



EERIKA KOSKINEN

## Traumatic Spinal Cord Injury

Current Epidemiology in Finland  
and Evaluation of Cervical Injury  
by Diffusion Tensor Imaging



ACADEMIC DISSERTATION

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UNIVERSITY OF TAMPERE

EERIKA KOSKINEN

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## ACADEMIC DISSERTATION

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*To my family*



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# ABSTRACT

In traumatic spinal cord injury (TSCI), the neural tissue within the spinal canal is damaged by an external force resulting in the partial or complete loss of motor, sensory and autonomic function below the neurological level of the injury. TSCI is associated with permanent disabilities and leads to frequent complications that have substantial impacts on personal life and the health care system.

Although there is no cure for spinal cord injury (SCI), preventive measures are of great importance. Knowledge of the incidence and other epidemiological features of TSCI is essential both for prevention and for planning clinical and support services for this unique patient group. In addition, prediction of the neurological and functional outcomes for the patient early after injury is a prerequisite for planning efficient and effective rehabilitation as well as identifying the resources required after discharge. Moreover, knowledge of microstructural changes in the central nervous system after SCI is critical for developing and assessing the effectiveness of new treatments in the future.

The aims of this thesis were to 1) provide an epidemiological description of patients with SCI in Finland for medical care, follow-up planning and preventive initiatives; 2) evaluate the effects of SCI on spinal and cerebral white matter tracts using diffusion tensor imaging (DTI) and region-of-interest (ROI) methods; and 3) assess the ability of this method to link structure and clinical function in chronic SCI.

Epidemiological data were collected from all TSCI patients admitted to the newly appointed SCI centers in Oulu and Tampere University Hospitals (UHs) during the year following the national centralization of SCI care in Finland. Cervical spinal cord 3T magnetic resonance imaging (MRI) with DTI sequences was performed in 34 patients with chronic TSCI and 40 healthy control subjects. A comprehensive clinical and functional assessment was performed, and the association between acquired clinical data and DTI values was studied.

The incidence of TSCI in Finland was significantly higher than expected with a value of 38.1 per million in the hospital districts of Oulu and Tampere UHs, where all new SCI patients should be managed at SCI centers. Elderly people who had been injured by falling and had an incomplete cervical SCI constituted a significant

proportion of the newly injured patients. In addition, alcohol use contributed to a considerable number of injuries.

Spinal DTI values in the healthy adult population depended on the measurement level and white matter area of the spinal cord, but the effect of age on DTI metrics was small. The reproducibility of spinal measurements varied from good to excellent. In patients with chronic SCI, DTI detected pathological changes in both the spinal and cerebral white matter tracts at positions remote from the primary injury site that were observed using conventional MRI. In addition, some of the DTI values demonstrated significant relationships with the clinical parameters used to assess neurological deficit and disability after SCI.

In conclusion, the incidence of TSCI was higher than previously published in Finland or other Nordic countries. The epidemiological features followed the trends of developed countries, emphasizing the need to target prevention strategies towards the prevention of falls in the elderly and of alcohol-related injuries in the younger population. DTI changes in regions that were remote from the site of the primary injury were most likely due to secondary degeneration of white matter tracts after injury. This microstructural change was associated with the motor, sensory and functional state of the patient. DTI is a promising quantitative and objective tool for the assessment of patients with SCI. The ROI method can be considered clinically applicable to cervical spinal cord assessments, and a comprehensive normative database was established. However, longitudinal follow-up studies after acute injury are needed to assess the value of spinal and cerebral DTI in predicting recovery and in assessing the efficacy of novel treatments.

# TIIVISTELMÄ (ABSTRACT IN FINNISH)

Traumaattisessa eli tapaturmaisessa selkäydinvammassa (SYV) selkäydinkanavan sisällä kulkeva hermokudos vaurioituu ulkoisen voiman vaikutuksesta aiheuttaen potilaalle osittaisen tai täydellisen liikuntavamman ja tuntopuutoksen vamma-alueen alapuolisiin kehon osiin. Autonomisen hermoston vaurioituminen johtaa useiden muiden elinjärjestelmien toimintahäiriöihin. Selkäydinvammalla on laaja-alaisia vaikutuksia vammautuneen terveydentilaan ja elämäntilanteeseen, minkä vuoksi sen hoito vaatii monialaista ja -ammattillista osaamista.

Tieto tapaturmaisen selkäydinvamman epidemiologiasta on tärkeää mm. selkäydinvammoihin johtavien tapaturmien ehkäisemiseksi ja tarvittavien terveyspalvelujen kehittämiseksi. Mitä tarkemmin potilaan toipumista ja tulevaa toimintakykyä kyetään ennustamaan varhaisessa vaiheessa vammautumisen jälkeen, sitä yksilöllisemmin ja tehokkaammin voidaan suunnitella mahdollisimman suureen omatoimisuuteen tähtäävää kuntoutusta ja tukitoimia. Uusien hoitomuotojen kehitystyö ja tehon arviointi edellyttää vamman aiheuttamien hermorakenteiden muutosten yhä tarkempaa ymmärtämistä.

Tämän väitöstutkimuksen tavoitteena oli 1) selvittää tapaturmaisen SYV:n epidemiologinen tilanne Suomessa, 2) tutkia diffuusiokuvauksen (DTI) avulla onko SYV:lla vaikutusta selkäytimen ja aivojen valkean aineen hermoratoihin varsinaisen vaurioalueen ulkopuolella ja 3) arvioida onko mahdollisilla hermoratojen rakennemuutoksilla yhteyttä selkäydinvaurion laajuuden ja sen aiheuttaman toimintakyvyn heikentymisen kanssa.

Selkäydinvamman hoito keskitettiin Suomessa 1.5.2011 valtioneuvoston asetuksella Helsingin, Oulun ja Tampereen yliopistollisiin sairaaloihin. Tässä väitöstutkimuksessa esitetty epidemiologinen tieto on kerätty Oulun ja Tampereen yliopistollisissa sairaaloissa hoidetuista tuoreen tapaturmaisen SYV:n saaneista potilaista ensimmäisen vuoden ajalta asetuksen voimaantulon jälkeen. Diffuusiokuvantamista hyödyntävään tutkimukseen rekrytoitiin puolestaan potilaita, joiden kaularangan alueen selkäydinvammasta oli kulunut aikaa yli vuosi. Tämä tutkimusryhmä koostui yhteensä 34 potilaasta, joille tehtiin kaulaytimen ja aivojen diffuusiokuvantamisen lisäksi myös kattavat kliiniset tutkimukset vamman laajuuden ja toimintakyvyn selvittämiseksi. Kuvantamistutkimukset suoritettiin myös 40:lle terveelle verrokkihenkilölle.

Tapaturmaisen selkäydinvamman ilmaantuvuus Suomessa osoittautui selvästi aiempaa raportoitua suuremmaksi, ollen Pirkanmaan ja Pohjois-Pohjanmaan sairaanhoitopiirien alueella 38.1 miljoonaa henkilöä kohden. Muut tutkimuksessa esiintulleet epidemiologiset piirteet vastasivat pääpiirteittäin nykytilannetta muissa kehittyneissä maissa. Suurin erillinen potilasryhmä koostui yli 60 vuotiaista potilaista, jotka olivat saaneet kaatumisen seurauksena osittaisen kaulaytimen alueen selkäydinvaurion. Nuoremmassa ikäryhmässä iso osa vammoista oli tapahtunut alkoholinkäytön alaisena. Erityisesti nämä vaaratekijät tulisi huomioida suunnitellessa selkäydinvammaan johtavien tapaturmien ehkäisytoimenpiteitä.

Terveillä verrokkihenkilöillä kaulaytimen alueelta mitatut DTI arvot olivat riippuvaisia sekä selkäytimen mittaustasosta että –alueesta, mutta iän vaikutus DTI arvoihin oli pieni. Ytimen alueella käytetty mittausmenetelmä osoittautui kliinisesti käyttökelpoiseksi ja mittausten toistettavuus vaihteli hyvän ja erinomaisen välillä. SYV-potilaiden keskushermostossa todettiin itse vamma-alueen ulkopuolella vertailuarvoista poikkeavia DTI-arvoja. Nämä DTI-muutokset liittyvät todennäköisimmin akuutin vaurion käynnistämään hermoratojen etenevään degeneraatioon, eli rappeutumiseen ja ne korreloivat vamman aiheuttamien lihastoiminnan, tuntoaistin ja toimintakyvyn muutoksien kanssa. DTI-tutkimuksella voidaan saada määrällistä tietoa potilaan hermoratojen tilanteesta selkäydinvamman jälkeen. Tarvitaan kuitenkin lisäselvityksiä, erityisesti seurantatutkimuksia akuutin vamman jälkeen, jotta voidaan selvittää voidaanko DTI-tutkimusta hyödyntää käytännön työssä potilaiden ennusteen arvioimisessa ja tutkimuskäytössä hoitomuotojen tehon seurannassa.

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four original publications, which are referred to in the text using Roman numerals I-IV. The original publications have been reprinted with the permission of the copyright holders. In addition, some previously unpublished results are included in the thesis.

- I      Koskinen, E. A., Alen, M., Vaarala, E. M., Rellman, J., Kallinen, M., & Vainionpää, A. (2014). Centralized spinal cord injury care in finland: Unveiling the hidden incidence of traumatic injuries. *Spinal Cord*, 52(10), 779-784.
- II     Brander, A., Koskinen, E., Luoto, T. M., Hakulinen, U., Helminen, M., Savilahti, S., Ryymin, P., Dastidar, P. & Öhman, J. (2014). Diffusion tensor imaging of the cervical spinal cord in healthy adult population: Normative values and measurement reproducibility at 3T MRI. *Acta Radiologica*, 55(4), 478-85.
- III    Koskinen, E., Brander, A., Hakulinen, U., Luoto, T., Helminen, M., Ylinen, A., & Öhman, J. (2013). Assessing the state of chronic spinal cord injury using diffusion tensor imaging. *Journal of Neurotrauma*, 30(18), 1587-1595.
- IV     Koskinen, E. A., Hakulinen, U., Brander, A. E., Luoto, T. M., Ylinen, A., & Öhman, J. E. (2014). Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury. *Spinal Cord*, 52(3), 202-208.

# ABBREVIATIONS

AD	Axial Diffusivity
ADC	Apparent Diffusion Coefficient
AIS	ASIA Impairment Scale
ANOVA	Analysis of Variance
ASCIR	Australian Spinal Cord Injury Register
ASIA	American Spinal Injury Association
CNS	Central Nervous System
CST	Corticospinal Tract
CT	Computed Tomography
D	Diffusion Coefficient
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
FA	Fractional Anisotropy
FIM	Functional Independence Measure
fMRI	Functional Magnetic Resonance Imaging
HO	Heterotopic Ossification
ICC	Intra-class Correlation Coefficient
ISAFSCI	International Standards to document remaining Autonomic Function after Spinal Cord Injury
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LMN	Lower Motor Neuron
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
MVA	Motor Vehicle Accident
NLI	Neurological Level of Injury
NMR	Nuclear Magnetic Resonance
NSCISC	National Spinal Cord Injury Statistical Center
PLIC	Posterior Limb of the Internal Capsule
RD	Radial Diffusivity
RF	Radiofrequency
ROI	Region of Interest
SCI	Spinal Cord Injury
SCIM	Spinal Cord Injury Measure
SCIWORA	Spinal Cord Injury Without Radiological Abnormality

SD	Standard Deviation
SNR	Signal-to-Noise Ratio
TBI	Traumatic Brain Injury
TBSS	Tract-Based Spatial Statistics
TSCI	Traumatic Spinal Cord Injury
UH	University Hospital
UMN	Upper Motor Neuron
US	United States
VBA	Voxel-Based Analysis
VBM	Voxel Based Morphometry
WBA	Whole Brain Analysis
WISCI	Walking Index for Spinal Cord Injury
$\lambda$	Eigenvalue
$v$	Eigenvector



# 1. INTRODUCTION

Traumatic spinal cord injury (TSCI) results in motor, sensory and autonomic dysfunction, which affects multiple body systems and causes a life-long risk of various secondary complications. It has a considerable impact on the lives of injured individuals and their social surroundings.

In addition, spinal cord injury (SCI) causes substantial economic consequences. For example in Canada, the lifetime total direct costs associated with SCI range from 0.75 million to 1.7 million Canadian dollars for persons with incomplete paraplegia and complete tetraplegia, respectively. In addition, the indirect costs, or losses that occur due to the reduction in productivity, range from 0.7 to 1.3 million Canadian dollars (Krueger, Noonan, Trenaman, Joshi, & Rivers, 2013). Based on these rates, the estimated overall total lifetime economic burden associated with SCI in euros ranges from 1 to 2 million per person, depending on the level and completeness of the injury.

Although TSCI is potentially preventable, it is essential to understand the epidemiology of SCI to target preventive measures effectively to high-risk groups. In addition, up-to-date knowledge of local incidence rates and the epidemiological profile of SCI is important for strategic planning of clinical and supportive SCI services. In addition, in Finland, there was a government decree on May 1, 2011 to centralize acute care, sub-acute rehabilitation and life-long follow-up of SCI in three University Hospitals; therefore, the epidemiology of SCI was of great importance for planning and arranging adequate resources for appointed SCI centers in Helsinki, Oulu and Tampere. However, only one study has reported the incidence of TSCI in Finland during the last three decades (Ahoniemi, Alaranta, Hokkinen, Valtonen, & Kautiainen, 2008), and the incidence rates in other countries vary greatly among studies depending on, for example, geographical, cultural and methodological differences (B. B. Lee, Cripps, Fitzharris, & Wing, 2014).

At the level of the individual, accurate information about the prognosis and expected outcome is essential to answer patient questions about their future functional potential, to establish realistic goals and to produce effective and efficient rehabilitation after injury. In addition, the planning of post-discharge care and required facilities begins early after injury and must be based on a prediction of

the outcome following SCI (Ditunno, 1999). Currently, the prediction of prognosis after SCI is based primarily on information provided by both clinical examination using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirschblum, Burns et al., 2011) and conventional magnetic resonance imaging (MRI). However, ISNCSCI is prone to inter-rater variability, and the evaluation of patients who cannot reliably participate in the evaluation, for example because of young age, concomitant brain injury or the use of sedatives, can be difficult and inaccurate (Mulcahey, Gaughan, Betz, & Johansen, 2007; Mulcahey, Gaughan, Betz, & Vogel, 2007). Although conventional MRI is the imaging modality of choice for guiding management after injury (Daffner & Hackney, 2007; Lammertse et al., 2007) and appears to be of value in the prediction of prognosis (Andreoli et al., 2005; Bozzo, Marcoux, Radhakrishna, Pelletier, & Goulet, 2011; Miyaji, Furlan, Aarabi, Arnold, & Fehlings, 2007), the information provided is mostly qualitative.

In addition, in emerging clinical trials investigating experimental cell-based, pharmaceutical or rehabilitative interventions, there is a need for more specific and sensitive end-point measures that provide information about the condition of nerve fiber tracts using noninvasive techniques. Although most experimental trials focus on processes at the level of the injured spinal cord, the consequences of SCI at the cerebral level are worth noting when evaluating the potentiality and efficacy of various treatments.

Diffusion tensor imaging (DTI) is a relatively new MRI modality that has the advantageous feature of using diffusing water molecules to probe the tissue architecture (Basser & Pierpaoli, 1996). It can non-invasively produce quantitative information about the direction and integrity of cerebral and spinal white matter tracts and can reveal pathological changes in areas that appear normal using conventional MRI (Ellingson, Ulmer, Kurpad, & Schmit, 2008a; Ellingson, Ulmer, Kurpad, & Schmit, 2008b; Virta, Barnett, & Pierpaoli, 1999).

The general aims of this thesis are to provide an epidemiological description of patients with SCI in Finland, to evaluate the effects of SCI on spinal and cerebral white matter tracts by DTI and to assess the ability of this method to link structure and function in chronic SCI.

## 2. REVIEW OF THE LITERATURE

### 2.1 Traumatic Spinal Cord Injury (TSCI)

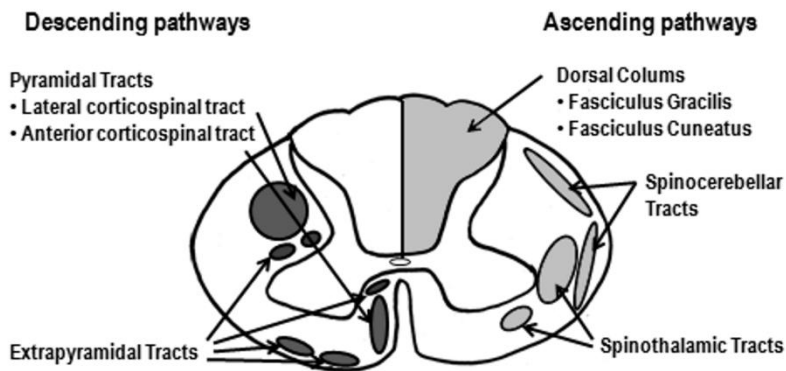
#### 2.1.1 *The Spinal Cord*

In this chapter, a brief review is presented of the important anatomical features of the spinal cord according to Baehr, Frotscher and Duus (2012) and Greenstein and Greenstein (2000).

The spinal cord runs within a bony vertebral canal and extends from the medulla oblongata to the level of the second lumbar vertebrae. Below that level, nerve roots from the lumbosacral segments ascend in the vertebral canal as the cauda equina. The spinal cord has been divided into 31 segments, each of which has an emerging pair of spinal nerves that transmit information to and from the peripheral nervous system. The spinal nerves are grouped as follows: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal. The butterfly-shaped gray matter is located in the inner part of the spinal cord and consists mainly of cell bodies, dendrites and axons. It is surrounded by the white matter, which is organized into three funiculi (anterior, lateral and posterior) in each half of the spinal cord. The descending and ascending axonal tracts running in these white matter funiculi convey sensory, motor and autonomic information between the peripheral nervous system and cerebral regions (Figure 1).

The corticospinal tract (CST) is a major descending pathway that participates in the control of voluntary movements in humans. The upper motor neuron (UMN) axons arise from the pyramidal cells in the precentral gyrus of the cerebral cortex and converge in the corona radiata. They descend through the capsula interna to the cerebral peduncle and further to the medullary pyramids. In pyramid decussation, approximately 90% of the fibers cross to the contralateral side and form the lateral corticospinal tract, which descends into the lateral funiculus of the spinal cord. Approximately 8% of the fibers continue in a straight path, forming the anterior corticospinal tract. In the anterior horn of the spinal grey matter, the UMNs synapse with the lower motor neurons (LMNs), which exit the spinal cord via spinal nerves. The majority of the sensory information is transmitted either via

the neospinothalamic tract in the lateral funiculus (temperature, pain and simple tactile sensations) or through the fasciculus gracilis and cuneatus in the posterior funiculus (position, movement, vibration, deep touch and two-point discrimination). From the thalamus, sensory tracts project through capsula interna to the primary sensory cortex in the postcentral gyrus. In addition, the autonomic nervous system pathways between the supraspinal regulatory centers and the effector organs travel in the white matter of the spinal cord. These neurons synapse on postganglionic neurons either in para- or prevertebral sympathetic ganglions or in parasympathetic ganglions near or within target organs.



**Figure 1.** A schematic representation of the spinal cord in cross-section and the location of the main white matter tracts.

### 2.1.2 *Definition of TSCI*

Traumatic spinal cord injury (TSCI) is defined by Kirshblum, Burns et al. (2011) as an impairment or loss of motor and/or sensory function due to damage to the neural elements within the spinal canal caused by an external force. The term SCI includes cauda equina and conus medullaris injuries and excludes brachial and

lumbosacral plexus lesions and injuries to peripheral nerves outside the neural canal. Tetraplegia refers to lesions in the cervical segments of the spinal cord that result in the impairment of function in all four limbs, trunk and pelvic organs. Paraplegia refers to lesions in the thoracic, lumbar or sacral segments of the spinal cord, and depending on the level of the lesion, it may involve the trunk, legs and pelvic organs.

### 2.1.3 *Pathophysiology*

An acute tear, compression or distortion of the spinal cord by external forces causes immediate death of the cells at the site of injury, resulting in a secondary injury that exacerbates the tissue damage via intricate mechanisms represented here according to the neuropathological reviews by Kakulas (1999) and Norenberg, Smith and Marcillo (2004). After a primary injury, immediate vascular damage leads to hemorrhage, ischemic changes and edema. An inflammatory response arises with neutrophil and then macrophage infiltration. Demyelination and death of oligodendrocytes are associated with neuron necrosis. Macrophages are responsible for removal of the damaged tissue, leading to the formation of cavities at the level of the lesion. Astrocytes form a glial scar, and collagenous fibrosis also appears in the area of the injury. Some peripheral types of remyelination occur through Schwann cell activity, and varying amounts of spinal cord tissue may be replaced by schwannosis. (Kakulas, 1999; Norenberg et al., 2004) In addition, many destructive responses, such as excitotoxicity, the formation of free radicals and lipid peroxidation, contribute to additional cell death during the acute and subacute phase following the initial trauma (Hagg & Oudega, 2006).

As a consequence of local neuronal injury in SCI, secondary degeneration can cause progressive and widespread changes in neural tracts at sites distant from the lesion over several years. Histologically, degeneration has been shown to spread in both anterograde and retrograde directions after SCI in humans (Bronson, Gilles, Hall, & Hedley-Whyte, 1978; Kakulas, 1999; Norenberg et al., 2004). Axonal changes, such as fragmentation and dying back, characterize the acute phase of degeneration, which is an active process triggered by rises in intracellular calcium levels. The acute phase of degeneration is followed by slow and progressive myelin degradation, which can continue for a number of years after the initial trauma (Kakulas, 1999; Norenberg et al., 2004). Demyelination is accompanied by astrogliosis, which eventually leads to isotropic scarring in regions where degeneration has occurred (Buss et al., 2004; Buss et al., 2005; Kerschensteiner, Schwab, Lichtman, & Misgeld, 2005). As an endpoint of neurodegeneration, the

spinal cord becomes atrophic after SCI (Cohen-Adad et al., 2011; Freund et al., 2011).

Secondary degeneration has even been shown to reach cerebral regions, and there is histological evidence of the atrophy of corticospinal neurons in humans after SCI (Yamamoto, Yamasaki, & Imai, 1989). Furthermore, the grey matter volume and thickness of the sensorimotor cortex (Henderson, Gustin, Macey, Wrigley, & Siddall, 2011; Wrigley et al., 2009) as well as the white matter volume in the corticospinal tract (Freund et al., 2011) have been shown to decrease after injury. In a recent study, such structural changes were shown to be progressive during the first year after injury, although the rate of atrophy decelerated in the area of the cranial CST after 6 to 12 months. In addition, these dynamic atrophic changes were associated with clinical scores that suggested better clinical outcomes with low volume changes in the cerebral CST after injury (Freund et al., 2013).

Functional magnetic resonance imaging (fMRI) has provided evidence of cortical reorganization, which compensates for sensorimotor loss after SCI. In humans, both a spatial shift and changes in the magnitude of cortical activation have been reported to occur in motor and sensory areas (Freund et al., 2011; Henderson et al., 2011; Jurkiewicz, Mikulis, McIlroy, Fehlings, & Verrier, 2007). Functional alterations, such as unmasking of latent lateral connections in the cortex, likely provide a partial explanation for the changes in activation observed by fMRI. However, in animal studies, structural alterations, such as remodeling of synaptic structures, axonal sprouting and the formation of new connections, have also been demonstrated in the cortex together with reorganization (Das & Gilbert, 1995; Florence, Taub, & Kaas, 1998; B. G. Kim, Dai, McAtee, Vicini, & Bregman, 2006). In addition, the reorganization of motor and sensory processing and the formerly mentioned structural changes have been shown to occur in subcortical regions of the brain (Ramu, Herrera, Grill, Bockhorst, & Narayana, 2008) and at the level of the spinal cord (Ghosh et al., 2010; Hill, Beattie, & Bresnahan, 2001) after experimental SCI.

#### **2.1.4      *Clinical Consequences***

In association with the impairment of voluntary motor and sensory functions below the level of the injury, SCI affects somatic and autonomic nervous control of the blood vessels, respiratory tract, sweat glands, bowel, urinary bladder and sexual organs, causing detrimental conditions and leading to secondary complications (A. Krassioukov et al., 2012). Of the various consequences of SCI, the decrease in the ability to walk or move has been reported to be the most

difficult to address, followed by decreases in sexual function, bladder control, and the ability to control the bowel, as well as pain (E. G. Widerstrom-Noga, Felipe-Cuervo, Broton, Duncan, & Yeziarski, 1999).

After cervical and high thoracic SCI, the majority of patients experience respiratory failure and complications, the risk of which depends on the level and completeness of the injury (Jackson & Groomes, 1994). Hypoventilation and atelectasis are common when breathing is dependent mainly on a functional diaphragm. Autonomic nervous system dysfunction leads to bronchospasm and increases the production of secretions, the clearing of which becomes difficult with the decreased effectiveness of coughing (Berlly & Shem, 2007). There is a high risk of developing pneumonia in patients with SCI, which, together with respiratory dysfunction, may be related to the dysphagia and aspiration that are common in patients with acute cervical cord injury (Jackson & Groomes, 1994; Shin, Yoo, Lee, Goo, & Kim, 2011).

Depending on the level of the injury, sympathetic cardiovascular dysfunction after SCI could affect heart rate, cardiac contractility and vascular tone. Major cervical or high thoracic injury usually leads to bradycardia, a low resting blood pressure and orthostatic hypotension. In addition, physiologic responses to exercise can diminish (Ravensbergen et al., 2014). After injuries at the level of T6 or above, there is a risk for autonomic dysreflexia. As a response to a triggering event below the level of the injury, episodes of extreme hypertension and heart rate abnormalities with various signs and symptoms of autonomic overactivity can occur (A. V. Krassioukov, Furlan, & Fehlings, 2003a). Patients with SCI are also susceptible to deep vein thrombosis (Chung, Lee, Kim, & Eoh, 2011).

Sympathetic decentralization after high SCI causes disturbances in thermoregulation. In subjects with a major injury, the core temperature can vary along with ambient temperatures, increasing the risk of hyperthermia in warm environments and of hypothermia in cold environments (Guttmann, Silver, & Wyndham, 1958). In addition, physical exercise can increase the risk of hyperthermia, mainly because of a reduced capacity for sweating below the level of the injury (Price, 2006). After acute SCI, tetraplegic patients can present a high fever without evidence of infection or any other definable cause (Ulger, Dilek, Karakaya, Senel, & Sarihasan, 2009).

Neurogenic bladder and bowel dysfunction can be of either the LMN or the UMN type. SCI above the level of T12 causes excessive anal sphincter and colonic wall tonus, producing fecal distention of the colon. In the LMN bowel, there is no reflex peristalsis of the colon, which together with a flaccid sphincter, typically results in constipation with fecal incontinence (Stiens, Bergman, & Goetz, 1997). Patients with suprasacral SCI can have involuntary reflex bladder activity with

incontinence and/or detrusor sphincter dyssynergia, whereas in LMN syndrome, urinary retention often occurs as a manifestation of areflexia of the detrusor (Weld & Dmochowski, 2000). Voiding dysfunctions, especially without proper management, can result in complications, such as urinary tract infections, urinary calculi and renal failure (Cardenas & Hooton, 1995; Kuhlemeier, Lloyd, & Stover, 1985).

Sexual dysfunction in men after SCI usually manifests as erectile dysfunction, which is generally more severe in patients with LMN injury. In addition, anejaculation and reduced semen quality decrease male reproductive potential (F. Biering-Sorensen & Sonksen, 2001). As in men, SCI has several effects on the sexual ability of women, resulting in diminished sexual arousal and a reduced probability of achieving orgasm (Sipski, Alexander, & Rosen, 2001). Nevertheless, the ability to become pregnant is usually not reduced after a transient period of amenorrhea that typically follows the acute injury (Rutberg, Friden, & Karlsson, 2008).

Spasticity can develop following UMN injury. It affects over 60% of patients with TSCI and can be particularly problematic following incomplete cervical lesions. Increased muscle tone and reflex movements elicited by movement or tactile stimulation can be painful and restrict daily living activities (Skold, Levi, & Seiger, 1999).

Chronic pain after SCI is common. Approximately 60% of TSCI patients suffer from nociceptive, neuropathic or visceral pain, and one-third of these patients rated the pain as at least severe (Siddall, Taylor, McClelland, Rutkowski, & Cousins, 1999). After acute injury, the most prevalent types of pain are trauma related musculoskeletal pain and neuropathic pain at the level of the injury. In turn, neuropathic pain below the level of the injury usually develops months or years after the injury. In addition, degenerative changes, overuse syndromes and postural abnormalities are usually responsible for the musculoskeletal pain in patients with chronic SCI (Siddall, McClelland, Rutkowski, & Cousins, 2003).

In heterotopic ossification (HO), extra osseous bone is formed in soft tissues, usually around the joints below the neurological level of the injury. This phenomenon causes swelling of the soft tissues and decreases in the range of motion of the joint. HO usually develops a few months after injury and can lead, at worst, to ankylosis of the joint (Van Kuijk, Geurts, & van Kuppevelt, 2002). Osteoporosis is very common in patients with SCI and increases the risk of fractures, especially in the lower extremities (Jiang, Dai, & Jiang, 2006).

Individuals with SCI are prone to pressure ulcers starting from day one, and the prevalence increases with time after the injury (Johnson, Gerhart, McCray, Menconi, & Whiteneck, 1998).



In addition to physical deficits, SCI induces psychosocial stress that can lead to psychological difficulties. Approximately 30% of SCI patients suffer from clinically significant depression, and the rate seems to change little with time after the injury. Coping strategies appear to be important for psychological outcomes, whereas anxiety or depression are unpredictable based on the level of the injury and functional independence (Kennedy & Rogers, 2000; Pollard & Kennedy, 2007).

## **2.1.5      *Evaluation***

### **2.1.5.1 *Clinical and Functional Assessment***

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) provides a standardized clinical tool for examining, describing and documenting the current neurological impairment of patients with SCI to achieve consistent and reliable data for clinical care and research studies (Kirshblum, Burns et al., 2011; Kirshblum, Waring et al., 2011). Since its development in 1982, many revisions have been made, and the latest version was published in 2011.

Several measures of neurological damage can be determined after standardized examination of sensory and motor functions based on the detailed instructions of the ISNCSCI. The numerical sensory score and sensory level, i.e., the most caudal normally innervated dermatome, are determined after examining light touch and pin prick sensations within each dermatome of the body and scoring the results on a three-point scale (0, 1 or 2). The motor score and motor level, in turn, refer to the results obtained from examining and recording the strength of certain key muscle functions of the extremities using a six-point scale (0 to 5). The neurological level of injury (NLI) is the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body. In turn, determination of the completeness of the injury is based on the definition of sacral sparing. Sacral sparing refers to the preservation of either sensation in the S4-5 dermatome or awareness of deep anal pressure or voluntary anal sphincter contraction. The injury is defined as incomplete when there is the presence of sacral sparing and complete when there is no sacral sparing. The American Spinal Injury Association (ASIA) Impairment Scale (AIS) designation is used to grade the degree of impairment. An AIS grade of A represents complete injury, AIS B represents motor complete-sensory incomplete injury, AIS C and D are incomplete motor and sensory injuries and AIS E means normal motor and sensory functions

at the time of the examination. The ISNCSCI worksheet contains detailed instructions for AIS determinations (Appendix 1).

The physical examination according to ISNCSCI and, in particular, the resulting level of neurological injury, completeness of the lesion and initial strength of the muscles, are important predictors of the expected recovery and outcome after SCI. For example, the probability that an initially complete injury will convert to an incomplete injury within one year is significantly lower than the likelihood of conversion from grades AIS B or C to higher AIS levels (Fawcett et al., 2007; Spiess et al., 2009). In addition, the recovery of upper extremity strength, lower extremity motor function, sensory recovery and the prognosis for walking after injury can be predicted based on the standardized physical examination (Burns, Golding, Rolle, Graziani, & Ditunno, 1997; Ditunno, Cohen, Hauck, Jackson, & Sipski, 2000; Waters, Adkins, Yakura, & Sie, 1993; Waters, Adkins, Yakura, & Sie, 1994; Waters, Adkins, Yakura, & Vigil, 1994). The results of ISNCSCI also provide an estimate of the achievable functional performance after SCI, which can be used, for example, to establish goals during the rehabilitation phase (Consortium for Spinal Cord Medicine, 2000). In general, the greatest gains in motor skills occur during the first 3 months, with the greatest recovery observed by 9 months (Fawcett et al., 2007). Improved recovery has been demonstrated in patients with incomplete injuries compared to those with complete injuries, whose recovery is usually limited to levels near the NLI (Ditunno et al., 2000; Spiess et al., 2009; Waters et al., 1993; Waters et al., 1994).

Several outcome measures, such as the Functional Independence Measure (FIM), Spinal Cord Injury Measure (SCIM) and Walking Index for Spinal Cord Injury (WISCI) are used to assess disability in the SCI population. WISCI is designed to evaluate walking capacity after SCI (Ditunno et al., 2000), and both FIM (Keith, Granger, Hamilton, & Sherwin, 1987) and SCIM (Catz, Itzkovich, Agranov, Ring, & Tamir, 1997) include subscores for a wide range of items in areas of mobility, locomotion, self-care, sphincter management and respiration. FIM as a general measure was initially designed for stroke patients, but nevertheless, it has been widely used to measure the functional ability of SCI patients and was even included previously as a part of the ISNCSCI (Dahlberg, Kotila, Kautiainen, & Alaranta, 2003; Hall, Cohen, Wright, Call, & Werner, 1999; Maynard et al., 1997). SCIM, in turn, was developed specifically for patients with SCI. The most recent version, SCIM III, has been shown to be a valid and reliable measure of the functional ability and changes specific to SCI (Anderson et al., 2011; Itzkovich et al., 2007).

Use of the International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI) is recommended as a part of the

clinical evaluation of patients with SCI. Assessment of remaining autonomic functions by ISAFSCI takes into account both the reported history and the results of a physical examination assessing the effects of SCI on cardiovascular, bronchopulmonary, sudomotor, bowel, urinary bladder and sexual functions (A. Krassioukov et al., 2012).

The International Spinal Cord Injury Data Sets were created to collect consistent data in a uniform manner for the purposes of daily clinical practice and research studies. They include core, basic and extended datasets (F. Biering-Sorensen et al., 2006; F. Biering-Sorensen et al., 2012). The core dataset includes background information about SCI and the patient, including for example data regarding age at the time of injury, etiology and characterization of the injury and the neurological state of the patient (M. DeVivo et al., 2006). The basic datasets were created primarily to record information about SCI-related issues in daily practice, and the extended datasets permit a more detailed data acquisition mainly for research purposes (F. Biering-Sorensen et al., 2006; F. Biering-Sorensen et al., 2012).

### ***2.1.5.2 Radiographic Evaluation***

The bony anatomy of the spine in trauma patients is generally assessed by computer tomography (CT) or plain radiography. From those, CT allows the 2D and 3D reconstructions improving the detection of bony injuries and helping in surgical planning. Therefore, it has become the most common and recommended method for the evaluation of patients with high risk for spinal trauma. (Holmes & Akkinepalli, 2005) However, magnetic resonance imaging (MRI) is recommended as a primary imaging modality for evaluating the spinal cord after injury. MRI enables the localization of the injury and is sensitive enough to evaluate the degree of compression and the presence of ligamentous injuries (Daffner & Hackney, 2007; Lammertse et al., 2007). Together with clinical findings, information regarding the degree and type of spinal MRI changes, especially in sagittal T2 sequences, can be used to determine the prognosis after injury. Patients with initial hemorrhagic lesions on the MRI more commonly have complete AIS A injuries with a poor prognosis, but a normal MRI predicts good recovery. Between these two scenarios, in terms of the initial neurological impairment and recovery, are patients with spinal edema, with a prognosis for resolution that is better with single-level edema when compared to patients with more diffuse edema (Andreoli et al., 2005; Bozzo et al., 2011; Ramon et al., 1997; Shimada & Tokioka, 1999). In addition, MRI characteristics, such as spinal swelling and the severity of spinal cord

compression, provide predictive information (Miyanji et al., 2007; Selden, Quint, Patel, d'Arcy, & Papadopoulos, 1999). The presence of hemorrhage and the rostral limit and length of the edema have also been shown to correlate with functional outcomes assessed by FIM scores (Flanders, Spettell, Friedman, Marino, & Herbison, 1999). The risen availability of MRI has obscured the use of the clinical term SCIWORA, i.e. SCI without radiological abnormality, in the medical literature. Therefore, the cases of neurologically evident SCI without any fracture, dislocation or malalignment detected by plain radiography or CT and with normal MRI has suggested to define, for example, as "real SCIWORA" or SCI without neuroimaging abnormality. (Yucesoy & Yuksel, 2008) In patients with chronic SCI, atrophy, myelomalacia, syrinx formation and cord compression can be detected in MRI (Curati, Kingsley, Kendall, & Moseley, 1992).

### **2.1.6      *Management***

The management of SCI has advanced during the 20th century. With the first SCI units established in 1936 in the United States (US) and in 1944 in England, SCI developed from an untreatable ailment into one that could be treated (Donovan, 2007). At present, all phases of care, including physical, physiological and social rehabilitation as well as life-long follow-up, are internationally recommended to be provided within a defined SCI system of care. The Cochrane review did not find a sufficient level of evidence to support the early referral of SCI patients to specialized centers (L. Jones & Bagnall, 2004). However, based on less stringent evidence, expert panels strongly recommend early transfer to integrated multidisciplinary specialized centers of care to decrease the overall mortality, number and severity of complications and length of stay (Consortium for Spinal Cord Medicine, 2008; Parent, Barchi, LeBreton, Casha, & Fehlings, 2011).

There are no common guidelines or determined requirements for specialized SCI care centers. Similarly, the organization, systems of care and services available differ widely among SCI rehabilitation units in different countries (New et al., 2013). However, the following components and functions for the optimal management of SCI have been emphasized in the literature in the pursuit of the prevention of complications, comprehensive rehabilitation, smooth integration into the community and cost effectiveness (Divanoglou, 2010; Emerich, Parsons, & Stein, 2012; Frankel, 1987; Guttmann, 1967; Parent et al., 2011): 1) in the acute phase, a specialized center for SCI should be capable of admitting a patient within hours of the injury and of providing rapid access to MRI and surgery with a spinal surgical team, if needed; 2) the many aspects of care and rehabilitation require the

implementation of a multidisciplinary team comprising nurses, different therapists and social workers in sufficient numbers and with specialized expertise in the care of SCI; 3) it is recommended that the physician directing the care of SCI patients possess special expertise in and work full-time with patients with SCI; 4) due to the multisystemic nature of this condition, medical management also demands the expertise and collaboration of several consulting physicians; 5) medical support services, and technical facilities for specialized care and rehabilitation should be adequate; and 6) research is considered an important part of the SCI system of care.

During the very first hours and days after an injury, the acute management of SCI is focused on life-saving interventions, neuroprotection and the prevention of complications. Spinal immobilization at the scene of the accident, cardiorespiratory stabilization, an early and accurate evaluation and surgical spinal stabilization are all aimed at reducing the progress of neural injury (Consortium for Spinal Cord Medicine, 2008). Early decompression within 24 hours of acute SCI is associated with an improved neurological outcome when compared to patients with surgery over 24 hours after the injury (Fehlings et al., 2012). Moreover, early surgery seems to decrease medical complications, shorten the length of stay in the hospital and lower the financial burden on the health care system (Bourassa-Moreau, Mac-Thiong, Feldman, Thompson, & Parent, 2013; Fehlings et al., 2012; Mac-Thiong, Feldman, Thompson, Bourassa-Moreau, & Parent, 2012). No pharmacologic agents have been shown to conclusively improve neurological outcomes after injury (Wilson, Forgione, & Fehlings, 2013). In contrast, comprehensive bowel, bladder and pulmonary management, skin protection and the prophylaxis of venous thromboembolism and stress ulcers are essential to prevent common and costly secondary complications. In addition, it is important to consider the psychological and social changes and needs of the patients from day one after injury (Consortium for Spinal Cord Medicine, 2008).

During the subacute period of inpatient rehabilitation, measures to prevent complications are maintained. The other main objectives of the rehabilitation phase are to optimize neurological recovery, develop compensatory skills and assess the equipment and house/workplace adjustments necessary to permit effective functionality and maximize independence in the environment of the patient after discharge (Emerich et al., 2012). The comprehensive education of patients and family members regarding various SCI-related issues is an important part of the rehabilitation process. Sufficient knowledge and adequate self-management skills are essential for coping with SCI after inpatient rehabilitation. In addition, vocational rehabilitation and peer mentoring as well as the sharing of information

about adapted sports and recreational activities facilitates community integration after injury (Emerich et al., 2012).

The multiple physiological problems that occur after SCI are usually life-long, and as a result of ageing and other life situation changes, patients can encounter new challenges, associated conditions and complications. Life-long follow-up with regular evaluations in specialized SCI centers enables the prevention, recognition, and care of medical, functional and psychosocial issues and the coordination of required services (Emerich et al., 2012).

While clinical trials investigating SCI cures have been inconclusive thus far, pre-clinical research has shown promise. There are many approaches to repairing the injury: reducing the effects of the damage, encouraging correct neuronal function and connections, enhancing regeneration and axon growth, replacing lost nerve cells, inhibiting scar and gliosis formation and reducing neurocircuit deficits (Donovan, 2007; Onifer, Smith, & Fouad, 2011; Tetzlaff et al., 2011).

