



Diffusion Tensor Imaging in Spinal Cord Injury: A Review

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Abstract

Magnetic resonance diffusion tensor imaging (DTI) is a recent technique that can measure the direction and magnitude of diffusion of water. It is widely being utilized to evaluate several brain and spinal cord pathologies. The objective of this review is to evaluate the importance of the DTI in patients with spinal cord injury (SCI). It aims to review various articles on DTI SCI and includes both animal and human studies. This will help to describe the current status of the clinical applications of DTI and show its potential as a helpful instrument in clinical practice. The PubMed database was searched for articles relating to the application of DTI in SCI. Relevant articles were also used for the review. A variety of DTI parameters have been studied in various articles. The standard parameters are fractional anisotropy (FA) values, apparent diffusion coefficient (ADC) values, radial diffusivity values, and axial diffusivity values, followed by tractography. FA and ADC values are the most commonly used parameters. The findings observed in most of the studies are increased FA and reduced ADC values following injury to the spinal cord. DTI data metrics possess the potential to become a potent clinical tool in patients with SCI. It is helpful for diagnosis, prognosis, treatment planning, as well as to evaluate the recovery. Nonetheless, to overcome the limitations and determine its reliability clinically, more research has to be performed.

Keywords

- ▶ diffusion tensor imaging
- ▶ spinal cord injury
- ▶ apparent diffusion coefficient
- ▶ fractional anisotropy
- ▶ axial diffusivity
- ▶ radial diffusivity

Introduction

Traumatic spinal injuries can be disastrous and distressing, especially when there is associated neurologic damage. They can have a negative impact on the lives of individuals—physically, mentally, and financially. It is accompanied by high mortality and debility. It can leave the individual with long-term disabilities needing costly rehabilitation treatment. The severity of the injury decides the extent of deficit and degree of neurological damage.¹

Diagnostic imaging is essential in evaluating and detecting spinal trauma. The assessment of patients with injury has undergone progressive changes over several years.²

Accurate diagnosis of spinal cord injury (SCI) forms the basis of clinical treatment. Currently, magnetic resonance imaging (MRI) is very well recognized for detecting SCI.³

The routinely performed conventional MRI can demonstrate soft-tissue changes, edema, hemorrhage, and SCIs in patients with spinal trauma. Trauma to the spinal cord can damage the myelinated fibers of the cord and nerve roots leading to myelopathy. Pathologically, this can lead to Wallerian degeneration of the cord. These changes can be seen as increased signal intensity on T2-weighted images in MRI.⁴ This can help foresee the neurologic outcomes in the affected patients.⁵

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Methodology

This review was prepared using articles from the PubMed database. Articles published between 2001 and May 2021 were searched. Phrases such as “diffusion tensor imaging” and “spinal cord injury” were used to search the articles. Article selection was limited to humans. Articles were added to the final review only after reading the titles and abstracts of the shortlisted articles. Citations from the shortlisted articles were scrutinized to search for relevant articles.

All articles that contained necessary information about the use of diffusion tensor imaging (DTI), specifically in imaging SCI, were included in the review. Articles that included the principles of DTI, its advantages, limitations, and clinical applications were also included. The final result included background on DTI, spinal injury mechanism, prognosis, and limitations.

There were total 266 publications that suited the criteria “DTI spinal cord injury.” This was narrowed down to 140 by selecting the “human” species. Relatable articles were searched from the citations of shortlisted articles.

Principles of DTI

In 1994, Basser et al⁷⁰ demonstrated that DTI was significantly better at visualizing microstructures than other magnetic resonance (MR) sequences, namely T1- and T2-weighted images. DTI is based on measuring the direction of diffusion of extracellular water molecules inside white matter fiber. Water diffusion is restricted in the axons by the cell membrane and the myelin sheath barriers. As a result, diffusion is high along the white matter tracts and low perpendicular to the matter tracts.⁶

DTI is capable of measuring this magnitude and the direction of diffusion of the water molecules.⁷ Magnetic gradients are applied in various spatial directions to achieve this, i.e., to measure the diffusion anisotropy of water molecules in the axonal tracts noninvasively *in vivo*.³ The axons in the white matter of the spinal cord are directed longitudinally; therefore, maximum diffusion of water occurs in this direction. Gray matter lacks such organization. Thus, DTI can distinguish between structures of high and low anisotropy.⁸

