation. Complete C4-C8 lesions usually have adequate spontaneous ventilation Thoracic lesions usually have adequate ventilation but impaired coughing ability. Tetraplegic or high paraplegic (Th1-Th6) patient have an increased risk of pneumonia due to paresis of the diaphragm and intercostal muscles. Being ventilator-dependent carries a high risk of acute mortality, as well as a major reduction in life expectancy where pneumonia and other respiratory conditions remain the leading cause of death (2, 38).

Urinary bladder

Urinary tract infection is the most common infection following a SCI with manifesting symptoms like fever, neuropathic pain, increased spasticity, autonomic dysreflexia and urinary incontinence. In high-income countries, urinary tract infections is a major cause for re-hospitalization and in developing countries a common cause for premature mortality (148, 149).

Thermoregulatory dysfunction

A SCI above Th6 level usually leads to a difficulty in maintaining a normal body temperature at both high and low ambient temperatures. Poikilothermia is when a SCI patient has a problem maintaining a core temperature irrespective of surrounding temperature (1).

SCI care management

In Sweden at present, there are 6 clinics specialized on rehabilitation after a SCI. All SCI patients are initially treated as individuals with multiple trauma at an intensive care unit. Rehabilitation then continues at a specialized SCI ward until the patient is ready to proceed to outpatient rehabilitation. Patients in Sweden are traditionally, after in-patient and out-patient rehabilitation, offered regular follow-ups at one of the specialist clinics from 1 year post injury and regularly during the rest of their lives. The follow-up should be annual, according to international standards. In addition to vulnerability in most organ systems, following a SCI, problems related to the aging process also have become significant factors in the life-long management of the SCI patient. To emphasize the importance of regular follow-ups, studies shows that in the USA, around 30% of the SCI patients are re-hospitalized at one or more occasions following injury. Most common causes are diseases in the urinary system, diseases of the skin, musculoskeletal problems as well as respiratory, circulatory and digestive problems (28).

The follow-up includes interviews, examinations and questionnaires to obtain the information needed for this patient group, to be able to prevent ill-health, to enable early diagnosis and to treat complications. A checklist is commonly used for review of common problems, with variations in content existing between different clinics.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AIMS

Aims of the thesis

The overall aim of this thesis was to contribute to a scientific ground regarding the need for CVD-related screening and prevention after SCI. Also, the aim was to screen the state of health among SCI patients to be able to understand more about how to give adequate counseling, advice and regime.

Specific aims:

Paper I	To assess risk factors for CVD at different BMI values in persons with wheelchair dependent paraplegia after SCI.
Paper II	To examine whether self-reported physical activity of a moderate/vigorous intensity influences risk markers for CVD in persons with paraplegia due to SCI.
Paper III	To survey the incidence of clinical risk markers and its correlation with established clinical measurements for CVD in a heterogeneous SCI patient population.
Paper IV	To assess the prevalence of pain, anxiety and depression in a consecutive sample of chronic SCI patients in Northern Sweden.


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3 | MATERIALS AND METHODS

Materials and methods

Design

Papers I-IV use a cross-sectional study design.

Study populations

Papers I and II comprised 135 and 134 participants (age range 18-79 years) respectively with post-traumatic SCI, paraplegia since at least 1 year (range 1-48 years). The participants had a neurological level of lesion below Th1 and ASIA Impairment Scale (AIS) grade A, B or C. All participants were living in the greater Stockholm area. Data were collected between November 2006 and December 2007. 153 persons, who consecutively attended the annual follow-up, fulfilled the criteria and were asked to participate in the study. The study comprises about 88% of the total regional population with wheelchair dependent paraplegia.

Table 3. Basic characteristics in study 1 of 135 persons (104 men, 31 women) with paraplegia.

Variable	Whole group (n=135)
Age, years (SD)	47.8 (13.7)
Injury duration, years (SD)	18.4 (12.3)
Level of injury (*n*)	
- Th1-Th6	45 (AIS A: 39, B: 4, C: 2)
- Th7-Th12	66 (AIS A: 56, B: 5, C: 5)
- L1-L4	24 (AIS A: 14, B: 4, C: 6)

SD: standard deviation

Table 4. Basic characteristics of 134 wheelchair-dependent individuals with posttraumatic spinal cord injury, paraplegia AIS grade A, B or C for at least one year.

Variable	Whole group (n=134)	Men (n=103)	Women (n=31)	p-value
Age, years, mean (SD)	47.8 (13.8)	47.9 (13.0)	47.3 (16.4)	0.778
Injury duration, years, mean (SD)	18.5 (12.3)	18.2 (12.4)	19.6 (12.2)	0.416
Level of injury (%)				0.798
Th1-Th6	34	33	36	
Th7-L4	66	67	64	

SD: standard deviation

In Papers III and IV, data were collected at the Neurorehabilitation Outpatient Clinic in Umeå, Sweden, between August 2012 and December 2014. All consecutive patients were invited to participate, and 78 of the 81 patients (age range 22-75 years) that were assessed during the period (96% of the patients) gave their informed written consent and were included in the studies. Time since injury was 1-53 years.