## 2.2 Epidemiology of TSCI

Globally, there is considerable variation in the published incidence rates and other epidemiological features of TSCI depending, for example, on geographical and cultural differences, population characteristics, inclusion criteria and differences in data collection. In addition, most studies did not include pre-hospital data, and hence, patients who died at the scene of the accident were not included in the collected data (Ackery, Tator, & Krassioukov, 2004; Wyndaele & Wyndaele, 2006). Differences in pre-hospital and hospital management and the accuracy of the medical diagnosis could also explain some of the discrepancy, especially between developed and developing countries (Chiu et al., 2010). Nations with similar economies tend to have similarities in incidence rates and other features of TSCI (Ackery et al., 2004).

### 2.2.1 *Incidence*

In the US, the National Spinal Cord Injury Statistical Center (NSCISC) has reported the annual incidence of TSCI to be approximately 40 cases per million. This estimate is a projection based on several studies implemented prior to the 21st century (National Spinal Cord Injury Statistical Center [NSCISC], 2013). In a more recent study in the US, a cumulative incidence of 56.4 per million people ranging in age from 18-109 years was discovered based on nationwide emergency department

utilization rates between 2007 and 2009 (Selvarajah et al., 2014). In Canada, the incidence of TSCI was estimated using formerly published regional rates and resulted in 41 cases per million people per year in 2010 (Noonan et al., 2012). In Australia, the reported incidence estimate for 2007-2008 was 15 new cases per million people per year in the age group of 15 years and older based on the Australian Spinal Cord Injury Register (ASCIR) (Norton, 2010). In 2012, Rahimi-Movaghar and colleagues (2013) reviewed 29 papers from 19 different developing countries and found an incidence of 25.5 cases per million people per year (range, 2.1-130.7).

According to B. B. Lee et al. (2014), the median value for the incidence of TSCI in Western Europe is 16 cases per million. Recent European studies published after the 20th century have reported annual incidence estimates of TSCI to reach 11.7 cases per million in The Netherlands (Nijendijk, Post, & van Asbeck, 2014), 13.1 per million in Ireland (R. J. O'Connor & Murray, 2006), 13.4 per million in Spain (Van Den Berg, Castellote, Mahillo-Fernandez, & de Pedro-Cuesta, 2011) and 39.7 per million in Estonia (Sabre et al., 2012) when considering all age groups. In the age group over 15 years old, the incidence rates were 19.4 cases per million in France (Albert, Ravaut, & Tetrafigap group, 2005) and 33.6 cases per million in Greece (Divanoglou & Levi, 2009).

In addition, incidence data are available from all of the Nordic countries. In Denmark, based on records from two specialized rehabilitation hospitals, an incidence rate of 9.2 cases per million in all age groups was calculated for the period from 1975-1984 (E. Biering-Sorensen, Pedersen, & Clausen, 1990). In the Stockholm region of Sweden, the incidence was 19.6 cases per million among new patients aged 16 years or older in 2007 (Divanoglou & Levi, 2009). In Western Norway and Iceland, the most recent annual incidence rates were assessed based on hospital records and were 26.3 cases per million in 1997-2001 (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a) and 33.5 cases per million in 2005-2009 (Knutzdottir et al., 2012) in all of the age groups, respectively.

In Finland, several studies have considered the incidence of TSCI, but only two were published during the new millennium. Härkönen and colleagues studied TSCIs treated at the Central Hospital of Tampere from 1968-1975 and discovered an annual incidence of 8.5 cases per million across all of the age groups. (Harkonen, Lepisto, Paakkala, Patiala, & Rokkanen, 1979) Based on statistics from the National Board of Health, Rokkanen et al. (1988) found an incidence of 54 cases per million for spinal injuries associated with spinal cord or nerve root lesions from 1969-1976. In the study reported by Tarkkanen (1991), the true incidence of TSCIs among persons of working age was 34.2 cases per million inhabitants from 1970-1984, which included deaths during the primary phase. Ahoniemi et al. (2008)

found an incidence of 13.8 cases per million among patients aged 16 years and over who were referred to the Käpylä Rehabilitation Center during the observation period between 1976 and 2005. According to the study reported by Puisto et al (2010), the annual incidence of SCI in the pediatric population aged 0 to 17 years was 4.3 cases per million children between 1997 and 2006.

### **2.2.2      *Prevalence***

There are relatively few studies of the prevalence of TSCI globally, and there are even some continents without any reliable data. In the US, the prevalence rates published during the previous three decades have ranged from 473 to 1009 cases per million, (M. J. DeVivo, Fine, Maetz, & Stover, 1980; Ditunno & Formal, 1994; Ergas, 1985; Griffin, O'Fallon, Opitz, & Kurland, 1985; Harvey, Rothschild, Asmann, & Stripling, 1990; Lasfargues, Custis, Morrone, Carswell, & Nguyen, 1995) and an estimate from Canada in 2010 reached 1298 cases per million (Noonan et al., 2012). In Australia, the prevalence in 1997 was estimated to be 681 cases per million (P. J. O'Connor, 2005). Scattered rates have also been published in India (236 cases per million) (Razdan, Kaul, Motta, Kaul, & Bhatt, 1994), Iran (440 cases per million) (Rahimi-Movaghar et al., 2009) and Egypt (180 cases per million) (El Tallawy et al., 2013).

The only prevalence studies from Europe originate from Nordic countries. In the catchment area of the Stockholm Regional SCI Center, the prevalence was found to be 227 cases per million in 1995 (Levi, Hultling, Nash, & Seiger, 1995). In Helsinki, Finland, Dahlberg and co-workers found a prevalence rate of 280 cases per million in 1999 (Dahlberg, Kotila, Leppanen, Kautiainen, & Alaranta, 2005). In Western Norway, the prevalence was estimated to be 365 cases per million in 2002 (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a) and the most recent study from Iceland revealed a nationwide prevalence rate of 526 cases per million in 2009 (Knutsdottir et al., 2012).



## 2.2.3 *Demographic Characteristics and Trends*

### 2.2.3.1 *Age and Sex*

According to many studies, the average age at the time of injury is increasing concurrently with the increasing proportion of new patients older than 55-60 years of age. This phenomenon is leading to the presence of two incidence peaks: one among young adults and the other among the elderly (Ahoniemi et al., 2008; M. J. DeVivo & Chen, 2011; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012; Pickett, Campos-Benitez, Keller, & Duggal, 2006; Van Den Berg et al., 2011; Norton, 2010). Recently published mean ages at the time of injury were 42.4-50.4 years in the US (Selvarajah et al., 2014; NSCISC 2013), 42 in Australia (Norton, 2010), 52 in Canada (Thompson, Mutch, Parent, & Mac-Thiong, 2014) and from 38-48.9 years (mean of 44 years) in Nordic countries (Ahoniemi et al., 2008; Divanoglou & Levi, 2009; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012). The age-adjusted incidence of TSCI in children is low (Pickett et al., 2006; Puisto et al., 2010).

Men are more prone to SCI, and the majority of studies show a male-to-female ratio of 3-4:1 (Ackery et al., 2004). However, the percentage of women has been increasing slightly over the decades. This is probably due in large part to the increasing number of injuries in older age groups, when injuries are typically more evenly split between men and women (M. J. DeVivo, 2012). Incident cases in developing countries seem to have a lower mean age and a higher male-to-female ratio in comparison to developed countries (Rahimi-Movaghar et al., 2013).

### 2.2.3.2 *Mechanism of Injury*

Traditionally, transportation, especially motor vehicle accidents (MVA), has been the leading cause of injury in most countries, typically comprising 35-45% of the incident cases and being most common in young and middle aged persons (Knutsdottir et al., 2012; Pickett et al., 2006; Van Den Berg et al., 2011; NSCISC 2013; Norton, 2010). There are opposing trends in the incidence rates of MVAs in different countries. In a Norwegian study, the incidence of MVA-related injuries increased, especially among young men, between 1952-2001 (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a), but in Australia, the rate of transportation accidents declined during the period from 1986-1997 (P. J. O'Connor, 2006). In both studies, the change in rates was reflected especially in young males. In addition, since 1973,

the percentage of injuries resulting from transportation has decreased in the US; however, this etiology has increased again during more recent periods (NSCISC, 2013).

The proportion of falls as a cause of TSCI has risen during recent decades, especially in the age group over 60 years, in which falls are usually the leading etiology of TSCI in Western countries (M. J. DeVivo & Chen, 2011; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Van Den Berg et al., 2011). For example in the US, Iceland and Estonia, the proportions of fall in that age group were 56.8%, 55% and 72.4%, respectively. In some studies, falls have even become the most common cause of injury over transportation in analyses of the entire population (Ahoniemi et al., 2008; Divanoglou & Levi, 2009; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Sabre et al., 2012; Selvarajah et al., 2014). Elderly falls more often occur from a low height (at or less than one meter), and high falls mainly occur in younger age groups (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012; Selvarajah et al., 2014). In a region of Stockholm, 4 out of 22 injuries caused by falls were intentional, leading to a proportion of 8.5% of injuries caused by falls in the whole population were from suicide attempts (Divanoglou & Levi, 2009). Prevalence studies from Sweden and Finland showed suicide attempt rates of 4.0% (Levi et al., 1995) and 10.0% (Dahlberg et al., 2005), respectively. In a Swedish study, 85.7% of such injuries occurred due to jumping from a high place.

Sports usually contribute approximately 10% or less of all cases of TSCI, and this association is emphasized in younger age groups (Ackery et al., 2004; Chen, Tang, Vogel, & Devivo, 2013; Thompson et al., 2014). For example, in the US, diving alone was the fourth most common etiology of TSCI in the age group from 16-30 (8.5% of the injuries) (Chen et al., 2013). In Finnish studies, diving accounted for 6.6-9.0% of the injuries in the whole study population (Ahoniemi et al., 2008; Dahlberg et al., 2005).

In the US, violence, mainly gunshot wounds, has caused more than 20% of the TSCIs in the 20th century, but this rate has declined to 14.3% since 2010 (NSCISC, 2013). In Europe, violence as an etiology of TSCI is rather uncommon. For example, in Sweden and Finland 2% (Divanoglou & Levi, 2009) and 2.7% (Ahoniemi et al., 2008) of injuries, respectively, are caused by an assault.

In developing countries, etiologies can be more heterogeneous, reflecting the lives of the people in different countries. For example, in South Africa, gunshot injuries are the most frequent cause of injury (36%) (Hart & Williams, 1994), but in Bangladesh, 63% of injuries are caused by falling mainly from trees and while carrying heavy loads on the head (Hoque, Grangeon, & Reed, 1999).

### **2.2.3.3 Other Risk Factors**

TSCI seems to have a higher incidence on Saturday and Sunday in comparison to weekdays (Chen et al., 2013; R. J. O'Connor & Murray, 2006). Moreover, a cyclic seasonal variation was noticed in a large study in the US. The lowest incidence occurred in February and the highest in July, which was also the peak month for diving and motorcycle injuries (Chen et al., 2013).

Alcohol consumption preceded TSCI in 43.2% of the cases in Estonia, and 52.7% of the patients who were injured by diving were under the influence of alcohol (Sabre et al., 2012). In Western Norway, 21% of TSCI patients had consumed alcohol prior to the accident (Sabre, Hagen, Rekand, Asser, & Korv, 2013), and studies from Greenland and the US have reported the usage of alcohol as a contributing factor in approximately 50% of TSIs (Burke, Linden, Zhang, Maiste, & Shields, 2001; Pedersen, Muller, & Biering-Sorensen, 1989).

## **2.2.4 Severity of the Injury**

The cervical cord, especially at the C4 and C5 levels, is the most common site of injury, and thus more than 50% of TSCI patients are referred to as tetraplegic (NSCISC 2013; Norton, 2010). Among paraplegic patients, more than half (approximately 30% of all TSIs) have injuries in the thoracic spine; the remainder have lumbar or sacral injuries. After the mid-cervical region, the second most common neurologic levels of injury are T12-L1 in the area of the thoracolumbar junction (NSCISC 2013; Norton, 2010).

The severity of SCI is usually reported by combining the level of the lesion and the completeness of the lesion, both of which are assessed using the ISNCSCI. According to recent reports, incomplete tetraplegia is the most common injury category in Western countries and is usually followed by incomplete paraplegia, complete paraplegia and complete tetraplegia (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; NSCISC 2013; Norton, 2010). In recent decades, the proportion of incomplete tetraplegia has increased, especially among elderly people injured by falling (Ahoniemi et al., 2008; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012; Nijendijk et al., 2014; NSCISC, 2013). Otherwise, the level and completeness of the injury are associated with the etiology of the injury. For example, the majority of motorcycle accidents have resulted in complete SCI, and diving injuries result in tetraplegia (Chen et al., 2013).

According to the 2013 NSCISC report, 39.5% of TSIs are accompanied by at least one of the following associated conditions, which were documented

according to the recommendations of the International SCI Core Data Set (M. DeVivo et al., 2006): moderate to severe traumatic brain injury (Glasgow Coma Scale (GCS) score of 12 or below), non-vertebral fractures requiring surgery, severe facial injuries affecting sensory organs, major injury requiring chest-tube or mechanical ventilation, traumatic amputations of an arm or a leg, severe hemorrhaging, or damage to any internal organs requiring surgery (NSCISC, 2013).

Many cases of SCI are accompanied by concomitant traumatic brain injury (TBI). A study from Norway reported a dual diagnosis in 46.7% of cases (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010b), and in a study in the US, 60% of the TSCI patients had concomitant TBI (S. Macciocchi, Seel, Thompson, Byams, & Bowman, 2008). In both studies, most of the TBIs were classified as mild. Moreover, in a Finnish study, 74.0% of TSCI patients were diagnosed with TBI in a rehabilitation setting (Tolonen, Turkka, Salonen, Ahoniemi, & Alaranta, 2007). TBI is most prevalent in TSCI patients who are injured by motor vehicle accidents and falls. In addition, cervical cord injury, the completeness of the injury and the use of alcohol prior to the injury were found to be risk factors for dual diagnosis (Hagen, Eide, Rekand, Gilhus, & Gronning et al., 2010b; S. Macciocchi et al., 2008). Neuropsychological symptoms of TBI can complicate the rehabilitation process, and TSCI patients with this co-morbidity have been reported to achieve diminished functional recovery during the rehabilitation phase (S. N. Macciocchi, Bowman, Coker, Apple, & Leslie, 2004).

## **2.2.5      *Survival and Mortality***

In general, mortality after SCI has decreased dramatically since the Second World War; however patients with TSCI still have an increased risk for death, and life expectancy remains below normal (Ahoniemi, Pohjolainen, & Kautiainen, 2011; Hagen, Lie, Rekand, Gilhus, & Gronning, 2010; Yeo et al., 1998). Tetraplegia, complete injury and older age at the time of injury are the most common risk indicators for death (Ahoniemi et al., 2011; Hagen, Lie et al., 2010; Lidal et al., 2007). Previously, urinary tract complications were the most common cause of death after TSCI, but with improved management of the neuropathic bladder, the situation has changed (Soden et al., 2000). In a recent Finnish study, the predominant causes of death were cardiovascular diseases (20.7%), suicide (10.7%), external causes (of which 28/40 were intoxication) (9.5%) and respiratory disease (8.6%) (Ahoniemi et al., 2011). The frequency of causes of death in relation to the general reference population are usually highest for pneumonia, septicemia, suicide and diseases of the urinary system, and mortality rates for ischemic heart disease

are similar to those of the general population (Hagen, Lie et al., 2010; Hartkopp, Bronnum-Hansen, Seidenschnur, & Biering-Sorensen, 1997; Soden et al., 2000).

## 2.3 Diffusion Tensor Imaging (DTI) in TSCI

### 2.3.1 *Overview of the Method*

#### 2.3.1.1 *Magnetic Resonance Imaging (MRI)*

This chapter provides a brief review of magnetic resonance imaging (MRI), according to Kozlowski (2009) and Pipe (2009). Nearly two-thirds of the human body consists of water molecules. The nucleus of the hydrogen atom in the water molecule includes one positively charged proton that spins around its axis creating an electromagnetic field. In MRI, a large ensemble of these microscopic magnetic fields are aligned parallel to a strong external magnetic field that serves as an axis around which they will precess with a certain frequency, similarly to a spinning top. The frequency of precession depends on the strength of the external magnetic field and the characteristics of the nucleus itself. Radiofrequency (RF) pulses with the same specific frequency generate a perpendicular magnetic field, synchronize the random precession and turn the magnetization vectors of the protons away from the external magnetic field. Concurrently, the protons absorb energy and become excited to a higher energy state. These processes create a nuclear magnetic resonance (NMR) signal as the varying magnetic flux induces a voltage that can be measured with coils in the MRI device. After the RF pulse, the magnetization vectors begin to return to the original orientation, the protons return to random precession, excitation begins to relax and the signal attenuates.

#### 2.3.1.2 *Diffusion*

Diffusion or Brownian motion refers to the completely random displacement of molecules due to thermal energy. The diffusion coefficient,  $D$ , characterizes this thermal motion and is usually expressed in units of square millimeters per second ( $\text{mm}^2/\text{s}$ ). This constant is dependent on the temperature, molecular weight and viscosity of the solution (Beaulieu, 2002; D. K. Jones, 2009). When considering biological tissues, the apparent diffusion coefficient (ADC) is used as a diffusion

constant to incorporate the effects of cellular structures and active processes within tissues on diffusion (Le Bihan et al., 1986). If diffusion is equivalent in all directions, it is called isotropic, whereas the term diffusion anisotropy is used when diffusion is restricted in some directions (Beaulieu, 2002).

### *2.3.1.3 Diffusion Imaging*

The basics of diffusion-weighted imaging (DWI) are described in this paragraph according to Mori & Zhang (2006) and Mukherjee, Berman, Chung, Hess, and Henry (2008). In DWI, the MR signal is sensitized to the diffusion of water molecules by applying a pair of gradient pulses. In a homogeneous magnetic field, all of the protons in the hydrogen atoms precess with a certain frequency, providing the same signal frequency. Because the frequency of precession is dependent on the strength of the magnetic field, the use of a linearly varying magnetic field gradient over the volume of interest causes the protons to precess with different frequencies depending on their position along the gradient axis. After the gradient pulse ends, the signals from the protons gradually return to the same frequency, but their phases are no longer the same. When a second gradient pulse is applied with the same amplitude and duration but with the opposite polarity, the gradients have an opposite effect on the proton phase. In addition, the refocusing is perfect in each location if the position of the water molecules remains the same. If the water molecules move between two opposite gradient pulses, the overall phase coherence decreases, causing MR signal attenuation. Therefore, in a created diffusion-weighted image, regions with high diffusion appear with low signal intensity and vice versa. Using a spin-echo MRI technique, two gradients have the same polarity due to the application of a 180- degree refocusing pulse between them.

From the imaging parameters of the MRI, the b-value is a measure of diffusion weighting and determines the strength, duration and timing of diffusion gradients. The greater the b-value, the stronger the diffusion weighting (Le Bihan, 1991). To obtain quantitative information regarding diffusion, two separate scans with different b-values are needed to calculate the ADC within each voxel of the imaged volume. The first measurement with a very low b-value or without diffusion gradients results in a non-diffusion weighted signal, and the second, with a higher b-value, results in a diffusion-weighted signal. The amount of signal intensity decay between the measurements contains the diffusion information along the applied gradient axis. Considering these data together, quantitative ADC maps can be obtained (Le Bihan et al., 1986; Mori & Zhang, 2006). Because the diffusion in

tissues is not usually isotropic, it is standard practice to improve the accuracy of the measurement using the average ADCs derived from at least 3 orthogonal gradient directions:  $ADC = (ADC_x + ADC_y + ADC_z) / 3$  (Basser & Pierpaoli, 1996).

#### **2.3.1.4 Diffusion Tensor Imaging**

In an isotropic medium such as free water, diffusion can be represented as a sphere and characterized by a single scalar ADC that is equivalent in each direction. In some biological tissues, especially in the white matter of nervous tissue, the ADC depends on the direction in which it was measured. The ADC is higher in parallel with nerve fiber bundles than in the perpendicular direction, indicating anisotropic diffusion (Chenevert, Brunberg, & Pipe, 1990; Thomsen, Henriksen, & Ring, 1987).

This asymmetrical diffusion pattern, with different diffusion properties in different directions, can be modeled by a three-dimensional ellipsoid in which the orientation of the longest axis, which has the highest ADC, represents the local fiber orientation. The concept of diffusion tensor provides a simplified mathematical model to estimate microscopic diffusion properties, such as the magnitude, the degree of anisotropy and the principal orientation, by performing six or more diffusion-weighted measurements in independent directions (Basser, Mattiello, & LeBihan, 1994). After creating a symmetric 3x3 matrix, called a tensor, from these measurements, it is mathematically possible to determine the six requisite properties of the three-dimensional diffusion ellipsoid. Three eigenvalues or diffusivities ( $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$ ) and three eigenvectors ( $v_1$ ,  $v_2$  and  $v_3$ ) describe the length and orientation of the longest, middle and shortest axes of the ellipsoid, respectively (Basser, Mattiello, & LeBihan, 1994).

### **2.3.2 Quantifying Diffusion Properties**

To further characterize the features of diffusion within a voxel, the eigenvalue information can be combined in several ways. The mean of the three eigenvalues describes the diffusivity of water without directional preferences and is usually called the mean diffusivity (MD), which is equivalent to the ADC averaged over all directions in a voxel (Basser & Pierpaoli, 1996). The greatest eigenvalue or diffusivity ( $\lambda_1$ ) along the principal direction of diffusivity is often called the axial diffusivity, (AD), whereas the average of the second and third eigenvalue is known as the radial diffusivity (RD) and provides the magnitude of diffusion

perpendicular to the neural fibers (Basser, 1995; S. K. Song et al., 2002). From calculated indices that characterize diffusion anisotropy, the fractional anisotropy (FA) is the most used in the literature. It is a normalized variance of the three diffusivities and describes the degree of directional dependence of diffusion ranging from 0 for a completely isotropic medium and 1 for diffusion that occurs completely along the principal axis (Basser & Pierpaoli, 1996) (see Table 1).

Based on the assumption that the orientation of the primary eigenvector in the diffusion ellipsoid represents the fiber orientation in a voxel, directionally encoded colored FA maps can be created to visualize the direction of the white matter tracts on 2D images (Pajevic & Pierpaoli, 1999). The same postulate enables 3D voxel-by-voxel tracking of individual neural fibers by tractography to visualize, localize and quantitatively assess neural pathways (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Mori, Crain, Chacko, & van Zijl, 1999). However, the DTI values of specific white matter areas in clinical studies are usually quantified from either a circular or freehand region of interest (ROI) that is placed manually on images separately for each subject (Hakulinen et al., 2012). In turn, voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) are useful approaches for whole-brain analysis between two groups of subjects without any hypothesis a priori (S. M. Smith et al., 2006).



Table 1. Overview of the most common diffusion tensor imaging indices used in the literature.

	Abbreviation	Definition	Equation	Unit
Eigenvalues	$\lambda_1, \lambda_2$ and $\lambda_3$	length of the longest, middle and shortest axes of the diffusion ellipsoid		mm <sup>2</sup> /s
Apparent Diffusion Coefficient	ADC	magnitude of diffusion without directional preferences	$ADC = (\lambda_1 + \lambda_2 + \lambda_3)/3$	mm <sup>2</sup> /s
Mean Diffusivity	MD	magnitude of diffusion without directional preferences	$MD = ADC$	mm <sup>2</sup> /s
Fractional Anisotropy	FA	degree of directional dependence of diffusion	$FA = \sqrt{\frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$	Scalar, from 0 to 1
Axial Diffusivity	AD	magnitude of diffusion along the principal direction of diffusivity	$AD = \lambda_1$	mm <sup>2</sup> /s
Radial Diffusivity	RD	magnitude of diffusion perpendicular to the principal direction of diffusivity	$RD = (\lambda_2 + \lambda_3)/2$	mm <sup>2</sup> /s

### 2.3.3 DTI Values in Healthy Central Nervous Tissue

In addition to the directional coherence of neural fibers, the axon count, fiber diameter, density and degree of myelination have an effect on DTI values (Beaulieu, 2002; Le Bihan, 1995; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996; Schwartz et al., 2005). From the longitudinal structural compartments of the neural tissue, intact axonal membranes have been indicated to be the most important factor for anisotropy, and the myelination of axons has a modulating effect (Beaulieu & Allen, 1994; Beaulieu, 2002; Gulani, Webb, Duncan, & Lauterbur, 2001).

In general, FA values are higher and ADC values are lower in the white matter when compared to the gray matter (Vedantam et al., 2013). Because of the variation in tissue composition and axonal morphometry, DTI values also vary in different intact cerebral (Brander et al., 2010; C. E. Lee, Danielian, Thomasson, & Baker, 2009) and spinal (Onu et al., 2010; Rossi et al., 2008) white matter tracts. In the brain parenchyma, higher regional FA values are detected in areas with tightly packed and parallel neural tracts, such as the corpus callosum. In contrast, in areas with a less coherent fiber architecture and crossing fibers, such as in the centrum semiovale, anisotropy is considerably lower in the DTI measurements (Brander et

al., 2010; Hakulinen et al., 2012; C. E. Lee et al., 2009). In addition, variation in DTI metrics of individual spinal white matter funiculi with varying fiber diameters, myelination and spacing has been detected, although the results are not in complete concordance (Onu et al., 2010; Rossi et al., 2008; Vedantam et al., 2013).

In the spinal cord, DTI values vary depending on the spinal level. In most studies, the magnitude of the FA has been found to decrease in the rostral to caudal direction both throughout the whole spinal cord (Ellingson, Ulmer, Kurpad, & Schmit, 2008a) as well as between cervical cord levels (Lindberg, Feydy, & Maier, 2010; Mamata, Jolesz, & Maier, 2005; T. Song et al., 2011; Vedantam et al., 2013). Compared to the FA, the inverse evolution of the ADC between different cervical cord levels has also been found in some studies (Cheran et al., 2011; Shanmuganathan, Gullapalli, Zhuo, & Mirvis, 2008), but in general, the ADC has been shown to be relatively constant throughout the spinal cord (Ellingson, Ulmer, Kurpad, & Schmit, 2008b; Lindberg et al., 2010; S. A. Smith et al., 2010; T. Song et al., 2011). In addition, in the brain parenchyma, ADC values show less regional variation than the FA (Brander et al., 2010). From directional diffusivities, AD has been shown to be higher in the cervical spine compared to the thoracolumbar regions (Ellingson, Ulmer, Kurpad, & Schmit, 2008b), whereas an increase in RD has been demonstrated in the rostrocaudal direction of the cervical cord (S. A. Smith et al., 2010).

With normal aging, FA values have been shown to decrease and ADC values to increase in the cerebral white matter. These changes appear to be regionally selective such that frontal and parietal white matter show greater changes in diffusion characteristics with age in comparison to the occipital and posterior areas (Abe et al., 2002; Hsu et al., 2008; Salat et al., 2005). Some studies have also reported gender-related differences in cerebral white matter DTI values (Hsu et al., 2008). In addition, spinal DTI metrics appear to be age-dependent. In particular, FA has demonstrated inverse correlations with age in addition to (Mamata et al., 2005; Van Hecke et al., 2008) or without a significant impact of age on the ADC values (Lindberg et al., 2010; Petersen et al., 2012; Vedantam et al., 2013). In a recent study, no gender differences in spinal DTI values were found (Vedantam et al., 2013).

### 2.3.4 *Interpreting Changes in DTI Values*

In the nervous tissue, water molecules diffuse inside, outside, around and through different structures, encountering many obstacles. In diffusion imaging, all of this complex thermal motion and ADCs in different compartments are measured with a single tensor per voxel, and the interpretation of changes in DTI values is not straightforward (Le Bihan et al., 2001; Sotak, 2004). In clinical studies, measurements are usually performed with a b-value of approximately 1000 s/mm<sup>2</sup>. With this amount of diffusion weighted, the changes in ADC are suggested to be especially sensitive to alterations in the diffusion coefficient of the extracellular space and its fractional volume relative to the intracellular volume (Le Bihan et al., 2001; Sotak, 2004). A case in point is the decrease in ADC that occurs during the acute stage after an ischemic stroke together with cellular swelling via cytotoxic edema, which leads to a decrease in the extracellular volume fraction and restriction of water molecule movement (Ahlhelm, Schneider, Backens, Reith, & Hagen, 2002; Albers, 1998). In addition, an increase in cellularity, for example in neoplasia, can decrease ADC (Guo, Cummings, Dash, & Provenzale, 2002). In contrast, an increase in the magnitude of diffusion has been reported in connection with conditions such as vasogenic edema (Lu et al., 2004) and inflammation (Tievsky, Ptak, & Farkas, 1999), which are characterized by an accumulation of water in interstitial spaces. Similarly, after the subacute phase of ischemic stroke, diffusivity in affected region increases in all directions and elevates the ADC or MD significantly, reflecting the loss of normal tissue architecture and accumulation of water in the extracellular spaces and in cystic cavities formed in the damaged tissue (Pierpaoli et al., 2001).

A reduction in diffusion anisotropy has generally been associated with the loss of structural orientation and integrity of fibers in the nervous system, but the decrease in the FA value can result from three different changes in directional diffusivities: an increase in RD, a decrease in AD or both (Mori & Zhang, 2006). Based on animal studies, it has been hypothesized that alterations in AD and RD may underlie changes in nervous tissue beyond FA. An elevation in RD is usually linked to demyelination, but a decrease in AD is associated with axonal injury (S. K. Song et al., 2002; S. K. Song et al., 2003). These changes in directional diffusivities are detected in the same timeframe as axon and myelin degradation in the acute stage of secondary neural degeneration. Although FA decreases during both the early acute phase and sub-acute phase during secondary degeneration, it is attributed to a decrease in AD due to axonal degeneration in the early acute phase and to an increase in RD due to demyelination during the sub-acute phase (Cohen-Adad, Leblond et al., 2011; Concha, Gross, Wheatley, & Beaulieu, 2006; S. K. Song

et al., 2003). The chronic phase of secondary degeneration is characterized by both axonal and myelin degradation as well as by the formation of isotropic gliosis (Buss et al., 2004). Analogously, the DTI values measured in the area of degenerated fibers usually display a marked decrease in FA and a small increase in ADC in connection with decreasing AD and increasing RD values (Pierpaoli et al., 2001). In comparison to the marked increase in diffusivity at the site of direct neural injury, the relative preservation of ADC during secondary degeneration may be due to the formation of gliosis and increases in extracellular matrices, restricting the mobility of water molecules in the area of the degenerating fibers (Pierpaoli et al., 2001).

At the macroscopic level, crossing fibers can affect FA, RD or AD values without any pathological alterations in the microstructure of the nerve fibers in question, because the principal direction of diffusivity in a voxel can be aligned with fibers other than those of the underlying structure in question. In addition, pathological changes that produce a decrease in anisotropy can cause biases in the eigenvectors and result in uncertainty regarding the interpretation of DTI values (Pierpaoli et al., 2001; Wheeler-Kingshott & Cercignani, 2009). Furthermore, many acquisition and analysis-related technical matters, such as physiological motion, image noise and partial volume effects, can cause artifacts and affect the diffusion values (Basser & Jones, 2002).

### **2.3.5      *Spinal DTI in Patients with TSCI***

An overview of the study protocols used for DTI studies in patients with SCI is presented in Table 2.

Table 2. The research protocols used for the diffusion tensor imaging studies in patients with SCI in this thesis.

First author	Year	Patients n/age	Controls n/age	Time since injury	Level of injury	Completeness of injury	MRI	DTI method	DTI metrics	Image plane	Placement of ROIs	Measurement levels	Measures for severity
Spinal DTI for patients with chronic SCI													
Ellingson	2008	10/37	13/25	> 4 years	C5-T11	4 AISA, 6 incompl	1.5T	ROI	FA, AD, RD, ADC	axial	1 per level: whole cord	all cervical levels, lesion level, high cervical level	completeness and the level of injury
Chang	2010	10/47.5	10/32.4	> 1 month	C4-C5	1 AISA, 3 B, 5 C, 1 E	1.5T	ROI + traktogr.	FA, ADC	axial	4 per level: anterior, posterior, lateral x 2	C3-T1	abnormal motor and sensory levels in the ISNCSCI
Cohen-Adad	2011	14/45	14/45	25±35 years	C3-C7	2 AISA, 5 B, 4 C, 3 D	3T	HARDI, ROI	FA, RD, AD, MD	axial	2 per level: dorsal, ventrolateral	cervical levels with no pathology in T2	ISNCSCI motor and sensory scores
Petersen	2012	19/59.7	28/58	2 months - 8 years, mean 32 months	C3-C8	2 AISA, 2 B, 3 C, 12 D	3 T	ROI	FA, RD	axial	5 per level: whole cord, lateral x 2, posterior x 2	C2, C5, T5, lumbar enlargement	AIS grades
Freund	2012	9/45.7	10/38.8	14.8±7.2 years	C5-C8	2 AISA, 1 B, 2 C, 4 D	1.5T	ROI	FA	axial	3 per level: whole cord and lateral x 2	high cervical cord C1-C3	Action Research Arm Test, 9-Hole Peg Test maximum voluntary contraction
Mulcahey	2012	10/15.5	-	chronic	C1-C5	3 AISA, 4 B, 2 C, 1 D	3T	ROI	FA, AD, RD, MD	axial	1 per level: whole cord	all cervical levels	all of the ISNCSCI-values

### Spinal DTI for patients with acute SCI

Shanmuganathan	2008	16/45.7	8/34.2	32±22 hours	Cervical	Not specified	1.5T	ROI	FA, ADC, RA	sagittal	-	upper, mid and lower cervical levels	quadriplegic vs diplegic and monoplegic
Cheran	2011	25/39.7	11/31.5	acute	C4-C7	5 AIS A, 7 B, 3 C, 9 D, 1?	1.5T	ROI	FA, AD, RD, MD	sagittal	-	upper, mid and lower cervical levels	ISNCSCI motor score
Vedantam	2013	12/54.7	12/52.2	3.6±0.9 day	C3-C8	1 AIS A, 1 B, 2 C, 8 D	1.5T	ROI	FA	axial	3 per level: whole cord and lateral x 2	high cervical cord, C1-C2	ISNCSCI motor and sensory scores and AIS grades

### Cerebral DTI for patients with SCI

Guleria	2008	20M/42, 2F/24	13/11M/40, 2F/22	3-24 months	C2-C5	22 AIS A	1.5T	ROI	FA, MD	-	-	medulla, pons, cerebral peduncles, PLIC, corona radiata	-
Wrigley	2009	15/41	27/37	24-390 months	T1-T10	15 AIS A	3T	WBA + tractogr.	FA in WBA, FA, MD, AD, RD in tractogr.	-	-	tractogr.: pyramidal or pons and cerebral peduncle, PLIC	injury level
Freund	2012	9/47.5	14/40.1	14.8±7.2 years	C5-C8	2 AIS A, 1 B, 2 C, 4 D	1.5T	WBA + ROI	FA, MD, AD, RD	-	-	pyramids, cerebral peduncle, PLIC, cortex: M1 hand and leg areas	ISNCSCI motor score, Action Research Arm Test, 9-Hole Peg Test, maximum voluntary contraction
Wei	2008	15/35.7	12/34.6	54-186 days	C1-L1	5 AIS A, 9 incompl.	3T	TBSS + ROI	FA	-	-	ALIC, PLIC, forceps minor, corpus callosum	-

SCI, spinal cord injury; n, number; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; ROI, region of interest; AIS, American Spinal Injury Association Impairment Scale; FA, fractional anisotropy; ADC, apparent diffusion coefficient; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; RA, relative anisotropy; HARDI, high angular resolution diffusion imaging; M, male; F, female; WBA, whole brain analysis; ISNCSCI, International Standards for Neurological Classification of SCI; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule; TBSS, tract-based spatial statistics

### **2.3.5.1 Patients with Chronic SCI**

Fractional anisotropy is the most used DTI value quantified in studies of chronic SCI. A decrease in FA values has been shown at the levels of direct neural lesions (Ellingson, Ulmer, Kurpad, & Schmit, 2008a) as well as in cervical levels that appear normal on conventional MRI. Changes that are remote from the injury site are generally suggested to reflect the secondary degeneration of descending and ascending neural pathways after injury (Chang, Jung, Yoo, & Hyun, 2010; Cohen-Adad et al., 2011; Freund et al., 2012; Petersen et al., 2012).

Results showing changes in diffusivity values are more variable. At the lesion level, ADC, AD and RD values have been shown to increase in chronic SCI (Ellingson, Ulmer, Kurpad, & Schmit, 2008a). At spinal levels with no MRI pathology, some studies did not report significant effects of SCI on directionally averaged diffusion (Chang et al., 2010; Cohen-Adad et al., 2011); in one study, the ADC even decreased (Ellingson, Ulmer, Kurpad, & Schmit, 2008a). Considering directional diffusivities at locations remote from the injury, both a decrease in AD with an increase in RD without a significant change in MD (Cohen-Adad et al., 2011) and a decrease in RD and AD values with decreasing ADC (Ellingson, Ulmer, Kurpad, & Schmit, 2008a) have been detected. In one study, RD showed no significant change (Petersen et al., 2012).

In chronic SCI, FA values, which are interpreted to show the integrity of white matter tracts, are associated with the severity of the injury and show a positive correlation with the sum of the motor and sensory score (Cohen-Adad et al., 2011) and with the AIS scale (Petersen et al., 2012) evaluated clinically using the ISNCSCI. In addition, the number of abnormal FA levels in the area of the cervical spinal cord has been shown to correlate with the number of abnormal motor levels (Chang et al., 2010). In turn, RD, which is thought to mainly reflect the integrity of the myelin, has demonstrated a negative association with the ISNCSCI motor and sensory score (Cohen-Adad et al., 2011), but no correlation was found for the AIS grade (Petersen et al., 2012). However, in complete SCI, FA has been shown to be lower and RD higher at the level of the lesion compared to values in patients with incomplete injury. In addition, the same DTI values also appeared to depend on the lesion level (Ellingson, Ulmer, Kurpad, & Schmit, 2008a). In a study with pediatric SCI patients, a negative association was detected between ISNCSCI scores and RD, AD and MD values. In the same study, the DTI diffusivity indices and FA value seemed to have significantly stronger correlations with clinical scores than with conventional MRI findings (Mulcahey et al., 2012). Beyond the relatively robust motor scores of the ISNCSCI, the fine motor

performance of the hand has been associated with the FA values measured from the area of right CST (Freund et al., 2012).

### ***2.3.5.2 Patients with Acute TSCI***

Analogously to the changes in diffusivity in the area of the acute ischemic lesion, the ADC has been demonstrated to decrease after an acute cervical TSCI, even throughout the cervical spinal cord, but the reduction in FA values was limited to a smaller area (Cheran et al., 2011) or did not occur (Shanmuganathan et al., 2008). However, at the exact site of injury, the reduction in FA, which is driven mainly by the reduction in AD, seems to be a more significant change than ADC (Cheran et al., 2011; Shanmuganathan et al., 2008). In a recent study, the FA values measured in an area of intact cervical cord above the acute injury were lower compared to the controls and correlated positively with the upper limb motor score and the AIS grade derived from the ISNCSCI (Vedantam, Eckardt, Wang, Schmit, & Kurpad, 2013). In contrast, a paradoxical increase in FA with increasing injury severity were detected in patients with non-hemorrhaging SCI around the injury site concomitantly with decreasing MD, AD and RD values (Cheran et al., 2011). In DWI studies, the low ADC following an acute injury has also been shown to predict poor functional recovery (Endo, Suzuki, Utsunomiya, Uenohara, & Tominaga, 2011; Tsuchiya, Fujikawa, Honya, Tateishi, & Nitatori, 2006).

### ***2.3.6 Cerebral DTI in Patients with TSCI***

Currently, only a few DTI studies have investigated the cerebral white matter microstructure by DTI after SCI. In a whole-brain analysis (WBA) of DTI values, lower FA and higher MD values have been detected in primary motor and sensory cortices and the immediately adjacent white matter, as well as in the superior cerebellar cortex. In addition, only changes in FA were detected in the area of the CSTs and the medial prefrontal, anterior cingulate and precuneus cortices (Wrigley et al., 2009). In the same study, a reduction in FA and AD and an increase in MD were also detected in a tractography of the CST (Wrigley et al., 2009). Using a WBA method, another research group showed significant changes in FA only in the right posterior limb of the internal capsule (PLIC) and left hand area of the primary motor cortex (Freund et al., 2011). However, in the first study, the patient population consisted only of subjects with complete injury; in another study, the patient population was more heterogeneous with respect to the disability.



A hypothesis-driven ROI analysis throughout the area of the cerebral CST has been used in two studies. The first study showed decreased FA in the bilateral pyramids and the right leg area of the primary motor cortex, AD was reduced in the right cerebral peduncle, and RD was increased in the right pyramid and cerebral peduncle (Freund et al., 2011). In another study that consisted only of patients with complete injury, a significant reduction in FA and increase in MD were noted in the medulla, pons, cerebral peduncles and PLIC. In addition, at the level of the corona radiata, FA values were higher and MD values lower in SCI patients compared to controls (Guleria et al., 2008). An examination of the change in DTI indices over the time since injury showed that the FA values decreased and MD increased progressively in the caudal part of the cerebral CST from 3 to 12 months after injury, suggesting progression of secondary degeneration. In turn, an opposite trend in FA was observed at the level of the PLIC and corona radiata. These inverse changes in FA in the cranial region of the CST were suggested to reflect subcortical plasticity after SCI (Guleria et al., 2008). In the only published study utilizing TBSS after SCI, no significant between-group differences in FA were detected (Wei et al., 2008).

