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Advancing Imaging Technologies for Patients with Spinal Pain: With a Focus on Whiplash Injury

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ABSTRACT

Background Context: Radiological observations of soft-tissue changes that may relate to clinical symptoms in patients with traumatic and non-traumatic spinal disorders are highly controversial. Studies are often of poor quality and findings inconsistent. A plethora of evidence suggests some pathoanatomical findings from traditional imaging applications are common in asymptomatic participants across the life span, which further questions the diagnostic, prognostic, and theranostic value of traditional imaging. While we do not dispute the limited evidence for the clinical importance of most imaging findings, we contend that the disparate findings across studies, may in part be due to limitations in the approaches used in assessment and analysis of imaging findings.

Purpose: The purpose of this clinical commentary is to 1) briefly detail available imaging guidelines, 2) detail research based evidence around the clinical use of findings from advanced, but available, imaging applications (e.g. fat/water MRI and magnetization transfer imaging), and

3) introduce how evolving imaging technologies may improve our mechanistic understanding of pain and disability, leading to improved treatments and outcomes.

Study Design/Setting: Non-systematic review of the literature

Methods: A narrative summary (including studies from the authors' own work in whiplash injuries), of the available literature is provided. Relevant disclosures: JE reports relevant activities outside the body of work as 35% investment/ownership in a medical consulting start-up, Pain ID, LLC and an NIH grant (2014-2019) R01 R01HD079076. DW reports relevant activities outside the body of work including speaking/teaching arrangements, Scientific Advisory Board duties, Grants (CIHR and Canadian Pain Society). MH, RC, and AS confirm no relevant disclosures.

Results: An emerging body of evidence suggests that the combination of existing imaging sequences and/or the use of developing imaging technologies in tandem with a good clinical assessment of modifiable risk-factors, may provide important diagnostic information towards the exploration and development of more informed and effective treatment options for some patients with traumatic neck pain.

Conclusions: Advancing imaging technologies may help to explain the seemingly disconnected spectrum of biopsychosocial signs and symptoms of traumatic neck pain.

INTRODUCTION

With an increasingly ageing population, healthcare spending is expected to increase dramatically.[1, 2] In the United States, dollars spent on healthcare is greater than any other country in the world,[3] with the largest increase in spending between 1996-2013 for musculoskeletal disorders such as neck and low back pain.[2] Despite the rising expenditures, little appreciable change in neck and low back pain prevalence has occurred either in the United States or across the globe.[4-7] Efforts to control spending and improve outcomes must consider the expense associated with delivery of interventions and diagnostic tests with little evidential support. Unnecessary imaging for patients with low back and neck pain has rightly received wide criticism [8-10], and triggered important work examining behaviors in physicians (and patients), aimed at reducing imaging overutilization. [9-11]

Routine use of early diagnostic imaging tests is challenged for multiple reasons. Numerous studies demonstrate abnormal or variant morphology of the cervical [12] and lumbar [10, 13-17] spines of asymptomatic participants (false positives), [18] and other studies highlight the lack of imaging findings in some patients injured from whiplash [19-22] or suffering from low back pain (potential false negatives).[9, 14, 23] Few studies have investigated the longitudinal predictive value of imaging findings in the lumbar [24] and cervical spine, [19, 22] and most importantly there is currently little evidence that magnetic resonance imaging (MRI) findings help identify those who respond best to specific interventions.[25]

On the other hand, while some imaging findings are common in those without pain, several findings (e.g. disc degeneration, Modic change, annular tear, disc herniation,) have been shown to be substantially more common in those with low back pain [18, 26] and traumatic neck pain (e.g. muscle fatty infiltrates) [27-33] than those without. Such discrepant findings have created a clinical (and research) dilemma that we believe is due partly to a lack of high quality studies and many perhaps misguided attempts to investigate the usefulness of imaging in understanding spinal pathology.