Table 5. Patient descriptors for 78 patients with SCI, ASIA impairment scale grade A-D for at least one year.

Variable	Whole group (n=78)	Men (n=61)	Women (n=17)	p-value
Age, years, mean (SD)	50.2 (14.4)	50.9 (12.1)	47.6 (13.6)	0.380
Injury duration, years, mean (SD)	14.5 (12.5)	13.1 (12.1)	19.4 (13.0)	0.045
Tetraplegia/ paraplegia (%)	50.0/50.0	54.1/45.9	35.3/64.7	0.170
Wheelchair dependence (%)	70.5	70.5	70.6	0.994
AIS score (%)				0.578
A (complete)	64.0	65.6	58.8	
B	2.5	1.6	5.9	
C	2.5	1.6	5.9	
D	31.0	31.1	29.4	
Physical activity ≥30 min/day ≥5 days/week (%)	32.1	31.1	35.3	0.748
Smokers	1	0	1	

SD: standard deviation

Measurements

Body weight was measured in kilograms on a calibrated scale. In Papers I and II, body height was obtained by patient report. In Papers III and IV, body height was obtained by measuring with the patient lying supine on a bed, using a meter stock. BMI was then computed as body weight (m) divided by the square of body height (m) (150).

Blood pressure, systolic (SBP) and diastolic (DBP), was measured in mmHg, recorded on the left arm with a calibrated manometer after 30 minutes of rest in Paper I and Paper II. In Paper III, blood pressure was measured after 10 minutes of rest.

Blood glucose concentrations and a lipid panel (i.e. TC, LDL, HDL, LDL/HDL quota, TG) were quantified in whole blood drawn from a superficial vein after an overnight, midnight fast and then analyzed. The lipid panel contained total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol quota (LDL/HDL) and triglycerides (TG).

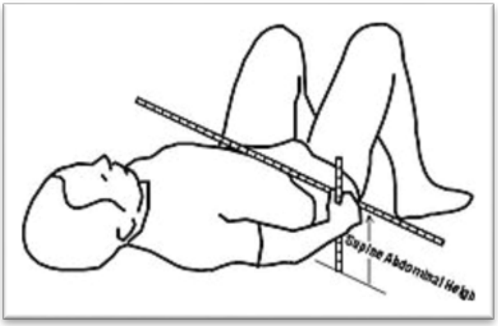
Dyslipidemia was operationalized as at least one pathological lipid level according to guidelines and/or ongoing drug treatment for DL (54). The cut-off levels were as follows: TC≥5.0mmol/L, LDL≥3.0mmol/L, HDL≤1.0mmol/L (men) and HDL≤1.3mmol/L (women), LDL/HDL-quota≥5.0, TG>1.7mmol/L.

Diabetes mellitus was operationalized as ongoing drug treatment for this disorder or an increased fasting blood glucose level ≥6.1mmol/L, according to WHO guidelines (54).

Hypertension was defined as SBP ≥140mmHg and/or a DBP ≥90mmHg and/or ongoing drug treatment for HTN. The HTN criterion score, when a participant had multiple risk factors, was set at a SBP of ≥130mmHg and a DBP of ≥85mmHg (151).

Sagittal abdominal height was measured with a meter stock (cm) and a spirit level with the patient lying on a bed, with hips and knees in 90 degrees of flexion (Figure 6). The measure was done at the end of a normal expiration at the level of the umbilicus. According to the cut-off limits used in the general population in Sweden, a sagittal abdominal height (SAH) <22cm for men and <20cm for women were considered normal (152, 153).

Figure 6. Measuring sagittal abdominal height.



Waist circumference was measured in cm at the level of the umbilicus, using a stretch-resistant measuring tape with the patient lying on a bed (60). An increased waist circumference (WC) was defined as values exceeding one or both of two cut-off points. The lower cut-off point was ≤94cm for men and ≤80cm for women. The higher cut-off point was ≤102cm for men and ≤88cm for women. Values in excess of the lower cut-off point is considered to be associated with an "increased risk", and values in the excess of the higher cut-off to be associated with a "substantially increased risk" of CVD (154).

Data pertaining the patients' age, injury duration, current medication and smoking habits were retrieved from the patients' files.

Physical activity, a questionnaire adapted and tested for the SCI population was used (155, 156). The questionnaire targets the following characteristics: type or types of physical activity, frequency, duration and intensity of physical activity. A minimum level of 30 minutes physical activity each day of the week was set as the cut-off. The participants were dichotomized into two groups based on their self-report; either they performing physical activity on a moderate and/or vigorous level >30 minutes per day, or not. In paper III the cut-off comprised a level of physical activity, reported in a questionnaire, corresponding to a minimum of 30 minutes at least 5 days per week.

Pain was assessed by asking the patients to register presently experienced pain above, at and/or below injury level on VAS. The ranged from 0-100, where 0 was no pain and 100 the worst possible pain. The pain intensity level was scored by measurement in millimeters of the distance from the no pain end of the line. A rating of 0-4mm was considered as no pain, 5-44mm as mild pain, 45-74mm as moderate pain and 75-100mm as severe pain (157). Patients, currently on daily pain medication, were registered as having pain problem, regardless of their VAS values.