The cerebral microstructural changes observed by DTI have been demonstrated to relate both to macrostructural changes in the spinal cord and to cortical reorganization after SCI. To be precise, the reduced cross-sectional spinal cord area predicted an increase in RD in the right cerebral peduncle, whereas a reduced pyramidal FA was associated with an increase in activation in the fMRI in the area of the primary motor cortex leg area during handgrip (Freund, Wheeler-Kingshott et al., 2012). In addition, lower regional grey and white matter volumes were detected by voxel- based morphometry (VBM) in the same regions in which degeneration-associated changes in DTI values were located after SCI (Freund et al., 2011; Wrigley et al., 2009). Moreover, post-injury DTI changes in the spinal cord have been shown to correlate positively with respective remote DTI alterations in the area of the cerebral CST (Freund, Schneider et al., 2012).

### 3. AIMS OF THE STUDY

- 1) To determine the incidence of newly injured patients with TSCI who were admitted to two of three SCI centers during the first year after national centralization of SCI care in Finland (Study I).
- 2) To analyze epidemiological characteristics and outcome data for a population-based cohort of new TSCI patients who were injured during one year (Study I).
- 3) To characterize diffusion tensor imaging (DTI) metrics across the cervical spinal cord in a healthy population and study the impact of age and gender on these values (Study II).
- 4) To quantitatively assess the state of the cervical spinal cord using DTI in patients with chronic traumatic cervical SCI and to determine whether trauma-induced microstructural changes quantified by DTI are associated with clinical neurological deficits and the functional state of the patients (Study III).
- 5) To quantitatively assess the state of the cerebral corticospinal tract using DTI in chronic traumatic SCI and to investigate the association of DTI metrics both with clinical measures and with spinal macrostructural changes assessed by conventional MRI (Study IV).

## 4. SUBJECTS AND METHODS

### 4.1 Design and Ethical Aspects

The study design of Study I is a prospective, population-based epidemiological study in two of three newly appointed SCI centers, Oulu and Tampere University Hospitals (UH) in Finland. Following institutional and governmental regulations, study approval was obtained from both the Oulu and the Tampere UH administration. Ethical committee approval was not required because all of the data were collected during standard practice.

Studies II, III and IV are a part of the broader Spinal Cord Injury Series of the Tampere-Retrospective Study (SCISSORS), which consists of cervical spinal cord injury patients and trauma control subjects. The study aims to examine SCI from a multidisciplinary perspective in a case-controlled manner to enhance the clinical assessment and treatment of this specific patient group. The study group includes researchers from the areas of neurosurgery, neurology, neuroradiology, neuropsychology, urology and sleep medicine. Ethical approval for the study was obtained from the Ethical Committee of Pirkanmaa Hospital District, Finland. Written informed consent was obtained from each participant.

### 4.2 Subjects

#### 4.2.1 *Patients with Acute TSCI*

The Oulu and Tampere UHs are the only trauma, intensive care, neurosurgery and spine surgery units in the Northern Ostrobothnia Hospital District and the Pirkanmaa Hospital District, respectively. Thus, all new SCI patients in these hospital districts should be seen in the SCI centers. In addition, during the study period, SCI patients were referred to the Oulu and Tampere SCI centers from several hospitals in 12 other hospital districts (population 2,146,830). Consequently, the whole catchment area of the SCI centers makes up 3,065,946 (56.5%) of the population in Finland and the sub-populations in the catchment

areas of Oulu and Tampere UH SCI centers were 739,475 and 2,326,471, respectively (see Table 3).

**Table 3.** Distribution of patients with acute traumatic SCI who were admitted to the Oulu and Tampere SCI centers over a one-year period according to the hospital districts.

Hospital District	Number of patients	%	Population
Pirkanmaa Hospital District ‡	22	28.6	518,157
Päijät-Häme Hospital District	6	7.8	213,542
Kanta-Häme Hospital District	8	10.4	175,472
South Ostrobothnia Hospital District	6	7.8	198,944
Varsinais-Suomi Hospital District	1	1.3	472,139
Satakunta Hospital District	2	2.6	224,934
Vaasa Hospital District	6	7.8	168,111
Etelä-Savo Hospital District	1	1.3	104,803
Central Finland Hospital District	3	3.9	250,369
North Ostrobothnia Hospital District ‡	13	16.9	400,959
Lappi Hospital District	4	5.2	118,189
Kainuu Hospital District	1	1.3	77,435
Central Ostrobothnia Hospital District	1	1.3	78,237
Länsi-Pohja Hospital District	3	3.9	64,655
Total	77	100.0	3,065,946

‡ Pirkanmaa Hospital District and North Ostrobothnia Hospital District are the hospital districts of the Tampere and Oulu University Hospitals, respectively.

After the centralization of SCI care, both Oulu and Tampere UHs introduced a new clinical practice in which a multidisciplinary SCI rehabilitation team is routinely informed of all patients who are admitted to the hospital with a new SCI and persistent impairment or loss of motor and/or sensory function regardless of the cause, level or completeness of the injury. However, this practice does not apply to patients with progressive neurological diseases, such as multiple sclerosis or amyotrophic lateral sclerosis. The consultant specialist physician from the SCI

unit, with the support of the rehabilitation team, performs a clinical evaluation and plans the rehabilitation. SCI is classified as traumatic if the damage to neural elements within the spinal canal is caused by an external force.

The results of the first year after starting the new protocol are presented: Tampere UH: January 1, 2012 to December 31, 2012 and Oulu UH: May 1, 2012 to April 30, 2013. Currently, there are data missing from the third SCI center in Helsinki University Central Hospital because the unit opened during the second half of 2013 with an outpatient clinic.

#### **4.2.2      *Patients with Chronic Cervical TSCI***

All consecutive patients with chronic traumatic cervical spine injuries (n=88) who were admitted to either the ward or an outpatient clinic in Tampere UH between 1989 and 2010 were contacted for participation in the study in 2011. The inclusion criteria for the patients were as follows: i) age over 18 years, ii) resident of the hospital district, iii) clinically significant neurological findings due to a traumatic cervical spinal cord injury after 24 hours of monitoring in the hospital and iv) time since injury greater than one year. The exclusion criteria were as follows: i) known neurological illness other than spinal cord injury, ii) respiratory arrest, iii) contraindications to MRI and iv) refusal to participate in the study.

The final population of chronic traumatic SCI patients consisted of 34 patients. In the study examining cervical DTI (Study III), an additional 6 patients with poor MRI image quality (e.g., artifacts due to the vertebral fixation material) were excluded. Thus, the final SCI population sample in that study consisted of 28 patients.

#### **4.2.3      *Control Subjects***

The control subjects were recruited from orthopedically injured patients who were evaluated in the Emergency Department of Tampere UH. A total of 609 patients with ankle injuries were screened for inclusion in the study. The aim was to enroll five male and five female subjects from each of the following age groups: 18-30, 31-40, 41-50 and 51-60 years old. The control sample was collected primarily for a mild TBI study, and thus, the enrollment criteria differed from those used for the chronic SCI patients. The inclusion criteria were as follows: i) age 18-60 years, ii) being a resident of the university hospital district and iii) ankle trauma. The exclusion criteria were: i) neurological problems, ii) psychiatric problems, iii)

history of traumatic brain injury, iv) former neurosurgical procedure, v) problems with hearing or vision, vi) first language other than Finnish, vii) contraindications to MRI and viii) refusal to participate in the study. The final sample (mean age $\pm$ SD of 40.4 $\pm$ 12.3) included 20 male (39.8 $\pm$ 11.8) and 20 female (41.1 $\pm$ 13.2) subjects.

## 4.3 Collection of Clinical Data

All of the data from patients with acute SCI (Study I) were collected during standard practice or was retrospectively recorded from the medical records. The patients with chronic SCI (Study III and IV) were examined at an outpatient SCI clinic in Tampere UH. The control subjects (Study II, III and IV) were thoroughly evaluated relative to the TBI study.

The epidemiological characteristics of patients with both the acute and chronic SCI were collected and classified using the International SCI Core Data Set. (M. DeVivo et al., 2006) The ISNCSCI was used to evaluate and classify the neurological consequences of spinal cord injury. The completeness of the injury was defined according to the ASIA impairment scale (AIS) (Kirshblum et al., 2011; Kirshblum, Waring et al., 2011).

In Studies III and IV, the level of disability was assessed using the motor subscale (range 13-91) of the Functional Independence Measure (FIM) which consists of subscores for self-care, sphincter control, mobility and locomotion (Hall et al., 1999; Maynard et al., 1997). The medical condition of the subjects was assessed according to the International Classification of Diseases and Related Health Problems 10<sup>th</sup> revision (ICD -10) (Ashley, 1990). The Basic Pain Data Set was used to collect data from patients who suffered from neuropathic pain that was related to the SCI (E. Widerstrom-Noga et al., 2008). Information on current medications at the time of the examination was classified into 17 subgroups according to the Finnish Commercial Drug Catalog (Pharmaca Fennica), which was categorized based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System codes.

## 4.4 MRI and DTI Examinations

The MRI examinations of the brain and spinal cord were performed using a 3T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany). A 12-channel head coil and a 4-channel neck coil were used simultaneously.

The spinal cord series included a sagittal T2 turbo spin echo (TSE) (TR 3500 ms, TE 108 ms, flip angle 160°, 1 average, FOV 280, matrix 288 x 384, slice/gap 3.0/0.3 mm, ETL 34), and an axial T2\*-weighted multi-gradient echo combination series (TR 506 ms, TE 14 ms, flip angle 30°, 1 average, FOV 160 mm, matrix 256 x 256, slice/gap 3.0/0.3 mm) was acquired. The voxel size of the T2\* images was 0.6 x 0.6 x 3.0 mm. DTI data were acquired using axial multidirectional diffusion weighted (MDDW) echo planar imaging sequences (TR 4000 ms, TE 103 ms, 4 averages, FOV 152 mm, matrix 128 x 128, slice/gap 4.0/1.2 mm, b-factor 0 and 1000, 20 diffusion directions). The voxel size was 1.2 x 1.2 x 4.0 mm. Cardiac gating was not used. The scan time for the DTI sequence was 5 minutes and 50 seconds.

The MRI protocol of the brain included a sagittal T1-weighted series (TR 750 ms, TE 7.3 ms, slice/gap 5.0/1.5 mm, FOV 220), an axial T1 series (TR 600 ms, TE 6.8 ms, slice/gap 4.0/1.2 mm, FOV 220), an axial T2 TSE series (TR 5600 ms, TE 109 ms, flip angle 120°, slice/gap 4.0/1.2 mm, FOV 220), an axial FLAIR (TR 5500 ms, TE 87 ms, TI 1922 ms, flip angle 150°, slice /gap 4.0/1.2 mm, FOV 220), a coronal T2 TSE series (TR 5990, TE 109, flip angle 120°, FOV 220 slice/gap 3.0/0.6 mm) and an axial susceptibility-weighted (SWI) series (TR 27, TE 20, flip angle 15°, slice 1.5 mm, FOV 230). The parameters for the DTI sequence of the brain were TR 5144 ms, TE 92 ms, FOV 230, matrix 128 x 128, 3 averages, slice/gap 3.0/0.9 mm, b-factor 0 and 1000 s/mm<sup>2</sup>, and 20 diffusion gradient orientations.

## 4.5 Image Analysis

Interpretation of the imaging findings on conventional MRI scans was performed by a neuroradiologist. Region of interest (ROI) DTI measurements were performed either by a neuroradiologist or physicist using the commercially available software Neuro3D (Siemens Healthcare, Malvern, PA, USA). The ROIs were manually placed on axial images of the color-coded FA maps and automatically transferred onto non-diffusion-weighted b<sub>0</sub> images and ADC maps.

The ROIs were centered in the area of interest, taking care to avoid border areas, CSF spaces and neighboring tracts.

Levels for the spinal cord measurements (Study II and III) were determined using sagittal T2 anatomical images. Whole spinal cord ROIs were drawn using a freehand technique and small circle ROIs were used for individual funiculi.

In Study II, FA and ADC values of the whole cord were measured at spinal levels C2-C7. At the C3 level, FA, ADC and directional diffusivities (AD and RD) were derived from the measured  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$  eigenvalues from the ROIs covering the whole cord as well as the lateral (right and left) and posterior funiculi.

In Study III, the FA and ADC were assessed for the whole cord and for the lateral funiculi both at the level of the spinal cord lesion and at cervical level C2-3 above the primary lesion. At the C2-3 level, the AD and RD were also calculated for the whole cord area. The DTI values from the left and right lateral funiculus were averaged per level measured. At the levels of the spinal cord lesions, the majority of the gray and white matter contrast was lost, causing the reliable placement of the ROI to be difficult. Consequently, measurements indicating “the lesion level” were performed at the level just above the most cranial border of the lesion. Due to artifacts from the vertebral fixation material, 10 of the images from the lesion level were excluded, and DTI measurements could be reliably performed for 18 of the 28 patients. In the control subjects, DTI values were measured at the C2-3, C3-4, C4-5 and C5-6 levels. All of the cranial levels of the spinal cord lesions, which were observed on the conventional MRI, were situated between segments C2 to C6. Thus, the mean DTI values among the healthy controls from the C2-3 to C5-6 levels were used as reference values for the lesion level measurements in SCI patients.

In Study IV, for the cerebral measurements, circular ROIs (19 mm<sup>2</sup>) were manually placed in the following anatomical locations: i) the cerebral peduncle, ii) the posterior limb of the internal capsule (PLIC) (anterior and posterior), iii) the posterior part of the corona radiata (anterior and posterior) and iv) the centrum semiovale (anterior, center and posterior). The ROIs were placed bilaterally on all locations, and the FA and ADC from the left and right structures were averaged per level measured.

The signal-to-noise ratio (SNR) was determined according to NEMA Standards

1-2008, including the following expression for SNR:  $SNR = \frac{S}{image\_noise}$ ,

where S = signal, and the image noise is estimated with the Rayleigh distribution:

$image\_noise = \frac{SD}{0.66}$  . SNR measurements from the images of three healthy



subjects were used. For the spinal cord (Study II), the signal was measured from one ROI centered in the spinal cord and four ROIs located outside of the anatomical structures in one of the  $b = 0$  s/mm<sup>2</sup> images at the C3 level. For the cerebral measurements (Study IV), the ROI was placed on the left side of each region of the  $b = 0$  s/mm<sup>2</sup> image. The mean value for SNR was  $18.3 \pm 5.0$  for the spinal measurements and  $30.5 \pm 3.6$  for the cerebral measurements.

## 4.6 Statistical Analysis

In Study I, epidemiological data for the patients with acute TSCI were analyzed as a whole but also grouped according to hospital district and age. Continuous variables are presented as the mean, standard deviation (SD), median and range. The Mann-Whitney test was used to calculate differences between patient groups. For categorical variables, numbers and percentages are shown, and the differences between groups were examined using Fisher's exact test. Statistical significance was set at  $p < 0.05$ . Incidence rates were calculated using the population available on the December 31, 2012 from the Official Statistics of Finland. (Official Statistics of Finland [OSF]).

In Study II, the DTI values are presented as the mean and SD. The FA and ADC measures of the different cervical levels were compared using repeated measures analysis of variance (ANOVA). The effect of age and gender on DTI values was tested by linear regression. To use age as a dichotomous variable in the analyses, the subjects were divided into two age groups: aged  $< 40$  and  $\geq 40$  years. Linear regression adjusted by age and gender was used to compare DTI values between individual funiculi. Due to multiple correlations, the statistical significance was set at  $p < 0.01$ . The mean DTI value differences between whole cord and funiculi were tested with repeated measures ANOVA with confidence interval adjustment (Bonferroni,  $p < 0.05$ ).

In Studies III and IV, the DTI values are presented as the mean, SD and median. Patients with chronic SCI were not gender-matched or age-matched with the control subjects; therefore, the analyses were performed using linear regression adjusted for age in Study III and for age and gender in Study IV. Correlations were calculated by partial correlation, with age (Study III) and age and gender (Study IV) as the controlling factors. The clinical variables used in the correlations included the ISNCSCI-derived total motor score, motor subscore for the upper and lower extremities, total sensory score, single neurological level and the motor subscale of FIM. Clinical variables (Study III) and DTI values (Study IV) were correlated with the most cranial level of the spinal cord lesion and with the length of the lesion in

millimeters assessed by conventional MRI. To use the single neurological level and the most cranial level of the lesion in the correlations, each vertebral level was sequentially numbered in the craniocaudal direction. For further comparisons, the patient population was divided into two groups according to the completeness of the injury: AIS A and AIS B-E. All of the parameters were ranked before the analyses. Due to multiple comparisons, the statistical significance level was set at  $p < 0.01$ .

Intra-observer reproducibility (intra-class correlation coefficient, or ICC) was assessed for cerebral and spinal DTI values, and inter-observer repeatability was assessed for the spinal DTI values measured from healthy volunteers (Studies II and IV). To assess the reproducibility of the measurements, the subjects were re-measured by the same examiner who performed the initial measurements. In addition, the spinal DTI values were measured by two other examiners.

The SPSS software program (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp.) was used to perform all of the statistical analyses.

## 5. RESULTS

### 5.1 Incidence of TSCI

A total of 77 patients with TSCI were admitted to the Oulu and Tampere UHs during a one-year follow-up period. The annual incidence rate was 25.1 per million people for all TSCI patients admitted to the Oulu and Tampere SCI centers. In the hospital districts of the Oulu and Tampere UHs, the incidence of TSCI was 38.1; in the area of other hospital districts, the patients referred to the SCI centers showed an incidence of 19.6 per million (see Table 4).

To facilitate comparison with earlier incidence rates from Finland, the incidences were also calculated for subpopulations under and over 16 years. In the age group over 16 years, the annual incidence per million people for the entire area was 29.8 (subpopulation of 2,516,942), whereas in the area of the Oulu and Tampere UHs hospital districts, the incidence in that age group was 46.0 per million (subpopulation of 739,338). Two children under 16 years of age were injured during the follow-up period, resulting in an incidence of 3.6 per million in a subpopulation of 549,004.

### 5.2 Epidemiological Features of Patients with Acute TSCI

The epidemiological features of patients with acute SCI (Study I) are presented in Table 4. Table 5 shows the treatment periods and outcome data.

**Table 4.** Epidemiological characteristics of new patients with traumatic spinal cord injury (TSCI) in two of three SCI centers in Finland over a one-year follow-up period. Comparisons between patient groups according to age and hospital district (Study I, reprinted with permission).

	All	Under 60	Over 60		Hospital districts of Oulu and Tampere UH	Other hospital districts in the SCI centers catchment area	
				p			p
Population	3 065 946	2 242 163	823 783		919 116	2 146 830	
Number of cases	77	29	48		35	42	
Incidence/million	25.1	12.9	58.3		38.1	19.6	
Gender (male/female)	2.1/1	2.6/1	1.8/1	0.617	1.9/1	2.2/1	0.810
Age at injury, mean±SD	58.7±19.8	37.8±15.4	71.3±7.8		55.7±20.1	61.2±19.4	
median (range)	63.4(2.8-89.5)	41.3(2.8-59.6)	70.4(60.2-89.5)	<b>0.000</b>	62.3(6.3-78.2)	64.5(2.8-89.5)	0.192
Injury etiology (%)							
Sports	6(7.8%)	6 (20.7%)	-		1 (2.9%)	5(11.9%)	
Assault	1(1.3%)	1 (3.4%)	-		1 (2.9%)	-	
Transport	14 (18.2%)	11 (37.9%)	3 (6.3%)		6 (17.1%)	8 (19.0%)	
Fall	50 (64.9%)	9 (31.0%)	41 (85.4%)		24 (68.6%)	26 (61.9%)	
Other traumatic cause	6 (7.8%)	2 (6.9%)	4 (8.3%)	<b>0.000</b>	3 (8.6%)	3 (7.1%)	0.526
Neurological level of injury (%)							
Tetraplegia	54 (70.1%)	15 (51.7%)	39 (81.3%)		23 (65.7%)	31 (73.8%)	
Paraplegia	23 (29.9%)	14 (48.3%)	9 (18.8%)	<b>0.010</b>	12 (34.3%)	11 (26.2%)	0.464
C 1-4	34 (44.2%)	8 (27.6%)	26 (54.2%)		12 (34.3%)	22 (52.4%)	
C 5-8	15 (19.5%)	6 (20.7%)	9 (18.8%)		8 (22.9%)	7 (16.7%)	
T 1-T 12	18 (23.4%)	10 (34.5%)	8 (16.7%)		9 (25.7%)	9 (21.4%)	
L 1-S 5	5 (6.5%)	4 (13.8%)	1 (2.1%)	<b>0.026</b>	3 (8.6%)	2 (4.8%)	0.509
Unknown	5 (6.5%)	1 (3.4%)	4 (8.3%)		3 (8.6%)	2 (4.8%)	
ASIA Impairment Scale (%)							
AIS A	14 (18.2%)	6 (20.7%)	8 (16.7%)		3 (8.6%)	11 (26.2%)	
AIS B	12 (15.6%)	5 (17.2%)	7 (14.6%)		5 (14.3%)	7 (16.7%)	
AIS C	7 (9.1%)	2 (6.9%)	5 (10.4%)		4 (11.4%)	3 (7.1%)	
AIS D	39 (50.6%)	16 (55.2%)	23 (47.9%)		19 (54.3%)	20 (47.6%)	
AIS E	2 (2.6%)	-	2 (4.2%)	0.897	2 (5.7%)	-	0.178
Unknown	3 (3.9%)	-	3 (6.3%)		2 (5.8%)	1 (2.4%)	

p-values <0,05 in bold and underlined

UH, University Hospital; SD, standard deviation; ASIA, American Spinal Injury Association; AIS A, motor-sensory complete; AIS B, motor complete-sensory incomplete; AIS C-D, motor-sensory incomplete; AIS E, normal examination

**Table 5.** Management, treatment periods and outcomes of new patients with traumatic spinal cord injury (TSCI) in two of three SCI centers in Finland over a one-year follow-up period. Comparisons between patient groups are according to the age and hospital district (Study I, reprinted with permission).

	All	Under 60	Over 60		Hospital districts of Oulu and Tampere UH	Other hospital districts in the SCI centers catchment area	
				p			p
Number of cases	77	29	48		35	42	
Vertebral injury (%)	64 (83.1%)	23 (79.3%)	41 (85.4%)	0.539	27 (77.1%)	37 (88.1%)	0.234
Associated injury (%)	9 (11.7%)	5 (17.2%)	4 (8.3%)	0.285	4 (11.4%)	5 (11.9%)	1.000
Spinal surgery (%)	72 (93.5%)	27 (93.1%)	45 (93.8%)	1.000	31 (88.6%)	41 (97.6%)	0.171
Days hospitalized, mean±SD	70.5±59.0	90.1±66.9	58.6±50.8		71.8±66.4	69.4±52.9	
median (range)	60.0(2-273)	104.0(2-273)	40.5 (4-199)	<b><u>0.046</u></b>	46.0(2-273)	63.5(4-170)	0.984
Days in ICU, mean±SD	n=44: 10.6±17.3	n=14: 15.7±27.4	n=30: 8.2±9.6		n=15: 9.4±11.8	n=29: 11.2±19.8	
median (range)	3.5(1-106)	4.0(2-106)	3.0(1-35)	0.182	3.0(1-35)	4.0(2-106)	0.772
Place of discharge (%)							
Private residence	41 (53.2%)	23 (79.3%)	18(37.5%)		25 (71.4%)	16 (38.1%)	
Hospital	24 (31.2%)	2 (6.9%)	22 (45.8%)		5 (14.3%)	19 (45.2%)	
Nursing home	4 (5.2%)	-	4 (8.3%)		1 (2.9%)	3 (7.1%)	
Assisted living residence	5 (6.5%)	4 (13.8%)	1 (2.1%)		2 (5.7%)	3 (7.1%)	
Group living situation	-	-	-		-	-	
Deceased	3 (3.9%)	-	3 (6.3%)	<b><u>0.000</u></b>	2 (5.7%)	1 (2.4%)	<b><u>0.010</u></b>
The ability to move at the time of discharge (%)	(n=74)	(n=29)	(n=45)		(n=33)	(n=41)	
Walking without equipments	22 (29.7%)	10 (34.5%)	12 (26.7%)		15 (45.5%)	7 (17.1%)	
Walking with a stick or crutch	6 (8.1%)	4 (13.8%)	2 (4.4%)		3 (9.1%)	3 (7.3%)	
Walking with a walker	5(6.8%)	1 (3.4%)	4 (8.9%)		-	5 (12.2%)	
Using a wheelchair	29 (39.2%)	11 (37.9%)	18 (40.0%)		12 (36.4%)	17 (41.5%)	
Using an electric wheelchair	7 (9.5%)	2 (6.9%)	5 (11.1%)		2 (6.1%)	5 (12.2%)	
Bed patient	5(6.8%)	1 (3.4%)	4 (8.9%)	0.600	1 (3.0%)	4 (9.8%)	<b><u>0.046</u></b>

p-values <0,05 in bold and underlined

UH, university hospital; SD, standard deviation; ICU, intensive care unit

**Table 5.** Management, treatment periods and outcomes of new patients with traumatic spinal cord injury (TSCI) in two of three SCI centers in Finland over a one-year follow-up period. Comparisons between patient groups are according to the age and hospital district (Study I, reprinted with permission).

	All	Under 60	Over 60	p	Hospital districts of Oulu and Tampere UH	Other hospital districts in the SCI centers catchment area	p
Number of cases	77	29	48		35	42	
Vertebral injury (%)	64 (83.1%)	23 (79.3%)	41 (85.4%)	0.539	27 (77.1%)	37 (88.1%)	0.234
Associated injury (%)	9 (11.7%)	5 (17.2%)	4 (8.3%)	0.285	4 (11.4%)	5 (11.9%)	1.000
Spinal surgery (%)	72 (93.5%)	27 (93.1%)	45 (93.8%)	1.000	31 (88.6%)	41 (97.6%)	0.171
Days hospitalized, mean±SD	70.5±59.0	90.1±66.9	58.6±50.8		71.8±66.4	69.4±52.9	
median (range)	60.0(2-273)	104.0(2-273)	40.5 (4-199)	<b><u>0.046</u></b>	46.0(2-273)	63.5(4-170)	0.984
Days in ICU, mean±SD	n=44: 10.6±17.3	n=14: 15.7±27.4	n=30: 8.2±9.6		n=15: 9.4±11.8	n=29: 11.2±19.8	
median (range)	3.5(1-106)	4.0(2-106)	3.0(1-35)	0.182	3.0(1-35)	4.0(2-106)	0.772
Place of discharge (%)							
Private residence	41 (53.2%)	23 (79.3%)	18(37.5%)		25 (71.4%)	16 (38.1%)	
Hospital	24 (31.2%)	2 (6.9%)	22 (45.8%)		5 (14.3%)	19 (45.2%)	
Nursing home	4 (5.2%)	-	4 (8.3%)		1 (2.9%)	3 (7.1%)	
Assisted living residence	5 (6.5%)	4 (13.8%)	1 (2.1%)		2 (5.7%)	3 (7.1%)	
Group living situation	-	-	-		-	-	
Deceased	3 (3.9%)	-	3 (6.3%)	<b><u>0.000</u></b>	2 (5.7%)	1 (2.4%)	<b><u>0.010</u></b>
The ability to move at the time of discharge (%)	(n=74)	(n=29)	(n=45)		(n=33)	(n=41)	
Walking without equipments	22 (29.7%)	10 (34.5%)	12 (26.7%)		15 (45.5%)	7 (17.1%)	
Walking with a stick or crutches	6 (8.1%)	4 (13.8%)	2 (4.4%)		3 (9.1%)	3 (7.3%)	
Walking with a walker	5(6.8%)	1 (3.4%)	4 (8.9%)		-	5 (12.2%)	
Using a wheelchair	29 (39.2%)	11 (37.9%)	18 (40.0%)		12 (36.4%)	17 (41.5%)	
Using an electric wheelchair	7 (9.5%)	2 (6.9%)	5 (11.1%)		2 (6.1%)	5 (12.2%)	
Bed patient	5(6.8%)	1 (3.4%)	4 (8.9%)	0.600	1 (3.0%)	4 (9.8%)	<b><u>0.046</u></b>

p-values <0,05 in bold and underlined

UH, university hospital; SD, standard deviation; ICU, intensive care unit

### 5.2.1 Risk Factors

The mean age at injury was 58.7 years, and the proportion of patients older than 60 years was 62.3%. The age distribution of all of the TSCI patients are shown in Figure 2.

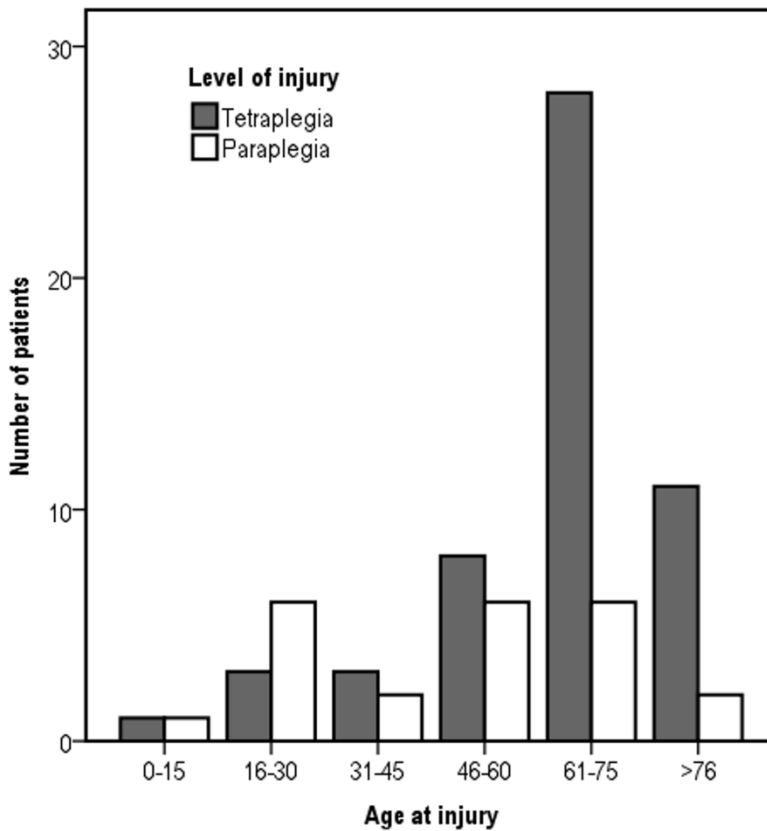
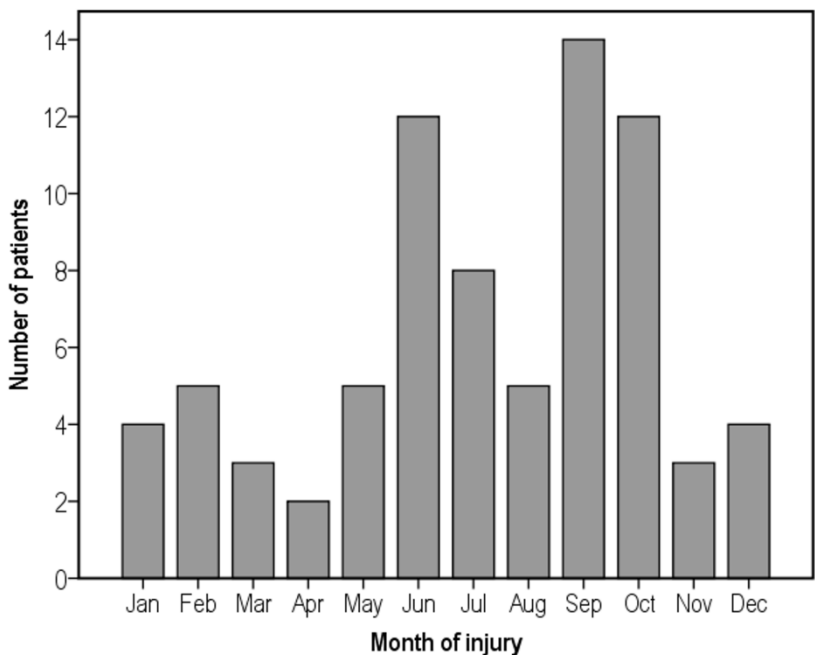


Figure 2. The age distribution and level of injury of all patients with traumatic spinal cord injury (SCI) in two of the three SCI centers in Finland over a one-year follow-up period.

In the entire population of 77 patients, 52 (67.5%) were male, resulting in a male-to-female ratio of 2.1/1. The preponderance of men was higher in the group of patients aged <60 years (2.6/1) than in the older age group (1.8/1).

The peak months for injuries were June, September and October, and the incidence of injuries as a whole appeared to increase during the summer and autumn months (see Figure 3).



**Figure 3.** The distribution of new patients with traumatic spinal cord injury by month.

The majority of TSCIs (57.1%) occurred between Friday and Sunday. The emphasis on injuries on the weekends was particularly pronounced in the younger age group, in which 72.4% of the patients were injured on Friday, Saturday or Sunday (see Table 6).

There was a statistically significant difference between patients under and over 60 years of age when considering alcohol consumption prior to injury. In the age group <60 years, 58.6% of the patients reported alcohol use or a positive test for alcohol at the time of injury compared to the 27.1% in the group of older patients



(Table 6). In the younger age group, alcohol was a contributing factor in 6 out of 11 (54.5%, male/female 5/1) transportation accidents, 8 out of 9 (88.9%, M/F 6/2) falls and 1 out of 6 (16.7%, M/F 1/0) injuries that occurred during participation in sports. In addition, 82.4% (n=14) of the younger patients who were under the influence of alcohol at the time of injury were injured during the weekend, from Friday to Sunday. In the older age group, the corresponding numbers were 1 out of 3 (33.3%, M/F 1/0) for transportation accidents and 12 out of 41 (29.3%, M/F 11/1) for falls.

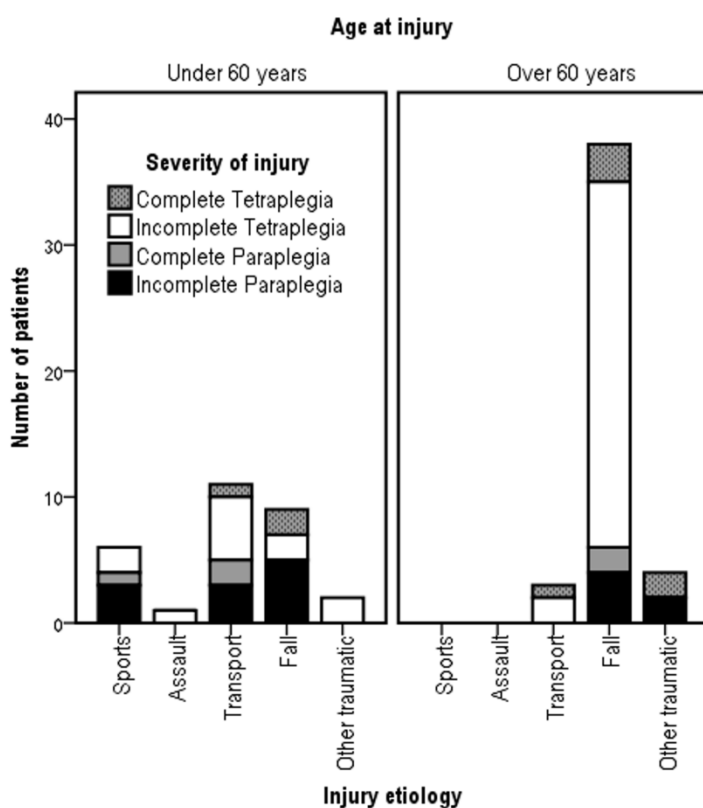
**Table 6.** The day of injury and alcohol consumption prior to the injury of all patients with traumatic spinal cord injury (SCI). Comparison between patient groups according to age.

	All	Under 60	Over 60	p
Number of cases	77	29	48	
Day of injury				
Monday	15 (19.5%)	1 (3.4%)	14 (29.2%)	
Tuesday	5 (6.5%)	2 (6.9%)	3 (6.3%)	
Wednesday	5 (6.5%)	3 (10.3%)	2 (4.2%)	
Thursday	8 (10.4%)	2 (6.9%)	6 (12.5%)	
Friday	9 (11.7%)	5 (17.2%)	4 (8.3%)	
Saturday	19 (24.7%)	10 (34.5%)	9 (18.8%)	
Sunday	16 (20.8%)	6 (20.7%)	10 (20.8%)	0.060
Alcohol				
Yes	30 (39.0%)	17 (58.6%)	13 (27.1%)	
No	39 (59.6%)	10 (34.5%)	29 (60.4%)	<b><u>0.013</u></b>
Unknown	8 (10.4%)	2 (6.9%)	6 (12.5%)	

p-values <0,05 in bold and underlined

## 5.2.2 External Causes of Injury

Falling was the most common cause of injury in the entire population (64.9%), followed by transportation accidents (18.2%). There was a statistically significant difference in etiology between the age groups. In the age group  $\geq 60$  years old, 85.4% of the patients were injured by falling; in the younger age group, transportation was the most common cause of injury (37.9%), and the proportion of falls was 31.0%. All of the injuries due to sports occurred among patients under 60 years of age (see Figure 4).



**Figure 4.** The severity of injury relative to the etiology in patients with traumatic spinal cord injury (SCI) younger than and older than 60 years of age in two of three SCI centers in Finland over a one-year follow-up period.

Among all 50 patients injured in falls, 30 (60.0%) fell from the same level, and 10 (20.0%) fell on stairs, 6 (12.0%) from a height > 1 m and 1 (2.0%) from a ladder. For 3 people (6.0%), falling was recorded as unspecific. Of all 50 patients injured in a fall, 9 were under 60 years of age; 6 of these patients were injured by falling from a height > 1 m and 3 fell from the same level.

### **5.2.3      *Severity of the Injury***

The neurological level of SCI classified by the ISNCSCI was mostly at the cervical level, and 70.1% of the patients were referred to as tetraplegic. The second most common injury was at the thoracic level, and injuries at the lumbosacral levels were less common. The most common segment was C4 (n=15, 19.5%), followed by C2 (n=9, 11.7%), C5 (n=7, 9.1%), C3 (n=6, 7.8%), C6 (n=6, 7.8%) and Th 11 (n=5, 6.5%). The injury was classified as complete (AIS A) in 18.2% of the cases, whereas 50.6% of the patients had an AIS D injury.

In the age group  $\geq 60$  years, 81.3% of the patients were tetraplegic, and the majority of the cervical injuries were at levels C1-4. In the younger age group, there was an even distribution between tetra- and paraplegia. Incomplete tetraplegia comprised 64.6% of all cases in the older age group, the percentages of incomplete paraplegia and complete tetraplegia were 12.5% each, and the percentage of complete paraplegia was 4.2%. In the younger age group, the corresponding figures were 41.4% for incomplete tetraplegia, 37.9% for incomplete paraplegia and 10.3% for both complete injury levels (see Figure 4).

### **5.2.4      *Management and Outcome***

The majority of patients (83.1%) had a spinal fracture and/or dislocation in addition to the SCI, and 93.5% of all cases underwent spinal surgery. Concurrently, 11.7% of the patients with SCI had at least one of the associated injuries categorized in the International SCI Core Data Set (M. DeVivo et al., 2006). The total length of stay in the acute care and rehabilitation facility ranged from 2 to 273 days (mean of 70.5 days). Home or another private residence was the most common place of discharge (53.2%), followed by other local hospitals (31.2%). At the time of discharge, 44.6% of the patients were able to walk with or without aids, and 39.2% used a manual wheelchair as equipment (see Table 5).

In relation to the total length of stay and the place of discharge, there was a statistically significant difference between patients under and over 60 years of age.

The younger group of patients had a longer length of stay in acute care and rehabilitation, after which they were discharged primarily to their home, but 45.8% of the patients over 60 years were discharged to another hospital, and only 37.5% went directly home (see Table 5).

A comparison of patients from the hospital districts of the SCI centers with those referred from other hospital districts in the SCI centers' catchment area revealed statistically significant differences only in relation to the place of discharge and the ability to move at the time of discharge. Patients from the Oulu and Tampere UHs districts were mainly discharged home (71.4%) and the place of discharge was a private residence in 38.1% and another hospital in 45.2% of the cases in the group of patients from other hospital districts. In turn, the percentages of patients who were able to walk with or without equipment were 54.5% and 36.6%, respectively (see Table 5).

### 5.3 Clinical Findings for Patients with Chronic Cervical TSCI

The clinical characteristics of the SCI patients and controls are shown in Table 7 (Studies II, III and IV). The final population of chronic traumatic SCI patients consisted of 34 patients, all of whom were included in Study IV. From those patients, 28 were included in Study III, and their numbers and percentages are presented in parentheses [n, (%)].

Of the patients with SCI, 18 (52.9%) [17 (60.7%)] patients had other chronic medical problems, among which the most common was disease of the circulatory system (n=9, 26.5%) [9, 32.1%] and disease of the musculoskeletal system and connective tissue (n=7, 20.6%) [7, 25.0%]. Twenty-eight (82.4%) [24, 85.7%] patients used permanent medication; 15 (44.1%) [12 (42.9%)] patients used pain medication; 12 (35.3%) [11 (39.3%)] patients used a prophylactic antibiotic; 9 (26.5%) [9 (32.1%)] patients used drugs for the cardiovascular system; and 13 (38.2%) [9 (32.1%)] patients used muscle relaxants. Thirteen (38.2%) [11(39.3%)] patients with SCI suffered from neuropathic pain.

