The role of diffusion tensor imaging in the diagnosis, prognosis, and assessment of recovery and treatment of spinal cord injury: a systematic review

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OBJECTIVE Diffusion tensor imaging (DTI) is an MRI tool that provides an objective, noninvasive, in vivo assessment of spinal cord injury (SCI). DTI is significantly better at visualizing microstructures than standard MRI sequences. In this imaging modality, the direction and amplitude of the diffusion of water molecules inside tissues is measured, and this diffusion can be measured using a variety of parameters. As a result, the potential clinical application of DTI has been studied in several spinal cord pathologies, including SCI. The aim of this study was to describe the current state of the potential clinical utility of DTI in patients with SCI and the challenges to its use as a tool in clinical practice.

METHODS A search in the PubMed database was conducted for articles relating to the use of DTI in SCI. The citations of relevant articles were also searched for additional articles.

RESULTS Among the most common DTI metrics are fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. Changes in these metrics reflect changes in tissue integrity. Several DTI metrics and combinations thereof have demonstrated significant correlations with clinical function both in model species and in humans. Its applications encompass the full spectrum of the clinical assessment of SCI including diagnosis, prognosis, recovery, and efficacy of treatments in both the spinal cord and potentially the brain.

CONCLUSIONS DTI and its metrics have great potential to become a powerful clinical tool in SCI. However, the current limitations of DTI preclude its use beyond research and into clinical practice. Further studies are needed to significantly improve and resolve these limitations as well as to determine reliable time-specific changes in multiple DTI metrics for this tool to be used accurately and reliably in the clinical setting.

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KEYWORDS diffusion tensor imaging; spinal cord injury; fractional anisotropy; MRI; magnetic resonance imaging

Spinal cord injury (SCI) is a prevalent problem affecting 17,700 new people every year in the US. It is estimated that approximately 288,000 people live with an SCI in the US. It is important to have quantifiable modalities in SCI to provide support for clinical decision making. One of those objective modalities is MRI, and more specifically diffusion tensor imaging (DTI) in patients with SCI (Figs. 1 and 2).

DTI was first described by Basser et al. in 1994 in a study demonstrating that this imaging modality was significantly better at visualizing microstructures than other MR sequences, namely T1- and T2-weighted images (Fig. 3). DTI measures the direction of diffusion of water molecules inside tissues. In the axon, water diffusion is mostly limited by the cell membrane and myelin sheath barriers; this leads to a gradient with high diffusion in the direction parallel to the white matter tracts and low diffusion perpendicular to the white matter tracts. Disruption of the biological barriers is thought to result in increased radial diffusivity (RD) by providing an alternate, perpendicular path for water diffusion.

Diffusion is measured in different ways in DTI: the axial diffusivity (AD), radial diffusivity (RD), fractional anisotropy (FA), and mean diffusivity (MD). These metrics are derived from the diffusion tensor and provide information about the structure and function of the white matter tracts. Changes in these metrics can reflect changes in tissue integrity and can be used to assess the extent of injury, predict outcomes, and monitor recovery. Although DTI has shown promise in the assessment of SCI, its clinical utility is limited by several factors, including the complexity of the diffusiontensor, the variability of the results, and the lack of standardized protocols for data analysis. Further research is needed to address these limitations and to develop DTI as a reliable tool for the diagnosis and management of SCI.
two most frequently used measurements are fractional anisotropy (FA), the extent to which diffusion is limited to specific directions, and mean diffusivity (MD), the overall amount of diffusion in a sample or voxel (Fig. 4). FA is a measure of microstructural integrity because it is sensitive to microstructural changes in the spinal cord, but it is not specific to underlying pathological causes. In contrast, MD is a measure of membrane density and is more sensitive for changes in cellularity, edema, and necrosis.

The purpose of this review was to describe the current state of DTI as a potential clinical tool for the assessment and management of SCI. We aimed to summarize the most up-to-date advances in DTI and its potential utility in diagnosis, prognosis, assessment of recovery, and of therapeutic interventions.

Methods
This review was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.42

Search Criteria
The MEDLINE database (via PubMed) was searched for articles published between January 2000 and April 2017 with the following search terms: “diffusion tensor imaging” AND “spinal cord injury”. The search was narrowed by selecting the “human” link for species and limiting the results. After reviewing title and abstract, the articles were then included in the final review. The citations from the preselected articles were then screened for additional relevant articles (Fig. 5).