Anxiety and depression were assessed by HADS, in which the patients were asked to rate their feelings during the last week. The instrument comprises 14 items and two subscales with 7 items each to screen for both anxiety and depression. The answers were given on a 0-3-scale where higher scores indicate more distress. Each subscale ranges from 0-21, where clinically relevant evaluation cut-offs for both anxiety (HADS-A) and depression (HADS-D) are suggested. A score $\geq$11 is considered a clinically significant disorder with a score between 0-7 is considered as normal. A score from 8-10 is suggested as a mild disorder (158-160).

Statistical methods

Paper I: Values were described as mean$\pm$SD. Differences in numerical values were calculated using Mann-Whitney U-test, categorical differences were calculated using Chi-square test.

Paper II: Analyzing group variables, results were described by mean and standard deviation (SD). Differences between groups in numerical values were calculated using Mann-Whitney U-test accounting for non-normality. Simple and multiple linear and logistic regression models were set up to produce crude and adjusted estimates of the relationship between physical activity ($\geq$30 minutes per day) and the CVD risk markers, accounting for potential confounding from factors (e.g. age, sex and education). All continuous CVD risk markers were studied using linear regression.

Paper III: Values are described as mean$\pm$SD. Differences in numerical values were calculated using Mann-Whitney U-test, categorical differences were calculated using Chi-square test.

Paper IV: Differences in numerical values were calculated using Mann-Whitney U-test, categorical differences were calculated using Chi-square test. Correlations were calculated using Pearson Correlation test.

A p-value of less than 0.05 was considered significant in all studies. PASW Statistics 18 (IBM Corporation, Armonk, NY, USA) and IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

Ethics

Study I and II were approved by the Regional Ethical Review Board, Stockholm, Sweden. Study III and IV were approved by the Regional Ethical Review Board in Umeå, Sweden.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4 RESULTS

Results

Paper I

Prevalence of risk factors for cardiovascular disease stratified by body mass index categories in patients with wheelchair-dependent paraplegia after spinal cord injury

Regardless of BMI level, more than 80% of the patients in the study, both men and women, had one or more CVD risk factor, as shown in Table 6 and 7.

Patients with HTN had significantly higher BMI than patients with no HTN (25.4±4.2 vs 23.7±3.7, p=0.023) and patients with DM also had a significantly higher BMI (27.8±3.5 vs 24.1±3.8 p=0.001), but only in men. There was a higher prevalence of HTN in men than in women (44.2% vs 22.6%, p=0.030). No gender differences were found concerning DM and DL.

Lower-level paraplegics (injury at or below Th7) had both significantly higher SBP (133.7±23.1 vs 121.1±20.3, p=0.003) and DBP (79.9±10.9 vs 74.5±13.0, p=0.022) than patients with higher-level paraplegia (injury at or above Th6). Low-level paraplegics also had a higher prevalence of HTN than high-level paraplegics (77% vs 23%, p=0.034).

Table 6. Distribution of risk factors for cardiovascular disease at different body mass index categories in the study group.

BMI level	HTN (*n*=73) %	DM (*n*=13) %	DL (*n*=109) %
<22 (n=33)	25	0	21
22<23 (n=14)	10	8	11
23<24 (n=18)	8	0	16
24<25 (n=13)	10	8	9
25<30 (n=44)	31	54	33
≥30 (n=13)	16	30	10
Total (n=135)	100	100	100

BMI =body mass index, HTN=hypertension, DM=diabetes mellitus, DL=dyslipidemia

Table 7. Prevalence (%) of risk factors for cardiovascular disease at different body mass index categories in the study group.

BMI level	HTN (*n*=73) %	DM (*n*=13) %	DL (*n*=109) %
<22 (n=33)	33	0	72
<23 (n=47)	30	2	76
<24 (n=65)	29	2	81
<25 (n=78)	32	3	68
25<30 (n=44)	43	16	82
≥30 (n=13)	70	31	85

BMI =body mass index, HTN=hypertension, DM=diabetes mellitus, DL=dyslipidemia

Paper II

Self-reported physical activity and risk markers for cardiovascular disease

Physical activity ≥30 min per day was reported to have been performed by 20.1% of the patients with a mean total amount of 53 min/week±134 min and with a mean amount of weekly moderate/vigorous physical activity of 107±182 min. Examples of physical activities were strength exercise, hand-cycling and wheeling.

The physically active group were significantly younger (40.6±9.2 vs 49.6±14.2, p=0.001) and had lower DBP (71.9±9.2 vs 79.3±12.0, p=0.007) compared to the non-physically active group. SBP was also lower in the physically active group but that difference disappeared after adjusting for age, while DBP remained lower in the physically active group.

There was no significant difference in blood lipids, and a tendency to significant difference in BMI levels and LDL/HDL-quota between the physically active and not physically active.

Significantly higher SBP, lower HDL, higher LDL/HDL-quota and higher TG were found in men than women.

Table 8. A comparison of risk markers for cardiovascular disease between the groups of subjects with different physical activity levels.