The data collected are then reconstructed to form three-dimensional images of the brain and spinal cord white matter tracts. This makes use of specialized fiber tracking algorithms.⁹ Tractography shows the architectural orientation of tissues. They are often described as representing axons or nerve fibers individually, but in physical terms, they are just the lines representing the maximum diffusion.¹⁰

Metrics in DTI

The commonly exploited DTI parameters comprise of:

- **Fractional anisotropy (FA):** It is a unitless scalar metric, based on the motional anisotropy of water molecules,

which can range from 0 (isotropy) to 1 (maximum anisotropy). This results in the formation of a color map representing the degree of anisotropy and the fiber direction.^{3,11}

- **Mean diffusivity (MD):** It shows the average diffusivity over all the sampled directions, i.e., the average of three eigenvalues at each voxel.¹¹
- **Axial diffusivity (AD):** It is also denoted as longitudinal diffusivity. It measures the diffusion of water molecules along the long axis of the fiber of the white matter tract, i.e., parallel to the axonal tract.
- **Radial diffusivity (RD):** It is also denoted as transverse diffusivity. It is the average diffusion of water molecules along the two minor axes of the fiber of the white matter tract, i.e., perpendicular to axons.

Applications

DTI is a new imaging modality whose usage is still being explored. It has abundant applications in diagnosing imaging. Some of the examples are:

- **Amiotrophic lateral sclerosis (ALS):** It is a fatal disorder affecting the nerve cells in the brain and the spine, leading to increasing muscle weakness by wasting. Two previous meta-analyses demonstrated a decrease in FA in patients with ALS. Thus, FA serves as a promising biomarker for ALS.^{12,13} Certain studies have also used other DTI parameters, namely AD, RD, and MD, to assess ALS.^{14,15}
- **Multiple sclerosis (MS):** It is an autoimmune disease of the central nervous system (CNS) attacking the myelinated axons of the CNS, and ultimately destroying it.¹⁶ It is characterized by chronic inflammation followed by demyelination, then gliosis, and, lastly, neuronal loss. MS lesions are by reduced FA values, which indicates structural disintegration.¹⁷ An increase in the AD values is noted, which is constant with Wallerian degeneration.¹⁸
- **Epilepsy:** Temporal-lobe epilepsy patients displayed increased apparent diffusion coefficient (ADC) and decreased FA in a sclerotic area of the hippocampal, which suggests structural disorganization.¹⁹ Similar findings were seen in the areas with cortical malformation, which showed normal findings in conventional MRI scans.²⁰ This advocates that DTI is a promising modality in refractory epilepsy patients for studying localized epileptogenic lesions.
- **Neurodegenerative disorders:** For example, Parkinson's disease (PD) and Alzheimer's dementia. These are the most common neurodegenerative diseases. The patients suffering from Alzheimer's dementia show an increasing decline in language, memory, problem-solving, and cognitive functions, while patients with PD show tremors, slow movements, behavioral problems, and balance and gait disturbances.²¹ Based on an assessment of the association between FA in the substantia nigra and clinical motor complaints, one study concluded that DTI could be beneficial for assessing clinical severity.²² DTI provides promising biomarkers for the clinical symptoms of PD, according to a recent meta-analysis of data from 958

patients and 764 controls in 43 trials. Furthermore, a sub-analysis of data from nine studies found that FA was lower in the substantia nigra of PD patients than in control subjects, with a significant effect size.²³ DTI has also been used to identify biomarkers for Alzheimer's dementia since DTI has the budding potential to identify patients with pathologies of white matter.¹⁷

- **Ischemic strokes:** In the acute phase, FA is increased, which reduces markedly in the chronic phase for up to 6 months after stroke due to the structural disorganization of white matter, which is ischemic. The ADC remains elevated in the chronic phase.²⁴
- **Traumatic brain injury (TBI):** Microscopic injury to axons following mild TBI cannot always be detected in conventional imaging of the brain.²⁵ Damage to the brain's white matter unrecognized in conventional sequences increases the risk of longstanding functional and cognitive impairments. As such, one can infer that DTI is useful for identifying unseen lesions and understanding the pathophysiology of mild TBI.²⁶
- **SCI:** Like TBI, DTI may also be beneficial to define the white matter fibers that are abnormal and not detected in the routine MRI imaging of the spine.⁹ Fiber tractography in DTI can demonstrate the integrity of the cord and help in providing necessary information about the pathophysiology. FA values help predict the patient outcome in spinal cord lesions; if the FA values are >0.6, better is the outcome in the acute period.²⁷ Thus, DTI may soon be used as possible biomarkers to quantitatively analyze the integrity of the axon to predict locomotor function.²⁸ Another application of DTI is diffusion tensor tractography, which enables three-dimensional demonstration of the white matter fibers (axons).¹
- **Major depressive disorder (MDD):** Disturbance of the neural circuits that are involved in the processing of affective and cognitive functions significantly contributes to the pathophysiology of MDD.^{29,30} Microstructural abnormalities have been found in several DTI studies of the white matter tracts in MDD patients.³¹
- **Preoperative planning** for the treatment of brain tumors.