In this clinical commentary, we draw from existing and emerging research to 1) briefly detail available imaging guidelines, 2) present research based evidence around the potential clinical use of findings from advanced but accessible imaging applications (e.g. fat/water MRI and magnetization transfer imaging), and 3) introduce evolving imaging technologies that may improve our mechanistic understanding of pain and disability, ultimately leading to improved treatment outcomes.

IMAGING GUIDELINES

We do not dispute the universal guideline recommendations to avoid routine, non-indicated imaging for spinal pain, and we further endorse that routine imaging should not be conducted once the patient has been medically screened and determined to not have serious pathology. Furthermore, we agree with Chou et al [15] who state

'…addressing inefficiencies in diagnostic testing could minimize potential harms to patients and have a large effect on use of resources by reducing both direct and downstream costs. In this area, more testing does not equate to better care. Implementing a selective approach to [spinal imaging] *as suggested by the American College of Physicians and American Pain Society guideline on low back pain, would provide better care to patients, improve outcomes, and reduce costs.' [page 181]*

The primary evidence-derived imaging guideline for health care providers in the United States is the American College of Radiology Appropriateness Criteria (ACR-AC). Relevant to this paper are the ACR-AC clinical conditions of a) Chronic Neck Pain,[34] b) Suspected Spine Trauma,[35] and c) Low Back Pain.[36] Readers are encouraged to revisit the 'clinical conditions' and subcategories (or variants) of the ACR-AC guidelines detailed above.

The authors support the value of these well established and expert-derived guidelines that imaging is appropriately not recommended for the majority of patients with spinal pain. However, despite the proposed benefits of following the guidelines (cost-savings, reductions in exposure to ionizing radiation, avoiding the identification of pathology that may simply represent normal variants, and potentially misinforming clinical decision-making), adherence to guidelines is quite variable, [37-39] and it is largely unknown if adherence results in improved outcomes. Furthermore, there remains a lack of a gold standard quantitative metric for diagnosing low back and neck pain. Without a gold standard against which to compare, it is impossible to investigate whether diagnosis improves outcomes in our current landscape of care. Secondly, the presence of pathology in some people with low back and neck pain should not be dismissed as a normal variant on grounds they are also present in some without these conditions. Accordingly, there is an urgent need to perform high quality prospective imaging studies with quantitative measures using existing (T1-, T2-weighting) and other developed, *but not an exhaustive list of*, techniques (Fat/Water MRI or Magnetization Transfer Imaging) to better understand which imaging findings are and are not important.

A potential outcome of ongoing research and development could be that emerging technologies and research findings afford the opportunity to interrogate our own clinical instincts when managing patients with more complex, and seemingly unexplainable, signs and symptoms. Moreover, such knowledge would provide for the judicious use of carefully selected quantitative imaging sequences in tandem with known psychosocial risk factors that improve diagnostics, and hopefully improve outcomes.

Not forgetting the Bio in the Bio-Psycho-Social Model of Spinal Pain

A potential risk of the strong push to reduce inappropriate imaging in clinical practice is to 'forget' a biological component of spinal pain and to stifle important research that aims to better understand the contribution of local lumbar and cervical pathology to spinal pain. It is widely accepted that low back and neck pain are complex multifactorial conditions with both spinal (e.g. local biological contributors) and extra-spinal contributors (e.g. psychosocial factors); however, much research[40-42] has focused on the extra-spinal domains and, with some exceptions, [43-46] largely ignores the potential contribution of local pathology. We argue that high quality imaging research (especially those using new technology and advanced standardized analysis approaches) investigating the potential biological contributors to spinal pain form an important part of this inquiry. Without a better mechanistic understanding of the many biological contributors, it is likely the personal, societal, and economic burden of spinal pain will remain unchanged and enormous.