Variable	Whole group (n=134)	≥30minutes /day (n=27)	<30minutes /day (n=107)	p-value
BMI, mean (SD)	24.2 (4.5)	23.1 (3.4)	24.5 (4.7)	0.053
SBP(mmHg),mean (SD)	129.7 (23.0)	121.6 (11.8)	131.7 (24.6)	0.023
DBP(mmHg),mean (SD)	77.9 (11.8)	71.9 (9.2)	79.3 (12.0)	0.007
Blood glucose (mmol/L),mean (SD)	5.2 (1.4)	5.0 (1.0)	5.2 (1.5)	0.649
TC, mean (SD)	4.8 (1.0)	4.9 (0.7)	4.8 (1.0)	0.423
HDL, mean (SD)	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)	0.332
LDL, mean (SD)	3.0 (0.9)	3.2 (0.6)	3.0 (1.0)	0.276
LDL/HDL quota, mean (SD)	2.8 (1.5)	3.1 (1.0)	2.7 (1.6)	0.072
TG, mean (SD)	1.3 (0.8)	1.4 (0.8)	1.3 (0.8)	0.875

SD: standard deviation; BMI: body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TG: triglycerides

Paper III

Dyslipidemia is common after spinal cord injury – independent of clinical measures

A majority, 87.2% of the patients had at least one of the diagnoses screened for in this study, i.e. DM, DL, HTN and/or overweight/obesity.

DL was present in 81% of all patients in the group with a BMI being significantly higher among patients with DL (25.5±4.6 vs 24.4±9.1, p=0.041). However, 46.7% of the patients with DL had a BMI below 25.

A majority of the patients with abdominal measures below recommended cut-off values had DL, as presented in Table 9. It also was found that DL correlated with SAH and WC above cut-off-level (SAH 22/20cm, p=0.002, WC 94/80cm, p=0.001, WC 102/88cm, p=0.033).

Four patients had anti-diabetic medication. Among the nine patients (11.5%) who were on medication for high serum lipids, TC and LDL was lower (4.4±0.77 vs 5.1±1.02, p=0.021 and 2.6±0.85 vs 3.4±0.96, p=0.029).

SBP was significantly higher among paraplegics than tetraplegics (133.7±16.7 vs 119.7±24.8, p=0.003) and not wheelchair dependent (NWD) patients registered both higher SBP (135.0±20.2 vs. 123.2±22.2, p=0.031) and DBP (80.9±10.1 vs. 76.0±19.3, p=0.039) than wheelchair dependent (WD) patients. No difference in BP were seen between men and women.

Patients (n=14, 17.9%) on HTN medicine had higher SBP (145.9±20.8 vs. 122.5 ±20.2, p=0.000) and DBP (83.4±10.1 vs.76.1±10.0, p=0.009) than patients without HTN medicine.

Physical activity at least 30min/day, 5 days a week at a moderate to vigorous level was reported by 32.1% of the patients and there was no difference found between physically active and non-physically active as regards of clinical abdominal measures or BMI, blood pressure, serum lipid values, blood glucose or DL.

Table 9. Frequency of dyslipidemia in SCI patients with anthropometric data below the recommended cut-off levels.

Variables (%)	Whole group (n=78)	Men/Women (n=61/17)	Tetraplegia/Paraplegia (n=39/39)	WD/NWD (n=55/23)
Normal SAH	61.5	57.1/80.0	64.3/58.3	60.9/66.7
WC below 94/80cm	60.7	58.3/75.0	60.0/61.5	56.5/80.0
WC below 102/88cm	73.5	70.0/88.9	61.9/82.1	71.4/78.6

SAH: sagittal abdominal height, WC: waist circumference, WD: wheelchair dependent, NWD: non-wheelchair dependent.

Paper IV

Pain, anxiety and depression in spinal cord injured patients

Pain above, at and below injury level was reported present in 32.1% (VAS 11.8±19.2, range 20-60mm), 24.4% (VAS 8.2±15.4, range 10-50mm) and 57.7% (VAS 23.3±23.6, range 20-80mm) of the patients respectively. Pain and/or having continuous pain medication at the time of the examination was present in 79.5% of the patients. Twenty-nine patients (37.2%) were prescribed continuous medication due to neuropathic pain where pain medicated patients registered significantly higher pain than patients without medication (35.9±24.3 vs 15.9±20.0, p=0.000). Pain divided into grades of severity is shown in Table 10.

No difference was found regarding presence of pain between men and women but women had significantly higher registered mean pain (VAS 15.9±20.7 vs 6.1±13.1. p=0.037). No differences in pain prevalence were found between tetraplegics and paraplegics. However, paraplegics had more severe pain above injury level than tetraplegics (VAS 17.2 vs 6.4, p=0.018).

Pain was as common among the incomplete as the complete injuries but patients with incomplete injury registered more pain below injury than patients with incomplete injury (VAS 31.0±26.0 vs 18.5±20.8, p=0.037).

WD patients had more severe pain above injury than NWD (14.5±18.2 vs 5.2±17.3, p=0.012), but there was no difference in prevalence of pain between the groups.