**Table 7.** Clinical characteristics of patients with chronic cervical spinal cord injury (entire group, AIS A and AIS B-E) and control subjects.

	Controls (n=40)	Patient group in Study IV			Patient group in Study III		
		Patients (n=34)	AIS A (n=10)	AIS B-E (n=24)	Patients (n=28)	AIS A (n= 7)	AIS B-E (n= 21)
Age (years)	40.6±12.2	57.5±14.5	51.3±15.7	60.1±13.4	59.9±13.3	54.2±14.6	62.3±12.5
Gender (male/female)	20/20	27/7	7/3	20/4	22/6	4/3	18/3
Time since injury (years) (mean±SD) (range)		13.9±12.1 (1.0-43.1)	23.5±13.1 (6.4-38.2)	9.9±9.3 (1.0-43.1)	13.1±13.1 (1.0-43.1)	26.4±14.2 (6.4-38.2)	8.7±9.5 (1.0-43.1)
Injury etiology							
Sports		6 (17.6%)	2 (20.0%)	4 (16.7%)	3 (10.7%)	1 (14.3%)	2 (9.5%)
Assault		1 (2.9%)		1 (4.2%)	1 (3.6%)		1 (4.8%)
Transport		12 (35.3%)	5 (50.0%)	7 (29.2%)	10 (35.7%)	3 (42.9%)	7 (33.3%)
Fall		13 (38.2%)	3 (30.0%)	10 (41.7%)	12 (42.9%)	3 (42.9%)	9 (42.9%)
Other traumatic cause		2 (5.9%)		2 (8.3%)	2 (7.1%)		2 (9.5%)
ASIA impairment scale (AIS)							
AIS A		10 (29.4%)			7 (25.0%)		
AIS B		1 (2.9%)			1 (3.6%)		
AIS C		4 (11.8%)			3 (10.7%)		
AIS D		18 (52.9%)			16 (57.1%)		
AIS E		1 (2.9%)			1 (3.6%)		
ISNCSCI single neurological level							
C1		2 (6.1%)			2 (7.4%)		
C2		4 (12.1%)			3 (11.1%)		
C3		5 (15.2%)			5 (18.5%)		
C4		11 (33.3%)			9 (33.3%)		
C5		5 (15.2%)			4 (14.8%)		
C6		1 (3.0%)					
C7		1 (3.0%)			1 (3.7%)		
C8		3 (9.1%)			2 (7.4%)		
T11		1 (3.0%)			1 (3.7%)		
ISNCSCI motor score (max. 100)		63.4±33.8	20.4±15.5	81.3±20.1	66.0±34.0	19.6±17.3	81.8±20.6
ISNCSCI sensory score (max. 224)		123.5±65.1	42.0±16.8	160.6±39.0	130.0±66.0	40.6±15.6	163.3±40.2
FIM physical subscore (max. 91)		65.8±28.6	41.1±28.3	76.0±22.0	67.1±28.5	40.1±29.6	76.1±22.1

ASIA, American Spinal Injury Association; AIS A, motor-sensory complete; AIS B, motor complete-sensory incomplete; AIS C-D, motor-sensory incomplete; AIS E, normal examination; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; FIM, Functional Independence Measure

## 5.4 Clinical Findings for Healthy Control Subjects

Eighteen (45.0%) of the control subjects demonstrated a diagnosed disease. Six of the patients had a disease of the circulatory system (15.0%), and 4 (10.0%) patients had a disease of the musculoskeletal system and connective tissue. Thirteen (32.5%) control subjects used some permanent medication. The most prevalent group used drugs for the cardiovascular system (n=6, 15.0%). None of the control subjects presented neuropathic pain.

## 5.5 Conventional MRI Findings

Conventional magnetic resonance imaging (MRI) findings for the patients with chronic cervical SCIs are listed in Table 8. None of the control subjects had significant structural abnormalities on conventional MRI scans.

Of the 28 patients in Study III, a focal post-traumatic lesion on either the sagittal or axial T2/T2\*-weighted sequences was found in 23 (82.1%) patients, 3 of whom had two separate lesions. In addition to the findings listed in Table 7, six of the patients displayed a diffuse high signal intensity in the dorsal funiculus at levels above the primary lesion on the axial T2\* images. In five of these patients, the clinical cord injury was complete (AIS A), and in one patient, the motor injury was complete and the sensory injury was incomplete (AIS B). This finding probably represents secondary anterograde (Wallerian) degeneration of the ascending tracts and was not apparent on the sagittal T2 images.

Patients in Study IV with the mentioned abnormalities in conventional brain imaging sequences were not excluded because the abnormalities were considered ordinary for the patient and for the age groups in question. In addition, excluding microangiopathy, the abnormalities were not located in the area of the ROI measurements.

**Table 8.** Conventional magnetic resonance imaging (MRI) findings for patients with chronic cervical spinal cord injury (Studies III and IV).

<b>MRI findings of the spinal cord</b>	<b>Patients in Study IV (n=34)</b>	<b>Patients in Study III (n=28)</b>
Spinal surgery	23 (67.6%)	19 (67.9%)
Fixation material	15 (44.1%)	13 (46.4%)
Narrow spinal canal	11 (32.4%)	10 (55.6%)
Medulla atrophy	21 (61.8%)	18 (64.3%)
Medulla lesion	29 (85.3%)	23 (82.1%)
one	24 (70.6%)	20 (71.4%)
two	5 (14.7%)	3 (10.7%)
Main lesion		
length (mm)	18.3±14.4	18.1±14.5
width (mm)	8.3±2.8	8.4±2.6
cranial level	C2-C6	C2-C6
caudal level	C3-T1	C3-T1
<b>MRI findings of the brain</b>		
Microangiopathy (moderate to severe)	4 (11.8%)	
Lacunar ischemic lesions	1 (2.9%)	
DAI-type microhemorrhage	14 (41.2%)	
n = 1	11 (32.4%)	
n = 2-5	3 (8.8%)	
Post-traumatic lesion	8 (23.5%)	
diameter < 1 cm	4 (8.8%)	
diameter 1-2 cm	4 (8.8%)	
Punctate white matter hyperintensities	20 (58.8%)	
n = 1-10	13 (38.2%)	
n = > 10	7 (20.6%)	

MRI, magnetic resonance imaging; DAI, diffuse axonal injury

# 5.6 Cervical DTI in Healthy Controls

## 5.6.1 DTI Values at Different Cervical Levels

The mean FA and ADC values for whole cord measurements at levels C2-C7 are shown in Table 9. There were significant differences between spinal levels for both FA and ADC ( $p<0.001$ ). The FA values decreased gradually in a rostral to caudal direction and an inverse trend was observed for the ADC values (see Figure 5).

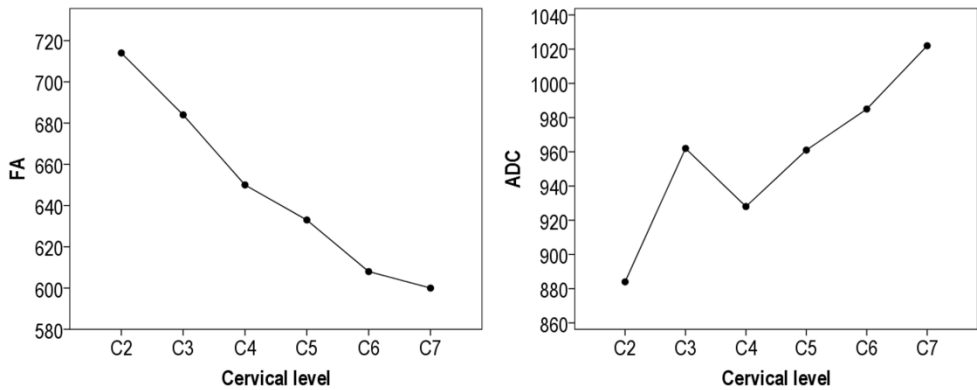
**Table 9.** Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values for the entire cord area at different cervical levels, C2-C7 (Study II, reprinted with permission).

	FA Mean±SD	ADC Mean±SD
C2	0.714 ± 0.074	0.884 ± 0.118
C3	0.684 ± 0.053	0.962 ± 0.091
C4	0.650 ± 0.058	0.928 ± 0.092
C5	0.633 ± 0.060	0.961± 0.078
C6	0.608 ± 0.057	0.985 ± 0.084
C7	0.600 ± 0.055	1.022 ± 0.106

ADC \* 10<sup>-3</sup> mm<sup>2</sup>/s

FA, fractional anisotropy; ADC, apparent diffusion coefficient; SD, standard deviation





**Figure 5.** Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values for the whole cord area at different cervical levels in healthy control subjects. (The FA values are multiplied by 1000. ADC, AD and RD  $\times 10^{-3} \text{ mm}^2/\text{s}$ .)

### 5.6.2 Comparison of DTI Values between Funiculi

At the C3 level, there were no significant differences in FA values between funiculi. The ADC, AD and RD values were all lower in the left and right lateral funiculi when compared with the values in the posterior funiculus (ADC left and right funiculi,  $p < 0.001$ ; AD left and right funiculi,  $p < 0.001$ ; RD right funiculus,  $p = 0.005$ ; RD left funiculus,  $p = 0.003$ ). Between the left and right funiculi, there were no significant differences in the DTI metrics (see Table 10).

Whole cord values for FA and AD were significantly lower but the values for RD were significantly higher compared to the values for the individual funiculi. The ADC values for the whole cord were significantly higher than those for the lateral funiculi but were significantly lower than those for the posterior funiculus.

**Table 10.** Mean ( $\pm$ SD) diffusion tensor imaging values of the whole cord and individual white matter funiculi at the cervical C3 level.

	DTI metrics	Whole cord	Right lateral funicle (I)	Left lateral funicle (II)	Posterior funicle (III)	Differences between funiculi
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
a	FA	0.687 $\pm$ 0.058	0.773 $\pm$ 0.086	0.773 $\pm$ 0.083	0.764 $\pm$ 0.069	-
b	ADC	0.951 $\pm$ 0.105	0.909 $\pm$ 0.132	0.890 $\pm$ 0.148	1.012 $\pm$ 0.139	IIIb vs Ib, IIb**
c	AD= $\lambda$ 1	1.859 $\pm$ 0.129	1.951 $\pm$ 0.184	1.939 $\pm$ 0.186	2.145 $\pm$ 0.168	IIIc vs Ic, IIc**
d	RD	0.497 $\pm$ 0.107	0.399 $\pm$ 0.135	0.389 $\pm$ 0.138	0.443 $\pm$ 0.143	IIId vs Id, IID*
e	$\lambda$ 2	0.591 $\pm$ 0.121	0.470 $\pm$ 0.115	0.481 $\pm$ 0.156	0.523 $\pm$ 0.163	IIIe vs Ie*
f	$\lambda$ 3	0.403 $\pm$ 0.097	0.319 $\pm$ 0.136	0.297 $\pm$ 0.128	0.364 $\pm$ 0.130	IIIf vs If, IIIf*

ADC, AD, RD and  $\lambda$ 2-3  $\times 10^{-3}$  mm<sup>2</sup> / s

\* $\leq 0.01$ ,

\*\* $\leq 0.001$

DTI; diffusion tensor imaging, FA, fractional anisotropy; ADC, apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; SD, standard deviation

### 5.6.3 Age and Gender Differences in DTI Values

For all of the DTI metrics, there were only two statistically significant differences between the age groups  $<$  and  $\geq 40$  years. Among older subjects, FA values at the C6 level ( $p=0.004$ ) and the  $\lambda$ 2 value for the left lateral funiculus ( $p=0.006$ ) were lower than those determined for the younger age group. There were no significant differences in any of the DTI metrics between male and female subjects.

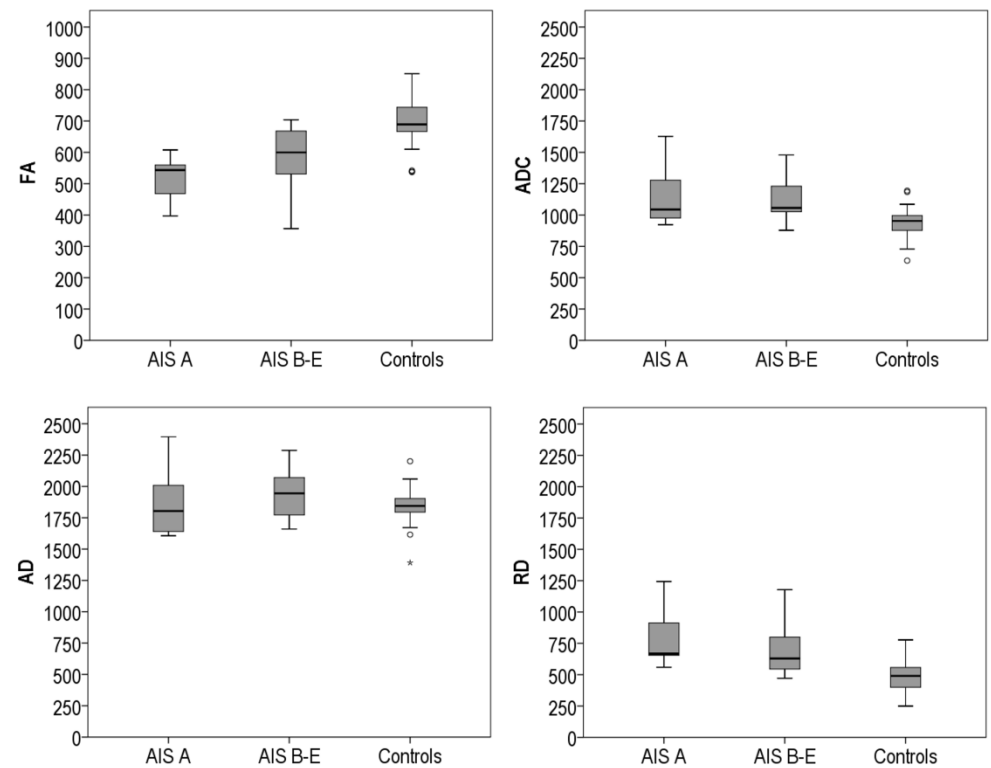
## 5.7 DTI in Patients with Chronic Cervical TSCI

### 5.7.1 *Spinal and Cerebral DTI values*

The measured spinal DTI metrics are summarized in Table 11 for the lesion level and in Table 12 for the upper cervical cord level C 2-3. Table 13 shows the cerebral FA and ADC values. Controls were compared to the entire group of patients with SCI and to the AIS A (complete SCI) and AIS B-E (incomplete SCI) subgroups. Furthermore, a comparison between the AIS A and AIS B-E groups was performed.

Spinal measurements (Study III) demonstrated lower FA values and higher ADC values in all of the patient groups with chronic SCI compared to the healthy control subjects at both the lesion and the upper cervical cord levels. In addition, the RD values increased at the upper cervical cord level. FA values in the patient group with complete injury were lower than those in patients with incomplete injury, but the difference did not reach statistical significance. (Figure 6)

**Figure 6.** Fractional anisotropy (FA), apparent diffusion coefficient (ADC), and axial (AD) and radial diffusivity (RD) values for the whole cord area at the upper cervical cord level C2-3 in patients with complete (AIS A) and incomplete (AIS B-E) cervical spinal cord injuries and in healthy control subjects. (The FA values are multiplied by 1000. ADC, AD and RD \*10<sup>-3</sup> mm<sup>2</sup>/s.)



**Table 11.** Diffusion tensor imaging (DTI) values at the lesion level in patients with chronic spinal cord injury and in control subjects (controls = mean of diffusion tensor parameters for healthy volunteers at levels C2-C3 to C5-C6) (Study III, reprinted with permission).

	Controls		Patients (18)			AIS A (3)			AIS B-E (15)			p AIS A vs. AIS B-E
	Med.	Mean±SD	Med.	Mean±SD	p	Med.	Mean±SD	p	Med.	Mean±SD	p	
Whole cord												
FA	0.67	0.67±0.06	<b>0.53</b>	<b>0.51±0.09</b>	<b>0.000**</b>	<b>0.41</b>	<b>0.38±0.05</b>	<b>0.001**</b>	<b>0.54</b>	<b>0.53±0.07</b>	<b>0.000**</b>	<b>0.020*</b>
ADC	0.95	0.95±0.10	<b>1.13</b>	<b>1.14±0.18</b>	<b>0.000**</b>	<b>1.36</b>	<b>1.31±0.19</b>	<b>0.001**</b>	<b>1.06</b>	<b>1.10±0.16</b>	<b>0.000**</b>	0.120
Lateral funicles												
FA	0.75	0.74±0.07	<b>0.52</b>	<b>0.51±0.11</b>	<b>0.000**</b>	<b>0.42</b>	<b>0.38±0.08</b>	<b>0.001**</b>	<b>0.56</b>	<b>0.54±0.10</b>	<b>0.000**</b>	<b>0.042*</b>
ADC	0.93	0.94±0.13	<b>1.05</b>	<b>1.14±0.20</b>	<b>0.000**</b>	<b>1.34</b>	<b>1.31±0.30</b>	<b>0.003**</b>	<b>1.04</b>	<b>1.10±0.17</b>	<b>0.000**</b>	0.250

ADC, AD and RD \*10<sup>-3</sup> mm<sup>2</sup>/s

Comparisons adjusted with age by linear regression.

p\*<sup><</sup>0.05, \*\*p<sup><</sup>0.01

FA, fractional anisotropy; ADC, apparent diffusion coefficient; Med, Median; SD, standard deviation; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C-D motor-sensory incomplete; AIS E normal,

**Table 12.** Diffusion tensor imaging (DTI) values at cervical level C2-3 in patients with chronic spinal cord injury and control subjects (Study III, reprinted with permission).

	Controls (40)		Patients (28)			AIS A (7)			AIS B-E (21)			p AIS A vs. AIS B-E
	Med.	Mean±SD	Med.	Mean±SD	p	Med.	Mean±SD	p	Med.	Mean±SD	p	
Whole cord												
FA	0.69	0.70±0.07	<b>0.58</b>	<b>0.57±0.09</b>	<b>0.000**</b>	<b>0.54</b>	<b>0.51±0.08</b>	<b>0.000**</b>	<b>0.60</b>	<b>0.58±0.09</b>	<b>0.000**</b>	<b>0.030*</b>
ADC	0.95	0.94±0.11	<b>1.05</b>	<b>1.13±0.20</b>	<b>0.000**</b>	<b>1.04</b>	<b>1.16±0.28</b>	<b>0.005**</b>	<b>1.06</b>	<b>1.12±0.18</b>	<b>0.000**</b>	0.681
AD	1.84	1.84±0.13	1.93	1.93±0.22	0.369	1.80	1.87±0.30	0.640	1.94	1.95±0.18	0.122	0.450
RD	0.49	0.48±0.12	<b>0.67</b>	<b>0.73±0.22</b>	<b>0.000**</b>	<b>0.67</b>	<b>0.80±0.27</b>	<b>0.000**</b>	<b>0.63</b>	<b>0.70±0.20</b>	<b>0.000**</b>	0.153
Lateral funicles												
FA	0.77	0.77±0.08	<b>0.57</b>	<b>0.57±0.12</b>	<b>0.000**</b>	<b>0.57</b>	<b>0.51±0.11</b>	<b>0.000**</b>	<b>0.60</b>	<b>0.59±0.12</b>	<b>0.000**</b>	0.094
ADC	0.88	0.89±0.12	<b>1.08</b>	<b>1.15±0.28</b>	<b>0.000**</b>	<b>0.97</b>	<b>1.19±0.43</b>	<b>0.004**</b>	<b>1.09</b>	<b>1.13±0.22</b>	<b>0.000**</b>	0.759

ADC, AD and RD \*10<sup>-3</sup> mm<sup>2</sup>/s

Comparisons adjusted with age by linear regression

p\*<sup><</sup>0.05, \*\*p<sup><</sup>0.01

FA, fractional anisotropy; ADC, apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; Med, Median; SD, standard deviation; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C-D motor-sensory incomplete; AIS E normal,

Brain analysis (Study IV) showed lower FA in the posterior ROIs of the centrum semiovale both in the whole patient group and in the patient group with complete SCI compared to the controls. In addition, in the latter group of more severely injured patients, the FA value for the cerebral peduncle was lower and the ADC value of the posterior centrum semiovale was higher than those of the healthy controls; however, these differences did not reach statistical significance. There was also a difference, although it was not significant, in the FA and ADC values determined for the posterior centrum semiovale between patient groups with complete and incomplete injuries.

**Table 13.** Cerebral diffusion tensor imaging values in patients with chronic spinal cord injury and control subjects (Study IV, reprinted with permission).

	Controls (N=40)			Patients (=34)			AIS A (n=10)			AIS B-E (n=24)			p AIS A vs AIS B-E
	Med.	Mean±SD		Med.	Mean±SD	p	Med.	Mean±SD	p	Med.	Mean±SD	p	
<b>Cerebral peduncle</b>													
FA	0.79	0.80±0.04		0.78	0.78±0.06	0.175	<b>0.74</b>	<b>0.74±0.06</b>	<b>0.036*</b>	0.78	0.79±0.05	0.996	0.093
ADC	0.75	0.75±0.05		0.75	0.76±0.06	0.048	0.77	0.77±0.07	0.156	0.75	0.75±0.05	0.050	0.562
<b>Posterior limb of the internal capsule</b>													
Anterior FA	0.70	0.70±0.04		0.70	0.70±0.04	0.830	0.70	0.69±0.02	0.406	0.71	0.71±0.04	0.375	0.171
Anterior ADC	0.71	0.71±0.03		0.69	0.70±0.04	0.496	0.69	0.70±0.02	0.830	0.69	0.70±0.04	0.478	0.633
Posterior FA	0.71	0.70±0.04		0.72	0.72±0.04	0.074	0.72	0.71±0.04	0.116	0.73	0.72±0.04	0.083	0.855
Posterior ADC	0.71	0.71±0.02		0.70	0.70±0.03	0.600	0.70	0.70±0.02	0.286	0.71	0.71±0.03	0.788	0.575
<b>Posterior part of the corona radiata</b>													
Anterior FA	0.47	0.48±0.07		0.48	0.48±0.06	0.496	0.48	0.48±0.04	0.711	0.48	0.48±0.07	0.496	0.665
Anterior ADC	0.67	0.67±0.05		0.71	0.72±0.06	0.195	0.69	0.70±0.05	0.232	0.72	0.73±0.07	0.374	0.729
Posterior FA	0.53	0.53±0.06		0.54	0.53±0.08	0.768	0.54	0.52±0.08	0.909	0.53	0.53±0.08	0.832	0.805
Posterior ADC	0.71	0.72±0.04		0.73	0.73±0.04	0.249	0.71	0.72±0.03	0.420	0.73	0.73±0.05	0.494	0.704
<b>Centrum semiovale</b>													
Anterior FA	0.61	0.62±0.06		0.57	0.57±0.09	0.483	0.58	0.57±0.06	0.067	0.55	0.57±0.10	0.959	0.463
Anterior ADC	0.71	0.72±0.04		0.73	0.74±0.06	0.547	0.72	0.73±0.04	0.465	0.74	0.75±0.07	0.668	0.781
Central FA	0.60	0.60±0.08		0.61	0.60±0.07	0.270	0.60	0.59±0.07	0.937	0.61	0.60±0.07	0.138	0.267
Central ADC	0.72	0.72±0.04		0.72	0.74±0.07	0.967	0.71	0.72±0.06	0.646	0.73	0.75±0.07	0.531	0.597
Posterior FA	0.56	0.57±0.05		<b>0.52</b>	<b>0.52±0.06</b>	<b>0.008**</b>	<b>0.50</b>	<b>0.48±0.08</b>	<b>0.000**</b>	0.52	0.53±0.05	0.352	<b>0.013*</b>
Posterior ADC	0.72	0.73±0.04		0.74	0.75±0.06	0.465	<b>0.76</b>	<b>0.78±0.09</b>	<b>0.023*</b>	0.73	0.74±0.04	0.491	<b>0.025*</b>

ADC \*10<sup>-3</sup>mm<sup>2</sup>/s

Comparisons adjusted with age and gender by linear regression.

p\* < 0,05, \*\*p < 0,01

FA, fractional anisotropy; ADC, apparent diffusion coefficient; Med, Median; SD, standard deviation; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C-D motor-sensory incomplete; AIS E normal.

### 5.7.2 *Clinical Correlations*

Partial correlations (with age in study III and with age and gender in study IV as controlling factors) between the DTI values, conventional MRI findings and clinical findings (ISNCSCI and FIM) are shown in Table 14 for spinal and in Table 15 for cerebral measurements. Neither the spinal nor the cerebral DTI values were statistically associated with the time since injury.

Among the DTI metrics measured from the area of the spinal cord, significant correlations with the ISNCSCI and FIM scores were found mostly in the FA. At the lesion level, the positive association of FA to the ISNCSCI motor score for the lower extremities and to FIM mobility and locomotion subscores were strong. At the upper cervical cord level, FA correlated moderately and positively with all of the clinical parameters. In addition, RD at the upper cervical cord level and the length of the spinal cord lesion assessed by conventional MRI were negatively associated with some of the clinical scores.

Significant correlations between cerebral DTI values and ISNCSCI parameters were mainly found for the measurements obtained for the posterior part of the centrum semiovale. In that area, there was a moderate and positive relationship between FA values and a moderate and negative association between ADC values and the motor and sensory scores for the ISNCSCI. In addition, the FA values for the PLIC were moderately correlated with certain clinical and MRI-derived parameters.



**Table 14.** Partial correlations (age as a controlling factor) for diffusion tensor imaging values and conventional magnetic resonance imaging findings with clinical scores (Study III, reprinted with permission).

	ISNCSCI scores					FIM scores				
	Mtot	Mue	Mle	Stot†	NL	Ftot	Fcare	Fspc	Fmob	Floc
<b>DTI, Lesion level (n=18)</b>										
<b>Whole cord</b>										
FA	<b>0.67*</b>	0.54	<b><u>0.76**</u></b>	0.56	-	-	-	-	<b><u>0.73**</u></b>	0.57
ADC	-	-	-	-	-	-	-	-	-0.50	-
<b>Lateral funicles</b>										
FA	<b>0.67*</b>	-	<b><u>0.74**</u></b>	0.54	-	0.53	-	0.49	<b><u>0.75**</u></b>	<b><u>0.71**</u></b>
ADC	-	-	-	-	-	-	-	-	-	-
<b>DTI, C 2-3 level (n=28)</b>										
<b>Whole cord</b>										
FA	<b>0.56*</b>	<b>0.49*</b>	<b>0.52*</b>	<b><u>0.66**</u></b>	-	<b>0.51*</b>	<b>0.48*</b>	<b>0.56*</b>	<b>0.58*</b>	<b>0.56*</b>
ADC	-	-	-	-	-	-	-	<b>-0.51*</b>	-	-
AD	-	-	-	-	-	-	-	-	-	-
RD	-0.45	-	-0.45	<b>-0.50*</b>	-	-0.42	-	<b>-0.55*</b>	-0.49	-0.47
<b>Lateral funicles</b>										
FA	<b>0.55*</b>	0.46	<b>0.55*</b>	<b><u>0.62**</u></b>	-	<b>0.56*</b>	<b>0.49*</b>	<b>0.57*</b>	<b><u>0.62**</u></b>	<b><u>0.61**</u></b>
ADC	-	-	-	-	-	-	-	-	-	-
<b>MRI findings (n=23)</b>										
Lesio, cranial limit	-	-	-	-	-	-	0.42	0.43	0.47	-
Lesio, length	<b>-0.54*</b>	-	<b>-0.56*</b>	<b><u>-0.77**</u></b>	-	-	-	-	-0.42	-0.44

p≤0.05, p≤0.01\*in bold, p≤0.001\*\* in bold and underlined

† 2 sensory scores missing, (n=26/16/21 respectively)

FA, fractional anisotropy; ADC, apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; Mtot, total motor score; Mue, motor score of the upper extremities; Mle, motor score of the lower extremities; Stot, total sensory score; NL, single neurological level; FIM, Functional Independence Measure; Ftot, FIM motor subscale; Fcare, FIM self care subscore; Fspc, FIM sphincter control subscore; Fmob, FIM mobility subscore; Floc, FIM locomotion subscore

**Table 15.** Partial correlations (age and sex as controlling factors) between cerebral diffusion tensor imaging values and clinical findings (Study IV, reprinted with permission).

Brain DTI values	ISNCSCI parameters				Spinal Cord MRI		
	Mtot	Mue	Mle	Stot†	NL	CL	LL
<b>Cerebral Peduncle</b>							
FA	-	-	-	-	-	-	-
ADC	-	-	-	-	-	-	-
<b>PLIC</b>							
Anterior FA	-	0.414	-	<b>0.493*</b>	-	0.456	-
Anterior ADC	-	-	-	-	-	-	-
Posterior FA	-	-	-	-	-	-	-
Posterior ADC	-	-	-	-	-	-	-
<b>Corona Radiata</b>							
Anterior FA	-	-	-	-	-	-	-
Anterior ADC	-	-	-	-	-	-	-
Posterior FA	-	-	-	-	-	-	-
Posterior ADC	-	-	-	-	-	-	-
<b>Centrum Semiovale</b>							
Anterior FA	-	-	-	-	-	-	-
Anterior ADC	-	-	-	-	-	-	-
Central FA	-	-	-	-	0.411	-	-
Central ADC	-	-	-	-	-	-	-
Posterior FA	0.426	<b>0.460*</b>	-	<b>0.482*</b>	-	-	-
Posterior ADC	-0.425	<b>-0.505*</b>	-	<b>-0.554*</b>	-	-	<b>0.493*</b>

p<0.05, p\* $<$ 0.01 in bold

†Two sensory scores missing n=32, ‡ n=29

FA, fractional anisotropy; ADC, apparent diffusion coefficient; PLIC, posterior limb of internal capsule; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; Mtot, total motor score; Mue, motor score of the upper extremities; Mle, motor score of the lower extremities; Stot, total sensory score; NL, single neurological level; CL, cranial level of lesion in conventional MRI; LL, lesion length

## 5.8 Reproducibility of the DTI Measurements

For measurements of the whole cord at different levels, the mean intra-class correlation coefficients (ICCs) for intraobserver variation for FA and ADC were 0.87 (range 0.81 – 0.96) and 0.70 (range 0.42 – 0.94), respectively, indicating excellent and good repeatability. For the interobserver variation between two observers, the mean ICC values for FA and ADC were 0.80 and 0.71, respectively, and among three observers were 0.78 and 0.67, respectively.

At the C3 cervical level for measurements of the whole cord and lateral and posterior funiculi, the mean ICCs for the intraobserver variation were as follows: FA, 0.76; ADC, 0.77;  $\lambda_1$ , 0.69;  $\lambda_2$ , 0.79; and  $\lambda_3$ , 0.73. These values indicated at least good agreement. For the interobserver variation between two/three observers, the mean ICC values for FA were 0.80/0.66, and those for ADC were 0.74/0.57.

For the cerebral measurements, the mean ICC values for the intraobserver variation for FA and ADC were 0.67 (range, 0.40-0.88) and 0.72 (range, 0.58-0.85), respectively, indicating good agreement.

## 6. DISCUSSION

### 6.1 Incidence of TSCI

The initial stages following the national centralization of SCI care revealed in practice that the former incidence estimates of TSCI in Finland were exiguous in terms of the current situation. Subsequently, after a one-year follow-up period, the annual incidence of TSCI in the entire catchment area was 25.1 cases per million; in the UH districts with integrated trauma and SCI centers, it was 38.1 cases per million. In fact, the calculated incidence rates proved to be two- to three-fold greater than those reported in the only incidence study published during the past two decades in Finland (Ahoniemi et al., 2008).

Ahoniemi and co-workers (2008) reported an incidence of 13.8 cases per million in the population older than 16 years old, but our recent findings for that same age group were 29.8 in the entire catchment area and 46.0 in the hospital districts of the SCI centers. Above all, a part of that difference was due to the different study samples. Our epidemiological data were collected for all of the new patients who were admitted to the SCI centers, whereas Ahoniemi and colleagues identified patients using the registers of the Käpylä Rehabilitation Centre. This institute for rehabilitation has been the only private center in Finland to care for patients with SCI immediately after the acute hospital phase. However, only a portion of SCI patients, mostly those of working age and those with injuries covered by private insurance systems, has been referred to the Käpylä Rehabilitation Centre after injury. Information about the remainder of the TSCI patients who were rehabilitated in public hospitals or health centers are missing from the register.

In contrast, the likelihood of missing cases in our study should be low, especially when considering the rates from the hospital districts of the Oulu and Tampere UHs, which are the only trauma units in the area. In the area of the other hospital districts, the coverage is less certain because a portion of the SCI patients, for example those with minor motor disabilities, may not have been referred to the SCI centers but were treated in local hospitals. Especially the Kuopio and Turku UHs have their own trauma, intensive care, neurosurgery, spine surgery and rehabilitation units to be used for the care of SCI patients, too. In addition, after

centralization, both the Oulu and the Tampere UHs adopted a systematic practice of screening all new patients who were suspected to have an SCI by a specialist rehabilitation doctor working in an SCI unit. With the increased awareness of spinal injuries during centralization, this new practice could have increased the identification of TSCI cases, revealing the hidden incidence. Both of these explanations are likely to be applicable to patients from the hospital districts of the Oulu and Tampere UHs, who appeared to be less disabled compared to with patients referred from other hospitals.

A direct comparison of our incidence rates with those reported in previous studies in Finland is more complicated due to the different sampling methods. Unlike in our study, which includes patients with milder injuries, Härkönen and colleagues (1979) reported a hospital-based incidence of 8.5 cases per million only for severe SCI. Rokkanen and associates (1988) calculated an incidence of cases of 54 per million simultaneously for traumatic SCI and nerve root lesions. In turn, the study reported by Tarkkanen (1991) documented an incidence of 34.2 per million only among patients of working age and, unlike in our study, also included deaths during the primary phase.

The information provided by the studies of Rokkanen et al. and Tarkkanen were obtained mainly from various national statistics, such as discharge reports, which could overestimate the incidence of traumatic SCI (Hagen, 2014). In our population-based study, identification of the patients was conducted during the acute phase, mainly by physicians who specialized in surgery. In addition, case ascertainment was performed by a consultant physician specialist in the SCI unit. This practice should minimize the risk of false-positive cases.

Excluding the study reported by Ahoniemi et al. (2008), all of the former studies in Finland reported incidence rates that were more than three decades old. During the past decades, the annual incidence of TSCI in Norway has been shown to increase (Hagen, 2014). Although such a trend was not found in the rehabilitation population in Finland (Ahoniemi et al., 2008), the increase in incidence was possible over the years as well as in our country, and that increase could have affected the discrepancy between the incidence rates of TSCI from different decades.

When comparing our incidence rates with those of international studies, the incidence in the area of the hospital districts of the Oulu and Tampere UHs of 38.1 cases per million was comparable to the recent rates from Estonia (39.7 cases per million) (Sabre et al., 2012) and approached the incidence estimates of TSCI in the US (40 cases per million) (NSCISC, 2013) and Canada (41 cases per million) (Noonan et al., 2012). In turn, the incidence of TSCI in the entire catchment area of 25.1 cases per million was more equivalent to recent rates from other Nordic

countries of 19.6 cases per million in Sweden (Divanoglou & Levi, 2009), 26.3 cases per million in Norway (Hagen, 2014) and 33.5 cases per million in Iceland (Knutsdottir et al., 2012). In relation to the median value of TSCI in Western Europe of 16 cases per million (B. B. Lee et al., 2014), our incidence rates were substantially higher. Nonetheless, a very recent study from the US has reported an incidence of 56.4 cases per million in the age group over 18 years (Selvarajah et al., 2014), exceeding even the annual incidence of 46.0 in our study population over 16 years old in the hospital districts of the SCI centers.

The true incidence rate of TSCI should also include data from patients who died prior to hospital admission. In the majority of the studies reporting incidence rates, similarly to our study, these deaths have not been taken into account. In their review, Wyndaele and Wyndaele (2006) described a prehospital mortality rate ranging from 15 to 56%. Thus, further studies are needed to determine the true incidence of TSCI in Finland in addition to additional follow-up to confirm the results of our one-year follow-up period.

De Vivo, Biering-Sorensen, New and Chen (2011) have prepared a recommendation for standardized data analysis and reporting for the studies of SCI, which probably will facilitate the comparison between different studies in the future.

## 6.2 Epidemiological Features of Patients with Acute TSCI

In our study, the mean age at injury was 58.7 years, which is one of the highest values documented in Western countries, exceeding, for example, the mean age range from 38 to 48.9 years reported previously in Nordic countries (Ahoniemi et al., 2008; Divanoglou & Levi, 2009; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012). However, it is comparable to very recent studies from Canada and the US, in which the mean ages were 52.1 (Thompson et al., 2014) and 50.3 years (Selvarajah et al., 2014), respectively. Different study samples in part explain the difference between studies, but a steady increase in the age at injury has been observed over decades in many countries including Finland (Ahoniemi et al., 2008; M. J. Devivo, 2012; Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012; Pickett et al., 2006; Van Den Berg et al., 2011). An increasing trend in older adults who experience TSCI has resulted in another prevalent group of new SCI patients with different epidemiological characteristics, in addition to patients who are injured as young adults.

Furthermore, in our study, the patient groups under and over 60 years of age differed significantly in several characteristics.

MVAs are usually the leading cause of injury in young and middle-age persons. This was also observed in our study, in which 37.9% of the patients under 60 years of age were injured in transportation accidents, but falling, which was the main injury etiology in the entire population, made up 31% of the injuries. Consistent with international studies, every injury due to sports in our TSCI population occurred in the younger age group (Chen et al., 2013; Thompson et al., 2014; Norton, 2010).

It is also noteworthy that all of the patients injured in high falls ( $> 1$  m) were under 60 years of age, and a majority of them had consumed alcohol prior to the injury. In our study, we did not classify suicide attempts separately. However, based both on clinical experience and on former studies from Finland and Sweden (Dahlberg et al., 2005; Levi et al., 1995), it can be assumed that a portion of the high falls that were documented in our study were intentional.

Alcohol consumption prior to TSCI was recorded in 39.0% of the cases in the entire population, but in the group of patients under 60 years of age, almost two-thirds had used alcohol prior to the injury. In that age group, 88.9% of the falls and 54.5% of the transportation accidents occurred under the influence of alcohol. When considering the contribution of alcohol use to injuries in patients  $< 60$  years, there was a conspicuous male preponderance. For those injuries, the male-to-female ratio was 4.7:1, but it was 2.6:1 for all of the injuries in that age group. In addition, the vast majority of alcohol-related injuries occurred from Friday to Sunday. These findings are consistent with Finnish drinking habits. In Finland, alcohol consumption is traditionally focused on weekends from Friday to Sunday, during which two-thirds of drinking events and 4 out of 5 drunken states occur. In addition, Finnish men drink alcohol more than twice as much as their female counterparts, and drunkenness is most common in the 20-29 years age group (Karlsson, Kotovirta, Tigerstedt, & Warpenius, 2013). In Nordic countries, alcohol consumption is highest in Finland, and Norway comes in fourth after Denmark and Sweden (Karlsson et al., 2013). In agreement with these data, only 21% of the TSCI patients had consumed alcohol prior to injury in Norway (Sabre, Hagen, Rekand, Asser, & Korv, 2013). In contrast, in Estonia, where alcohol consumption is high, that proportion was almost equal to the Finnish figures at 43.2% (Karlsson et al., 2013; Sabre, Rekand, Asser, & Korv, 2013).

In the age group over 60 years, the incidence of TSCI was high at 58.3 cases per million, and 85.4% of the patients had been injured by falling. Of those falls, 65.9% occurred on the same level and 24.4% occurred on/from stairs. The majority of

the patients had incomplete tetraplegia (64.6%), and among the cervical injuries, 82.9% were at levels C 1-4.

This most recent epidemiological profile of elderly TSCI patients in Finland confirms the trends observed in previous studies. Ahoniemi and colleagues (2008) demonstrated that the annual incidence of new TSCIs and the proportion of falls increased in persons 55 years and over in Finland over a 30-year period. In addition, the proportions of tetraplegia and incomplete injuries rose over the same time. Moreover, Kannus et al. reported, based on data from the National Hospital Discharge Register, a steep increase in the incidence of fall-related SCIs among older Finns between 1970 and 1995. (Kannus, Niemi, Palvanen, & Parkkari, 2000) An increasing trend of incomplete tetraplegia due to falls among the elderly has also been observed in other Nordic and European countries (Hagen, Eide, Rekand, Gilhus, & Gronning, 2010a; Knutsdottir et al., 2012; Van Den Berg et al., 2011) as well as on other continents (M. J. Devivo, 2012; P. J. O'Connor, 2006; Thompson et al., 2014). In the most recent studies from Finland, the incidence of fall-induced cervical spine injuries, including SCIs, continues to increase among older adults. The authors noted that demographic changes were insufficient to explain this trend. With the ongoing ageing of the population, the number of these injuries reported annually is predicted to be even 50% higher in the year 2030 compared with the values documented in 2011 (Kannus, Palvanen, Niemi, & Parkkari, 2007; Korhonen, Kannus, Niemi, Parkkari, & Sievanen, 2014). A similar increasing trend is also seen in the case of TBIs in Finland. (Korhonen, Niemi, Parkkari, Sievänen & Kannus, 2013)

Accurate explanations for the increasing numbers of fall-induced injuries among older adults remain uncertain (Kannus et al., 1999). It has been assumed that the survival of frail and less healthy persons to older ages has increased and that these functionally less capable elderly are more prone to falls and injuries. In addition, an increased body weight, less active lifestyle, use of alcohol and sedative medications and a greater occurrence of medical conditions have been suggested to contribute to impaired performance and increased risk of falling (Kannus et al., 1999; Kannus et al., 2000; Kannus, Sievanen, Palvanen, Jarvinen, & Parkkari, 2005).