DTI as a Diagnostic Tool for SCI

DTI has been extensively used in the imaging of the brain and spinal cord. DTI is an effective tool to diagnose SCI and can locate the area of injury to the spinal cord and identify its severity.^{2,32}

DTI metrics can be quantified at specific levels of the spinal cord using MR postprocessing software, and for easier interpretation, these data are to be displayed in a visual format. The various metrics calculated in DTI in patients with SCI include FA, MD, radial anisotropy, RD, and ADC values.⁶

- **FA values:** Numerous studies on humans and animals with SCI have shown that the mean FA value is considerably reduced in both compared with healthy controls.³³⁻³⁵ D'souza et al found that in patients with a cervical spine injury, FA values at the injury level were

less as compared with levels above or below the injury.² As the severity of the SCI and the level of stenosis of the canal increase, the FA value decreases.³⁶

- **MD values:** It has been observed that the MD values increase after acute injury to the spinal cord.³⁷⁻³⁹ D'souza et al discovered a remarkably significant increase in MD values at the level of the injured spinal cord, but not at the level above or below the injury.²
- **ADC values:** ADC shows the magnitude of diffusion of water molecules inside a tissue, and changes in this value represent a change in the structure of the tissue. Various studies show inconsistent findings for ADC values in patients with SCI. In a study performed by Ellingson et al, it was discovered that a low ADC value was obtained at 2 weeks following SCI, anterior and inferior to the site of injury, while a slight decrease in ADC is seen at the level of injury.⁴⁰
- In another study, Shanmuganathan et al found a considerable decrease in ADC values in the cervical spinal cord at the injury site; however, a decrease in ADC was found above and below the level of injury as well.⁵ Contrary to this, increased ADC values were observed by Song et al in patients with the spinal cord as compared with controls.⁴¹ No significant change was found in ADC values by Petersen et al following SCI.⁴² A slight increase was found in ADC values by Li et al in mild SCI as compared with healthy controls while a low ADC value was obtained in moderate and severe SCIs.⁴³
- **AD and RD values:** The integrity of the myelin sheath covering the axon inhibits the diffusion of water across the membrane. This results in increased AD. AD decreases with axonal injury.^{44,45} Contrary to this, increased demyelination and injury to the axon increases RD. AD and RD values are useful DTI metrics; however, they cannot be used exclusively on their own and remain too unpredictable to be used as a reliable method of diagnosing SCI.

DTI as a Prognostic Tool for SCI

According to histology research, post-injury neurological functional result is closely linked with axonal injury.^{46,47} DTI measures have been linked to histological axonal damage and functional recovery.^{48,49}

Ellingson et al discovered that in patients with cervical spondylosis, in modified Japanese Orthopaedic Association scores, FA values, ADC values, and DTI fiber tract density together were the best prognosticator of motor impairment. Their study showed that, at the region of compression of the spinal cord, higher FA, lower ADC, and a high fiber tract density were obtained, which corresponded with inferior neurological function.⁵⁰ Comparable results were obtained in other studies with modified Japanese Orthopaedic Association scores and increased track density.⁵¹

Some studies have used FA values to evaluate recovery following neuroprotective therapy. FA can assess the clinical outcome following acute compression and can be used as proper prognostic parameters. Early increases in FA values suggest an acute compression that may give a good prognosis

if immediately decompressed by performing surgery. This proposition, however, needs to be assessed in more studies. However, as of now, no sufficient data are available to assess the correlation between FA parameters and prognosis.²⁷

Discussion

DTI is widely being used in several brain and spinal cord studies for a variety of applications. Clinically, DTI has been used in the spinal cord in tumors, trauma, myelopathy, and inflammation.⁵² It has also shown usefulness in brain examination in patients with stroke, epilepsy, tumor, and other pathologies involving the white matter tracts. This provides a plus point in planning the treatment and also helps in the follow-up of cases. Because of its superior soft-tissue resolution, MR imaging has played an essential role in diagnosing spinal cord injuries. On traditional MR sequences, however, minor cord injuries are frequently missed, and the correlation between clinical severity of injury and pathology have shown that MR is less than satisfactory in numerous situations.⁵³