Mild or clinically significant psychological disorder for anxiety was reported by 14.1% and depression by 10.2% of the patients as shown in Table 11, with a mean HADS-A of 3.64±3.37 and a mean HADS-D of 3.44±3.12.

Younger patients had a higher HADS-A score and patients with mild or moderate/severe disorder were significantly younger (39.1±15.7 vs 52.0±13.4, p=0.005).

Seventeen (22%) patients had anti-anxiety medication where two of those patients had a HADS-A ≥8, while nine patients with HADS-A ≥8 did not have anti-anxiety medication.

No differences were found regarding HADS-A and HADS-D when comparing with men/women, tetraplegia/paraplegia, WD/NWD, complete/incomplete or physically active/not physically active.

Patients with anxiety and/or depression disorder had significantly higher VAS pain at injury level than patients with no anxiety and/or depression disorder, and no differences were found above and below injury level. Also, there was no difference in pain prevalence between patients with and without anxiety or depression disorder.

Table 10. Registered pain divided into grades of severity in 78 SCI patients.

VAS severity grade	Above injury level (%)	At injury level (%)	Below injury level (%)
No pain (0-4)	67.9	75.6	42.3
Mild (5-44)	24.4	20.6	37.1
Moderate (45-74)	7.7	3.8	19.3
Severe (75-100)	0.0	0.0	1.3

VAS: Visual Analogue Scale

Table 11. Registered anxiety and depression divided into HADS subscales in 78 SCI patients.

HADS subscales	HADS-A (%)	HADS-D (%)
Normal (0-7)	85.9	89.7
Mild disorder (8-10)	9.0	5.1
Clinically significant disorder (11-21)	5.1	5.1

HADS: Hospital Anxiety and Depression Scale


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5 DISCUSSION

Discussion

SCI persons in Sweden attend regular clinical follow-ups. Increased life expectancy has allowed secondary conditions and complications to emerge. As a consequence, in addition to traditional SCI complications, the need for focus on both physical and psychological health has increased. In this thesis focus is on some of those factors.

Clinical measurements

Up until recently, BMI cut-off limit 25 has been used on the SCI population, which is the cut-off limit for the general population to describe a higher risk for CVD. However, this limit has been suggested to be lowered, as it is inconsistently related to CVD risk factors and in not valid in estimating obesity in persons with SCI (60, 161). The cut-off limit for overweight for SCI patients are at present recommended to be set at BMI$\geq$22 (62). One of very few studies made on SCI women has also suggested lowering of BMI cut-off regarding obesity to BMI 28 for paraplegia and BMI 21 for tetraplegia (162). The reason for this is the changed body composition that follows a SCI and a paralysis. With a paralysis comes a loss of lean body mass (i.e. loss of muscle and bone tissue) (60, 61), which leads to an underestimation of the degree of obesity in persons with SCI (163). For instance, an increase in body fat mass might occur without an increase in body weight and thereby no increase in BMI.

An accurate BMI is not easy to assess due to the difficulty in obtaining a correct body height. Measuring body height by using a meter stock in a patient group where joint contractures (for example joint of hips, knees and ankles), spinal deformities, vertebral body compressions etc. often are present are a great challenge to the clinicians and may give inaccurate measures. Also, obtaining body height by patients' report has a well-known bias, where overestimation of body height by recall is a common fenomenon. In addition, the SCI patient group is a very heterogenous group, which gives very different body compositions depending on injury level (i.e. tetraplegia or paraplegia) and completeness of injury, i.e. if it is a complete or incomplete injury and therefore leads to a big variety in remaining muscle mass and bone tissue.

As shown in Paper I and Paper III in this thesis, BMI has a limited value as a clinical instrument for the SCI patient group. The difficulties in assessing a correct body height, changes in body composition and the great heterogeneity among the SCI, diminishes the value of BMI as a clinical instrument for the SCI population, especially as an instrument when assessing risk for CVD.

However, there were some correlations between BMI and risk markers for CVD, where in Paper I, SCI patients with HTN had significantly higher mean BMI than non-hypertensive subjects and patients with DM had significantly higher mean BMI than patients without DM, but only in men.

The prevalence of DM has been reported to be 13-22% in the SCI population (164-166), which is higher when compared to the general population in Sweden (6.3%) and USA (11.2% in the group <60 years) (166, 167). DM is correlated to overweight/obesity in the general population and is, in the SCI population, likely related to changes in body composition due to paralysis, metabolic changes and greater adiposity above and below the NLL (168). In Paper I the DM prevalence was 16% and in Paper III 5%.

In persons with SCI, HTN is a two-sided issue, where patients with injuries above Th6 often suffer from hypotension and therefore in some way are protected against HTN. This is due to a lower level of activity in the sympathetic nervous system (1, 169, 170). Persons with lower level of injury, i.e. Th7 and below, on the other hand have similar HTN issues as the general population (166). Risk factors for HTN, especially among paraplegics, are for instance overweight/obesity and physical inactivity, risk factors that are highly prevalent in this patient group and also among the patients in this thesis. If there is a HTN diagnosis made, it is important to verify the underlying cause and if it might be caused by autonomic dysreflexia or a renal problem etc.