The majority of falls in our older study population occurred on the same level with presumably less trauma energy compared to the high falls that were more common in younger patients. In addition, most of the injuries among older patients resulted in an incomplete cervical lesion. Degenerative diseases of the cervical spine, such as reduced spinal canal diameter, spondylosis and ossification of the posterior ligament, have been shown to increase the risk for SCI caused by relatively minor trauma (Nakae et al., 2010). In our study, we did not assess the radiological features of the acute TSCI patients. However, the frequency of cervical



spinal stenosis is higher in patients over 60 years of age compared to younger patients (Selden et al., 1999), and furthermore, more than 70% of subjects with cervical injury in this older age group have been reported to have severe pre-existing spinal stenosis (Hagen, Aarli, & Gronning, 2005).

The prevalence of medical co-morbidities prior to SCI is higher in elderly individuals, who also appear to experience more secondary complications during hospitalization (M. J. DeVivo, Kartus, Rutt, Stover, & Fine, 1990; A. V. Krassioukov, Furlan, & Fehlings, 2003b; Scivoletto, Morganti, Ditunno, Ditunno, & Molinari, 2003). Both patients with an older age and those who acquire SCI as a result of a fall seem to benefit from rehabilitation; however, they achieve less independence in some areas, such as bladder and bowel management and mobility, when compared to younger patients and to patients injured by other etiologies (Hagen et al., 2005; Kennedy, Cox, & Mariani, 2013; Scivoletto et al., 2003). For those reasons in part, there was a significant difference in the place of discharge between the younger and older age groups in our study despite equivalent completeness of the injuries and ambulation. Although the vast majority of patients under 60 years of age were discharged directly to their home following rehabilitation, 45.8% of the older patients required a subsequent stay in another hospital prior to being discharged home or to an assisted living residence.

The first year charges for SCI caused by falls, which usually result in incomplete injury, seem to be lower in relation to other main etiologies. However, the annual charges thereafter are third after MVA and sports-related SCIs because older people are more prone to fall-induced SCIs and are more likely to require attended care and nursing home services (M. J. DeVivo, 1997).

These age-related differences address the need for multidisciplinary and comprehensive medical care as well as tailored rehabilitation programs for this increasing population of TSCI patients with special needs. Because elderly people with a TSCI seem to be a growing problem that will increasingly challenge health and support services in the future, effective fall-prevention strategies are also needed. Strength and balance training, vitamin D and calcium supplementation, reduction of psychotropic medication, cataract surgery and professional home hazard assessments and modifications have been shown to reduce the risk of falling in elderly people (Kannus et al., 2005) and should be implemented more widely in that population in the future. Moreover, despite the relatively strict alcohol policy in Finland, there remains clear need for more efficient preventive measures to reduce alcohol-related injuries in all of the age groups, especially among men. It is worth noting that based on the lifetime cost of an SCI in Canada (Krueger et al., 2013), a prevention program that prevents only one major TSCI could cost almost 1 million euros and still save a great deal of money.

## 6.3 Cervical DTI in Healthy Controls

The application of DTI in the spinal cord is challenging. The small size of the spinal cord and the individual white matter tracts stress the need for high spatial resolution (Mukherjee et al., 2008; Stroman et al., 2014). Nevertheless, the spatially non-uniform magnetic field environment of tissues and materials with different magnetic properties, such as bone, soft tissues and air, that are in close proximity to one another results in image distortion and a loss of signal intensity. In addition, the physiological motion of cerebrospinal fluid flow, cardiac and respiratory cycles, and oropharyngeal motion, causes substantial image artifacts. (Mukherjee et al., 2008; Stroman et al., 2014)

A comparison of spinal DTI values between different studies with varying MRI scanner types, acquisition parameters, measurement methods and sample populations is not straightforward (Mukherjee et al., 2008). For example, the voxel size and the number of diffusion gradient directions, both of which are important factors in SNR, are shown to affect FA values, which tend to be higher with a low SNR (Santarelli, Garbin, Ukmar, & Longo, 2010). Therefore, a local series of normative DTI values with optimized acquisition parameters should be created in each institution if the DTI values are to be used in research or in a clinical setting.

To provide a reliable interpretation of DTI findings for individual patients or patient populations, it is important to be aware of variations in normative DTI values with respect to factors that potentially affect them. As in many other studies (Ellingson, Ulmer, Kurpad, & Schmit, 2008b; Lindberg et al., 2010; Mamata et al., 2005; T. Song et al., 2011; Vedantam et al., 2013), the FA decreased linearly in the rostral-caudal direction in our population of healthy subjects. The proportion of grey/white matter varies at different spinal levels and could partially explain the dependence of FA on the segmental level (Wheeler-Kingshott et al., 2002). In addition, disruption of the directional coherence of fibers by emerging brachial plexus nerve roots in the lower cervical levels (Wheeler-Kingshott et al., 2002) and the different percentages of axons with a large-diameter between higher and lower SC levels have been suggested to account for some of the differences (Ellingson, Ulmer, Kurpad, & Schmit, 2008b). Consistent with the studies of Shanmuganathan et al. (2008) and Cheran and colleagues (2011), we found an inverse relationship between ADC and FA, with the highest ADC values at the lower level of the cervical spinal cord. In contrast, many studies have reported no statistically significant differences in ADC between the spinal levels (Ellingson, Ulmer, Kurpad, & Schmit, 2008b; Lindberg et al., 2010; S. A. Smith et al., 2010; T. Song et al., 2011). However, in these studies, the number of healthy volunteers was smaller (up to 24) compared to our study with a larger sample size of 40. When SNR is

also shown to vary according to the cervical cord levels (Vedantam et al., 2013), the different measurement levels used in different studies complicates the comparison of acquired DTI metrics between studies.

At present, studies reporting DTI values for individual spinal cord white matter funiculi are relatively sparse, and the results are partially conflicting (Onu et al., 2010; Rossi et al., 2008; S. A. Smith et al., 2010; Vedantam et al., 2013). Although Smith and co-workers (2010) did not detect differences in any of the DTI metrics between funiculi, both Rossi et al. (2008) and Onu and associates (2010) reported significantly higher FA values in dorsal compared with lateral funiculi. Moreover, the latter study reported the lowest FA values for the ventral funiculus. (Onu et al., 2010) In accordance with our study, Vedantam et al. (2013) failed to reveal a difference in FA values between the lateral and posterior funiculi, but the FA of the ventral funiculus was lower compared to the other white matter areas. In addition, consistent with that study, both the directional diffusivities and the ADC in our study were significantly higher in the dorsal funiculus than in the lateral funiculi. (Vedantam et al., 2013) Similarly, Onu et al. (2010) did not detect a difference in the AD of RD between the dorsal and lateral funiculi, but the RD values for the ventral funiculus were significantly higher than those determined for the lateral and dorsal funiculi.

The differences in DTI metrics between white matter funiculi have been suggested to be due to differences in axon morphometry and spacing, which has been reported to correlate with DTI values in histological studies (Schwartz et al., 2005). However, partial volume effects from adjacent structures are likely to affect spinal DTI values. In the study reported by Onu and associates (2010), two ROIs were designated in the area of the dorsal funiculi to avoid a partial volume effect from the corticospinal fluid in the median fissure. In turn, similarly to our group, Vedantam and others (2013) used only one ROI positioned in the midline of the dorsal funiculi, which could increase the ADC and decrease the FA in that area and partially explain the diversity in the formerly mentioned results. Contamination of the ROI by grey matter is especially likely to occur in the anterior spinal cord ROI (Hesseltine et al., 2006) and could affect the especially low FA and high RD in that area demonstrated by Onu and collaborators (2010).

The impact of age on DTI values seems to be exiguous in our study. In a recent study, Vedantam et al. (2013) showed no significant association between age and DTI values in subjects under 55 years of age, but the FA was linearly and negatively associated with age in the age group ranging from 55 to 85 years. This finding could explain the contradictory results documented in previous literature. The studies reported by Mamata et al. (2005) and Petersen and co-workers (2012) demonstrated a significant impact of age on DTI values, but other studies have

shown no association between these variables (Cui, Wen, Hu, Li, & Luk, 2011; Hesselstine et al., 2006). A closer examination of those studies showed that the age range appeared to be wider (Mamata et al., 2005) and the mean age higher (Petersen et al., 2012) in studies with significant age correlations than in those lacking a consistent relationship between age and DTI metrics (Cui et al., 2011; Hesselstine et al., 2006). This phenomenon may explain the findings in our recent study of a mean age of 40.4 years and an age range of 18-60 years without consistent associations between age and DTI values. In addition, in a study reported by Lindberg and associates (2010), a healthy population with a mean age of 43 years showed only a trend toward a negative correlation between age and FA in the lateral part of the spinal cord.

## 6.4 DTI in Patients with Chronic Cervical TSCI

The primary aim in studies III and IV was to quantitatively assess the state of spinal and cerebral white matter in chronic cervical SCI using the DTI and ROI method. DTI measurements in the spinal and cerebral regions were focused on the area of the corticospinal tract (CST), which is the major descending pathway that contributes to the control of skilled motor movements in humans (Lemon, 2008). In the spinal cord, the majority of CST fibers run in lateral funiculi and are covered by circular ROIs. In addition, DTI values are calculated from the whole cross-section of the cord, because in individual SCI patients, spinal gray and white matter structures may become indistinguishable by injury, and it is often impossible to perform more detailed measurements near the injury site.

### 6.4.1 *Spinal DTI*

In line with a study reported by Ellingson and others (Ellingson, Ulmer, Kurpad, & Schmit, 2008a), FA and ADC values measured at the level of the lesion were significantly reduced and increased, respectively, in patients with both complete and incomplete chronic SCI compared to healthy controls. In addition, the FA values of patients with complete SCI seemed to be lower than those in patients with incomplete injury. However, perhaps due to the relatively small number of subjects in the first aforementioned patient group, the difference did not reach statistical significance. The significant DTI alterations in the injury site likely reflect consequences of both direct and secondary neural injury as well as the effects of secondary neural degeneration. Although disruption of coherent axonal

architecture is likely to reduce FA values, the increase in ADC is probably a primary consequence of the accumulation of extracellular water in the area of the damaged tissue (Pierpaoli et al., 2001).

Even if the conventional MRI showed no signs of a primary lesion in the upper cervical cord area at the level of C2-3, the FA, ADC and RD values were significantly altered in our patient population. In five of these patients, the ISNCSCI-derived single neurological level was located between C1-2, and it is probable that a portion of the change in DTI metrics, especially in those individuals, was caused by a direct injury. However, the remainder of the patients had a clinical neurological level below C3, and the contribution of the effects of anterograde and retrograde secondary degeneration to the observed DTI changes rostral to the lesion was likely substantial. In support of this assumption, six patients with a complete injury showed a diffuse high signal intensity in the dorsal funiculus on the T2\* images, likely representing anterograde degeneration of the sensory tracts (Valencia & Castillo, 2006).

In concordance with our results, a reduction in FA values rostral to the lesion has been observed in previous studies (Chang et al., 2010; Cohen-Adad et al., 2011; Ellingson, Ulmer, Kurpad, & Schmit, 2008a; Freund, Schneider et al., 2012; Petersen et al., 2012). In addition, the findings reported by Cohen-Adad et al. (2011) also demonstrated an increase in RD. However, in contrast to the majority of those studies, which demonstrated no change in directionally averaged diffusion in the area of the intact spinal cord after injury, the ADC was significantly increased in our patient population. In general, the increase in ADC in the area of degenerated tracts, in which myelinated axons are replaced by astrogliosis, has been shown to be smaller than at the site of direct injury (Pierpaoli et al., 2001). It is possible that our larger patient population resulted in an increase in ADC rostral to the lesion, which has not been observed in previous studies with fewer subjects.

However, the FA value appeared to be the most sensitive DTI parameter in chronic SCI, followed by RD. In most cases, the previous literature demonstrated an association between clinical disability and a reduction in FA (Chang et al., 2010; Freund, Schneider et al., 2012; Petersen et al., 2012), yet some studies, consistent with our results, also showed a relationship between an increasing RD and disability (Cohen-Adad et al., 2011; Ellingson, Ulmer, Kurpad, & Schmit, 2008a). Moreover, in the study reported by Ellingson et al., the decrease in FA and increase in RD were able to discriminate patients with complete and incomplete injuries, but in our study, only a difference in FA was observed between these patient groups (Ellingson, Ulmer, Kurpad, & Schmit, 2008a).

The clinical and functional state of SCI patients tends to be worse with decreasing FA values. At the lesion level, the motor deficit of the lower extremities

in particular increases, and functional ability in the areas of mobility and locomotion decreases along with an increasing disruption of the axonal architecture caused by direct injury. Rostral to the lesion, the reduction in FA, which is likely induced by axonal degeneration and demyelination, was moderately associated with both motor and sensory outcomes as well as with all of the functional subscores. In addition, in other studies, spinal FA values have been shown to correlate with the completeness of the injury (Ellingson, Ulmer, Kurpad, & Schmit, 2008a), AIS grade (Petersen et al., 2012), sum of the ISNCSCI motor and sensory scores (Cohen-Adad et al., 2011) and fine motor skills of the hand (Freund, Schneider et al., 2012). However, no previous studies in adults have investigated DTI values in patients with chronic SCI using the entirety of the ISNCSCI parameters or with any instrument used to assess functional disability.

Our findings support earlier assumptions that DTI indexes measured rostral to the spinal lesion provide clinically relevant information about the condition of the nerve fiber tracts, enabling the use of those values as noninvasive imaging biomarkers following SCI. In addition, the results seems to be comparable regardless of the placement of ROIs either to encompass the whole area of the cord or a part of the lateral white matter. Thus, it appears that reliable DTI measures can be obtained, at least in chronic SCI, despite the difficulty associated with the distinction of spinal gray and white matter after injury and in spite of imaging artifacts caused by bone/soft tissue injuries and fixation materials at the level of the lesion.

## **6.4.2      *Cerebral DTI***

Although degeneration associated DTI changes after SCI in the intact upper cervical cord have been detected in several studies, the publications concerning cerebral DTI metrics after injury are relatively sparse. In general, DTI studies, which include only patients with complete injury (Guleria et al., 2008; Wrigley et al., 2009), have shown more extensive injury-related cerebral DTI changes compared to studies with heterogeneous patient populations (Freund et al., 2012; Wei et al., 2008).

Histologically, there is evidence for cerebral retrograde CST degeneration after SCI in humans as high as the pons concurrently with the loss of large pyramidal cells in the precentral gyrus suggesting atrophic changes in the soma of the damaged axons (Yamamoto et al., 1989). In fact, the distribution of cerebral DTI value differences between SCI patients and healthy controls in our patient population can be interpreted to correspond to the extent of histological changes

in the formerly mentioned case report. Hypothetically, in the area of the cerebral peduncles, reduced FA values without a change in ADC could represent retrograde CST degeneration that continues from the spinal cord to the region of the brain stem. In turn, changes in both FA and ADC immediately under the primary sensorimotor cortex (in the posterior part of the centrum semiovale) may potentially reflect atrophy of the neuronal soma. The finding that DTI changes both in the brain stem and centrum semiovale occurred primarily in the patient group with complete SCI strengthens the assumption that these values are associated with microstructural changes induced by trauma. However, due to multiple comparisons, the statistical significance was set at  $p < 0.01$ , and the only statistically significant differences in DTI metrics were detected in the FA of the posterior centrum semiovale.

When proceeding cranially from the spinal cord to the area of the brainstem, the DTI changes suggesting degeneration were subtle in our study and consisted only of a slight reduction in FA in patients with a complete injury. In previous studies using the ROI method, Guleria and associates (2008) discovered decreased FA and increased ADC values throughout the brainstem, and Freund, Wheeler-Kingshott et al. (2012) demonstrated alterations in FA and RD in the pyramids and changes in AD and RD in the cerebral peduncles. Lower FA values were also detected by Wrigley et al. (2009) in the WBA of the DTI indices in the area of the pons and pyramids.

In the area between the brainstem and cortex, the CST runs through the PLIC and the posterior part of the corona radiata. All of the formerly mentioned studies showed reduced FA values in SCI patients in the area of PLIC, indicating post-injury disruption of the white matter tracts in that area (Freund, Wheeler-Kingshott et al., 2012; Guleria et al., 2008; Wrigley et al., 2009). Moreover, in two out of three of these studies, DTI alterations were noticed in the area of the corona radiata. In the study reported by Wrigley and co-workers (2009), the FA in the corona radiata was reduced, but in contrast to expectations, the FA and ADC in the other study were increased and decreased, respectively (Guleria et al., 2008). These inverse changes in FA and ADC, from which the increase in FA also propagated with the time since injury, were suggested to reflect the subcortical plasticity found in experimental studies after SCI (Guleria et al., 2008; Ramu et al., 2008). In our study, no alterations in DTI values were detected between patients and control subjects in those areas. Nevertheless, the FA values for the PLIC were moderately related to certain clinical variables and tended to increase, especially with better sensory function. It can be hypothesized that in our patient population, the white matter tracts in the PLIC may also be affected by SCI.

Only a few human studies have demonstrated grey matter loss in the area of the sensorimotor cortex after SCI (Freund et al., 2011; Henderson et al., 2011; Wrigley et al., 2009). These findings may reflect, at least in part, the shrinkage of pyramidal neurons after CST injury observed previously both in lower primates (Wannier, Schmidlin, Bloch, & Rouiller, 2005) and humans (Yamamoto et al., 1989). In addition to volume changes, Wrigley and co-workers (2009) also detected a significant decrease in FA and an increase in ADC in the region of the primary motor cortex and the immediately adjacent white matter. Corresponding volume and DTI value differences, indicating cortical microstructural changes after SCI, have also been shown in the patient population reported by Freund et al. (Freund et al., 2011; Freund, Wheeler-Kingshott et al., 2012) In our study, the posterior ROIs in the centrum semiovale (the white matter area directly underneath the grey matter) were located in approximately the same area in which the motor CST and sensory projections traveled from and to the cortex, respectively (Seo, Chang, & Jang, 2012; Yamada et al., 2007). Therefore, based on emerging clinical correlations, the observed DTI changes in that area in our patient population likely describe the neuronal degenerative changes caused by SCI.

Freund and colleagues have shown a complex association between spinal and cortical atrophy, spinal and cerebral microstructural integrity, cortical reorganization and fine-motor functions of the hand in chronic SCI using multimodal MRI. (Freund et al., 2011; Freund, Wheeler-Kingshott et al., 2012; Freund, Schneider et al., 2012) For example, they showed that axonal CST degeneration in the atrophic spinal cord is associated with upper limb function and parallels cranial CST degeneration. (Freund, Schneider et al., 2012) In our study, the extent of the lesion in the spinal cord, in the form of the lesion length on conventional MRI, was associated with remote cerebral degeneration. In addition, although many previous studies have demonstrated a link between spinal DTI values and clinical scores, we have demonstrated for the first time to the best of our knowledge an association between cerebral DTI changes and clinical disability after SCI. Consistent with the findings in the area of the spinal cord, FA decreased and ADC increased together with increasing disability.

## 6.5 Strengths and Limitations

In this thesis, detailed clinical data were collected from patients with acute and chronic SCI according to international recommendations. In the epidemiological study, the evaluation of patients by specialists in the field minimized the risk of false positive cases that may be included in retrospective register studies.



Concomitantly, the risk of missing cases was reduced, at least in the areas of the Oulu and Tampere UH districts, with integrated trauma and SCI centers, in which all patients with suspected SCI come to the attention of the physicians working in the SCI units. In addition, the epidemiological study in two of three SCI centers in Finland provided good national coverage despite the missing data from Helsinki UH. However, the study period was short, and the incidence rates did not include patients who died prior to hospital admission.

In our DTI studies, the cardiac gating technique was not used to image of the spinal cord. It would have diminished corticospinal fluid flow-related artifacts but concurrently lengthened the acquisition time and increased the number of artifacts caused by swallowing and respiratory movements. In general, better spatial resolution would have increased the specificity of the characterization of individual spinal cord columns. For example, the possibility of examining the dorsal columns separately could have provided a more accurate indication of sensory function in our patient population. However, that procedure would have required a longer acquisition time, which may not have been reasonable considering the patients in question, especially the most disabled patients. Moreover, the reproducibility of the ROI method is good for spinal measurements and is easy to apply in clinical practice. In addition, measurements for the area of whole cord ROIs appeared to result in clinically relevant DTI metrics, even if the measurement area also included grey matter.

In the area of the cerebral CST, we again used the ROI with an a priori hypothesis to explore SCI-induced changes. However, the evidence suggests that SCI can cause other significant cerebral changes beyond this descending tract (Wrigley et al., 2009), but these changes could not be verified in the present study. In addition, the small ROIs represent only a part of the area in question, and possible pathological changes may remain outside the measurement area. Moreover, it was not possible to definitively separate the motor and sensory tracts travelling next to each other in some cerebral areas, complicating the interpretation of the results. However, the repeatability of the method was also good in this area.

The mean ages of our healthy subjects were relatively low, and the age range was limited when considering the progressively aging patient population with SCI in Finland, which likely diminished the effect of age on DTI values in our results. However, the subjects in our present series were enrolled in an age- and sex-stratified manner to obtain one of the largest and most presentable series of healthy spinal cord DTI data published.

Our patient population with chronic SCI was larger than those in previous DTI studies and provided a wide range of age and neurological disabilities that represent the entire spectrum of adult tetraplegic SCI patients. In fact, the mean age of the

patients with chronic SCI in Studies III and IV ( $58 \pm 19.8$  years) corresponds well to the mean age of patients with acute SCI ( $57.5 \pm 14.5$ ) in our recent epidemiological study (Study I). In addition, the proportions of AIS A (motor and sensory complete) and AIS D (motor and sensory incomplete) injuries in those populations were quite similar to one another: 29.4% AIS A and 52.9% AIS D in the patients in Studies III and IV versus 18.2% AIS A and 50.6% AIS D in the patients in Study I.

The broad spectrum of patients could also be regarded as a weakness of the study when considering factors that could have affected the cerebral DTI values. For example, although patients with other known neurological diseases and injuries were excluded from the study, our patient population included a few subjects with moderate-to-severe microangiopathy, and the presence of undiagnosed TBI could not be excluded based on MRI findings. However, TBI and microangiopathy-related abnormalities on the MRI are ordinary for the patient and age group in question, and except for microangiopathy, the abnormalities were not located in the area of the DTI measurements. Although the wide range of neurological disabilities in our patient population probably aided in the identification of clinical correlations, a greater number of patients with complete injuries may have resulted in more changes in the DTI with respect to the healthy controls, at least in the cerebral area.

Another weakness of our study was that our patient and control populations were not age- or gender-matched. However, the confounding effects of age and gender were addressed using statistical methods. In addition, considering spinal measurements, the presumptive effect of age on DTI values was small compared to the effect of injury.

In general, the greatest limitation to the applicability of our DTI results for clinical needs, for example in predicting the outcome after injury, was that our patient population included only patients with chronic SCI and that the demonstrated DTI changes reflected a relatively stable situation after injury. Therefore, likely in concordance with previous studies of chronic SCI patients (Freund, Wheeler-Kingshott et al., 2012; Wrigley et al., 2009), we did not detect a statistically significant correlation between DTI parameters and the time since injury in our patient population. In a recent study evaluating spinal cross-sectional area and cerebral volumetric changes following an acute SCI, progressive atrophy of the CST was demonstrated to occur during the first year after injury, and that change was related both to time and clinical improvement (Freund et al., 2013). However, the preceding studies with chronic patients provide a good foundation for needed corresponding studies in the field of DTI.

## 6.6 Future Perspectives

Further follow-up of SCI epidemiology in Finland is necessary to confirm our results for the first year after centralization of SCI care. Including the data from the third SCI center in Helsinki UH will expand the catchment area to encompass the entire country. The national SCI register is currently under active development and will likely facilitate the future follow-up of incidence and epidemiological features. The information provided by the register could also be used over the long term to monitor the impact of possible preventive measures. Moreover, with thorough information regarding the health of patients with SCI, the register will aid the development of patient care. To reveal the true incidence of TSCI in Finland, the number of patients who died at the scene of the accident must be explored separately in the future.

Our results for both spinal and cerebral DTI studies suggest that DTI can noninvasively link neural structure and clinical function in chronic SCI. In experimental studies, acute changes in DTI have been shown to help predict functional recovery (J. H. Kim et al., 2010). In humans, few studies have been conducted to examine the relationship between DTI values and clinical deficits in acute SCI (Cheran et al., 2011; Vedantam, Eckardt, Wang, Schmit, & Kurpad, 2014). However, additional evidence, especially longitudinal studies, are needed in the future to evaluate the presumptive change in DTI values with time after an acute injury and the association of that change with clinical recovery. This knowledge would facilitate the prognostication of recovery and our understanding of and ability to monitor the changes induced by treatment and rehabilitative interventions beyond ISNCSCI and conventional MRI. In daily practice, this information could aid in the development of rehabilitation goals consistent with the anticipated recovery and thus improve the effectiveness and efficiency of costly sub-acute rehabilitation. However, it should be noted that group level results in screened research populations are not directly applicable to individual clinical cases.

In the near future, it would also be interesting to explore the cerebral white matter tracts beyond CST and small ROIs in our patient population using TBSS, which has recently become available in our institution. In addition, analyses of the directional diffusivities from cerebral white matter areas could yield more detailed information regarding trauma-induced microstructural changes in the brain after SCI.

## 7. CONCLUSIONS AND MAIN FINDINGS

Based on the present results, the following conclusions can be made.

- 1) The incidence of TSCI was 25.1 per million people for all patients admitted to the Oulu and Tampere SCI centers and 38.1 per million people for the hospital districts of the Oulu and Tampere UHs.
- 2) The incidence of TSCI was extremely high among patients over 60 years of age, and the majority of these patients were injured by simple falls that resulted in an incomplete cervical injury. In the younger patient group, alcohol contributed to a high proportion of injuries, especially among young males.
- 3) Spinal DTI values that were measured using the ROI method in healthy adult populations depended on the measurement level. There were also significant changes in directional diffusivities between the dorsal and lateral white matter columns of the spinal cord. The effect of age on spinal DTI values was minimal in our population of healthy subjects under 60 years of age, and no gender differences were found. The intra- and interobserver reproducibility of the spinal measurements varied from good to excellent
- 4) In patients with chronic SCI, DTI detected pathological changes in spinal white matter areas. The extent of these changes had a significant relationship with parameters that are used clinically to assess neurological deficits and disability after SCI. DTI indices measured from whole cord area remotely from the primary site of the injury provided clinically relevant information about the condition of the nerve fiber tracts.
- 5) After SCI, DTI detected pathological changes in cerebral white matter areas also. These DTI abnormalities were associated both with the clinical state of the patient and the extent of the macroscopic lesions in the spinal cord detected by conventional MRI.

In summary, the main implications are listed below.

- 1) The incidence of TSCI in Finland was significantly higher than expected. The centralization of SCI care appeared to have resulted in a comprehensive patient sample, particularly in the hospital districts with SCI centers. However, a proportion of the differences in incidence rates between earlier estimates and our study were due to different study populations and methods.
- 2) The epidemiological characteristics of patients with TSCI in this study confirmed the trends observed in previous studies in Finland. This description could be utilized in developing care practices, in planning resources required for the proper operation of newly appointed and emerging SCI centers and in implementing preventive measures to control the increasing burden of TSCI in Finland.
- 3) To correctly interpret the patient-derived DTI metrics either in research or in clinical settings, it is important to compare them with the normative values that are measured in the corresponding spinal level and area and, at least in older patients, from healthy subjects with the same ages as the patients.
- 4) DTI can provide quantitative and objective information about the state of the central nervous system in a noninvasive manner, linking structure and clinical function in chronic SCI. The observed spinal and cerebral post-injury DTI changes were most likely due to degeneration, and in general, the FA value seemed to be the most sensitive parameter for the detection of that microstructural pathology. The method used for the spinal measurements minimized the effect of fixation materials and bone/soft tissue injuries that can complicate neuroimaging and image analysis close to the level of the lesion.

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## 120

[illegible]

## Muscle Function Grading

- 0 = total paralysis
- 1 = palpable or visible contraction
- 2 = active movement, full range of motion (ROM) with gravity eliminated
- 3 = active movement, full ROM against gravity
- 4 = active movement, full ROM against gravity and moderate resistance in a specific position
- 5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person
- 5\* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, edema) were not present
- NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal range of motion)

## Sensory Grading

- 0 = Absent
- 1 = Altered, either decreased/impaired sensation or hypersensitivity
- 2 = Normal
- NT = Not testable

## Non Key Muscle Functions (optional)

May be used to assign a motor level to differentiate AIS B vs. C

Movement	Root level
<b>Shoulder:</b> Flexion, extension, abduction, adduction, internal and external rotation	<b>C5</b>
<b>Elbow:</b> Supination	
<b>Elbow:</b> Pronation	<b>C6</b>
<b>Wrist:</b> Flexion	
<b>Finger:</b> Flexion at proximal joint, extension, Thumb: Flexion, extension and abduction in plane of thumb	<b>C7</b>
<b>Finger:</b> Flexion at MCP joint	
<b>Thumb:</b> Opposition, adduction and abduction perpendicular to palm	<b>C8</b>
<b>Finger:</b> Abduction of the index finger	<b>T1</b>
<b>Hip:</b> Adduction	<b>L2</b>
<b>Hip:</b> External rotation	<b>L3</b>
<b>Hip:</b> Extension, adduction, internal rotation	<b>L4</b>
<b>Knee:</b> Flexion	
<b>Ankle:</b> Inversion and eversion	
<b>Toe:</b> MP and IP extension	
<b>Hallux and Toe:</b> DIP and PIP flexion and abduction	<b>L5</b>
<b>Hallux:</b> Abduction	<b>S1</b>

## ASIA Impairment Scale (AIS)

**A = Complete.** No sensory or motor function is preserved in the sacral segments S4-S5.

**B = Sensory Incomplete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch or pin prick at S4-S5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

**C = Motor Incomplete.** Motor function is preserved below the neurological level\* and more than half of key muscle functions below the neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

**D = Motor Incomplete.** Motor function is preserved below the neurological level\*, and at least half (half or more) of key muscle functions below the NLI have a muscle grade  $\geq 3$ .

**E = Normal.** If sensation and motor function at least with the SNI/S4-S5 are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

\* For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The International Standards at this time allow even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for differentiating between AIS B and C, the **motor level** in each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the **neurological level of injury** is used.



## Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

- Determine sensory levels for right and left sides.**  
The sensory level is the most caudal intact dermatome for both pin prick and light touch sensation.
- Determine motor levels for right and left sides.**  
Defined by the lowest key muscle function that has a grade of at least 3 (on same testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).  
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level. If testable motor function above that level is also normal.
- Determine the neurological level of injury (NLI)**  
This refers to the most caudal segment of the cord with intact sensation and integrity (3 or more) muscle function strength, provided that there is normal intact sensory and motor function rostrally respectively.  
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
- Determine whether the injury is Complete or Incomplete.**  
i.e. absence of presence of Sacral Sparing  
If sensory and motor function is normal at S4-S5 sensory scores = 0 AND no motor function is preserved more than three levels below the NLI, then injury is **Complete**.  
Otherwise, injury is **Incomplete**.

## 5. Determine ASIA Impairment Scale (AIS) Grade:

**Is Injury Complete?** If YES, AIS=A and can record 27% lowest dermatome or myotome on each side with some preservation)  
**NO** ↓

**Is Injury Motor Complete?** If YES, AIS=B

**NO** ↓ (No-voluntary and contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?





ORIGINAL ARTICLE

# Centralized spinal cord injury care in Finland: unveiling the hidden incidence of traumatic injuries

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**Study design:** Population-based prospective study.

**Objectives:** To determine the incidence and evaluate the characteristics of newly injured patients with traumatic spinal cord injury (TSCI) admitted to two of the three national spinal cord injury (SCI) centers during the first year after the centralization of SCI care in Finland.

**Setting:** Oulu and Tampere University Hospital SCI centers, Finland.

**Methods:** The designated rehabilitation teams evaluated all of the patients with a new SCI and persisting neurological symptoms. The data were recorded according to the International Spinal Cord Injury Core Data Set.

**Results** In a 1-year period, 77 new patients with TSCI were admitted to the study centers serving a population of 3 065 946. In the whole catchment area, the mean annual incidence of TSCI was 25.1 per million, and in the hospital districts of the SCI centers, the incidence was even higher, at 38.1 per million. The mean age of the patients was 58.7 years. Falls were the leading cause of injury (64.9%), and the injury resulted in tetraplegia in 70.1% of the cases. Alcohol use was a contributing factor in 39% of the cases in the entire sample and in 58.6% of cases among patients aged younger than 60 years.

**Conclusion** The incidence rates of TSCI were markedly higher than expected, demonstrating the previously hidden morbidity. The epidemiological features of TSCI appeared to follow the trends in developed countries, highlighting the increasing incidence of cervical lesions due to falling among the elderly. The results need to be confirmed in an extended follow-up.

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## INTRODUCTION

Finland is a quite large and relatively sparsely populated Nordic country (303 891 km<sup>2</sup>, 5.4 million inhabitants), and its health care system is primarily public and financed by taxes. Traffic and occupational injuries are covered by the private insurance system, but the acute phase of severe injuries such as spinal cord injuries (SCIs) is always treated in public hospitals. Previously, the acute care and possible surgical management of new patients with SCI in Finland was divided into 21 different hospital districts responsible for organizing the specialized medical care. After acute care, some SCI patients, primarily those of the working-age, were referred to the private Käpylä Rehabilitation Centre. The rehabilitation of the remaining patients was performed primarily in the rehabilitation units of local hospitals or health centers with variable resources and protocols. In addition, depending on the area of Finland, there are wide variations in organizing the life-long follow-up, varying from follow-up at multidisciplinary SCI outpatient clinics to non-existent follow-up.

Internationally specialized SCI centers have been established to improve the care and recovery of the patients with SCI. Integrated multidisciplinary specialized SCI centers are supported by the tentative research data and expert panel recommendations to decrease the length of stay, overall mortality, and number and severity of complications.<sup>1,2</sup> To alter the heterogeneous and fragmented situation of SCI care in Finland, the patient organization has stressed the need to follow

international recommendations to centralize SCI care in integrated multidisciplinary SCI units with adequate resources. After years of effort, the new Health Care Act also contained a decree to centralize highly specialized medical care, including SCI care.<sup>3</sup> The decree took effect on 1 May 2011. The acute care, subacute rehabilitation and life-long follow-up of patients with SCI were centralized into three University Hospitals (UHs): Helsinki, Oulu and Tampere. A national SCI care advisory board, containing representatives from all five university hospitals and a patient organization, was established to guide the practical execution of the decree.

After the decree of centralization was issued, the epidemiology of SCI was of great importance in organizing the service and allocating the facilities and other resources in the SCI centers. However, there is no SCI registry in Finland, and only one report about the incidence of traumatic SCI (TSCI) was published in the past two decades. Ahoniemi *et al.*<sup>4</sup> reported an annual incidence rate of 13.8 per million in the population aged 16 years or older based on the data from the records of Käpylä Rehabilitation Centre over the period between 1976 and 2005. Studies from other Nordic countries have reported an annual incidence of TSCI reaching 9.2 per million inhabitants per year in Denmark,<sup>5</sup> 19.5 in the greater Stockholm region in Sweden,<sup>6</sup> 26.3 in western Norway<sup>7</sup> and 33.5 in Iceland.<sup>8</sup>

The aim of this study was to obtain population-based epidemiological and outcome data for medical care and follow-up planning as well as for preventive initiatives. Furthermore, our intention was to

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monitor the implementation of centralized care throughout the catchment areas.

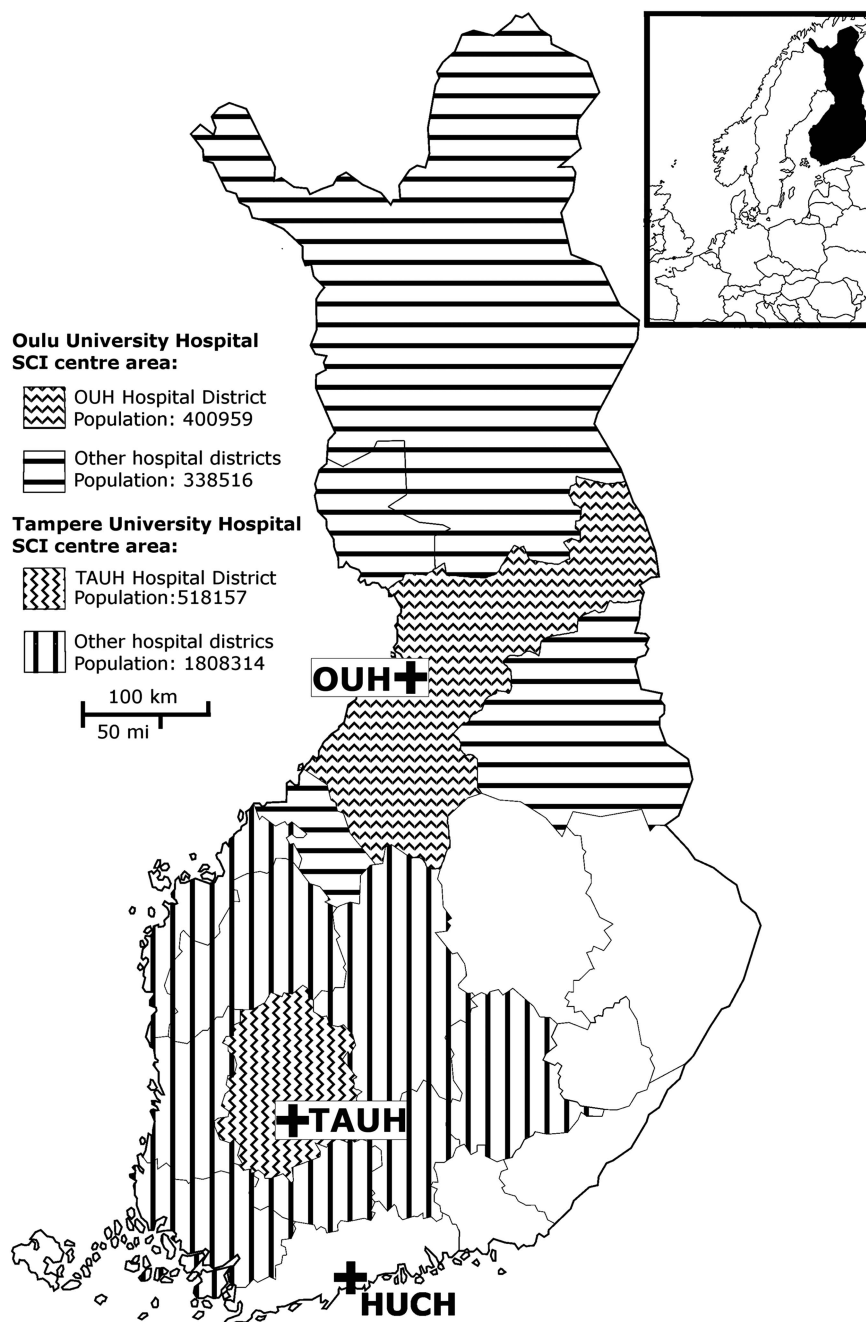
## MATERIALS AND METHODS

### Design

The study was a prospective 1-year population-based epidemiological study in two of the three newly appointed SCI centers in Finland, which covered 3 065 946 (56.5% of the population) individuals in all age groups during the study period. All patients with SCI caused by an external force were included in this study. Patients with non-traumatic etiologies were excluded.

Both the Oulu and Tampere UHs have previously provided general neurorehabilitation and used outpatient follow-up clinics for SCI patients for many years. These resources have now been increased, although Käpylä Rehabilitation Centre is still being used for some selected patients after the acute period and following evaluation in SCI centers. These rehabilitation periods were included in the study. The study areas and population are described in Figure 1.

Evaluation of new SCI patients admitted to these centers according to the International Spinal Cord Society (ISCoS) Core Data Set principles started in Tampere UH on 1 January 2012 and in Oulu UH on 1 May 2012. The results of the first year after starting the protocol are presented; Tampere UH: 1



**Figure 1** Finland is divided into 20 hospital districts in the mainland and one on the autonomous Åland Islands. The districts are responsible for specialized health care (tertiary care) and are municipality financed and governed. Five of these hospital districts are university hospital districts supporting the central hospital districts in their region and also providing government-defined highly specialized medical care. Spinal cord injury care is centralized in the university hospitals in Helsinki (HUCH), Oulu (OUH) and Tampere (TAUH).

January 2012 to 31 December 2013 and Oulu UH: 1 May 2012 to 30 April 2013. Currently, data from the third SCI center in Helsinki University Central Hospital are missing because the unit was opened only in the second half of the year 2013 in the form of an outpatient clinic.

Following institutional and governmental regulations, study approval was obtained from both the UH administrations. Ethics committee approval was not required, as all data were collected during the standard practice.

### Subjects and procedure

In both SCI centers, a multidisciplinary SCI rehabilitation team is routinely informed of all patients admitted to the hospital with a new SCI and persisting neurological symptoms, regardless of the cause, level or completeness of injury. However, this practice does not apply to patients with progressive neurological diseases, such as multiple sclerosis or amyotrophic lateral sclerosis. The consultant specialist physician of the SCI unit with the support of rehabilitation team performs the clinical evaluation and assessment to plan and initiate the rehabilitation and follow-up program.