A fundamental difficulty underlying almost all spinal imaging studies is the lack of a gold standard test to identify sources of spinal pain. Importantly, spinal pain, similar to abdominal pain or headache pain, is a symptom. Differentiating a painful structural change (e.g. disc degeneration) from a non-painful structural change remains a key challenge for the research community. Ultimately, the value of imaging findings from investigations of the spinal column[31, 47, 48] (and the brain [49-57]) will be demonstrated if such findings strongly predict important outcomes or identify phenotypes of patients who respond best to specific interventions.

MUSCLE FAT INFILTRATION AS A BIOLOGICAL MARKER OF DISEASE

The observation and description of muscle fatty infiltrates (MFI) has become increasingly common in the literature spanning acute and chronic whiplash, [27, 28, 32, 58, 59] low back pain,[60-63] spondylytic myelopathy [64], rotator cuff injury,[65-69] osteoarthritis,[70, 71] and spinal cord injury.[72, 73]

While some early studies suggest this finding may be associated with development of persistent pain and poor recovery in whiplash, [27, 28, 30, 31, 33] others report no association between measures of muscle structure (e.g. size without measuring fat) and symptoms.[20, 21] Accordingly, the causal relationships between changes in muscle structure, symptoms, and the mechanisms underlying their generation following whiplash are largely unknown. Irrespective of the condition, current theories behind the expression of MFI could include the result of trauma, age-related changes,[74, 75], ethnic differences,[76] spinal phenotypes,[43-46] disuse,[60, 61] or degeneration.[16]

Imaging of Whiplash Injury – Potential Pathology

Here we examine whiplash injury from a motor vehicle collision on grounds it is a common, yet enigmatic, condition whereby the role of imaging in clinical practice remains controversial.

Radiculopathy or myelopathy have their own distinctive clinical features, and accompanying abnormalities on radiography and MRI [77] yet the identification of salient pathologies of discs, ligaments, vertebral and carotid arteries, and facet joints that are related to the signs and symptoms of acute, or chronic whiplash remain obscure.[19, 78-84] Accordingly, whiplash continues to be conceptualized as an almost purely psychosocial phenomenon. [85]

Yet, it is possible that the lack of consistent imaging findings that are related to whiplash-related symptoms [20, 21, 28, 31, 33, 86] are the result of study limitations and differences in methodological approaches (e.g. Ultrasound imaging, fat/water imaging, T1-, T2-weighted, Proton-Density, or Gradient Echo sequences). Another limitation of existing studies of imaging findings using longitudinal research designs (within and beyond whiplash) is that few, if any, use more quantitative measurement tools. Rather, they have tended to rely on qualitative grades or scores. While qualitative grading is shown to be adequate and with acceptable utility in the clinical environment, they may be prone to more variability.[87-91] Few investigators report using even simple but critical methodological controls such as co-registration and how the slices were aligned in plane to reduce noise, and discrepant findings from repeated measures. [92] We argue a way forward is to explore and develop consensus driven standardized measurement approaches similar to what has been proposed for measuring the structure and composition of lumbar paravertebral muscles [93] and for quantifying the patient's pain experience using functional magnetic resonance (fMRI).[94]

The Progression Towards Fat/Water MRI (Muscle Fat Infiltration)

In traumatic whiplash, MFI is a potentially interesting marker as it is more common than in patients with non-traumatic neck pain[29, 30], suggesting that traumatic factors may play a role in their development [31] on standard T1-weighted images.[28] Considering a growing body of evidence around muscle degeneration,[59] these changes may represent one physiological contributor to poor functional recovery in a discrete number of patients with poor functional recovery following whiplash injury.

Imaging techniques such as fat/water MRI (detailed below) could help quantify the rapid onset of compositional changes in muscle, which may precede macroscopic muscle changes on standard T1-weighted sequences. A preliminary study,[31] case-series,[95] and interdisciplinary lines of work [96] suggests this may be the case for a subset of patients with whiplash, meaning these advances in imaging techniques could lead to more timely and effective intervention trials and thus, informed clinical decision-making.