Overweight and obesity, as mentioned above, are problems in this patient group with studies showing prevalence estimates of overweight or obesity between 40-66%, calculated with a BMI cutoff set at 25 (56-59). With reduced cutoff limit, the amount of SCI individuals with overweight/obesity increases. One study, where BMI was adjusted to 23, the prevalence of overweight was 37% and obesity 31%, i.e. 68% had a BMI above cutoff limit (59).

When it comes to SAH and WC, the same fenomenon as with BMI and DL was found. In paper III, the presence of DL (81%) was high, with a majority of the participants with SAH and WC below the recommended cut-off levels still had DL. However, methodologically, it has been shown that WC is a clinical examination that is practical to measure and easy to perform, compared with BMI and has a higher sensitivity than BMI (171). It has also been shown to be a good index for obesity-related CVD (60, 161, 171). The present suggested cut-off limit for WC are 94cm (171), while SAH cut-off used in paper III was set at 22cm for men and 20cm for women (152, 153). The relation between WC and increased all-cause mortality is shown. However, there are differences in cut-off limit recommendations for the general population in various countries. At the same time there is lack of data when it comes to appropriate cut-offs for other populations and ethnicities than a white population in North America, Australia and Europe (172). SAH and WC are probably better clinical measures than BMI, but still have limitations.

In the study group in Paper III, DL was often untreated or treated suboptimally, a result also found by others (173). As SCI persons have an increased prevalence of many risk markers for CVD it is of great importance that clinicians working with this patient group provide adequate treatment of DL and treat the SCI population as a high risk group for CVD (174, 175).

It is of great importance that people with SCI exercise regularly, together with adequate diet recommendations to both assess energy balance, to create a caloric deficit if needed, and to avoid/correct malnutrition. Therapeutic lifestyle interventions are also important to reduce weight, to reduce risk for HTN, DM and DL, and thereby reduce the risk for CVD. Interventions should also should include pharmacotherapy when needed as well as assistance with smoking cessation and moderation of alcohol consumption (1).

Physical activity

The amount of self-reported physical activity at least 30 minutes or more at a moderate or vigorous intensity, at least 5 days per week in the two study groups was low (20 and 32%) compared with the general Swedish population, where 65% have reported to be physically active equally or more than minimum recommendations (176). Patients who were physically active before the SCI were not more physically active than patients who were not physically active before the SCI. This is also shown in other studies, studies that also showed a decreasing amount of physical activity with increasing age and time since injury (177, 178). This might point to the many obstacles that are experienced by people with SCI when it comes to reasons for not being regularly physically active. It might be caused by one single factor or multiple factors. Common reasons given by SCI patients are economical, transportation problems, lack of interest, pain, internal barriers, the great amount of time it takes to prepare for physical activity (89, 90).

There was no difference in the amount of reported physical activity between WD and NWD patients, which could have been expected due to the fact that the patients in the NWD group have more muscle mass and function. This might indicate that the barriers perceived are the same, no matter the injury level and severity of injury. Therefore, it is of great importance that the SCI patients are given exercise advices, exercise plans, coupled with regular follow-ups, components that make the patients 2 to 3 times more likely to exercise (179). Also, it has been shown that persons with SCI prefer information about physical activity from their health care providers (180), which shows the importance and the need for regular follow-ups where SCI patients can be provided exercise prescriptions to increase the physical activity level.

In addition, SCI patients should be encouraged to be engage in ADL activities, like cleaning and shopping etc. A way to increase the likelihood of a SCI person being physically active might be to educate and involve family and personal assistance in the importance of regular exercise as well as to motivate and to allow the SCI person to be physically active in the everyday life.

In Paper IV there was no difference in presence of pain or pain intensity and no difference when comparing HADS-A and HADS-D between physically active or not physically active. There was no difference in the presence of risk markers for CVD between the physically active group compared to the not physically active, except for DBP in the study group with paraplegics only. In the heterogenous group in Paper III there was no differences found at all when analyzing risk markers for CVD between the physically active and not active. Men/women, tetraplegics/paraplegics and WD/NWD were equally physically active. An explanation might be that the intensity and frequency of physical exercise need to be increased compared to the WHO recommendations for the general population. Some studies on SCIs have shown that high-intensity physical activity might have a positive effect on blood lipid levels (86, 87), and other studies have shown that physical activity has a positive effect on CVD risk markers in persons with SCI together with a number of guidelines to increase physical fitness in the SCI population (80-83, 181). A problem for many SCI patients is that adequate physical activity level might be unreachable. The reasons can be disruption of sympathetic outflow, if injured above Th6, or it might be caused by a small remaining muscle mass with voluntary control.

However, until there are more evidence, the general recommendations for physical activity to improve cardiometabolic risk factors should be the same for the SCI population as it is for the general population.