The Oulu and Tampere UHs are the only trauma, intensive care, neurosurgery and spine surgery units in their own hospital districts, serving a population of 400 959 in Oulu and 518 157 in Tampere (Figure 1). Thus, all newly injured SCI patients in these hospital districts should come to the attention of these SCI centers. When considering the entire catchment area of SCI centers, there are several trauma and intensive care units, and referral to the SCI centers is less certain.

### Collection of clinical data

The International Standards for Neurological Classification of Spinal Cord Injury<sup>9</sup> were used to evaluate and classify the neurological consequence of SCI, and epidemiological characteristics were collected and classified using the International SCI Core Data Set.<sup>10</sup> In addition, the ability to move at the time of discharge was classified into six categories, and the influence of alcohol at the time of the injury was retrospectively recorded from the medical records.

### Statistical analyses

The incremental number of TSCI cases in all age groups and their clinical features over a consecutive 12-month follow-up period are reported in this article. Data were analyzed as a whole, but further comparisons were also drawn with regard to age and hospital district. Continuous variables are presented as the mean, (s.d.) and median (range). The Mann–Whitney test was used to calculate the differences between patient groups. For categorical variables, the number and percentage are shown, and the differences between groups were examined by Fischer's exact test. Statistical significance was set at  $P < 0.05$ . Incidence rates were calculated using the population on 31 December 2012 according to the Official Statistics of Finland.<sup>11</sup> SPSS version 20.0 (IBM, Armonk, NY, USA) was used to perform all of the statistical analyses.

## RESULTS

### Incidence

The incidence of TSCI is shown in Table 1. In the 1-year period, 77 new patients with TSCI were admitted to the Oulu and Tampere UH SCI centers. Of those patients, 35 were residents of the Tampere and Oulu UH's own hospital districts and 42 were referred from other hospital districts in the catchment area of the SCI centers. The annual incidence of TSCI patients in the entire catchment area was 25.1 per million, and that in the age group over 16 years was 29.8 per million in the subgroup population of 2 516 942 people. In the hospital districts of the Oulu and Tampere UHs with integrated trauma and SCI centers, the incidence was 38.1 per million inhabitants, and in the age group over 16 years, the incidence was 46.0 per million in the subgroup population of 739 338 people. There were only two cases of TSCI in the age group under 16 years presenting incidence of 3.6 per million in the population of 549 004.

**Table 1 Annual incidence of TSCI patients referred to two of the three SCI centers in Finland and the severity of the injuries**

	All	Hospital districts of Oulu and Tampere UH	Other hospital districts in the SCI centers catchment area
Population	3 065 946	919 116	2 146 830
Number of cases	77	35	42
Incidence/million	25.1	38.1	19.6
<i>Neurological category (%)</i>			
Ventilator dependent	4 (5.2)	2 (5.7)	2 (4.8)
C1–C4 AIS A, B, C	13 (16.9)	3 (8.6)	10 (23.8)
C5–C8 AIS A, B, C	4 (5.2)	2 (5.7)	2 (4.8)
T1–S5 AIS A, B, C	12 (15.6)	5 (14.3)	7 (16.7)
All AIS D	39 (50.6)	19 (54.3)	20 (47.6)
AIS E	2 (2.6)	2 (5.7)	—
Unknown	3 (3.9)	2 (5.7)	1 (2.4)

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; AIS A, motor–sensory complete; AIS B, motor complete–sensory incomplete; AIS C–D, motor–sensory incomplete; AIS E, normal examination; SCI, spinal cord injury; TSCI, traumatic spinal cord injury; UH, University Hospital.

### Characteristics of TSCIs

The epidemiological characteristics of the TSCI patients, the treatment periods, the outcomes and the comparisons between groups are shown in Table 2. Of all TSCI patients, 52 were male and 25 were female, giving a male-to-female ratio 2.1/1. The mean age at injury was 58.7 years, and falls were the leading cause of injury (64.9%), followed by transportation accidents (18.2%). The injury resulted in tetraplegia in 70.1% of cases and paraplegia in 29.9%. The place of discharge was most often a private residence, and 44.6% of the patients were able to walk without or with equipment at the time of discharge. The distributions of the place of discharge and the ability to move at the time of discharge differed significantly when comparing patients from the Oulu and Tampere UH's own hospital districts with patients referred from other hospital districts. The patients from Oulu and Tampere UH's own hospital districts were mainly discharged directly to the private residence (71.4%), whereas other hospital was the most prevalent place of discharge for the group of patients from other hospital districts (45.2%). In the same study groups, the proportions of patients able to walk without assistive devices at the time of discharge were 45.5% and 17.1%, respectively.

### Effect of age on injury characteristics

Of the patients with TSCI, 29 individuals were younger than 60 years and 48 were  $\geq 60$  years of age giving the incidence of 12.9 per million and 58.3 per million in the populations of 2242 163 and 823 783, respectively. (Table 2) The male-to-female ratio was higher among the younger age group (2.6/1) than in the older (1.8/1). In relation to the etiology of injury, the neurological level of injury, the total days hospitalized and the place of discharge, there was a statistically significant difference between patient groups by age. In the patient group  $\geq 60$  years of age, 85.4% were injured by falling, whereas among younger patients, transportation comprised 37.9% and falls 31.0% of the external causes of injury. In the older age group, 81.3% were tetraplegic, whereas in the younger age group, the distribution between tetra- and paraplegia was even. In the age group  $\geq 60$  years of age among the patients with tetraplegia, 72.2% had a high cervical neurological lesion (C1–C4). In the group of patients  $< 60$  years of



**Table 2** Epidemiological characteristics, treatment periods and outcomes of new patients with TSCI in two of the three SCI centers in Finland over a 1-year follow-up period

	All	Hospital districts of Oulu and Tampere UH	Other hospital districts in the SCI centers catchment area	P-value	Under 60	Over 60	P-value
Population	3 065 946	919 116	2 146 830		2 242 163	823 783	
Number of cases	77	35	42		29	48	
Gender (male/female)	2.1/1	1.9/1	2.2/1	0.810	2.6/1	1.8/1	0.617
Age at injury, Mean $\pm$ s.d.	58.7 $\pm$ 19.8	55.7 $\pm$ 20.1	61.2 $\pm$ 19.4		37.8 $\pm$ 15.4	71.3 $\pm$ 7.8	
Median (range)	63.4 (2.8–89.5)	62.3 (6.3–78.2)	64.5 (2.8–89.5)	0.192	41.3 (2.8–59.6)	70.4 (60.2–89.5)	<b>0.000</b>
<i>Injury etiology (%)</i>							
Sports	6 (7.8)	1 (2.9)	5 (11.9)		6 (20.7)	—	
Assault	1 (1.3)	1 (2.9)	—		1 (3.4)	—	
Transport	14 (18.2)	6 (17.1)	8 (19.0)		11 (37.9)	3 (6.3)	
Fall	50 (64.9)	24 (68.6)	26 (61.9)		9 (31.0)	41 (85.4)	
Other traumatic cause	6 (7.8)	3 (8.6)	3 (7.1)	0.526	2 (6.9)	4 (8.3)	<b>0.000</b>
Vertebral injury (%)	64 (83.1)	27 (77.1)	37 (88.1)	0.234	23 (79.3)	41 (85.4)	0.539
Associated injury (%)	9 (11.7)	4 (11.4)	5 (11.9)	1.000	5 (17.2)	4 (8.3)	0.285
Spinal surgery (%)	72 (93.5)	31 (88.6)	41 (97.6)	0.171	27 (93.1)	45 (93.8)	1.000
<i>Neurological level of injury (%)</i>							
Tetraplegia	54 (70.1)	23 (65.7)	31 (73.8)		15 (51.7)	39 (81.3)	
Paraplegia	23 (29.9)	12 (34.3)	11 (26.2)	0.464	14 (48.3)	9 (18.8)	<b>0.010</b>
C1–C4	34 (44.2)	12 (34.3)	22 (52.4)		8 (27.6)	26 (54.2)	
C5–C8	15 (19.5)	8 (22.9)	7 (16.7)		6 (20.7)	9 (18.8)	
T1–T12	18 (23.4)	9 (25.7)	9 (21.4)		10 (34.5)	8 (16.7)	
L1–S5	5 (6.5)	3 (8.6)	2 (4.8)	0.509	4 (13.8)	1 (2.1)	<b>0.026</b>
Unknown	5 (6.5)	3 (8.6)	2 (4.8)		1 (3.4)	4 (8.3)	
<i>ASIA Impairment Scale (%)</i>							
AIS A	14 (18.2)	3 (8.6)	11 (26.2)		6 (20.7)	8 (16.7)	
AIS B	12 (15.6)	5 (14.3)	7 (16.7)		5 (17.2)	7 (14.6)	
AIS C	7 (9.1)	4 (11.4)	3 (7.1)		2 (6.9)	5 (10.4)	
AIS D	39 (50.6)	19 (54.3)	20 (47.6)		16 (55.2)	23 (47.9)	
AIS E	2 (2.6)	2 (5.7)	—	0.178	—	2 (4.2)	0.897
Unknown	3 (3.9)	2 (5.8)	1 (2.4)		—	3 (6.3)	
<i>Total days hospitalized</i>							
Mean $\pm$ s.d.	70.5 $\pm$ 59.0	71.8 $\pm$ 66.4	69.4 $\pm$ 52.9		90.1 $\pm$ 66.9	58.6 $\pm$ 50.8	
Median (range)	60.0 (2–273)	46.0 (2–273)	63.5 (4–170)	0.984	104.0 (2–273)	40.5 (4–199)	<b>0.046</b>
<i>Days in ICU</i>							
Mean $\pm$ s.d.	<i>n</i> = 44 10.6 $\pm$ 17.3	<i>n</i> = 15 9.4 $\pm$ 11.8	<i>n</i> = 29 11.2 $\pm$ 19.8		<i>n</i> = 14 15.7 $\pm$ 27.4	<i>n</i> = 30 8.2 $\pm$ 9.6	
Median (range)	3.5 (1–106)	3.0 (1–35)	4.0 (2–106)	0.772	4.0 (2–106)	3.0 (1–35)	0.182
<i>Place of discharge (%)</i>							
Private residence	41 (53.2)	25 (71.4)	16 (38.1)		23 (79.3)	18 (37.5)	
Hospital	24 (31.2)	5 (14.3)	19 (45.2)		2 (6.9)	22 (45.8)	
Nursing home	4 (5.2)	1 (2.9)	3 (7.1)		—	4 (8.3)	
Assisted living residence	5 (6.5)	2 (5.7)	3 (7.1)		4 (13.8)	1 (2.1)	
Group living situation	—	—	—		—	—	
Deceased	3 (3.9)	2 (5.7)	1 (2.4)	<b>0.010</b>	—	3 (6.3)	<b>0.000</b>
<i>The ability to move at the time of discharge (%)</i>							
Walking without equipments	( <i>n</i> = 74) 22 (29.7)	( <i>n</i> = 33) 15 (45.5)	( <i>n</i> = 41) 7 (17.1)		( <i>n</i> = 29) 10 (34.5)	( <i>n</i> = 45) 12 (26.7)	
Walking with a stick or crutches	6 (8.1)	3 (9.1)	3 (7.3)		4 (13.8)	2 (4.4)	
Walking with a walker	5 (6.8)	—	5 (12.2)		1 (3.4)	4 (8.9)	
Using a wheelchair	29 (39.2)	12 (36.4)	17 (41.5)		11 (37.9)	18 (40.0)	
Using an electric wheelchair	7 (9.5)	2 (6.1)	5 (12.2)		2 (6.9)	5 (11.1)	
Bed patient	5 (6.8)	1 (3.0)	4 (9.8)	<b>0.046</b>	1 (3.4)	4 (8.9)	0.600

Abbreviations: ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; AIS A, motor–sensory complete; AIS B, motor complete–sensory incomplete; AIS C–D, motor–sensory incomplete; AIS E, normal examination; ICU, intensive care unit; TSCI, traumatic spinal cord injury UH, University Hospital.  
Comparisons between patient groups according to the hospital district and age.  
P-values <0.05 in bold and underlined.

age, 79.3% of the subjects were discharged home or to another private residence; in the age group  $\geq 60$  years, 37.5% were discharged to a private residence and 45.8% to another hospital.

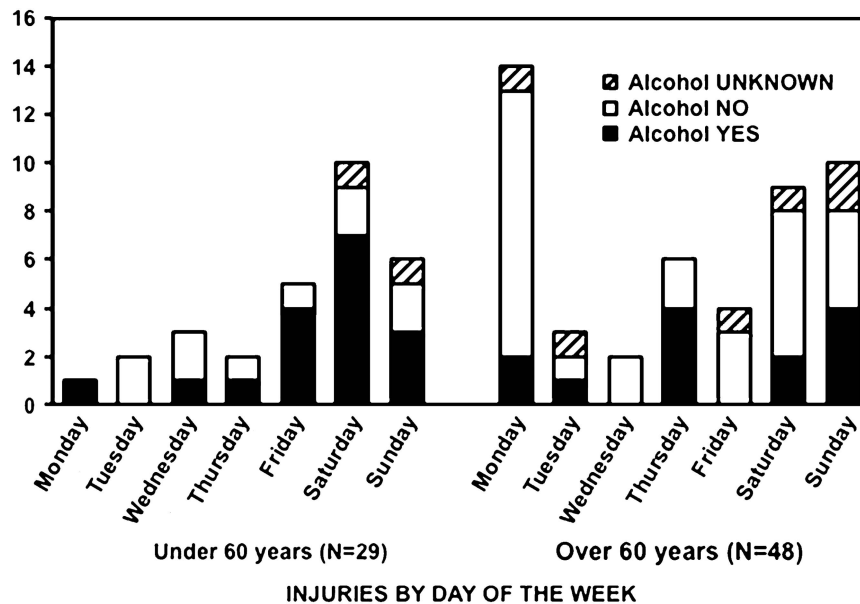
In addition, the patient groups exhibited statistically significant differences regarding alcohol consumption before the injury ( $P=0.013$ ). In the group of younger patients, 58.7% were injured under the influence of alcohol, whereas in the age group  $\geq 60$  years,

the figure was 27.1%. The peak days for occurrence in the younger group of patients were Friday to Sunday, during which over 70% of the injuries took place (Figure 2).

## DISCUSSION

The first year of centralized spinal cord care in Finland revealed a significantly higher incidence of TSCIs than expected, demonstrating





**Figure 2** Consumption of alcohol before injury in relation to the number of injuries by day of the week in traumatic spinal cord injury (TSCI) patients younger and older than 60 years.

the previously hidden morbidity. The annual incidence of TSCI in the entire catchment area was 25.1 per million; in the UH districts with integrated trauma and SCI centers, the incidence exceeded this, being 38.1 per million. The incidences in the population over 16 years were 29.8 and 46.0, respectively, being two- to threefold greater than that reported in a previous study from Finland, in which the incidence in this age group was 13.8 per million.<sup>4</sup>

When observing all age groups, the numbers in the entire catchment area are comparable to those in recent retrospective incidence reports from Norway and Iceland, at 26.3 and 33.5 per million inhabitants, respectively.<sup>7,8</sup> In addition, the incidence found in our study corresponds very well with the recently reported TSCI incidence estimate for Finland of 24.8 per million, which was based on a population-based regression model.<sup>12</sup> The incidence of TSCI in the hospital districts with integrated trauma and SCI centers, at 38.1 per million inhabitants, approaches the average incidence of 40 per million reported in the United States<sup>13</sup> and the recently published incidence estimate of 41 per million for Canada.<sup>14</sup>

The incidence in the hospital districts with SCI centers was twice as high as the incidence in the other hospital districts, at 19.6 cases per million, which referred patients to the study centers. There are some differences in the demographic characteristics of the populations, for example, the proportion of urban residents in the hospital districts. However, the most likely reasons behind the differences in the incidence are the incompleteness of centralized care and the more precise screening of acute trauma patients in SCI centers. These assumptions are supported by the slight, although not significant, difference in the ASIA Impairment Scale distribution and the lower proportion of independent walkers at discharge of the patients referred from other hospital districts. Most likely, the increasing awareness of spinal injuries among hospital staff and the systematic screening of new patients suspected of having SCI in established SCI centers has enhanced the identification of SCIs, particularly among patients with milder manifestations, revealing the hidden morbidity. Regardless of the degree of centralization, some patients from other hospitals may not have been referred to the SCI centers, for example, due to advanced age or minor motor disabilities. Differing procedures

between SCI centers and other hospitals result in different distributions of injury severity indicators, such as ASIA Impairment Scale and walking ability, and are also reflected in the place of discharge. The same reasons are those that are most likely behind the difference between our results and the previous report of Käpylä Rehabilitation Centre.<sup>4</sup> This hypothesis is also supported by our present finding of the increase in the mean age of occurrence from 42 years in a previous study<sup>4</sup> to 58.7 years in our study.

Although the change in the mean age may in part reflect the differences in the selected study samples, the recent literature has also shown an increasing age at injury as well as an increasing proportion of cervical injuries and injuries due to falls.<sup>8,13,15,16</sup> A similar tendency has been observed in Finland in recent decades.<sup>4,17</sup> In our entire TSCI cohort, 64.9% of the patients were injured by falling and 70.1% were tetraplegic, supporting the trends reported in previous studies. Moreover, in the age group  $\geq 60$  years in our study, over 80% of the patients were tetraplegic, and the number of upper cervical injuries (C1–C4) was almost threefold the number of lower cervical lesions. A similar tendency toward cervical injuries above C5 after the sixth decade has been detected previously.<sup>16,18</sup>

Interestingly, in our study, 85.4% of the patients 60 years of age or older were injured by falling, whereas patients under 60 years of age were primarily injured either in transportation accidents or by falling, which have traditionally been the main mechanisms of injury in the developed countries.<sup>19–21</sup> The increasing age-adjusted incidence of fall-induced fracture-associated spinal injuries in elderly persons has been observed previously in Finland.<sup>17</sup> Together with the aging of the population, this will challenge the health and support services, and older patients also have an increased frequency of complications and poorer prognosis.<sup>22</sup> As an illustration of the challenge, the place of discharge differed between the age groups in our study despite equivalence in the completeness of injuries and in the ability to move at the time of discharge from the SCI center. Almost 80% of the patients aged younger than 60 years were discharged home directly after treatment in an SCI center, whereas 45.8% of the patients aged 60 years or older required a subsequent stay in another hospital before discharge home or to an assisted living residence. These findings

emphasize the definitive need to target preventive measures against falls in elderly people.

In the younger patient groups, one of the key prevention areas should consider certain activities, such as driving and swimming, under the influence of alcohol. In our study, almost two-thirds of the patients younger than 60 years were injured under the influence of alcohol. When considering the entire sample, 39% of the injuries were contributed by alcohol use. This is a similar proportion to that previously reported in Estonia,<sup>23</sup> whereas a study from the USA has reported the presence of alcohol to be a contributing factor to injury in nearly 50% of cases tested.<sup>24</sup> In addition, patients younger than 60 years of age were injured more often during weekends, most likely reflecting the prevailing binge drinking habits in Finland.<sup>25</sup>

The definitive strength of this study is the systematic clinical evaluation of all the new SCI patients according to the International SCI Core Data Set by specialist rehabilitation doctors working in SCI units. This practice both minimizes the risk of false-positive cases and leads to a low likelihood of missing cases, particularly in hospital districts with integrated trauma and SCI centers, as patients with milder injuries are also examined by specialists in the field. Although data from the Helsinki University Central Hospital were not available, the conduct of the study in two of the three SCI centers in Finland provides a good national coverage.

The major limitation of this study is the short 1-year study period. Therefore, a further follow-up to confirm the findings is necessary. Second, our data were based on the individuals admitted to the hospital and patients who died at the scene of the accident were not included, and this needs to be explored separately in the future. Thus, the incidence found in this study most likely represents the lower limit of the TSCI incidence.

Centralization of care resulted in a comprehensive SCI patient sample in the hospital districts with SCI centers, although centralization needs to be promoted in other hospital districts. The incidence rates of TSCI were surprisingly high, indicating the previously hidden morbidity. The epidemiological features of TSCI follow the trends of other developed countries, emphasizing the need to target prevention strategies toward fall prevention in the elderly and alcohol-related injuries in the younger population. The results need to be confirmed over an extended study period. The national SCI register is currently under development and will hopefully aid future follow-up of the epidemiology and development of patient care.

## DATA ARCHIVING

There were no data to deposit.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.


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# Diffusion tensor imaging of the cervical spinal cord in healthy adult population: normative values and measurement reproducibility at 3T MRI

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## Abstract

**Background:** Compared to diffusion tensor imaging (DTI) of the brain, there is a paucity of reports addressing the applicability of DTI in the evaluation of the spinal cord. Most normative data of cervical spinal cord DTI consist of relatively small and arbitrarily collected populations. Comprehensive normative data are necessary for clinical decision-making.

**Purpose:** To establish normal values for cervical spinal cord DTI metrics with region of interest (ROI)- and fiber tractography (FT)-based measurements and to assess the reproducibility of both measurement methods.

**Material and Methods:** Forty healthy adults underwent cervical spinal cord 3T MRI. Sagittal and axial conventional T2 sequences and DTI in the axial plane were performed. Whole cord fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were determined at different cervical levels from C2 to C7 using the ROI method. DTI metrics (FA, axial, and radial diffusivities based on eigenvalues  $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$ , and ADC) of the lateral and posterior funicles were measured at C3 level. FA and ADC of the whole cord and the lateral and posterior funicles were also measured using quantitative tractography. Intra- and inter-observer variation of the measurement methods were assessed.

**Results:** Whole cord FA values decreased and ADC values increased in the rostral to caudal direction from C2 to C7. Between the individual white matter funicles no statistically significant difference for FA or ADC values was found. Both axial diffusivity and radial diffusivity of both lateral funicles differed significantly from those of the posterior funicle. Neither gender nor age correlated with any of the DTI metrics. Intra-observer variation of the measurements for whole cord FA and ADC showed almost perfect agreement with both ROI and tractography-based measurements. There was more variation in measurements of individual columns. Inter-observer agreement varied from moderate to strong for whole cord FA and ADC.

**Conclusion:** Both ROI- and FT-based measurements are applicable methods yielding reproducible results for cervical spinal cord DTI metrics. Normative values for both measurement methods are presented.

## Keywords

CNS, MR diffusion/perfusion, spinal cord, adults, normal variants, tissue characterization

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## Introduction

While still mostly used in research, diffusion tensor imaging (DTI) of the brain is gradually developing into a clinical tool in the imaging of different white matter diseases. Only recently has the applicability of DTI been tested in spinal cord diseases. These first

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studies of spinal cord DTI have, however, already yielded promising results (e.g. in subjects with spinal cord trauma, demyelination as well as cervical spondylotic myelopathy). In these entities conventional magnetic resonance imaging (MRI) underestimates the total amount of damage revealing only the most severe lesions, whereas DTI better estimates the total lesion load. DTI results also show better correlation with the degree of clinical disability than conventional MRI (1–5). Compared to brain, the spinal cord is, however, a much more challenging target to DTI. The small size of the spinal cord and its surrounding vertebral bony elements as well as its physiologic macroscopic motion all present technical challenges to MR image acquisition. On the other hand, the tract anatomy of the spinal cord is much simpler than that of the brain because practically all fibers are oriented longitudinally. Various quantitative metrics can be derived from DTI data to provide information on tissue microstructure. Apparent diffusion coefficient (ADC) expresses the magnitude of the diffusion irrespective of directional dependence. From the three eigenvalues or directional diffusivities ( $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$ ) the diffusivity along the principal axis of the diffusion tensor,  $\lambda_1$ , is also called axial diffusivity. The average of the second and third eigenvalues  $\lambda_2$  and  $\lambda_3$  is referred to as radial diffusivity. Fractional anisotropy (FA) describes the degree of directional dependence/anisotropy of the diffusion and takes on values between zero (complete isotropic diffusion) and one (complete anisotropic diffusion) (6,7). Evidence suggests that orientation of fiber bundles, axonal diameter, density, and myelination influence diffusion metrics in the nervous system (8,9). Compared to brain DTI, there is a lack of normative databases of the DTI metrics of the spinal cord, which are however mandatory for the interpretation of measurements in individual patients. The aim of the present study was to establish normative reference values for cervical spinal cord (trauma) patients using region of interest (ROI) and fiber tractography (FT) methods which can be applied to individual clinical patients and to study the reproducibility of both methods.

## Material and Methods

### Subjects

This work is part of a larger spinal cord injury study, which consists of cervical spinal cord injury patients and trauma control subjects. The control subjects, representing the subjects of the present paper, were recruited among consecutive patients with ankle trauma (fracture or distension) of an emergency department of a university hospital. The aim was to enrol five male and five female subjects to each of the following

age groups: 18–30 years, 31–40 years, 41–50 years, and 51–60 years. The inclusion criteria were: aged 18–60 years, resident of university hospital district area, and ankle trauma. Exclusion criteria were: neurological problems, psychiatric problems, history of traumatic brain injury, former neurosurgical procedure, problems with hearing or vision, first language other than Finnish, contraindications to MRI, and refusal to participate. The final sample of subjects included 20 male and 20 female healthy subjects. The mean ages (SD) were: whole sample 40.4 (12.3), men 39.8 (11.8), and women 41.1 (13.2) years. None of the subjects had significant structural abnormalities on conventional MRI sequences. Written informed consent was obtained from each participant. Ethics approval for the study was obtained from the ethical committee of the local hospital district.

### MRI and DTI examinations

The MRI and DTI examinations were performed between September 2010 and October 2011 with a 3T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany). A 12-channel head coil and a 4-channel neck coil were used simultaneously. Sagittal T2 turbo spin echo (TSE) (TR, 3500 ms; TE, 108 ms; flip angle, 160°; average, 1; FOV, 280; matrix, 280×384; slice/gap, 3.0/0.3 mm; ETL, 34) and axial T2\*-weighted multigradient echo combination series (TR, 506 ms; TE, 14 ms; flip angle, 30°; average, 1; FOV, 160 mm; matrix, 256×256; slice/gap, 3.0/0.3 mm) were acquired. The voxel size of T2\* images was 0.6×0.6×3.0 mm.

DTI data were acquired using axial multidirectional diffusion-weighted echo planar imaging sequence (MDDW) (TR, 4000 ms; TE, 103 ms; averages, 4; FOV, 152 mm; matrix, 128×128; slice/gap, 4.0/1.2 mm; b-factor, 0 and 1000; 20 diffusion directions). The voxel size was 1.2×1.2×4.0 mm. Cardiac gating was not used. The scan time for the DTI sequence was 5 min 50 s.

### ROI and tractography measurements

The ROI measurements and tractographies were performed on a workstation using the commercially available software Neuro3D (Siemens Healthcare, Malvern, PA, USA).

The FA and ADC values of the whole cord were measured at C2, C3, C4, C5, C6, and C7 levels. Spinal cord levels were determined using the sagittal T2 anatomic sequence. The measurements were performed at the level of the center of the vertebral body to minimize artifacts (10,11). Measurements of the individual funicles (right and left lateral funicles and the



posterior funicle) were performed for FA, ADC, and eigenvectors  $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$  in addition to measurements of the whole cord at C3 vertebral body level. The ROIs were drawn on axial interpolated directionally color-encoded FA maps. Whole cord ROIs were drawn using freehand technique, for individual funicles small circle ROIs (4.3–5.8 mm<sup>2</sup>) were used. The ROIs were centered in the area of interest, taking care to avoid border areas and CSF spaces (Fig. 1). Tensor estimation and fiber tractographies were performed using vendor-provided software, which uses FACT (fiber assignment by continuous tracking) fiber tracking algorithm. Seed points were placed on axial interpolated directionally color-encoded FA maps. FA thresholding value of 0.2 and angulation threshold of 30 degrees turning angle were used.

Signal-to-noise ratio (SNR) of the measurements was determined by measuring the signal from one ROI centered in the spinal cord and four ROIs outside anatomical structures in one of the  $b = 0$  s/mm<sup>2</sup> images at C3 level. SNR was determined according to the NEMA Standards 1-2008 which includes the following expression for SNR:  $SNR = S/\text{image noise}$ , where  $S$  = signal, and image noise is estimated with Rayleigh distribution:  $\text{image noise} = SD/0.66$

The measurement was performed in three subjects yielding the average value for SNR  $18.3 \pm 5.0$ .

One of the authors, a neuroradiologist (AB) performed all first-line measurements. For assessment of measurement reproducibility 10 subjects were re-measured by the same examiner, as well as by two other examiners, a physicist with long experience of brain ROI measurements (UH) and a neuroradiologist with no previous experience of ROI measurements (SS). The primary ROI and FT measurements were performed during January 2012 and the re-measurements during March 2012.

## Results

### Measurements of the whole cord at different cervical levels

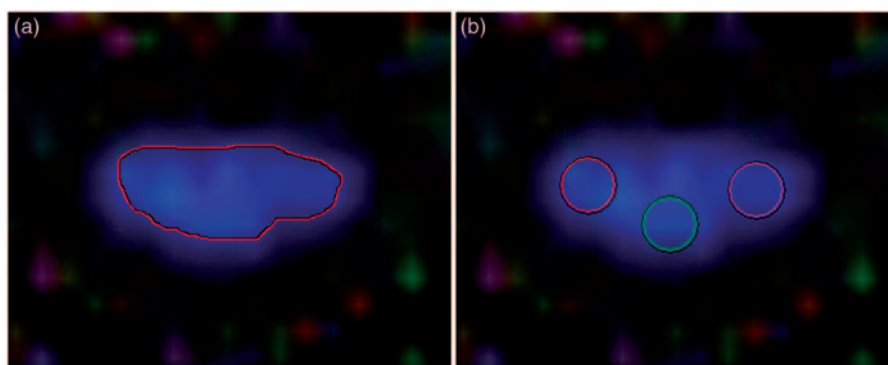
The mean FA and ADC values of the whole cord at different cervical levels are shown in Table 1 and Fig. 2. The FA values decreased and the ADC values increased almost linearly in the rostral to caudal direction from C2 to C7. The overall differences between cervical levels was tested with repeated measures ANOVA using gender as between subjects factor ( $P < 0.001$  for both FA and ADC values).

The effect of gender and age to the FA and ADC values was studied with linear regression. Using  $P < 0.01$  (due to multiple testing) as a level of significance there was no statistically significant difference between FA and ADC values of the female and male subjects. For the estimation of the age effect the subjects were divided in two age groups: those aged  $< 40$  years and those aged  $\geq 40$  years. The only significant difference between the two age groups was a lower FA value at C6 level for the older group ( $P = 0.004$ ).

**Table 1.** Means and SDs for whole cord FA and ADC at different cervical levels.

	FA	ADC*
C2	$0.714 \pm 0.074$	$0.884 \pm 0.118$
C3	$0.684 \pm 0.053$	$0.962 \pm 0.091$
C4	$0.650 \pm 0.058$	$0.928 \pm 0.092$
C5	$0.633 \pm 0.060$	$0.961 \pm 0.078$
C6	$0.608 \pm 0.057$	$0.985 \pm 0.084$
C7	$0.600 \pm 0.055$	$1.022 \pm 0.106$

\* $10^{-3}$  mm<sup>2</sup>/s



**Fig. 1.** (a) The placement of the freehand-ROI onto an axial color-coded FA map of the spinal cord for the measurements of the whole cord DTI metrics. (b) The placement of three circle ROIs for the measurement of the DTI metrics of the lateral and posterior funicles.

### Measurements of the funicles and the whole cord at C3 level

At C3 vertebral body level mean values for FA, ADC, axial ( $\lambda_1$ ), and radial (average of the sum of  $\lambda_2$  and  $\lambda_3$ ) diffusivities as well as individual eigenvalues  $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$  were measured separately for the left and right lateral funicles, the posterior funicle and the whole cord.

The mean values and SDs are given in Table 2.

The values of the individual funicles were compared with linear regression, adjusted with gender and age (dichotomous). For FA values no statistically significant differences between the funicles were found. Axial diffusivity and radial diffusivity of both lateral funicles were significantly lower than those of the posterior funicle. (Axial diffusivity  $P < 0.001$  for both lateral funicles, radial diffusivity  $P = 0.005$  for the right and  $P = 0.003$  for the left funicle).

The individual eigenvalues  $\lambda_1$  and  $\lambda_3$  values of both lateral funicles were significantly lower than those of the posterior funicle ( $\lambda_1$   $P < 0.001$  for both lateral funicles,  $\lambda_3$  right  $P = 0.008$  and left  $P = 0.001$ ).  $\lambda_2$  of the right lateral funicle was also significantly lower than that of the posterior funicle ( $P = 0.006$ ) but for  $\lambda_2$  of the left lateral funicle no significant difference was found. ADC values of the both lateral funicles were also significantly lower than that of the posterior funicle ( $P < 0.001$  for both lateral funicles). Between the left and right lateral funicles no significant differences were found for any of the measured DTI metrics.

Because measurements of the whole cord include both gray and white matter of the spinal cord, the

respective DTI metrics values could be expected to differ from those of the individual funicles, consisting of white matter. Values of the whole cord were for FA and  $\lambda_1$ /axial diffusivity significantly lower, for  $\lambda_2$  and  $\lambda_3$  and radial diffusivity significantly higher than those of the lateral and posterior funicles. These mean value differences were tested with repeated measures ANOVA using confidence interval adjustment (Bonferroni,  $P < 0.05$ ). ADC of the whole cord was significantly higher than ADC of the lateral funicles but significantly lower than that of the posterior funicle. Gender was not correlated with any of the DTI metrics.

Age did not affect the FA or ADC values. The only significant effect of age for the DTI metrics was significantly lower  $\lambda_2$  for the left lateral funicle ( $P < 0.006$ ) in the older age group.

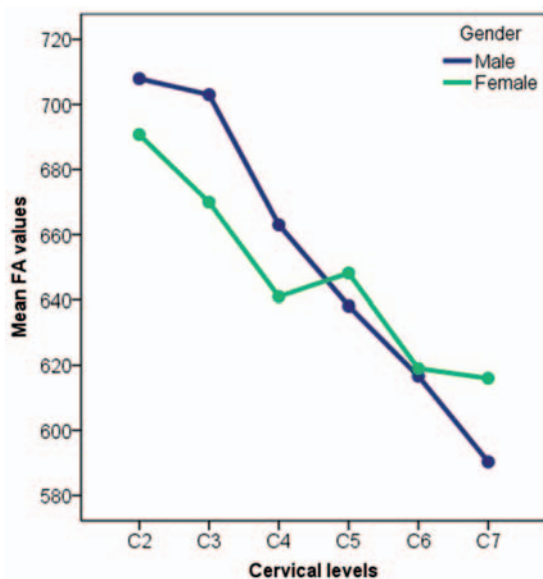
### Tractography-based measurements

The mean values for tractography-derived metrics are given in Table 3.

The values of the individual funicles were compared with linear regression, adjusted with gender and age (dichotomous).

The mean value for FA of the posterior funicle was higher than that of the both lateral funicles but the difference did not reach significance. For ADC no differences between the funicles were found.

FA of the whole cord was significantly lower than FA of the lateral and posterior funicles but the ADC values did not differ significantly between the whole cord and the individual funicles. Using the same dichotomy for age as described above there were no significant differences between FA, ADC or volumes of the funicles between age groups. For gender the only differences were found in the volumes of the funicles; the volumes for the whole cord as well as for the posterior funicle were significantly lower in women than in men.



**Fig. 2.** The FA values of the whole cord area at different cervical levels. The FA values are multiplied by 1000.

### Measurement reproducibility

Intraclass correlations (ICC) were used for testing the reproducibility of the measurements. For the measurements of the whole cord at different levels the mean ICC for intra-observer variation for FA was 0.871 (range, 0.811–0.959) indicating almost perfect agreement and for ADC the mean ICC was 0.701 indicating strong agreement (range, 0.420–0.943). For inter-observer variation between two observers (AB, UH) mean ICC for FA was 0.802 and for ADC 0.714 and between three observers (AB, UH, SS) for FA 0.784 and for ADC 0.666, respectively.

At C3 level the mean ICC value for intra-observer variation of the measurements of FA (lateral and posterior funicles and whole cord) was 0.755, for ADC

**Table 2.** Means and SDs of DTI metrics at C3 level.

	Right lat funicle	Left lat funicle	Posterior funicle	Whole cord
FA	0.773 ± 0.086	0.773 ± 0.083	0.764 ± 0.069	0.687 ± 0.058
$\lambda_1^*$ ( $\lambda^{\parallel}$ )	1.951 ± 0.184	1.939 ± 0.186	2.145 ± 0.168	1.859 ± 0.129
$\lambda_2^*$	0.470 ± 0.150	0.481 ± 0.156	0.523 ± 0.163	0.591 ± 0.121
$\lambda_3^*$	0.319 ± 0.136	0.297 ± 0.128	0.364 ± 0.130	0.403 ± 0.097
$\lambda^{\perp}$	0.399 ± 0.135	0.389 ± 0.138	0.443 ± 0.143	0.497 ± 0.107
ADC*	0.909 ± 0.132	0.890 ± 0.148	1.012 ± 0.139	0.951 ± 0.105

\* $\lambda_1$ – $\lambda_3$ ,  $\lambda^{\perp}$ , and ADC  $10^{-3}$  mm<sup>2</sup>/s.

$\lambda^{\parallel}$ ,  $\lambda_1$  = axial diffusivity;  $\lambda^{\perp}$ ,  $(\lambda_2 + \lambda_3)/2$  = radial diffusivity.

**Table 3.** Means and SDs of tractography-derived metrics.

	Right lat funicle	Left lat funicle	Posterior funicle	Whole cord
FA	0.562 ± 0.053	0.565 ± 0.061	0.576 ± 0.054	0.541 ± 0.036
ADC*	1.222 ± 0.174	1.196 ± 0.166	1.200 ± 0.152	1.232 ± 0.119
Volume (mm) <sup>3</sup>	811 ± 303	750 ± 296	840 ± 306	4515 ± 970

\* $10^{-3}$  mm/s<sup>2</sup>.

0.770, for  $\lambda_1$  0.690, for  $\lambda_2$  0.789 and for  $\lambda_3$  0.731. For inter-observer variation between two observers (AB, UH)/three observers (AB, UH, SS) mean ICC values for FA were 0.797/0.663 and for ADC 0.739/0.570.

For intra-observer variation of tractography-derived metrics of the whole cord ICC was for FA 0.931, for ADC 0.963 and for tract volume 0.905 indicating almost perfect agreement.

ICCs for inter-observer variation for the same metrics between two/three observers (AB, UH/AB, UH, SS) were for FA 0.523/0.645, for ADC 0.565/0.686, and for tract volume 0.242/0.352.

## Discussion

Studying healthy populations in order to determine normal values and their variation is a mandatory prerequisite for the interpretation of DTI measures in patient populations and individual patients. Compared to DTI of the brain, reports of normative DTI data of the spinal cord are at present relatively sparse. In addition, most studies consist of relatively small and arbitrarily enrolled samples of healthy subjects with unrepresentative age and gender distribution. The subjects of the present study have been enrolled systematically among previously healthy ankle trauma patients in order to get a representative sample of the adult population of male and female subjects including young to elderly adults aged 18–60 years. In this respect the present series can be considered one of the largest series of healthy spinal cord DTI data. We deliberately

chose to use ROI-measurement method and vendor-provided software because both can be easily applied to clinical patients without a need to laborious post-processing and manipulation of the DTI raw data. The DTI acquisition parameters were also selected as to enable applying in clinical patients.

Reported quantitative mean values and variations of individual DTI metrics of the spinal cord in healthy population vary in the literature. Acquisition parameters like voxel size and number of diffusion gradient directions have impact on FA values (12). Differences between sample populations, vendors and postprocessing softwares, and methods of measurement also contribute to the diversity of reported data. The FA values of the intact cervical spinal cord are mostly reported to lie between 0.6 to 0.7 with a standard deviation of 0.06–0.07, i.e. 10% of the reported value (13–17). In our series the mean value of the whole cord FA at C2 level was  $0.714 \pm 0.074$  and that of ADC  $0.884 \pm 0.118$  corresponding well to previous reports. Considering the principally longitudinal orientation of spinal cord nerve fibers, one would expect less variation of FA values in spinal cord than in brain. The measured FA of the whole cord represents the mean FA of white and grey matter combined and as such can be argued to be a rather robust and nonspecific measure. In individual patients it is, however, often impossible to perform more detailed measurements at least in sites of injury and for this reason whole cord measurements can be considered clinically relevant. Nonetheless, the possibility of targeting the measurement to individual funicles

ought to increase the clinical value and specificity because in some diseases motor and sensory tracts are selectively affected. The clinical picture of an incomplete spinal cord injury can vary considerably with respect to localization of the affected area, as well.