Inclusion Criteria
Articles that contained information relevant to the use of DTI in SCI were included. Articles that discussed the limitations precluding the use of DTI in SCI were also included.

Data Evaluation
Relevant results from individual articles were extracted and organized into the clinically relevant categories of diagnosis, prognosis, recovery, assessment of therapeutic interventions, and limitations.

Results
Our search resulted in 306 publications that were narrowed to 33 articles based on the inclusion criteria. The remaining 41 papers were found by searching the citations of identified articles (Fig. 5).

Utility of DTI as a Diagnostic Tool for SCI
DTI can identify the location and severity of injury to the spinal cord, and is therefore an important tool for diagnosis of SCI.15,27 Postprocessing MR software is available to quantify DTI metrics at specified spinal levels and can also be used to allow the data to be displayed in a visual format that allows easier interpretation (Fig. 6). Several metrics in DTI have been studied in SCI, including FA,
MD, radial anisotropy, RD, and apparent diffusion coefficient (ADC) values.

**FA Values**

The mean FA value has been consistently found to be reduced in both human and animal studies of individuals with SCI compared to healthy controls.²,⁶,¹⁰–¹²,¹⁴–¹⁶,²⁸,³²–³⁵,⁴⁰,⁴¹,⁴³,⁴⁵,⁴⁷,⁵¹,⁵⁵,⁵⁹,⁶⁸,⁷¹,⁷⁴ With respect to the level of spinal injury, D’souza et al. found that the mean FA values in cervical spine injury were significantly reduced compared to healthy controls at the level of injury but not at levels above or below the injury.¹⁵ FA levels have been shown to decrease with increasing canal stenosis, and several studies have shown a correlation between FA value reduction and severity of SCI.³³,⁴⁶

Asymmetrical FA values between left and right corticospinal tracts were found to moderately correlate with laterality of neurological symptoms and American Spinal Injury Association (ASIA) scores using tract-specific DTI (Fig. 7).³⁸

**MD Values**

Most commonly, MD values increase following acute SCI.¹⁰,¹⁴,¹⁵,⁴⁰,⁶⁵ D’souza et al. found a statistically significant increase in MD values post-SCI at the injured spinal level, but not at the level above or below the injury.¹⁵ They also found an inverse linear relationship between MD scores at the level of injury and clinical SCI assessment; the highest MD values represented worse clinical grades. Additionally, MD values have been found to change with age, further confounding the interpretation of results.⁶⁴

**ADC Values**

ADC is a measure of the magnitude of water molecule diffusion inside a tissue, and changes in this value represent a change in the tissue structure. The ADC values in SCI vary substantially by study. In their animal study,
Ellingson et al. found a decreased ADC value at 2 weeks after SCI in the cord rostral and caudal to the site of injury, whereas ADC values were only slightly decreased at the level of injury. In their cohort of patients with SCI, Shanmuganathan et al. also found significantly decreased ADC values in the cervical spine; however, this study found decreases at levels above, below, and at the site of injury. In contrast, Song et al. found elevated ADC values in SCI patients relative to controls and Petersen et al. found no significant change in ADC values after SCI. Importantly, Li et al. found that ADC values in mild SCI were elevated compared to healthy controls whereas they were decreased in moderate and severe SCI.

AD and RD Values
Axial diffusivity (AD) is usually high in spinal cord DTI due to axon and myelin integrity that inhibits water diffusion across the membrane, whereas AD decreases with axonal injury. In contrast, RD increases with increased demyelination and axonal injury. Although AD and RD values are a useful metric in DTI, they remain too inconsistent on their own to be used exclusively as a reliable method of diagnosing SCI.

Utility of Cortical DTI for SCI
There is evidence that DTI of cortical and brainstem structures demonstrates chronic changes after SCI and may contribute to assessing the severity and prognosis of, as well as recovery from, SCI. Sun et al. demonstrated significantly reduced FA and increased AD and RD values in both the cerebral peduncles and internal capsule in patients with cervical spine ASIA grade A/B SCI. Differences were also noted in cervical spine ASIA grade D and thoracic SCI, but were not statistically significant.

Utility as a Prognostic Tool
Postinjury neurological functional outcome is highly correlated with axonal injury as determined by histological analysis. DTI metrics correlate with histological axonal injury as well as functional recovery. Ellingson et al. found that the combination of DTI fiber tract density, FA values, and MD values were the best predictor of motor impairment in the modified Japanese Orthopaedic Association scores in cervical spondylosis. In their study, at the site of spinal cord compression, higher fiber tract density, lower FA, and higher MD were associated with worse neurological function. Similar results were found with maximum tract density and modified Japanese Orthopaedic Association scores.