Exercise should also be part of the SCI patients' weekly routine to improve strength, but it is unlikely to be an isolated method to achieve weight loss (182, 183). Improved strength, and thereby a positive change in body composition might, in time, lead to a reduced body weight through an enhanced resting metabolic rate. Improved strength and reduced weight are both important for the SCI persons ADL as well as injury prevention, especially to prevent or reducing shoulder pain. Exercise is also documented to have a positive impact on quality of life in persons with SCI (184).

Pain

Paper IV showed that pain registered with VAS was considered mild at all three levels; above, at and below injury level, compared with other studies that report a high prevalence of severe or excruciating pain (71, 185). A minority of the patients were on subscripted pain medication at the time of the study, but were included for the prevalence assessment. However, it is not possible to conclude the actual pain severity, without medication, in this patient group.

Pain below injury was significantly higher among incomplete SCIs, also showed by Sidall et al (71).

Paper IV studied the prevalence and level of pain. The results showed a high prevalence of pain (74.4%), but it is in parity with many other studies where around 70% of the individuals with SCI have persistent pain (186-189), and a recent systematic review showed an overall pain prevalence of 61±21% (70). Compared to the general population in Sweden (40-65% of the primary care patients, with approximately 30% of all general practice treatments) (190, 191), the prevalence of pain in this study group is high. The pain prevalence among women was not different when compared with men in the study. A difference found among the general population, where pain prevalence is higher among women (190). Women in Paper IV had higher registered pain at injury level, while other studies show varying results when it comes to differences in pain prevalence as well as pain intensity between men and women, but has found a greater use of both opioids and NSAID drugs among women than men (192, 193).

In Paper IV, 77.6% of the patients had pain below injury level (i.e. neuropathic pain) which is a higher prevalence than reported in other studies, where the prevalence of neuropathic pain is approximately 40% (71, 185, 194, 195). There was no difference in pain prevalence between complete and incomplete injuries, in contrast to a study by Mahnig et al. who found higher pain prevalence at and below injury level comparing those groups (185).

As persons with SCI have an increased risk for CVD it emphasizes the importance of adequate and sufficient treatment of pain, as it also might stand as an independent risk factor for CVD. However, neuropathic pain is very difficult to treat (196), especially neuropathic pain after a SCI (197-199).

The two most commonly used pharmacological medication against neuropathic pain in the study group are pregabalin and gabapentin. These medications are generally considered first-line agents on neuropathic pain (200, 201). Guidelines support the safety and efficacy of pregabalin, but long-term efficacy of pharmacologic agents for pain management in patients with SCI and neuropathic pain are still lacking. Gabapentin may be effective in some patients but has less support than pregabalin.

Nonpharmacological treatment strategies on neuropathic pain have few existing clinical trials. However, massage, acupuncture etc. are often reported to have a positive outcome by persons with SCI (197, 199, 202). Exercise to reduce pain has not yet been extensively tested.

The pain prevalence, and often the pain severity is high in this patient group and need adequate treatment. Pain is difficult to treat, why it need special attention from specialized clinics, with interdisciplinary and multimodal rehabilitation (203, 204). It is also important to note that most SCI patients have more than one pain problem (202, 205, 206). Important for a comprehensive pain management is therefore to differentiate a patient´s pain, when it comes to quality, location and factors increasing or decreasing the pain. An important notion, and of concern, is the high prevalence of drug abuse in the SCI population; almost twice as common as in the normal population (68, 207), as well as a high medication misuse (67, 68, 207).

Anxiety and depression

In Paper IV the results showed low scores on both HADS-A and HADS-D. Only 5.1% of the patients in study IV had HADS-A scores indicating mild or clinically significant disorder. HADS-D score equivalent to clinically significant disorder was present in 5.1% of the study group and only 8.9% that indicated mild depression. In comparison with the general population, this is a low depression prevalence, as the most common range globally is 8-12%. Anxiety affects 14% of the Europeans and approximately 18% of the Americans (208, 209), while he point prevalence for anxiety in Sweden is 5-8% (210). Also, compared with the SCI population, the prevalence of anxiety and depression in the group was low. Studies have shown presence of anxiety being 56% and depression 53% (185), while another study showed that major depression was around 20% (65).

In the general population, anxiety and depression is more frequent in women than in men. This was not the case in Paper IV, where no differences were found between men and women, however there were few women in the study group.

In Paper IV, there were no correlations between pain and anxiety/depression. There is an important connection found in the general population between pain and anxiety/depression that needs attention when diagnosing and treating patients with chronic pain. The correlation between pain and anxiety/depression is also found in SCI patients, as well as a correlation between pain and the risk for CVD. Both psychological and physical symptoms should therefore be diagnosed and treated and it is important that SCI patients have access to teams specialized on pain, anxiety and depression.

Strength and limitations

The two study groups are fairly small, but both groups were consecutively included and comprise a majority of the SCI patients in their respective geographical areas.

In this thesis DL is chosen as a risk marker, instead of focusing on separate blood lipids, as it is not known which blood lipids are of greater importance compared to others when it comes to risk for CVD. Using DL as a main risk marker for CVD might have limitations.