As many other researchers, (4,13,18–20) we found that FA and ADC values of the whole cord depend on the cervical level with FA decreasing from the upper to the lower levels. The reason for this dependence is not clear but can partly be attributed to larger central grey matter portion at the lower cervical level (17). It has also been suggested that brachial plexus nerve roots entering and leaving lower cervical spinal cord disrupt slightly the directional coherence of the fibers and decrease the FA value (21). There are also reports in which this difference has not been observable (14). We also found ADC increasing from the upper to the lower cervical levels. This is in accordance with reports by Shanmuganathan et al. and Cheran et al. (22,23) but many researchers have also reported no significant differences between the cervical levels in ADC or mean diffusivity (MD) values. In these studies the number of healthy control subjects has however been smaller than in the present study. In comparing the DTI metrics of the individual funicles we found no significant difference between the FA values of the lateral and dorsal funicles. However, both axial and radial diffusivities and ADC values of the lateral funicles were significantly lower than those of the dorsal funiculus. Tractography-derived FA of the dorsal funicle was higher than that of the lateral funicles, though without reaching significance. Recently, Onu et al. (24) reported significant differences in the FA and radial diffusivity values between individual spinal cord funicles. In their series the FA values of both lateral funicles were lower than that of the dorsal funicle. The FA value of the ventral funicle was found to be significantly lower than those of both the lateral and dorsal funicles. In turn the radial diffusivity was significantly higher in the ventral funiculus than in the dorsal and lateral funicles. Similar results for the FA values were reported by Rossi et al. (25). These differences could reflect the differences in axon diameter, axon density, and spacing between these funicles (26) containing different kind of tracts. Partly in accordance with our results, Smith et al. (27) using DTI and magnetization transfer did not find differences in DTI metrics between dorsal and lateral funicles. The spatial resolution of our raw data maps and the placement of ROIs in the color-coded FA maps did not allow us to measure the ventral funicle individually. Because of the small size of the target, partial volume effects of neighboring structures are likely to affect the DTI values in spinal cord regardless of the method used in placing the ROIs (1,14). As pointed out by Hesseltine et al. (1) the inclusion of

some gray matter into the ROI is especially likely to happen with the anterior spinal cord ROI which perhaps can partly explain its low FA values.

Because increasing age has been shown to decrease anisotropy and increase mean diffusivity in the brain (28), it would be natural to expect a similar effect in the spinal cord. There are contradictory results in the literature in this respect. Mamata et al. in a sample of 72 cervical spondylosis patients showed a weak positive correlation of ADC and a negative correlation of FA with age within the normal spinal cord area at C3–C4 level (18). In accordance, Petersen et al. found a significant impact of age on FA but not on ADC values among 28 healthy subjects (16). There are however also reports with no correlation of the DTI metrics with age (1,13), in concordance with our results. Van Hecke et al. using an automatic technique for tractography-based measurement showed a positive correlation of MD and eigenvalues with age and a negative correlation of FA with age that was not significant for the ROI-based segmentation (29). The importance of the possible effect of age to the DTI metrics is probably small for measurements in individual clinical patients. We did not find any significant gender differences, with the exception of the smaller volumes for the FT-measured whole cord as well as for the posterior funicle in women than in men. To our knowledge gender differences have not been reported for DTI of the spinal cord.

Concerning the reproducibility of cervical cord DTI, Mulcahey et al. recently reported a good to strong (ICC 0.75–0.95) reliability of cervical cord DTI with a test-retest design (30). In our study the scanning procedure was not repeated but the intra- and inter-observer variation of the measurements was studied by repeated measurements of the same data. Repeated ROI measurements of the whole cord showed an almost perfect agreement for intra-observer variation and a strong to almost perfect agreement for inter-observer variation. This finding has practical significance because ROI measurements are relatively easy to perform in anatomically simple structures as the spinal cord. The reproducibility of the FT-derived metrics was also almost perfect for whole cord FA and strong to almost perfect for ADC for intraobserver variation. Corresponding inter-observer agreements were moderate to strong for both FA and ADC. In clinical practice it seems wise to keep the number of examiners performing the measurements to a minimum if possible. The ROI- and tractography-based methods appear, however, not to be prone to significant differences between measurements made by several observers. Of the individual DTI-metrics, tract volume in FT had clearly the lowest inter-observer reproducibility compared to the other metrics.



Even though the data acquisition technique and measurement method we used was deliberately chosen such as to be easily applicable in clinical patients, it can also be considered a limitation of the study. With longer acquisition times better spatial resolution can be reached which diminishes partial volume effects and increases specificity in characterization of individual spinal cord columns. A weakness in the used measurement method was the centralizing of the dorsal funicle ROI in the midline, where it inevitably included the posterior median fissure which, although a narrow structure, will decrease the FA and increase ADC values. Also, using interpolated FA maps in drawing of the ROIs may add some partial volume effect to the measured areas. We also chose not to use cardiac gating technique, which would have diminished artefacts related to corticospinal fluid flow but on the other hand lengthened acquisition time and thus increased artifacts caused by swallowing and respiratory movement.

In conclusion, we present the normal values of DTI metrics of the cervical spinal cord in a population of 40 healthy adults with age range of 18–60 years and an equal number of male and female participants. The measurement techniques are easy to use and yield reproducible results allowing their application in clinical cervical spinal cord trauma patients.

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# Assessing the State of Chronic Spinal Cord Injury Using Diffusion Tensor Imaging

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## Abstract

The aim of this study was to quantify the association between diffusion tensor imaging (DTI) parameters of the cervical spinal cord and neurological disability in patients with chronic traumatic spinal cord injury (SCI). A cervical spinal cord 3T magnetic resonance imaging (MRI) with DTI sequences was performed on 28 patients with chronic traumatic SCI and 40 healthy control subjects. DTI metrics, including fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD), and radial diffusivity (RD), were calculated within the normal-appearing spinal cord area at levels C2 or C3. Clinical assessment of the patients was performed according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and the motor subscale of the Functional Independence Measure (FIM). The FA values of the patients with SCI were significantly lower than those of healthy control subjects ( $p < 0.000001$ ). In contrast, the ADC and RD values of these patients were significantly higher than those of control subjects (ADC  $p < 0.0001$ , RD  $p < 0.00001$ ). In patients with SCI, the FA values were positively correlated with the motor ( $r = 0.56$ ,  $p < 0.01$ ) and sensory ( $r = 0.66$ ,  $p < 0.001$ ) scores of ISNCSCI and with the motor subscale of FIM ( $r = 0.51$ ,  $p < 0.01$ ). DTI revealed spinal cord pathology, which was undetectable using conventional MRI. DTI changes in regions that were remote from the site of primary injury were most likely the result of secondary degeneration of white matter tracts. Decreased FA values were correlated with poorer motor and sensory function, as well as a lack of independence in daily living. DTI is a promising quantitative and objective tool that may be used in the clinical assessment of patients with SCI.

**Key words:** assessment tools; DTI; traumatic SCI

## Introduction

THE INCIDENCE of traumatic cervical spinal cord injury (SCI) appears to be increasing in developed countries, particularly in the elderly.<sup>1,2</sup> Cervical SCI causes different grades of motor and sensory deficits, autonomic dysfunction, and secondary problems, which together result in long-term disability and have a great impact on psychosocial coping.

Clinical examination and magnetic resonance imaging (MRI) are routinely used to evaluate the severity of SCI. Neurological examination using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) serves as the most commonly used method for the clinical definition and grading of the level and completeness of an injury.<sup>3</sup> Daily living activities are usually assessed using the Functional Independence Measure (FIM).<sup>4,5</sup> MRI findings such as hemorrhage and edema have been

shown to correlate with clinical impairment in acute cervical SCI. In addition, data from both MRI and ISNCSCI have been used to predict long-term outcome after SCI.<sup>6–9</sup> However, ISNCSCI is prone to some inter-rater variability, and the evaluation of children and patients with cognitive impairment is difficult because of inadequate cooperation.<sup>10,11</sup> Although conventional MRI can reliably depict focal injuries of the spinal cord parenchyma, the data will be mostly qualitative.

Diffusion tensor imaging (DTI) is a relatively new imaging method based on the diffusion of water molecules in tissues. Quantitative DTI parameters provide information on tissue microstructure in the nervous system.<sup>12</sup> The apparent diffusion coefficient (ADC) or mean diffusivity (MD) expresses the magnitude of the diffusion. Of the three directional diffusivity values ( $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$ ), the diffusivity along the principal axis of the diffusion tensor ( $\lambda_1$ ) is known as the axial diffusivity (AD), and the average

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of the second and third values ( $\lambda_2$ ,  $\lambda_3$ ) is referred to as the radial diffusivity (RD). Fractional anisotropy (FA) describes the degree of directional dependence/anisotropy of the diffusion, and it is represented as values between zero (complete isotropic diffusion) and one (complete anisotropic diffusion).<sup>13,14</sup>

DTI has been shown to have potential for the quantification of white matter pathology of the spinal cord. This technique has been successfully applied to multiple sclerosis (MS), spondylotic myelopathy, and SCI.<sup>15–18</sup> However, the patient populations used in previous studies on DTI parameters of patients with chronic SCI have been relatively small, and most of the DTI methodology was laborious to implement into clinical practice.<sup>18–21</sup>

The aim of this study was to quantitatively assess the state of the cervical spinal cord using DTI in patients with chronic traumatic cervical SCI, and to determine whether there are differences between DTI values with respect to the completeness of the SCI. We also investigated the correlations between DTI values and clinically relevant measures such as ISNCSCI and FIM. The association between conventional MRI findings and clinical parameters was also examined.

## Methods

### Study design and ethics

This study is part of the Spinal Cord Injury Series of Tampere-Retrospective Study. The study aims to examine SCI from a multidisciplinary perspective, in a case-control manner, to enhance the clinical assessment and treatment of this specific patient group. Ethics approval for the study was obtained from the Ethical Committee of Pirkanmaa Hospital District, Finland. A written informed consent was obtained from each participant.

### Subjects

All consecutive patients with a chronic traumatic cervical spine injury ( $n=88$ ) who were admitted to either the ward or an outpatient clinic in Tampere University Hospital between 1989 and 2010 were contacted for participation in the study in 2011. The inclusion criteria for the patients were as follows: 1) >18 years of age, 2) resident of the hospital district, 3) clinically significant neurological findings of a traumatic cervical SCI after 24 h of monitoring in the hospital, and 4) time since injury >1 year. The exclusion criteria were as follows: 1) known neurological illness other than SCI, 2) respiratory arrest, 3) contraindications to MRI, and 4) refusal to participate in the study. In addition, 6 patients with poor MRI image quality (e.g., artifacts from a vertebral fixation material) were excluded; the final SCI population sample consisted of 28 patients.

Patients with SCI were compared with an orthopedically injured control sample of 40 neurologically intact subjects. The control subjects were recruited from consecutive patients with ankle trauma from the Emergency Department of Tampere University Hospital. A total of 609 patients with ankle injury were screened for participation in this study. The aim was to enroll five male and five female subjects into each of following age groups: 1) 18–30, 2) 31–40, 3) 41–50, and 4) 51–60 years. The inclusion criteria were as follows: 1) age 18–60 years, 2) being a resident of the university hospital district, and 3) ankle trauma. The exclusion criteria were as follows: 1) neurological problems, 2) psychiatric problems, 3) history of traumatic brain injury (TBI), 4) former neurosurgical procedure, 5) problems with hearing or vision, 6) first language other than Finnish, 7) contraindications to MR, I and 8) refusal to participate. Of the final sample of 40 healthy subjects, 20 (50%) were male and 20 (50%) were female. The control sample was primarily collected for a mild TBI study, and, therefore, the enrollment criteria differed from the ones used with the SCI patients.

### Collection of clinical data and neurological scoring

All patients with SCI were examined at an outpatient clinic in Tampere University Hospital. The collection of clinical data was performed by the first author of this study. The etiology of the SCI was classified using the International SCI Core Data Set.<sup>22</sup> The ISNCSCI was used to evaluate and classify the neurological consequence of SCI.<sup>3</sup> Completeness of the injury was defined according to the American Spinal Injury Association (ASIA) impairment scale (AIS). A single neurological level represents the most caudal level of normal sensory and motor functions. The motor score (range 0–100) consists of five manually tested key muscle forces (range 0–5, where 0=total paralysis and 5=active movement against full resistance) for both the arms and legs. To determine the sensory score (range 0–224), light touch and pinprick sensations (range 0–2, where 0=absent and 2=normal sensation) were examined over dermatomes C2 to S4/S5. However, there are sensory data missing for two of the patients. The level of disability was assessed using the motor subscale of the FIM.<sup>4,5</sup> The motor subscale of the FIM (range 13–91) consists of subscores for self-care, sphincter control, mobility, and locomotion. Within each subscore, two or more specific items were evaluated in a strictly defined manner in terms of independence of function. Each item ranged in value from 1 to 7 (6–7=independent=capable of performing activity without supervision or help, 3–5=modified dependent, and 1–2=completely dependent).

The medical condition of the subjects was assessed according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD–10).<sup>23</sup> The Basic Pain Data Set was used to collect data from patients with neuropathic pain related to the SCI.<sup>24</sup> Information on the current medication at the time of examination was classified into 17 subgroups according to the Finnish Commercial Drug Catalog (Pharmaca Fennica), which was categorized on the basis of the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System codes.

### MRI

The MRI and DTI examinations were performed using a 3T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany). A 12 channel head coil and a 4 channel neck coil were used simultaneously. Sagittal T2 turbo spin echo (TSE) (TR 3500 ms, TE 108 ms, FlipAngle 160 degrees, 1 averages, field of view [FOV] 280, matrix 288×384, slice/gap 3.0/0.3 mm, echo train length [ETL] 34) and axial T2\*-weighted multigradient echo combination series (TR 506 ms, TE 14 ms, FlipAngle 30 degrees, 1 average, FOV 160 mm, matrix 256×256, slice/gap 3.0/0.3 mm) were acquired. The voxel size of the T2\* images was 0.6×0.6×3.0 mm. DTI data were acquired using axial multidirectional diffusion weighted echo planar imaging sequences (MDDW) (TR 4000 ms, TE 103 ms, 4 averages, FOV 152 mm, matrix 128×128, slice/gap 4.0/1.2 mm, b-factor 0 and 1000, 20 diffusion directions). The voxel size was 1.2×1.2×4.0 mm. Cardiac gating was not used. The scan time for the DTI sequence was 5 min and 50 sec.

### Image analysis

An evaluation of the conventional MRI scans was performed by a neuroradiologist (A.B.). The most cranial level of the lesion was assessed, and the craniocaudal length of the main lesion was measured in millimeters.

The region of interest (ROI) measurements were performed by a physicist (U.H.) using the commercially available software Neuro3D (Siemens Healthcare, Malvern, USA). The ROIs were manually placed on axial images of the color-coded FA maps and automatically transferred onto the non-diffusion-weighted b0 images and ADC maps. Spinal cord levels were determined using the



sagittal T2 anatomical images. Whole spinal cord ROIs were drawn using a freehand technique; however, for individual funicles, small circle ROIs were used. The ROIs were centered in the area of interest, taking care to avoid the border areas and cerebrospinal fluid (CSF) spaces (Fig. 1).

The mean values, standard deviations and median values of the FA and ADC were assessed for the whole cord and for the lateral funicles at cervical level C2–3 above the primary lesion and at the level of the spinal cord lesion (Figs. 2–4). At the C2–3 level, the AD and RD were also calculated for the whole cord area. The DTI values from the left and right funiculus were averaged per level measured. At the levels of the spinal cord lesions, the gray and white matter contrast was mostly lost, which made a reliable placement of the ROI difficult. Consequently, measurements indicating “the lesion level” were made at the level just above the most cranial border of the lesion. Because of the artifacts from the vertebral fixation material, 10 of the images from the lesion level were excluded, and DTI measurements could be reliably made for 18 of the 28 patients.

In the control subjects, the DTI values were measured at the C2–3, C3–4, C4–5 and C5–6 levels (Fig. 2). All of the cranial levels of the spinal cord lesions, which were observed in the conventional MRI, were situated between segments C2 and C6. Therefore, the mean DTI values among the healthy controls from the C2–3 to C5–6 levels were used as reference values for the lesion level measurements in SCI patients.

### Statistical analyses

Patients with SCI were not age-matched with the control subjects; therefore, the analyses were performed using linear regression, which was adjusted for age. Correlations with the DTI values and conventional MRI findings were calculated using a partial correlation with age as a control factor. Clinical variables used in the correlations included the ISNCSCI-derived total motor score, motor subscore for the upper and lower extremities, total sensory score, single neurological level, and FIM subscores of the motor subscale. Further comparisons of the patient population were divided into two groups on the basis of the completeness of the injury; AIS A and AIS B–E. Statistical analyses were performed under the guidance of a biostatistician (M.H.). Because of multiple comparisons, the statistical significance level was established at 1%. All of the parameters were ranked prior to the analyses. The SPSS program (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used to perform all of the statistical analyses.

## Results

### Clinical findings

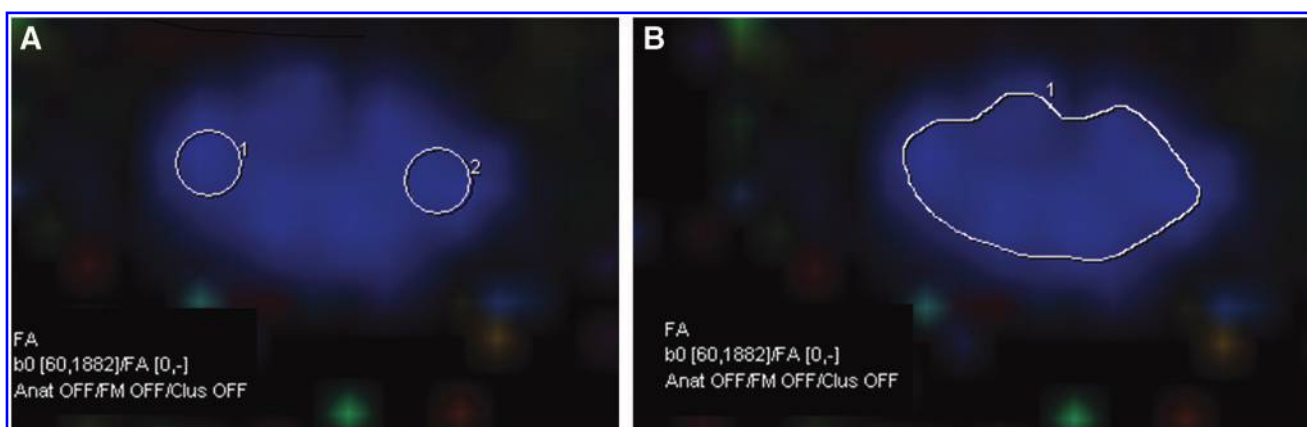
Clinical characteristics of the SCI patients (entire group, AIS A and AIS B–E) and control subjects are shown in Table 1. Of the patients with SCI, 17 (60.7%) patients had some chronic medical problems. The most common chronic medical problems were diseases of the circulatory system ( $n=9$ , 32.1%) and diseases of the musculoskeletal system and connective tissue ( $n=7$ , 25.0%). Twenty-four (85.7%) patients used some permanent medication; 12 (42.9%) patients used some pain medication; 11 (39.3%) patients used a prophylactic antibiotic; 9 (32.1%) patients used drugs for the cardiovascular system; and 9 (32.1%) patients used muscle relaxants. Eleven (39.3%) patients with SCI had neuropathic pain.

Eighteen (45.0%) of the control subjects had a diagnosed disease. Six of the patients had a disease of the circulatory system (15.0%), and four (10.0%) patients had a disease of the musculoskeletal system and connective tissue. Thirteen (32.5%) control subjects used some permanent medication. The largest group used drugs for the cardiovascular system ( $n=6$ , 15.0%). There were no control subjects who showed neuropathic pain.

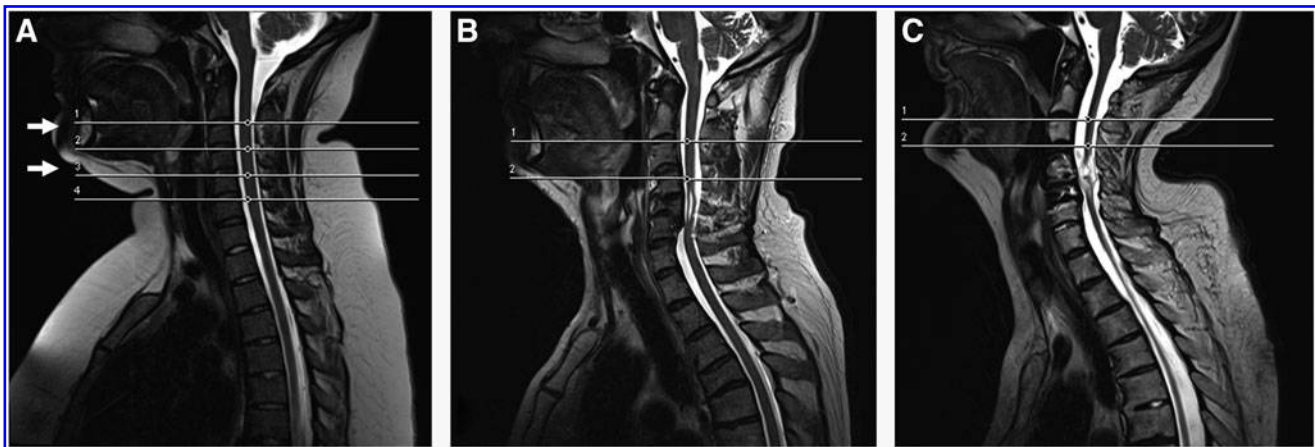
### Conventional MRI findings

A cervical cord operation was performed on 19 out of the 28 (67.9%) patients. A vertebral fixation material was found on 13 (46.4%) of the patients. The spinal canal was classified as narrow in 10 (35.7%) of the patients. A focal post-traumatic lesion on either the sagittal or axial T2 / T2\*-weighted sequences was found in 23 (82.1%) of the patients, of which 3 patients had two separate lesions. Five (17.9%) patients demonstrated no visible spinal cord lesions. The most cranial levels of the main lesions were situated between the C2 and C6 levels. The mean length of the main lesion was 18.1 mm (SD 14.5). Spinal cord atrophy was found in 18 (64.3%) patients. On axial T2\* images, six of the patients showed diffuse high signal intensity in the dorsal funicle at levels above the primary lesion (Fig. 3). In five of them, the clinical cord injury was complete (AIS A), and in one it was incomplete (AIS B). This finding probably represents secondary anterograde (Wallerian) degeneration of the ascending tracts, and was not apparent on sagittal T2 images.

None of the control subjects showed significant structural abnormalities on the conventional MRI sequences.



**FIG. 1.** The placement of the regions of interest (ROIs) on the fractional anisotropy (FA) maps. (A) Circular ROIs for the lateral funicles. (B) Freehand ROI for the whole spinal cord area.



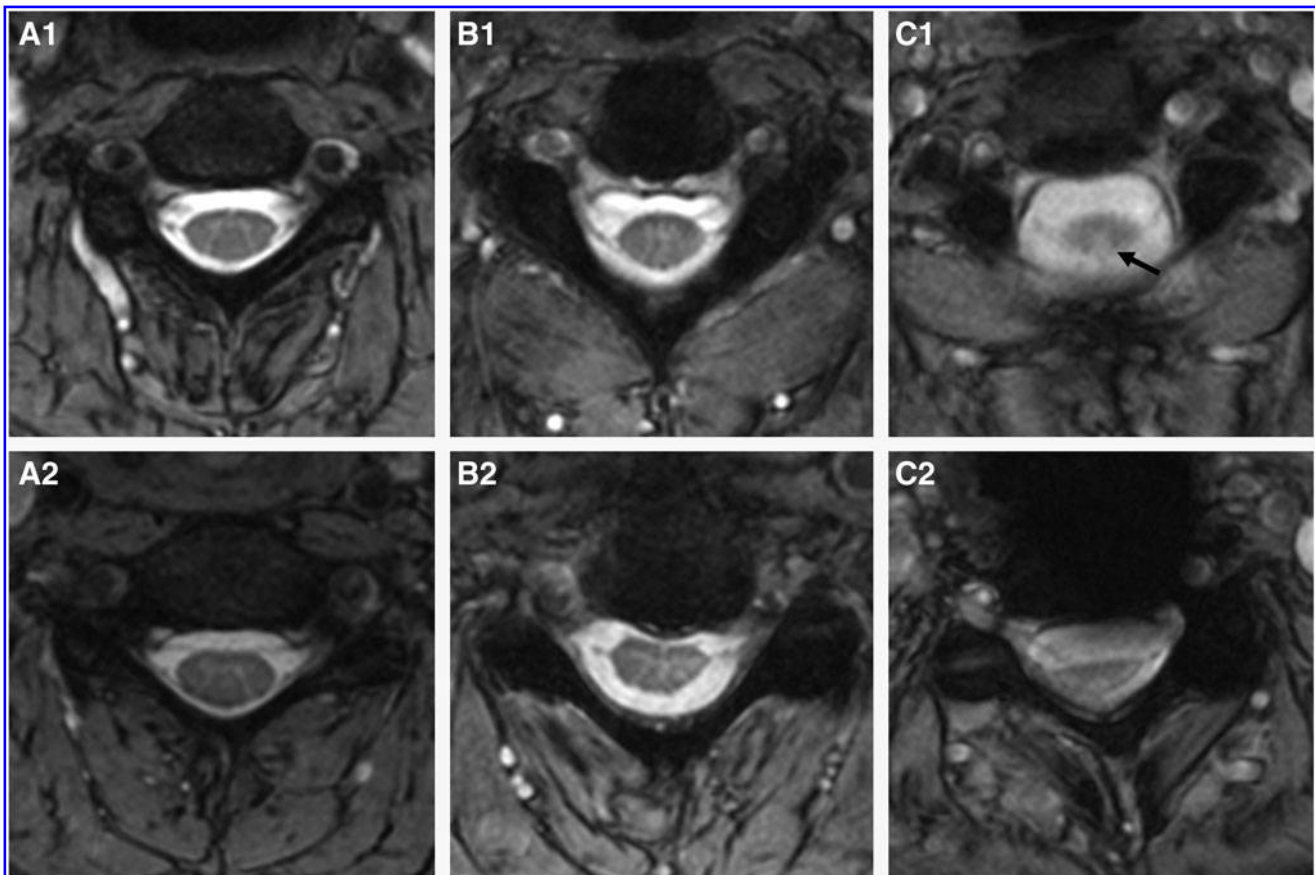
**FIG. 2.** Sagittal T2 images with horizontal white lines showing the measurement levels in a control subject (A) and patients with chronic traumatic spinal cord injury; American Spinal Injury Association impairment scale (AIS) D (B) and AIS A (C). The upper level is C2–3 in all patients and controls. The lower measurements of the patients were performed at or immediately above the lesion. Line 3 is the corresponding level in the control subject. The axial images of these levels are presented in Figures 3 and 4.

#### DTI parameters

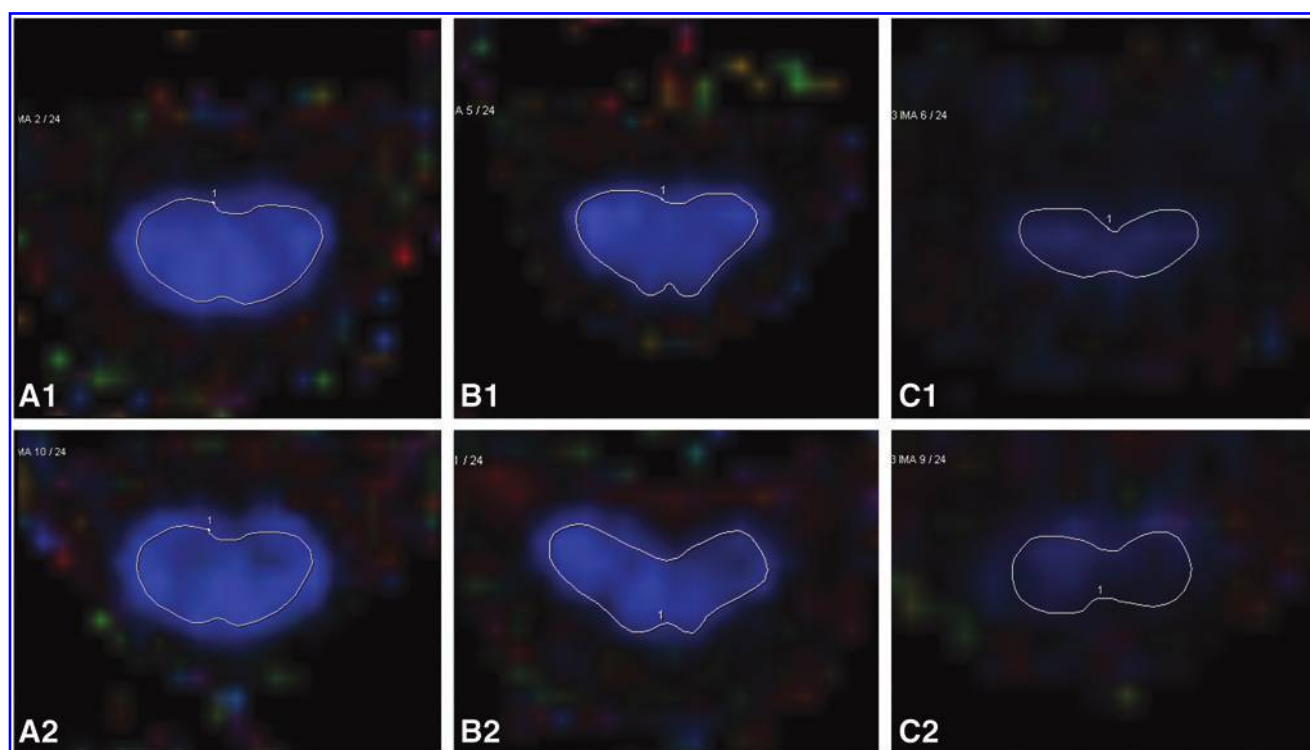
All of the measured FA, ADC, AD, and RD values are summarized in Tables 2 and 3. The control subjects were compared with the entire group of patients with SCI, both the AIS A subgroup and the AIS B–E subgroup. Furthermore, a comparison between the AIS A and AIS

B–E groups was performed. Patients with SCI demonstrated lower FA values and higher ADC values than did healthy control subjects at both the upper cervical cord and the lesion levels. In addition, the RD values were increased in patients at the upper cervical cord level.

Partial correlations (with age as a controlled factor) between the spinal DTI values, conventional MRI findings, and clinical findings



**FIG. 3.** Axial T2\* images of a control subject (A) and patients with chronic traumatic spinal cord injury; American Spinal Injury Association impairment scale (AIS) D (B) and AIS A (C). The upper row shows the upper measurement level (C2–3) of Figure 2 and the lower row shows the C4–5 level in the control subject and the lesion levels of the patients. In C1, the high signal intensity of the dorsal funicle indicating Wallerian degeneration in the patient with AIS A injury (black arrow) can be seen.



**FIG. 4.** Axial fractional anisotropy (FA) color maps corresponding to the same levels as in Figure 3: control subject (A) and patients with chronic traumatic spinal cord injury; American Spinal Injury Association impairment scale (AIS) D (B) and AIS A (C). The upper row shows the upper measurement level (C2–3) and the lower row shows the C4–5 level in the control subject and the lesion levels of the patients. The area inside white lines (the freehand ROI) is used for measurement of the diffusion tensor imaging (DTI) metrics. The corresponding FA values of these measurements are: 0.74 (A1), 0.67 (A2) in the control subject, 0.68 (B1), 0.52 (B2) in the patient with the AIS D lesion, and 0.40 (C1) and 0.32 (C2) in the patient with the AIS A lesion.

(ISNCSCI and FIM) are shown in Table 4. Significant correlations between the DTI values and ISNCSCI and FIM scores were mostly found in the FA. The length of the spinal cord lesion correlated with the ISNCSCI scores from the MRI findings.

## Discussion

In our series, significant alterations in spinal DTI values appeared in both patients with complete and those with incomplete SCI compared with healthy subjects. Some of the DTI values showed a moderate to strong correlation with the clinical parameters, which assessed neurological deficits and disability after SCI. DTI revealed pathological changes in the spinal cords of patients with chronic SCI, as well as in areas where conventional MRI was normal.

In agreement with previous studies on DTI and chronic SCI, we found that the FA values of the patients with SCI were lower than those of healthy controls at both the lesion and upper cervical cord level, which was intact on conventional MRI.<sup>18,19,21,25</sup> In our study, the decrease in FA values was significant in both patients with complete and those with incomplete SCI compared with healthy controls. There was also a difference, although not statistically significant, in the FA values regarding the completeness of the SCI. In contrast to most previous studies,<sup>18,19,21</sup> we found a significant increase in ADC values in patients with SCI at both the lesion and upper cervical cord levels. Ellingson and colleagues also showed higher MD values at the lesion level in patients with SCI. However, in the area of the intact spinal cord, the MD values were reduced in patients compared with healthy individuals.<sup>25</sup>

Although no sign of primary lesion on the conventional MRI at the C2–3 level was found in our patient population, a clinically defined single neurological level was located between C1 and C2 in five of the SCI subjects. Therefore, changes in the DTI values at the upper cervical cord level in these patients were most likely a direct result of the primary SCI. Nevertheless, the majority of the SCI patients demonstrated a single neurological level of C4 or lower. One possibility may be that the white matter tracts above the primary lesion level were also affected by secondary anterograde (Wallerian) and some retrograde degeneration.<sup>26</sup> In our sample, six of the most severely injured patients had diffuse high signal intensity in the dorsal funicle on T2\* images, probably representing secondary degeneration. In regions of isolated fiber bundles, such as the white matter tracts in the spinal cord, white matter degeneration in the chronic phase causes an increase in the MD and RD whereas FA and AD decrease.<sup>27</sup> In our study, the RD was higher in the patient groups than in the controls, but the AD values were consistent. Because the AD and RD were calculated from the ROIs that covered the entire cord area, the variability in the measurements was most likely diluted by the gray matter. A study conducted by Cohen-Adad and colleagues summarized the diffusion parameters between the areas of the white matter funicles at the vertebral levels remote from the lesion and demonstrated alterations in both the AD and RD values.<sup>21</sup>

In chronic SCI, the relationship between DTI values and some of the clinical ISNCSCI scores has been previously described. Chang and colleagues have reported that the number of abnormal FA levels in the cervical cord showed a statistically significant



TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS WITH SCI (ENTIRE GROUP, AIS A AND AIS B-E) AND CONTROL SUBJECTS

	Controls (n=40)	Patients (n=28)	AIS A (n=7)	AIS B-E (n=21)
Age (years)	40.6 ± 12.2	59.9 ± 13.3	54.2 ± 14.6	62.3 ± 12.5
Gender (male/female)	20/20	22/6	4/3	18/3
Time since injury (years)		13.1 ± 13.1	26.4 ± 14.2	8.7 ± 9.5
Injury etiology				
Sports		3 (10.7%)	1 (14.3%)	2 (9.5%)
Assault		1 (3.6%)		1 (4.8%)
Transport		10 (35.7%)	3 (42.9%)	7 (33.3%)
Fall		12 (42.9%)	3 (42.9%)	9 (42.9%)
Other traumatic cause		2 (7.1%)		2 (9.5%)
ASIA impairment scale				
AIS A		7 (25.0%)		
AIS B		1 (3.6%)		
AIS C		3 (10.7%)		
AIS D		16 (57.1%)		
AIS E		1 (3.6%)		
Single neurological level				
C1		2 (7.4%)		
C2		3 (11.1%)		
C3		5 (18.5%)		
C4		9 (33.3%)		
C5		4 (14.8%)		
C7		1 (3.7%)		
C8		2 (7.4%)		
T11		1 (3.7%)		
ISNCSCI motor score (max. 100)		66.2 ± 33.7	19.6 ± 17.3	81.8 ± 20.6
ISNCSCI sensory score (max. 224)		130.3 ± 65.6	40.6 ± 15.6	163.3 ± 40.2 <sup>a</sup>
FIM physical subscore (max. 91)		67.1 ± 28.5	40.1 ± 29.6	76.1 ± 22.1

<sup>a</sup>Missing sensory data for two patients.

ASIA, American Spinal Injury Association; AIS A, motor-sensory complete; AIS B, motor complete-sensory incomplete; AIS C-D, motor-sensory incomplete; AIS E, normal examination; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; FIM, Functional Independence Measure.

TABLE 2. DTI PARAMETERS AT LEVEL C 2–3 IN PATIENTS WITH SCI AND CONTROL SUBJECTS

	Controls (40)		Patients (28)		AIS A (7)		AIS B-E (21)		AIS A vs. AIS B-E
	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	
Whole cord									
FA	0.69	0.70 ± 0.07	<b>0.58</b>	<b>0.57 ± 0.09</b>	<b>0.54</b>	<b>0.51 ± 0.08</b>	<b>0.60</b>	<b>0.58 ± 0.09</b>	<i>p</i> = 0.030
			<i>p</i> < 0.001		<i>p</i> < 0.001		<i>p</i> < 0.001		
ADC * 10 <sup>-3</sup> mm <sup>2</sup> /s	0.95	0.94 ± 0.11	<b>1.05</b>	<b>1.13 ± 0.20</b>	<b>1.04</b>	<b>1.16 ± 0.28</b>	<b>1.06</b>	<b>1.12 ± 0.18</b>	<i>p</i> = 0.681
			<i>p</i> < 0.001		<i>p</i> = 0.005		<i>p</i> < 0.001		
AD * 10 <sup>-3</sup> mm <sup>2</sup> /s	1.84	1.84 ± 0.13	1.93	1.93 ± 0.22	1.80	1.87 ± 0.30	1.94	1.95 ± 0.18	<i>p</i> = 0.450
			<i>p</i> = 0.369		<i>p</i> = 0.640		<i>p</i> = 0.122		
RD * 10 <sup>-3</sup> mm <sup>2</sup> /s	0.49	0.48 ± 0.12	<b>0.67</b>	<b>0.73 ± 0.22</b>	<b>0.67</b>	<b>0.80 ± 0.27</b>	<b>0.63</b>	<b>0.70 ± 0.20</b>	<i>p</i> = 0.153
			<i>p</i> < 0.001		<i>p</i> < 0.001		<i>p</i> < 0.001		
Lateral funicles									
FA	0.77	0.77 ± 0.08	<b>0.57</b>	<b>0.57 ± 0.12</b>	<b>0.57</b>	<b>0.51 ± 0.11</b>	<b>0.60</b>	<b>0.59 ± 0.12</b>	<i>p</i> = 0.094
			<i>p</i> < 0.001		<i>p</i> < 0.001		<i>p</i> < 0.001		
ADC * 10 <sup>-3</sup> mm <sup>2</sup> /s	0.88	0.89 ± 0.12	<b>1.08</b>	<b>1.15 ± 0.28</b>	<b>0.97</b>	<b>1.19 ± 0.43</b>	<b>1.09</b>	<b>1.13 ± 0.22</b>	<i>p</i> = 0.759
			<i>p</i> < 0.001		<i>p</i> = 0.004		<i>p</i> < 0.001		

Comparisons adjusted with age by linear regression.

*p* < 0.01 in bold

DTI, diffusion tensor imaging; SCI, spinal cord injury; FA, fractional anisotropy; ADC, apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C-D, motor-sensory incomplete; AIS E, normal.

TABLE 3. DTI PARAMETERS AT THE LESION LEVEL IN PATIENTS WITH SCI AND CONTROL SUBJECTS

	Controls		Patients (18)		AIS A (3)		AIS B-E (15)		vs. AIS B-E
	Median	Mean $\pm$ SD	Median	Mean $\pm$ SD	Median	Mean $\pm$ SD	Median	Mean $\pm$ SD	
Whole cord									
FA	0.67	0.67 $\pm$ 0.06	<b>0.53</b>	<b>0.51 <math>\pm</math> 0.09</b> <i>p</i> < 0.001	<b>0.41</b>	<b>0.38 <math>\pm</math> 0.05</b> <i>p</i> = 0.001	<b>0.54</b>	<b>0.53 <math>\pm</math> 0.07</b> <i>p</i> < 0.001	<i>p</i> = 0.020
ADC $\times 10^{-3}$ mm <sup>2</sup> /s	0.95	0.95 $\pm$ 0.10	<b>1.13</b>	<b>1.14 <math>\pm</math> 0.18</b> <i>p</i> < 0.001	<b>1.36</b>	<b>1.31 <math>\pm</math> 0.19</b> <i>p</i> = 0.001	<b>1.06</b>	<b>1.10 <math>\pm</math> 0.16</b> <i>p</i> < 0.001	<i>p</i> = 0.120
Lateral funicles									
FA	0.75	0.74 $\pm$ 0.07	<b>0.52</b>	<b>0.51 <math>\pm</math> 0.11</b> <i>p</i> < 0.001	<b>0.42</b>	<b>0.38 <math>\pm</math> 0.08</b> <i>p</i> = 0.001	<b>0.56</b>	<b>0.54 <math>\pm</math> 0.10</b> <i>p</i> < 0.001	<i>p</i> = 0.042
ADC $\times 10^{-3}$ mm <sup>2</sup> /s	0.93	0.94 $\pm$ 0.13	<b>1.05</b>	<b>1.14 <math>\pm</math> 0.20</b> <i>p</i> < 0.001	<b>1.34</b>	<b>1.31 <math>\pm</math> 0.30</b> <i>p</i> = 0.003	<b>1.04</b>	<b>1.10 <math>\pm</math> 0.17</b> <i>p</i> < 0.001	<i>p</i> = 0.250

Controls = mean of diffusion tensor parameters for healthy volunteers at C2-C3 to C5-C6 levels.

Comparisons adjusted with age by linear regression.

*p* < 0.01 in bold.