Several approaches for quantitatively measuring the water and fat composition on a MR image exist. These include T1-weighted imaging and a dual acquisition method, where one image is fat suppressed [97] (water image) and a standard image (fat and water combined) is collected.[98] By removing the water from the co-registered combined image, muscle fat can be identified with high sensitivity and specificity.[31] A challenge with such an acquisition is its reliance on the uniform frequency difference between water and fat and this can be difficult to obtain when using higher magnetic fields (3Tesla and above) where chemical shift may feature. A fat suppressed inversion recovery sequence (e.g. short tau inversion recovery, or STIR) is promising, but as STIR nulls signal from fat species, the quantity of fat will be estimated rather than quantified and this may vary across ethnicities, [76] age, [74, 75], phenotypes, [43-46] and conditions whereby the composition of and temporal changes in muscle fat may differ**.**[92, 99]

A well-known alternative is the Dixon method [100] where data are collected at echo times when water and fat are in- and out-of-phase. The data can be used to generate a fat and water image but this is not without potential image distortions from field inhomogeneities.[101, 102] Current methods collect multiple echo time data to improve the estimation of the fat and water images and this has been applied successfully. [103, 104] The methods [33, 75, 105, 106] have been tested and used in animal- and human-based studies of the appendicular and axial muscle system collecting different echo times for generating a quantitative measure for fat/water composition. [98, 107]

While previous research across the globe has identified changes in the size, shape, and spatial distribution of MFI in paraspinal muscle following whiplash[27, 28, 31-33, 86] and in low back pain (and asymptomatic participants)[75, 76, 108], they are not typically reported in clinical practice, likely because radiologists are neither looking for them nor using the techniques that would enable them to observe and measure such changes. We are of the opinion, based on basic, [106] and clinical research, [31, 69, 75, 86, 105] that fat/water imaging is the preferred imaging method for quantifying MFI. We further expect that a richer investigative landscape for musculoskeletal conditions will result in diagnostic imaging standards based on sound biological, psychological and social parameters [109, 110] resulting in improved outcomes.

Magnetization Transfer Imaging of the Spinal Cord

The following two sections (Magnetization Transfer Imaging and Spinal Cord Toolbox) briefly detail new imaging techniques and mechanistic measurement tools that pertain to patients with suspected spine trauma and/or cervical cord involvement (e.g. whiplash, spinal cord injury, myelopathy) but, as yet, not patients with low back pain, shoulder dysfunction, or osteoarthritis where mechanistic origins are less grounded in trauma.

Magnetization Transfer Imaging (MT) has been used to provide a semi-quantitative metric for traumatic brain injury,[111, 112] peripheral neuropathies, [113] and is used clinically in diagnostic studies of neuronal degeneration in Multiple Sclerosis,[114] Alzheimer's,[115-119] and Parkinsons disease.[120, 121] MT provides an indirect measure of tissue integrity, relying on the exchange between saturated hydrogen molecules (protons associated with free water) and another pool of protons that belong to bound water residing on hydrophilic macromolecular surfaces (e.g. lipids and proteins).[122, 123]

Magnetization transfer imaging has demonstrated predictive value in determining sensory and motor disability levels following spinal cord injury, suggesting that a non-invasive MT measure of the cord *and* determination of impairment is possible.[124] It is our contention that MT imaging could provide a more sensitive measure of cellular level changes in the spinal cord and brain [27, 28, 32] in a discrete number of patients without radiologic abnormalities following whiplash,[95] and possibly concussion.[125]

Positive findings could inform the prognostic picture of and expected response to functional rehabilitation schemas by acutely characterizing the structure of white matter spinal pathways following head and neck trauma. Larger scaled prospective investigations involving patients with varying levels of condition-related disability and impairment are required before definitive conclusions can be drawn. **FIGURE 1** details the basic physics underlying Magnetization Transfer Imaging.