Framingham Risk Score was not chosen as a CVD risk predictor, as it has not been validated for use in persons with SCI. In addition, it is an instrument that to some extent is based on both blood pressure and BMI – two values that are difficult to use and interpret on SCI patients due to autonomic dysfunction and the earlier mentioned difficulties with obtaining an accurate BMI on the SCI patient.

The use of self-reported physical activity does probably not show the true frequency, activity time per week or work intensity. The physical activity done might therefore be overestimated and the intensity of a physical activity might be experienced differently between different individuals. However, in population-based studies, questionnaires are well-established to assess this type of information and to our knowledge, there is no golden standard when it comes to studies on physical activity in a SCI population.

A limitation with studying both pain and anxiety/depression with rating scores, is that patients in the study group could be under pharmacological treatment, which could affect the scores on VAS and HADS. However, the low presence of anxiety and depression might also indicate that the study group is well-medicated and well-rehabilitated. Paper IV did not include data on consequences of pain and anxiety/depression, such as daily activities, participation and quality of life. There are other instruments available to assess pain in this patient group that might be valuable in the future, e.g. International Spinal Cord Injury Pain (ISCIP) (185, 211).

Clinical implications

The results in this thesis suggest that the components studied, e.g. the risk markers for CVD, anthropometric measurements, physical activity, pain, anxiety and depression are all important parts of a follow-up of the SCI patients. When assessing CVD risk markers in this patient group, evaluation of serum lipids and blood pressure are probably of higher importance and more significant than calculating BMI levels. This calculation is also difficult to make as well as the changed body composition gives BMI even less value. However, overweight and obesity, common problems in this patient group, is something that needs attention. Dual X-ray Absorptiometry (DXA) might therefore be useful to create a golden standard to obtain adequate measures on body composition. SAH and WC seem to be better clinical measures than BMI, but also have its limitations.

It is also of great importance to screen for and treat DL (212, 213), HTN (169, 170, 214), central obesity (12), impaired fasting glucose and DM (11, 215), as a vast majority of both study groups had one or more of those risk markers. Risk markers that, according to convincing evidence, are a threat to the SCI person as it may be the cause of CVD.

Physical activity is still important and should be implemented as a regular part of the SCI patient's everyday life to increase strength to ease ADL; to achieve a possible change in body composition, to increase strength and to improve quality of life. However, this thesis suggests that physical activity is not the primary first hand choice when it comes to CVD prevention after a SCI. Life style intervention probably has to be combined with other measures.

As a suggestion, comprehensive therapeutic lifestyle intervention, with focus on dietary, exercise and behavioral components should be implemented in the treatment and prevention of CVD and overweight/obesity, together with pharmacological treatment when needed.

Pain is very common in the study group but the average level of pain was low, which might indicate that the patients in the study were well-medicated. However, international data shows the importance of adequate and sufficient pain management as well as the SCI patient having access to specialized care that includes both pharmacological and non-pharmacological treatments.

Even though anxiety and depression were found to be much less common in the study group than reported in other studies, psychological factors should be screened for and treated adequately.

Persons with SCI have to perform multiple procedures, follow many regimes and impose several lifestyle restriction on a daily basis. So before adding or implementing further restrictions and procedures to the persons in this patient group, it is of the greatest importance to assess the relevance and validity of the regime given.


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6 | SUMMARY AND CONCLUSIONS

Summary and conclusions

- Around 80% of the examined patients had at least one CVD risk marker irrespective of BMI level.
- DL was common for both men and women at all BMI levels.
- DL also seems not to be treated or undertreated in the group with different neurological lesion and functional levels.
- A majority of the patients with normal abdominal measures had DL.
- There was a high prevalence of HTN, especially in men.
- The patients reported a low prevalence of physical activity and no differences, except diastolic blood pressure, were found in blood glucose, clinical measures or serum lipids between physically active and not physically active patients.
- General anthropometric clinical measures did not seem to be valid for evaluating CVD risk in this SCI patient group.
- Pain was common in the patient group, however, most often on a mild to moderate level.
- Anxiety and depression were less common than reported in other studies.

This thesis shows the complexity and vulnerability that comes with a SCI as well as it emphasizes the importance of regular, life-long follow-ups by specialized clinics in various areas, depending on the SCI patients' specific, individual needs and a need for development of strategies for prevention and intervention of secondary conditions.

Acknowledgements

There are several people, without whom this thesis could never have been completed and I would like to extend my deepest gratitude to all of you.

Martin Fahlström, supervisor

Anna Ramnemark, assistant supervisor

Kerstin Wahman, assistant supervisor

Richard Levi, assistant supervisor

John E Lewis and Carina Boström, co-authors

All patients who participated in the studies

Colleagues and staff at the Department of Community Medicine and Rehabilitation, Umeå University

Colleagues at the Neurorehabilitation ward and outpatient clinic, Umeå University Hospital

Bill Olson, art-work

Mikke Hedberg, graphical design

Promobilia, financial support

My friends, wherever you are

My parents Stefan and Mona

My brother Jonas, my sister Anna and their families

Josefine, my beautiful wife, love of my life and best friend. Bene meritus!

Our beautiful children Vilmer, Signe, Cornelia, Christelle. You are awesome!

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