Utility in Assessment of Therapeutic Interventions
Gu et al. described an experiment in which rats underwent laminectomy with spinal cord contusion and subsequent injection of olfactory ensheathing cells. DTI was used to demonstrate SCI as well as axonal regeneration at
the injury epicenter, which was corroborated by histopathology. The study demonstrated increases in FA values and improved Basso-Beattie-Bresnahan scores with time.

In their animal model of SCI, Jirjis et al. used DTI to assess changes in histopathology and functional metrics at the cervical cord after injury, and compared these to changes in DTI after neuronal stem cell transplantation into thoracic spinal cord. FA, longitudinal diffusion, RD, and MD values increased in cervical segments in the stem cell–transplanted groups relative to controls. However, there was no significant change in functional recovery as assessed by Basso-Beattie-Bresnahan scores, suggesting that changes in DTI metrics may demonstrate changes in white matter recovery but may not always correlate to clinical improvement. Similar results were found by Bazley et al., who found increases in FA that correlated with improvements in cell survival and somatosensory evoked potentials after treatment of SCI with oligodendrocyte precursor cell transplantation.

Other MRI Modalities for SCI Assessment

The Brain and Spinal Injury Center (BASIC) scoring system was developed to evaluate T2-weighted MR images in patients with SCI. The BASIC grading system is...
based on axial T2-weighted images. The BASIC scale has 5 points—from 0 (no cord signal abnormalities) to 4 (in- tramedullary T2 hyperintensity with microhemorrhage). The authors of this study found good correlation with a high BASIC grade and a worse clinical SCI (higher ASIA grade). A limitation of the scale is the high variance of T2 signal in images obtained > 24 hours after injury. Nonetheless, the BASIC system would be easier to implement because T2 sequences are obtained routinely for patients with SCI.

Limitations of DTI Utility in SCI

Inconsistencies in the changes in DTI metrics among studies preclude this imaging modality from consistent and reliable clinical use. A potentially interesting solution to this problem is the use of machine learning via a training data set of injured and healthy patients that could serve to establish different metrics to improve diagnostic accuracy of DTI.

The specificity and sensitivity of DTI decreases with increasingly complex tissue. SCI results in several pathologies that are difficult to distinguish on DTI, including inflammation, edema, demyelination, and hemorrhage. Li et al. found that changes in ADC and FA values could be detected on 3.0-T machines, but changes in ADC values were not detected by a General Electric 1.5-T machine and changes in FA values were not detected by a Philips 1.5-T machine. A 3.0-T machine may be required for the reliable measurements of DTI metrics necessary for clinical use. DT image quality can be significantly reduced and result in artificial alteration of DTI metrics due to patient and physiological motion. Methods to improve motion correction have been developed with promising results.

Conclusions

DTI has great potential to provide an objective, in vivo clinical assessment of SCI. Several DTI metrics, and combinations thereof, have demonstrated significant correlations with clinical function in both animal models and humans. The applications of this tool encompass the spectrum of clinical and functional assessment in SCI including diagnosis, prognosis, recovery, and efficacy of treatments in both the spinal cord and potentially the brain. However, DTI carries several limitations that have prevented its transition beyond research into clinical practice. Further studies are needed to significantly improve and resolve these limitations as well as create standard, time-specific changes in DTI metrics that will be required for accurate and reliable use of DTI in the clinical setting. This review is limited by the absence of randomized controlled human trials and reliance on data from animal and class II–IV human studies.

Acknowledgments

Except for Fig. 5, all figures are research images that we obtained using Siemens Healthineers MR and/or CT scanners, and Figs. 6 and 7 were also processed using Siemens Healthineers postprocessing software (SyngoVia VB30A).

References

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**Author Contributions**

Conception and design: Martirosyan. Acquisition of data: Martirosyan, Zaninovich, Avila. Analysis and interpretation of data: Martirosyan, Zaninovich, Avila. Drafting the article: Zaninovich, Avila. Critically revising the article: Martirosyan, Becker, Hurlbert. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Martirosyan. Administrative/technical/material support: Martirosyan, Hurlbert. Study supervision: Becker, Hurlbert.

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