DTI, diffusion tensor imaging; SCI, spinal cord injury; FA, fractional anisotropy; ADC, apparent diffusion coefficient; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C-D, motor-sensory incomplete; AIS E, normal.

correlation with abnormal motor levels, but not with sensory levels.<sup>19</sup> Cohen-Adad and colleagues also detected a correlation between DTI parameters (FA and RD) and a combined variable consisting of the sensory and motor scores of the ISNCSCI.<sup>21</sup> Furthermore, in a study by Petersen and colleagues, the decrease of FA correlated with the completeness of SCI on the basis of the AIS scale.<sup>18</sup> In a study of pediatric SCI, the clinical findings showed a

statistically stronger correlation with the DTI values compared with the upper border of the SCI on conventional MRI.<sup>28</sup>

In our study, the FA values demonstrated a moderate to strong correlation with the motor and sensory scores of the ISNCSCI, but not with a single neurological level. There was also a moderate association between the sensory score and RD at the upper cervical cord level. These findings were consistent with earlier

TABLE 4. PARTIAL CORRELATIONS (AGE AS A CONTROLLED FACTOR) OF DTI PARAMETERS AND CONVENTIONAL MRI FINDINGS WITH CLINICAL SCORES

	ISNCSCI scores					FIM scores				
	Mtot	Mue	Mle	Stot <sup>a</sup>	NL	Ftot	Fcare	Fspc	Fmob	Floc
DTI, C 2–3 level ( <i>n</i> = 28)										
Whole cord										
FA	<b>0.56*</b>	<b>0.49*</b>	<b>0.52*</b>	<b>0.66**</b>	-	<b>0.51*</b>	<b>0.48*</b>	<b>0.56*</b>	<b>0.58*</b>	<b>0.56*</b>
ADC	-	-	-	-	-	-	-	<b>-0.51*</b>	-	-
AD	-	-	-	-	-	-	-	-	-	-
RD	-0.45	-	-0.45	<b>-0.50*</b>	-	-0.42	-	<b>-0.55*</b>	-0.49	-0.47
Lateral funicles										
FA	<b>0.55*</b>	0.46	<b>0.55*</b>	<b>0.62**</b>	-	<b>0.56*</b>	<b>0.49*</b>	<b>0.57*</b>	<b>0.62**</b>	<b>0.61**</b>
ADC	-	-	-	-	-	-	-	-	-	-
DTI, Lesion level ( <i>n</i> = 18)										
Whole cord										
FA	<b>0.67*</b>	0.54	<b>0.76**</b>	0.56	-	-	-	-	<b>0.73**</b>	0.57
ADC	-	-	-	-	-	-	-	-	-0.50	-
Lateral funicles										
FA	<b>0.67*</b>	-	<b>0.74**</b>	0.54	-	0.53	-	0.49	<b>0.75**</b>	<b>0.71**</b>
ADC	-	-	-	-	-	-	-	-	-	-
MRI findings ( <i>n</i> = 23)										
Lesio, cranial limit	-	-	-	-	-	-	0.42	0.43	0.47	-
Lesio, length	<b>-0.54*</b>	-	<b>-0.56*</b>	<b>-0.77**</b>	-	-	-	-	-0.42	-0.44

<sup>a</sup>Two sensory scores missing (*n* = 26/16/21 respectively).

*p* ≤ 0.05, \**p* ≤ 0.01 in bold; \*\**p* ≤ 0.001 in bold and underlined.

DTI, diffusion tensor imaging; FA, fractional anisotropy; ADC, apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; Mtot, total motor score; Mue, motor score for the upper extremities; Mle, motor score for the lower extremities; Stot, total sensory score; NL, single neurological level; FIM, Functional Independence Measure; Ftot, FIM motor subscale; Fcare, FIM self care subscore; Fspc, FIM sphincter control subscore; Fmob, FIM mobility subscore; Floc, FIM locomotion subscore.

studies, which showed that an increase in FA and a decrease in RD were associated with a better clinical outcome. Correlations between the DTI values and FIM appeared mostly in the FA, which decreased with increasing disability. In particular, the FA was moderately associated with all of the FIM motor subscores at the upper cervical cord level. At the lesion level, a strong correlation between the FA values and motor scores of the lower extremities was found. Moreover, correlations between the FA values and FIM scores were focused on the mobility and locomotion subscores.

The upper level of the lesion determined using conventional MRI did not correlate with any of the ISNCSCI parameters, particularly the clinically determined single neurological level. The length of the lesion moderately or strongly correlated with the motor and sensory scores, indicating that the clinical state of patients was worse with a longer lesion length. The association between the length of the lesion on conventional MRI and the degree of impairment has also been previously shown in acute and subacute SCI.<sup>8,29</sup> In our study, the conventional MRI findings and subscales of FIM were only modestly associated with each another. However, similar findings have been reported in a study of subacute SCI, which indicated that function was better when the location of the injury was lower on the spine and when the length of the injury was shorter.<sup>30</sup>

To the best of our knowledge, no previous studies in adults have investigated the DTI values of patients with chronic SCI using the entirety of the ISNCSCI parameters or with any instrument used to assess disability. Although the FA, ADC, and RD values in our study differed significantly between the patients and controls, the FA appeared to be the most sensitive parameter in describing the state of the spinal cord in the chronic phase of SCI. As a strength, our study population was larger than those in previous studies, and included SCI patients with variable neurological deficits and disability. The age range of the patients was broad (23–78 years), and included many elderly people.

In the present study, the placement of the ROIs was simple to put into practice. The results presented in this article also indicated that the measurements of the DTI values at the area of the intact upper spinal cord could provide clinically relevant information regarding the state of the chronic injury located below the level measured. This information could be useful in reducing the number of MRI artifacts and producing reliable DTI measures, because the measurement could be performed in regions where the vertebral fixation material and bone/soft tissue injuries did not distort the imaging data.

One weakness of our study was that the patients and control subjects were not age matched. In previous studies, the FA and ADC have been shown to decrease and increase with aging.<sup>31</sup> Moreover, there have also been studies that have reported no correlation between the DTI values and age.<sup>32,33</sup> However, the potential effect of age on DTI values was relatively small compared with the effect of the SCI. Age was also considered using statistical methods.

Overall, compared with the brain, the spinal cord is a substantially more challenging target for DTI analysis. The small size of the spinal cord, which is surrounded by vertebral bony element, as well as its physiological macroscopic motion, all present technical challenges to MRI image acquisition.<sup>34</sup> We chose not to use the cardiac gating technique, which would have diminished the corticospinal fluid flow-related artifacts and lengthened the acquisition time, thus increasing the number of artifacts caused by a swallowing and respiratory movement. The measurements were not strictly performed at the level of the center of the vertebral body, which could have also reduced some artifacts.<sup>35</sup>

In the future, DTI may provide a truly quantitative and objective method for assessing spinal cord and tissue microstructure in studies of novel treatments and in clinical settings. The pattern and direction of changes in DTI values, which were measured during the acute or subacute period of SCI, differed from those in chronic SCI. In addition, associations between the clinical scores and DTI values were inconsistent.<sup>36,37</sup> In animal studies, it has been suggested that the DTI values at the acute phase can predict recovery after SCI.<sup>38,39</sup> In the long-term, prospective human studies are required to examine the changes in DTI values and clinical state with respect to time after traumatic SCI, and to determine whether the DTI values in the acute phase have a predictive value for functional outcome.

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## Author Disclosure Statement

No competing financial interests exist.

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## ORIGINAL ARTICLE

# Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury

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**Study design:** Prospective clinical case–control study.

**Objectives:** The aim of this study was to use diffusion tensor imaging (DTI) to assess the state of cerebral white matter tracts after spinal cord injury (SCI). The DTI metrics were evaluated in relation to neurological deficits and to the size and level of the spinal cord lesions.

**Setting:** Tampere University Hospital, Tampere, Finland.

**Methods:** Thirty-four patients ( $n = 34$ ) with clinically complete and incomplete SCI were evaluated using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). DTI metrics (fractional anisotropy (FA) and apparent diffusion coefficient (ADC)) were calculated for multiple levels along the course of the corticospinal tract. The state of the spinal cord after injury was assessed using conventional magnetic resonance imaging (MRI). DTI parameters were compared with 40 orthopedically injured control subjects.

**Results:** Statistically significant differences in the DTI values between patients and controls were detected in the posterior area of the centrum semiovale. In this area, the FA values were lower in the patients compared with controls ( $P = 0.008$ ). For patients with clinically complete injury, the difference was even more significant ( $P = 0.0005$ ). Motor and sensory scores of the ISNCSCI correlated positively with FA and negatively with ADC values of the centrum semiovale. A moderate association was observed between the macroscopic changes in the spinal cord and the DTI abnormalities in the centrum semiovale.

**Conclusion:** In patients with chronic SCI, DTI changes can be observed in the cerebral white matter. These alterations are associated with the clinical state of the patients.

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**Keywords:** traumatic spinal cord injury; magnetic resonance imaging; diffusion tensor imaging; degeneration; cerebral white matter

## INTRODUCTION

Spinal cord injury (SCI) causes local destruction of nervous and vascular tissue in the spinal cord, which leads to dramatic changes in motor, sensory and autonomic functions. The neuropathological cascade induced by trauma continues in the subacute phase and can exacerbate the neuronal damage at the site of the primary lesion and in the surrounding area.<sup>1</sup> Anterograde and retrograde degeneration proceed along the spinal white matter tracts, resulting in axonal loss and demyelination.<sup>2,3</sup> This degeneration has been shown to extend cranially, even to cerebral regions.<sup>4</sup> In addition, the gray matter volume of the sensorimotor cortex has been shown to decrease after SCI.<sup>5,6</sup>

Diffusion tensor imaging (DTI), which is a method that measures the diffusion of water molecules in tissues, provides quantitative information about tissue microstructure. Among the parameters derived from DTI data, the apparent diffusion coefficient (ADC) or the mean diffusivity (MD) express the magnitude of the diffusion, and the fractional anisotropy (FA) describes the ease of water moving in one direction/degree of anisotropy of the diffusion.<sup>7,8</sup> In nervous tissue, the orientation of fiber bundles and the axonal diameter, density and myelination have an effect on DTI metrics.<sup>9,10</sup>

Numerous studies have demonstrated the ability of DTI to detect abnormalities in the spinal cord parenchyma, even in regions that are remote from the macroscopic lesions observed on conventional MRI scans. These results suggest secondary degeneration of the white matter tracts in the spinal cord.<sup>11–13</sup> Previously, abnormalities in DTI values of the cerebral corticospinal tract after SCI have also been reported. However, these studies consisted of relatively small samples and primarily included subjects with complete SCI.<sup>5,14,15</sup>

The purpose of this study was to quantitatively assess the state of the cerebral white matter tracts in chronic traumatic SCI using DTI in a generalizable sample of patients with both clinically complete and incomplete SCI. We also investigated the association of DTI values with clinical neurological deficit. Finally, the consequence of injury to the spinal cord was assessed using conventional MRI and the findings were correlated with cerebral DTI values.

## MATERIALS AND METHODS

### Study framework and statement of ethics

This study is part of the Spinal Cord Injury Series of Tampere-Retroprospective Study. The study aims to examine SCI from a multidisciplinary perspective, in a case–control setting, to enhance the clinical assessment and treatment of this

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specific patient group. The ethics approval for the study was obtained from the Ethical Committee of Pirkanmaa Hospital District, Finland. A written informed consent was obtained from each participant. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

## Subjects

All consecutive patients with a chronic traumatic cervical spine injury ( $n = 88$ ) who were admitted to either the ward or an outpatient clinic in Tampere University Hospital between 1989 and 2010 were contacted for participation in the study in 2011. The inclusion criteria were as follows: (i) age over 18 years, (ii) resident of the hospital district, (iii) clinically significant neurological findings due to a traumatic cervical spinal cord injury after 24 h of monitoring in the hospital and/or (iv) time since injury was greater than 1 year. The exclusion criteria were as follows: (i) known neurological illness other than spinal cord injury, (ii) respiratory arrest, (iii) contraindications to MRI and/or (iv) refusal to participate in the study. The final SCI population sample consisted of 34 patients. The main reason for exclusion was refusal to participate in the study ( $n = 17$ ).

Patients with SCI were compared with an orthopedically injured control sample of 40 neurologically intact subjects. The control subjects were recruited from consecutive patients with ankle trauma from the Emergency Department of Tampere University Hospital. A total of 609 patients with ankle injury were screened for participation. The aim was to enroll five male and five female subjects into each of following age groups: (i) 18–30, (ii) 31–40, (iii) 41–50 and (iv) 51–60 years. The inclusion criteria were as follows: (i) age 18–60 years, (ii) being a resident of the University Hospital district and (iii) ankle trauma. The exclusion criteria were as follows: (i) neurological problems, (ii) psychiatric problems, (iii) history of traumatic brain injury, (iv) former neurosurgical procedure, (v) problems with hearing or vision, (vi) first language other than Finnish, (vii) contraindications to MRI and (viii) refusal to participate. In our future studies, we are planning to examine the possible confounding effects of trauma-induced psychological stress on neuropsychological performance. Therefore, orthopedic controls were used instead of healthy volunteers.

## Collection of clinical data and neurological scoring

All patients with SCI were examined at an outpatient clinic in Tampere University Hospital. The collection of clinical data was performed by the first author of this study. The etiology of the spinal cord injury was classified using the International SCI Core Data Set.<sup>16</sup> The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) was used to evaluate and classify the neurological consequence of spinal cord injury.<sup>17</sup> The level of disability was assessed using the motor subscale of the Functional Independence Measure.<sup>18,19</sup>

The medical condition of the subjects was assessed according to the International Classification of Diseases and Related Health Problems 10th revision (ICD –10).<sup>20</sup> The Basic Pain Data Set was used to collect data from patients who suffered from neuropathic pain related to the SCI.<sup>21</sup> Information on the current medication at the time of examination was classified into 17 subgroups according to the Finnish Commercial Drug Catalog (Pharmaca Fennica), which was categorized on the basis of the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System codes.

## Magnetic resonance imaging (MRI)

The MRI examinations of the brain and spinal cord were performed using a 3T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany). A 12-channel head coil and a 4-channel neck coil were used simultaneously.

The spinal cord series included a sagittal T2 turbo spin echo (TR 3500 ms, TE 108 ms, flip angle 160°, 1 Average, FOV 280, Matrix 288 × 384, slice/gap 3.0/0.3 mm, ETL 34), and an axial T2\*-weighted multi-gradient echo combination series (TR 506 ms, TE 14 ms, flip angle 30°, 1 Average, FOV 160 mm, Matrix 256 × 256, slice/gap 3.0/0.3 mm) was acquired. The voxel size of the T2\* images was 0.6 × 0.6 × 3.0 mm.

The MRI protocol of the brain included a sagittal T1-weighted series (TR 750 ms, TE 7.3 ms, slice/gap 5.0/1.5 mm, FOV 220), an axial T1 series (TR 600 ms, TE 6.8 ms, slice/gap 4.0/1.2 mm, FOV 220), an axial T2 turbo spin echo series (TR 5600 ms, TE 109 ms, flip angle 120°, slice/gap 4.0/1.2 mm, FOV 220), an axial FLAIR (TR 5500 ms, TE 87 ms, TI 1922 ms, flip angle 150°, slice/gap 4.0/1.2 mm, FOV 220), a coronal T2 turbo spin echo series (TR 5990, TE 109, flip angle 120°, FOV 220 slice/gap 3.0/0.6 mm) and an axial susceptibility-weighted (SWI) series (TR 27, TE 20, flip angle 15°, slice 1.5 mm, FOV 230). The parameters for the DTI sequence of the brain were TR 5144 ms, TE 92 ms, FOV 230, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, b-factor 0 and 1000 s mm<sup>-2</sup> and 20 diffusion gradient orientations.

Interpretation of the imaging findings on the conventional MRI scans was performed by a neuroradiologist (AEB).

## DTI analysis

DTI measurements were performed by a physicist (UH) on a workstation using the commercially available software Neuro3D (Siemens Healthcare, Malvern, PA, USA).

Circular regions of interest (ROI; 19 mm<sup>2</sup>) were manually placed on color-coded axial FA maps of the brain. The ROIs were placed at the following anatomical locations (Figure 1): (i) the cerebral peduncle, (ii) the posterior limb of the internal capsule (PLIC) (anterior and posterior), (iii) the posterior part of the corona radiata (anterior and posterior) and (iv) the centrum semiovale (anterior, center and posterior). The ROIs were placed carefully to avoid border areas, such as areas overlapping with cerebrospinal fluid spaces and neighboring tracts. The ROIs were placed bilaterally on all locations, and DTI metrics from left and right structures were averaged per level measured. Median values, mean values and s.d. for FA and ADC were calculated.

Signal-to-noise ratio (SNR) was determined according to the NEMA Standards 1–2008, including the following expression for SNR:  $SNR = \frac{S}{\text{image\_noise}}$ , where  $S$  = signal, and image noise is estimated with Rayleigh distribution:  $\text{image\_noise} = \frac{s.d.}{0.66}$ . The SNR measurements were used from the images of three healthy subjects. The ROI was placed on the left side of each region of the  $b = 0$  s mm<sup>-2</sup> image.

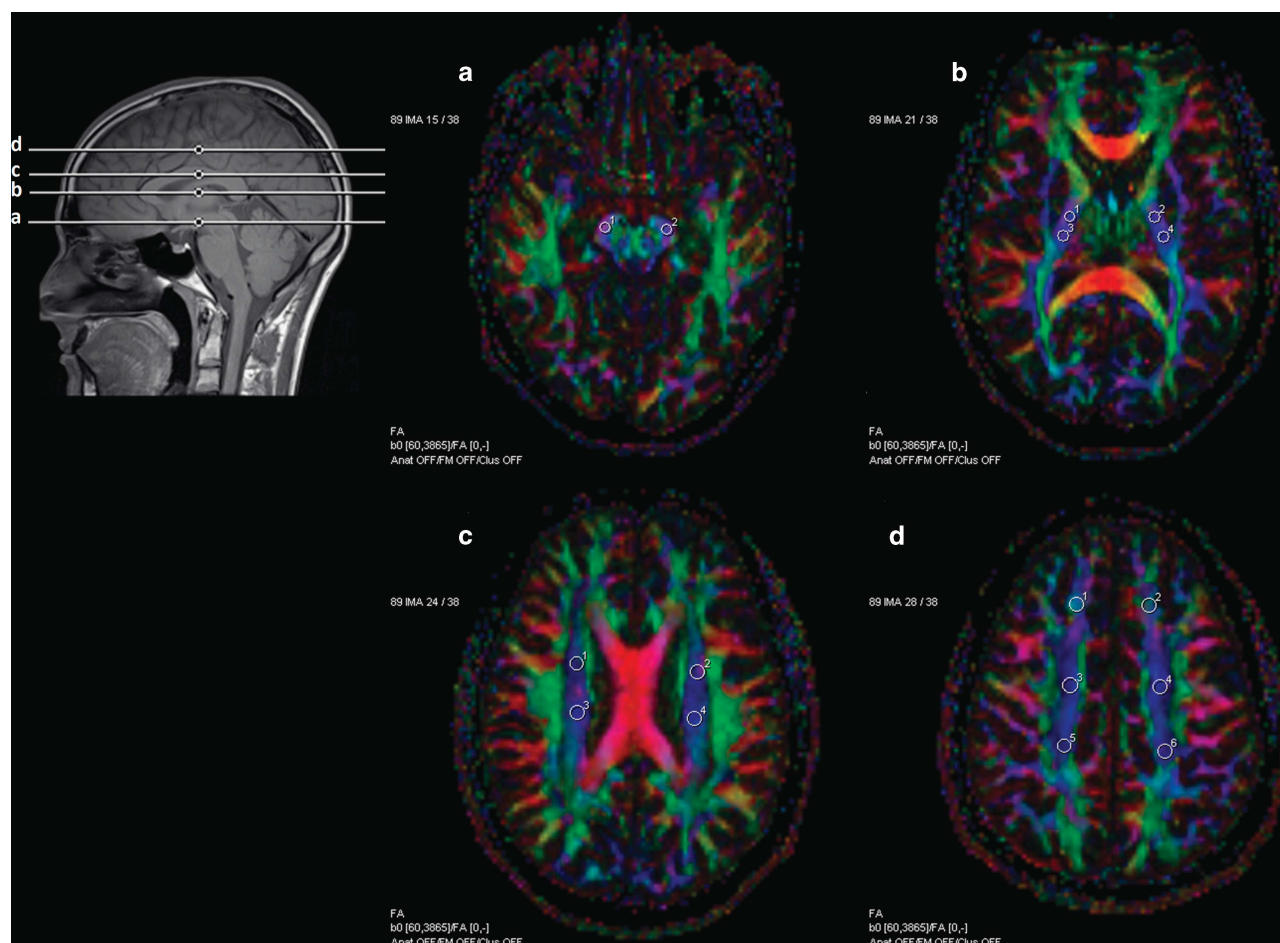
## Statistical analyses

Patients with SCI were not gender-matched or age-matched with the control subjects; therefore, the analyses were performed using linear regression adjusted for age and gender. Correlations were calculated by partial correlation, with age and gender as the controlling factors. The clinical variables used in the correlations were the ISNCSCI-derived total motor score, motor subscore for upper and lower extremities, total sensory score and single neurological level. DTI values were correlated with the most cranial level of the spinal cord lesion and with the length of the lesion assessed by conventional MRI. To correlate the single neurological level and the most cranial level of the lesion with DTI values, each vertebral level was sequentially numbered in the cranio-caudal direction. For further comparisons, the patient population was divided into two groups according to the completeness of the injury: AIS A and AIS B–E. All parameters were ranked before the analyses. Because of multiple comparisons, the statistical significance level was set at 1%. The intra-observer repeatability (intra-class correlation coefficient or ICC) and variability (coefficient of variation, or CV%) were assessed for FA and ADC values measured from healthy volunteers. The statistical analyses were performed under the guidance of a biostatistician. The SPSS program (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, IBM Corp.) was used to perform all statistical analyses.

## RESULTS

### Clinical findings

Clinical characteristics of the 34 SCI patients (whole group, AIS A and AIS B–E) and 40 control subjects are shown in Table 1. Of the patients with SCI, 18 (52.9%) patients had some chronic medical problems. The most common chronic medical problem was disease of the circulatory system ( $n = 9$ , 26.5%) and disease of the musculoskeletal system and connective tissue ( $n = 7$ , 20.6%). Twenty-eight (82.4%)



**Figure 1** The placement of the ROIs on the color-coded FA maps: (a) cerebral peduncle, (b) posterior limb of the internal capsule, (c) posterior part of the corona radiata and (d) centrum semiovale.

patients used some permanent medication; 15 (44.1%) patients used some pain medication; 12 (35.3%) patients used a prophylactic antibiotic; 9 (26.5%) patients used drugs for the cardiovascular system; and 13 (38.2%) patients used muscle relaxants. Thirteen (38.2%) patients with SCI suffered from neuropathic pain.

Eighteen (45.0%) of the control subjects demonstrated a diagnosed disease. Six of the patients had a disease of the circulatory system (15.0%) and 4 (10.0%) patients had disease of the musculoskeletal system and connective tissue. Thirteen (32.5%) control subjects used some permanent medication. The most prevalent group used drugs for the cardiovascular system ( $n=6$ , 15.0%). There were no control subjects who showed neuropathic pain.

### Conventional MRI findings

Twenty-nine (85.3%) patients with clinically defined spinal cord injury had a focal post-traumatic cord lesion on either the sagittal or axial T2/T2\* images. Five (17.2%) patients had two separate lesions. Five patients (14.7%) had no visible spinal cord lesions. The mean craniocaudal length of the main lesion was 18.3 mm (s.d.  $\pm 14.4$ ). The most cranial borders of the main lesions were located between levels C2 and C6. Spinal cord atrophy was found in 21 (61.8%) patients.

In the patients with no post-traumatic cord lesions, the average time between the SCI and MRI was 2.8 years (s.d.  $\pm 2.2$ ), the mean ISNCSCI motor score was 93.2 (s.d.  $\pm 6.4$ ) and sensory score was

192.0 (s.d.  $\pm 28.5$ ). In turn, in the patients with spinal cord atrophy, the time since injury was 14.3 years (s.d.  $\pm 11.4$ ), the ISNCSCI motor score was 50.0 (s.d.  $\pm 31.3$ ) and sensory score was 100.7 (s.d.  $\pm 60.6$ ).

Four (11.8%) patients had moderate to severe cerebral microangiopathy. One (2.9%) patient had lacunar ischemic lesions (size  $<1$  cm) in both cerebellar hemispheres, and one (2.9%) patient had a trigeminal schwannoma. Eleven (32.4%) SCI patients had single diffuse axonal injury (DAI) -type microhemorrhage, and three (8.8%) subjects had between two and five separate DAI lesions. Eight (23.5%) patients had an old post-traumatic parenchymal lesion, four of which were under 1 cm and four of which were 1–2 cm in diameter. Thirteen (38.2%) patients had between one and ten punctate white matter hyperintensities, and seven (20.6%) patients had more than ten punctate white matter hyperintensities. Patients with the above-mentioned abnormalities in conventional brain imaging sequences were not excluded because the abnormalities were considered ordinary for the patient and for the age groups in question and, except for microangiopathy, the abnormalities were not located in the area of ROI measurements.

None of the control subjects had significant structural abnormalities on conventional MRI scans.

### Relationship between clinical variables and cerebral DTI metrics

Table 2 summarizes the measured FA and ADC values. Controls were compared with the entire group of patients with SCI and to the AIS A

**Table 1** Clinical characteristics of SCI patients (entire group, AIS A and AIS B–E) and control subjects

	Controls (n = 40)	Patients (n = 34)	AIS A (n = 10)	AIS B–E (n = 24)
Age (years)	40.6 ± 12.2	57.5 ± 14.5	51.3 ± 15.7	60.1 ± 13.4
Gender (male/female)	20/20	27/7	7/3	20/4
Time since injury (mean ± s.d.)		13.9 ± 12.1	23.5 ± 13.1	9.9 ± 9.3
Median (range)		(8.8, 1.0–43.1)	(23.4, 6.4–38.2)	(6.8, 1.0–43.1)
<i>Injury etiology</i>				
Sports		6 (17.6%)	2 (20%)	4 (16.7%)
Assault		1 (2.9%)		1 (4.2%)
Transport		12 (35.3%)	5 (50%)	7 (29.2%)
Fall		13 (38.2%)	3 (30%)	10 (41.7%)
Other traumatic cause		2 (5.9%)		2 (8.3%)
<i>ASIA impairment scale (AIS)</i>				
AIS A		10 (29.4%)		
AIS B		1 (2.9%)		
AIS C		4 (11.8%)		
AIS D		18 (52.9%)		
AIS E		1 (2.9%)		
<i>ISNCSCI single neurological level</i>				
C1		2 (6.1%)		
C2		4 (12.1%)		
C3		5 (15.2%)		
C4		11 (33.3%)		
C5		5 (15.2%)		
C6		1 (3.0%)		
C7		1 (3.0%)		
C8		3 (9.1%)		
T11		1 (3.0%)		
ISNCSCI motor score (max. 100)		63.4 ± 33.8	20.4 ± 15.5	81.3 ± 20.1
ISNCSCI sensory score (max. 224)		123.5 ± 65.1	42.0 ± 16.8	160.6 ± 39.0
FIM physical subscore (max. 91)		65.8 ± 28.6	41.1 ± 28.3	76.0 ± 22.0

Abbreviations: ASIA, American Spinal Injury Association; AIS A, motor-sensory complete; AIS B, motor complete-sensory incomplete; AIS C–D, motor-sensory incomplete; AIS E, normal examination; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; FIM, Functional Independence Measure.

and AIS B–E subgroups. A comparison between the AIS A and AIS B–E subgroups was performed. Patients with SCI had lower FA values in the posterior ROIs of the centrum semiovale compared with the controls. In the patient group with clinically complete injury, the ADC values of the posterior centrum semiovale were higher and the FA values of the cerebral peduncle were lower than those of the healthy controls, although these differences did not reach statistical significance.

Partial correlations (age and gender as controlling factors) between cerebral DTI values and the clinical findings (ISNCSCI and MRI findings of the spinal cord lesion) are presented in Table 3. The FA values of the PLIC were moderately and positively associated with the motor score of the upper extremities and the total sensory score derived from the ISNCSCI and with the cranial level of the lesion in the conventional MRI. In the posterior part of the centrum semiovale, the FA values correlated moderately and positively and the ADC values correlated moderately and negatively with the motor and sensory scores of the ISNCSCI. In addition, the ADC values in the posterior part of the centrum semiovale were positively associated with the lesion length in the conventional MRI.

DTI values were not statistically associated with the time since injury.

### SNR analysis

The mean SNR value ( $\pm$  s.d.) of  $b=0$  s mm<sup>-2</sup> images for the all regions *in vivo* measurements was  $30.5 \pm 3.6$  (range 26.8–36.2).

### Intra-observer repeatability and variability of DTI measurements

The ICC results for FA and ADC were between 0.40 and 0.88 (mean 0.67) and 0.58 and 0.85 (mean 0.72), respectively, and 75.0% of the ICCs for FA and 93.8% for ADC were over 0.6. The CV% for FA and ADC varied between 3.8% and 20.3% and 3.0% and 13.3%, respectively. The CV% values were below 10% in 37.5% of the FA and 93.7% of the ADC measurements.

### DISCUSSION

The primary aim of this study was to quantitatively assess the state of cerebral white matter tracts of patients with chronic traumatic SCI by using DTI. In our study, statistically significant differences in DTI parameters between SCI patients and controls were detected only in the posterior area of the centrum semiovale, which approximately reflects the white matter in the subcortical area of the sensory-motor cortex. The associations of DTI values with clinical variables indicating SCI-related deficiencies were focused on the corresponding area. The minor findings in the cerebral peduncle and the PLIC suggest that the white matter tracts in those structures may be affected by SCI.



Few reports about the diffusion properties of the spinal cord in the chronic state of the injury have been published in the literature.<sup>11–13</sup> In those studies, DTI has been shown to estimate the total lesion load in the spinal cord better than conventional MRI. FA values have been proven to diminish in areas of the intact upper spinal cord after injury. Hypothetically, diminishing FA values reflects anterograde and retrograde degeneration of the white matter tracts.<sup>3</sup> Histologically, axonal loss, demyelination, gliosis, astrocytic scarring and an increase in the extracellular matrix are found in secondary degeneration of the white matter tracts.<sup>2</sup> From a DTI perspective, a decreased FA and an increased ADC or MD are associated with the aforementioned neuropathological changes.<sup>22</sup>

Currently, reports studying changes in the cerebral white matter tracts after SCI in humans are relatively sparse. Yamamoto *et al.*<sup>4</sup> observed histological evidence of retrograde degeneration after SCI in supraspinal areas reaching as high as the pons. In a study by Guleria *et al.*,<sup>14</sup> alterations in DTI metrics suggesting retrograde degeneration after SCI were shown along the corticospinal tract in the medulla, pons, midbrain and PLIC. Freund *et al.*<sup>15</sup> observed a reduction in the FA in patients with SCI in the pyramids and the PLIC. Although there were no significant differences in FA values at the level of the cerebral peduncles, axonal degeneration and demyelination-related alterations in directional diffusivities were noted. In a tractography study by Wrigley *et al.*,<sup>5</sup> the corticospinal tract revealed changes in DTI metrics, which were indicative of fiber loss.

We did not find any statistically significant differences between the DTI values of patients and controls in the area of cerebral peduncles,

which simply conveys motor information. However, the FA values appeared to be lower in patients with a complete SCI compared with the controls.

The majority of connections between the motor and sensory primary and supplementary cerebral cortex and subcortical structures travel through the PLIC and the posterior part of the corona radiata.<sup>23,24</sup> We did not find any significant differences in the DTI metrics between SCI patients and controls in these structures. Freund *et al.*<sup>14</sup> and Guleria *et al.*<sup>15</sup> showed reduced FA values but unchanged MDs in the PLIC after SCI compared with healthy subjects. Guleria *et al.*<sup>15</sup> reported a progressive increase in the FA values in the PLIC and corona radiata up to 12 months after injury. FA values in the corona radiata were eventually higher in subjects with SCI compared with the controls. They suggested that the increase in the FA values could be related to structural alterations of compensatory subcortical regeneration. In our sample, the FA values of the PLIC were moderately related to some clinical variables and tended to increase, especially with better sensory function. It can be hypothesized that in our patient population, the white matter tracts in the PLIC may also be affected by SCI.

In our study, the significant differences in DTI values between the patients and controls were focused on the posterior ROIs of the centrum semiovale. In this area, the FA values were significantly lower in the patients, especially in the patients with complete injury, compared with the controls. The ADC of the patients with complete injury was higher than the control values, although not reaching statistical significance. The posterior ROIs were located in approximately the same area where motor corticospinal and sensory

**Table 2** Diffusion tensor imaging parameters in patients with SCI and control subjects

	Controls (N = 40)		Patients (N = 34)			AIS A (n = 10)			AIS B–E (n = 24)			P-value, AIS A vs AIS B–E
	Med	Mean ± s.d.	Med	Mean ± s.d.	P-value	Med	Mean ± s.d.	P-value	Med	Mean ± s.d.	P-value	
Cerebral peduncle												
FA	0.79	0.80 ± 0.04	0.78	0.78 ± 0.06	0.175	<b>0.74</b>	<b>0.74 ± 0.06</b>	<b>0.036*</b>	0.78	0.79 ± 0.05	0.996	0.093
ADC	0.75	0.75 ± 0.05	0.75	0.76 ± 0.06	0.048	0.77	0.77 ± 0.07	0.156	0.75	0.75 ± 0.05	0.050	0.562
Posterior limb of the internal capsule												
Anterior FA	0.70	0.70 ± 0.04	0.70	0.70 ± 0.04	0.830	0.70	0.69 ± 0.02	0.406	0.71	0.71 ± 0.04	0.375	0.171
Anterior ADC	0.71	0.71 ± 0.03	0.69	0.70 ± 0.04	0.496	0.69	0.70 ± 0.02	0.830	0.69	0.70 ± 0.04	0.478	0.633
Posterior FA	0.71	0.70 ± 0.04	0.72	0.72 ± 0.04	0.074	0.72	0.71 ± 0.04	0.116	0.73	0.72 ± 0.04	0.083	0.855
Posterior ADC	0.71	0.71 ± 0.02	0.70	0.70 ± 0.03	0.600	0.70	0.70 ± 0.02	0.286	0.71	0.71 ± 0.03	0.788	0.575
Posterior part of the corona radiata												
Anterior FA	0.47	0.48 ± 0.07	0.48	0.48 ± 0.06	0.496	0.48	0.48 ± 0.04	0.711	0.48	0.48 ± 0.07	0.496	0.665
Anterior ADC	0.67	0.67 ± 0.05	0.71	0.72 ± 0.06	0.195	0.69	0.70 ± 0.05	0.232	0.72	0.73 ± 0.07	0.374	0.729
Posterior FA	0.53	0.53 ± 0.06	0.54	0.53 ± 0.08	0.768	0.54	0.52 ± 0.08	0.909	0.53	0.53 ± 0.08	0.832	0.805
Posterior ADC	0.71	0.72 ± 0.04	0.73	0.73 ± 0.04	0.249	0.71	0.72 ± 0.03	0.420	0.73	0.73 ± 0.05	0.494	0.704
Centrum semiovale												
Anterior FA	0.61	0.62 ± 0.06	0.57	0.57 ± 0.09	0.483	0.58	0.57 ± 0.06	0.067	0.55	0.57 ± 0.10	0.959	0.463
Anterior ADC	0.71	0.72 ± 0.04	0.73	0.74 ± 0.06	0.547	0.72	0.73 ± 0.04	0.465	0.74	0.75 ± 0.07	0.668	0.781
Central FA	0.60	0.60 ± 0.08	0.61	0.60 ± 0.07	0.270	0.60	0.59 ± 0.07	0.937	0.61	0.60 ± 0.07	0.138	0.267
Central ADC	0.72	0.72 ± 0.04	0.72	0.74 ± 0.07	0.967	0.71	0.72 ± 0.06	0.646	0.73	0.75 ± 0.07	0.531	0.597
Posterior FA	0.56	0.57 ± 0.05	<b>0.52</b>	<b>0.52 ± 0.06</b>	<b>0.008**</b>	<b>0.50</b>	<b>0.48 ± 0.08</b>	<b>0.000**</b>	0.52	0.53 ± 0.05	0.352	<b>0.013*</b>
Posterior ADC	0.72	0.73 ± 0.04	0.74	0.75 ± 0.06	0.465	<b>0.76</b>	<b>0.78 ± 0.09</b>	<b>0.023*</b>	0.73	0.74 ± 0.04	0.491	<b>0.025*</b>

Abbreviations: ADC, apparent diffusion coefficient; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C–D, motor-sensory incomplete; AIS E, normal; FA, fractional anisotropy; Med, Median.

Comparisons adjusted with age and gender by linear regression.

ADC ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ).

\* $P < 0.05$  in bold, \*\* $P < 0.01$  in bold.

**Table 3** Partial correlations (age and gender as controlling factors) between cerebral DTI values and clinical findings

Brain DTI values	ISNCSCI parameters					Spinal cord MRI	
	Mtot	Mue	Mle	Stot <sup>a</sup>	NL	CL <sup>b</sup>	LL <sup>b</sup>
<i>Cerebral peduncle</i>							
FA	—	—	—	—	—	—	—
ADC	—	—	—	—	—	—	—
<i>PLIC</i>							
Anterior FA	—	0.414*	—	<b>0.493**</b>	—	0.456*	—
Anterior ADC	—	—	—	—	—	—	—
Posterior FA	—	—	—	—	—	—	—
Posterior ADC	—	—	—	—	—	—	—
<i>Corona radiata</i>							
Anterior FA	—	—	—	—	—	—	—
Anterior ADC	—	—	—	—	—	—	—
Posterior FA	—	—	—	—	—	—	—
Posterior ADC	—	—	—	—	—	—	—
<i>Centrum semiovale</i>							
Anterior FA	—	—	—	—	—	—	—
Anterior ADC	—	—	—	—	—	—	—
Central FA	—	—	—	—	0.411*	—	—
Central ADC	—	—	—	—	—	—	—
Posterior FA	0.426*	<b>0.460**</b>	—	<b>0.482**</b>	—	—	—
Posterior ADC	−0.425*	<b>−0.505**</b>	—	<b>−0.554**</b>	—	—	<b>0.493**</b>

Abbreviations: ADC, apparent diffusion coefficient; CL, cranial level of lesion in conventional MRI; DTI, diffusion tensor imaging; FA, fractional anisotropy; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; LL, lesion length; MRI, magnetic resonance imaging; Mtot, total motor score; Mue, motor score of the upper extremities; Mle, motor score of the lower extremities; NL, single neurological level; PLIC, posterior limb of internal capsule; Stot, total sensory score.

\* $P < 0.05$ .

\*\* $P < 0.01$  in bold.

<sup>a</sup> $n = 32$ .

<sup>b</sup> $n = 29$ .

thalamocortical projections pass through the white matter area directly below the cortex.<sup>25,26</sup>

The motor and sensory scores of the ISNCSCI were positively related to the FA values and negatively related to the ADC values in the posterior part of the centrum semiovale. These findings suggest that the clinical state of the patient tends to be better with higher FA values and lower ADC values. Recently, the relationship between spinal DTI values and ISNCSCI scores has been reported in chronic SCI patients.<sup>12,27</sup> To the best of our knowledge, this is the first study concerning cerebral sensory-motor white matter tracts in which the association of DTI values to the neurological deficit of patients with SCI has been demonstrated.

In our study, no statistically significant correlation was found between DTI values and time since injury. This finding is in agreement with previous studies.<sup>5,15</sup>

There was a moderate association between macroscopic post-traumatic changes in the spinal cord and microstructural changes in the centrum semiovale. An increase in ADC in the posterior part of the centrum semiovale was positively correlated with the craniocaudal length of the spinal cord lesion. Only Freund *et al.*<sup>15</sup> have previously demonstrated a relationship between the peripheral macrostructural effects of SCI and the cerebral DTI values. In their study, one of the directional diffusivities, the radial diffusivity, in the right cerebral peduncle correlated negatively with the cross-sectional area of the spinal cord after injury.

Strength of our study was that the patient sample included SCI patients with a wide range of neurological deficits and disabilities.

This design provided us the possibility to examine DTI findings in relation to the completeness of the SCI. Our study sample was substantially larger than in previous studies, and a detailed data collection was performed.

Taking into account the repeatability of the measurements, the vast majority of the ICCs for FA and ADC were over 0.6 indicating at least substantial agreement.<sup>28</sup> In turn, the SNR was very well above 20 in all regions, which is considered to enable the measurement of reliable DTI values.<sup>29</sup>

Despite the detailed data collection and design, our study has several considerable limitations. To best of our knowledge, the patients with known neurological diseases, which could potentially have a confounding effect on cerebral DTI values, were excluded. However, some patients were injured over thirty years ago. Thus, the clinical information collected from the medical records of these patients cannot be considered as accurate as in the more modern records. For example, there is a high probability that our patient population includes subjects with undiagnosed TBI. In the literature, up to 70% of patients with traumatic SCI have been reported to have concomitant TBI,<sup>30</sup> and mild TBI has also been shown to cause DTI changes in the white matter.<sup>31</sup> Our sample includes few subjects with moderate to severe microangiopathy, which could also have an effect on DTI values. Another weakness was that the SCI patients and controls were not age- or gender- matched. The possible confounding effects of age and gender<sup>32</sup> were addressed with statistical methods. Lastly, the ROI method that we used did not allow us to separate the motor and sensory tracts. The measurements could represent different

white matter tracts in individual subjects, complicating the interpretation of the results. The small circular ROIs represent only a small sample of the larger tracts, and it is possible that the pathological changes were outside of the measurement area.

## CONCLUSION

Patients with chronic SCI have considerable DTI changes in the posterior area of the centrum semiovale. Cerebral microstructural changes detected by DTI are linked to the completeness of the injury and reflect the motor and sensory scores measured by the ISNCSCI. Macroscopic lesions in the spinal cord, visualized on conventional MRI, are associated with DTI abnormalities in the centrum semiovale.

## DATA ARCHIVING

There were no data to deposit.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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