The microstructural integrity of nerve fiber pathways is assessed using DTI, based on the simple concept of water molecule diffusion in vivo. DTI anisotropy indices can be calculated to assess changes in diffusion qualitatively using “fiber tracking techniques” (tractography) or quantitatively using DTI anisotropy indices.⁵⁴

Tractography provides tracking linear axons by providing a visual depiction and helps in assessing the diffusion of the examined structure. Diffusion direction can also be color coded, with red representing diffusion from left to right, green representing the anteroposterior flow, and blue representing craniocaudal diffusion. The tracts are always shown in blue in the spine since the fibers are primarily craniocaudal. The orientation of fibers and a stunning portrayal of tract rupture may be seen on spinal tractography, which is difficult to see on conventional MRI. This knowledge

aids in the clinical identification of damaged fiber pathways in the traumatic spinal cord.⁵⁵

Anisotropy indices, also known as DTI data metrics, give a numerical value to the diffusion in any given voxel. The most commonly used indices are FA and ADC. FA measures the “magnitude” of overall diffusion occurring in one voxel that can be accredited to anisotropic diffusion. It can take values between 0 and 1; 0 indicating isotropic diffusion, and 1 for anisotropic diffusion as in intact neurons. Damage to the axons causes the diffusion to become unrestricted and isotropic. ADC has low values if the nerve fibers are organized, while injured fibers show high ADC values.⁵⁶

A study performed by D'souza et al found that DTI proved better than conventional MRI scans in depicting subtle as well as obvious variations in cord integrity following injury. The spinal cord was assessed either way, qualitatively and quantitatively. Tractography was also performed, which revealed a break in the integrity of neurons. The quantitative assessment revealed a marked decrease in FA value while it noted that the MD value was statistically increased at the site of injury in comparison to controls during the acute phase of injury. FA showed a positive correlation with Frankel score, which gives a clinical measure of the motor as well as sensory status and helps in assessing the clinical severity of the injury.²

In another study performed by Mohamed et al, they found a similar striking positive correlation between FA indices at the region of trauma and Frankel score, which was obtained 1 to 2 months post injury. Even though a negative correlation was obtained between the mean MD and Frankel score, at the region of trauma, it was whatsoever statistically not significant. They also found that the correlation between the FA values and International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) determined scores for clinical severity of trauma was statistically significant in the pediatric study. Their study also demonstrated a decrease in the FA value in the distal cord if there was cervical injury and

Table 1 Comparison of diffusion tensor imaging matrices in various studies

Authors	FA values	ADC values	Indication
D'souza et al ²	0.43 ± 0.08	1.30 ± 0.24	SCI
Kamble et al ⁴	0.367 ± 0.14	–	SCI
Rao et al ³	0.220 ± 0.121	–	SCI
Alizadeh et al ⁵⁷	0.37 ± 0.09	1.01 ± 0.08	SCI
Alkadeem et al ¹	0.326 ± 0.135	1.319 ± 0.378	SCI
Mohamed et al ⁸	0.39	–	SCI
Koskinen et al ⁴⁹	0.51 ± 0.09 (whole cord)	1.14 ± 0.18 (whole cord)	SCI
Mulcahey et al ⁵⁸	0.28 ± 0.10	–	SCI
El Basset et al ¹⁰	0.238	1.466 (0.256)	Cord compression
Lee et al ⁵⁹	0.475	1.079 × 10 ⁻³	Cord compression
Tsuchiya et al ⁶⁰	–	3.30 ± 0.38 · 10 ³ (mm ² /s)	Myelomalacia
Cheran et al ³⁵	0.49 ± 0.13	0.83 ± 0.15	Nonhemorrhagic spinal injury

Abbreviations: ADC, apparent diffusion coefficient; FA, fractional anisotropy; SCI, spinal cord injury.

a decrease in FA value in the proximal cord in case of lower cord injury. This likely suggests that there is Wallerian degeneration in the cord following trauma, which can be perceived with the help of DTI.⁸ Other studies have documented that FA correlates with motor deficits can be a forecaster of longstanding motor recovery.⁴

A study performed by Demir et al on cervical compressive myelopathy showed a considerable reduction in FA and a rise in MD values, which had the normal impression in conventional sequences.⁶¹ This pattern of upsurge in MD with a fall in FA at the site of SCI has been noted in other studies as well.^{8,38,62} Similar findings have been seen in nontraumatic spinal cord pathologies as well.^{27,63,64} The reason for this is still uncertain.

Tsuchiya et al described that in the chronic phase of injury, the raised ADC values could be a result of edema, necrosis, and myelomalacia.⁶⁰ Song et al suggested that intervertebral disk herniation and consequent canal stenosis compressing the spinal cord could cause decrease in perfusion that might lead to ischemia and anoxemia and cellular membrane injury that could increase cellular membrane penetrability.⁴¹

Ducieux et al performed a study to investigate the application of the DTI parameters in acute, slowly progressive cord compression. The statistical values were used in detecting abnormal areas. They first measured DTI matrices at different levels of the spine. This aimed to check the physiologic hypothesis of variation in inflow and outflow of the inner spinal water, which could vary based on the cord level due to variation in the anatomy of the spinal vascular system. Their study revealed that ADC values could only be used in cases of chronic compression of the spinal cord due to its poor sensitivity and specificity. This could result from partial evaluation of diffusivity of water, caused due to the failure to detect in-/outflow of water in and about the cord fibers. On the contrary, the FA value showed high sensitivity and specificity in detecting anomalous areas within the cord in comparison to conventional T2-weighted sequences. This could be the result of a complete evaluation of the diffusivity of the water molecules by DTI. Reduced FA values were noted in the majority of patients, which was suggestive of either the decreased number of fibers or extracellular edema, or both. They concluded that the FA variation had a time-specific pattern, with a critical increase in values due to restriction in diffusivity and a late decrease in values as a result of an increase in diffusivity in the extracellular space.²⁷

Limitations of DTI in SCI

Imaging the spinal cord is technically challenging. This is due to a variety of reasons, for example, the small volume of the cord has low signal-to-noise ratio (SNR) and magnetic susceptibility artifact due to the adjacent bone.⁵

There is no adequate spatial resolution. Diffusion-weighted imaging visualization of the individual funiculi remains a problem, particularly in the lower thoracic cord.⁶⁵ DTI of the spinal cord is prone to artifacts arising from the presence of cardiac motion and respiratory motion, and pulsation artifacts arising from the cerebrospinal fluid.⁶⁶

In human SCI, the SNR is dissatisfactory in many studies, and anisotropy may be overestimated, particularly in the central gray matter, which has low anisotropy.⁶⁷ The usage of 3 T scanners to acquire the DTI images improves the SNR;⁶⁸ however, it is still not used universally.

According to Maier and Mamata, DTI of the spinal cord is more problematic. This was due to multiple reasons like: the presence of adjacent bony structures causes susceptibility variations that may cause severe image distortions; presence of lipids in the vertebral bodies and nearby structures can cause chemical-shift artifacts; or the presence of ghosting artifacts due to physiologic motion in the thorax and abdomen, which causes image distortion. Finally, it is not easy to obtain good SNR for obtaining a high-resolution image.⁶⁴

In a study performed by Rückenmarks and Rossi, a comparison was made between a 1.5 T and a 3 T MRI scanner. Their study included eight healthy volunteers and one patient. The volunteers were scanned at both the field strengths, i.e., 1.5 T and 3 T, while the patient was scanned at only 3 T. Their study concluded that a statistically significant ($p < 0.02$) improvement was seen in the image quality at higher field strength. The FA maps demonstrated superior quality at 3 T as compared with 1.5 T. However, similar ADC values were noted for both the field strengths.⁶⁹

Conclusions

We conclude that DTI parameters are seen to vary in the spinal cord succeeding injury, which is not demonstrated on conventional MRI. These variations in the cord are greatest at injury site. FA at the level of injury is more sensitive than the other parameters as well as T2-weighted imaging in detecting spinal cord abnormalities. The FA value was seen to significantly decrease while the MD value to increase. FA also showed a substantial correlation with the clinical grading. Thus, DTI could be used as an impartial imaging tool for predicting the functional outcome. Post-trauma fiber tracking is helpful for the evaluation of acute or slowly progressive cord compression. It also helps to assess the microstructural changes in areas of subtle damage that are otherwise invisible in conventional MRI.

Description

This article reports the current status of the clinical applications of DTI and shows its potential as a helpful instrument in clinical practice.

Conflict of Interest

None declared.

Acknowledgment

Not applicable.

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