Tools for Imaging Spinal Cord Pathways

The Spinal Cord Toolbox, an open-source image processing software, has been developed to facilitate the advancement of spinal cord imaging.[126] One key component of this software is the MNI-Poly-AMU T_2-weighted template, which allows for a fitting of spinal cord imaging data from anatomically varied participants into a standardized anatomical template of the spinal cord.[127] This important registration step in image processing permits researchers the opportunity to analyze precise anatomical locations of the cord, including gray matter, CSF, and specific white matter tracts, which can then be compared within- and between-subjects in a standardized manner.[128] In 2016, the Spinal Cord Toolbox was used to study spinal cord changes in patients with degenerative cervical myelopathy, using diffusion tensor imaging, MT, and T_2 weighted MRI.[129] Significant relationships between white matter injury and specific motor deficits, in an ipsilesional manner (i.e. right sided white matter damage correlated with right sided motor deficits) were observed.[129] Using the Spinal Cord Toolbox, and in accordance with the findings of Martin et al., preliminary work coming out of the Neuromuscular Imaging Research Laboratory at Northwestern University observed damage involving the lateral corticospinal tract that was associated with ipsilesional motor deficits in patients with incomplete spinal cord injury (Smith et al, in submission). The Spinal Cord Toolbox represents an innovative program with great potential to improve the segmentation, registration and calculation of spinal cord anatomical metrics (**FIGURE 2**) across a spectrum of patients with persistent spine-related disability (e.g. whiplash, known spinal cord injury, or myelopathy). Any indication for its use in patients with other musculoskeletal conditions whose mechanistic origins are less ground in trauma (e.g. low back pain or joint-related conditions) is, at this stage, unknown

WHERE TO GO FROM HERE

The current climate of rejecting imaging as a viable modality for spinal pain/disability appears to have been borne largely from a series of studies that found positive spinal imaging findings in asymptomatic cohorts.[12, 18, 130] and the appropriate desire to reduce some unnecessary imaging. While we do not dispute the value of this research, we see several clear reasons why high quality research into MRI findings remains important. Given the recurrent nature of most spinal pain and clear evidence that many MRI findings are more common in those who have spinal pain than those who do not [26, 131] we believe future research should focus on understanding the link between imaging findings and future spinal pain (e.g. the course of a current episode, development of recurrences, or persistent pain-related disability), rather than focusing on imaging findings in asymptomatic people that would not be sent for imaging in clinical practice.

CONCLUSION

Our intention is not to throw darts at our peers, nor is it to endorse imaging for all, or even most, people with traumatic or non-traumatic spinal pain. On the contrary, our intention is to refocus research and clinical efforts towards identifying the right evaluation, for the right patient, at the right time (acute, subacute, chronic stages). While we are not there yet, advancing imaging technologies, and pathological findings (or processes) may explain the seemingly disconnected spectrum of biopsychosocial signs and symptoms of chronic traumatic and non-traumatic neck and low back pain. The sequences and measures described are not meant to be exhaustive, rather they offer an encouraging preview of imaging findings that could eventually guide clinical treatment decisions by identifying spinal phenotypes with a target to determine which patients respond best to specific interventions. Current and future research investigations should aim to enhance tomorrow's imaging guidelines towards providing appropriate directives for the timely performance of imaging in tandem with consideration of the psychosocial factors that are unique to the individual person seeking our care.

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FIGURE LEGENDS:

FIGURE 1 – Basic Physics underlying Magnetization Transfer Imaging. Typical MRI imaging draws it signal from protons associated with free water. There is also a pool of protons bound to macromolecules – such as the myelin surrounding an axon. If one compares the resonance spectra of these 2 pools, free water has a sharp resonance peak and long T2, whereas Macromolecular protons have a broad spectrum and an ultra-short T2 (~100μs) making imaging of this group difficult. By use of an off-resonance radiofrequency pulse before imaging, one can selectively saturate the macromolecular pool of protons. Although the relaxation will not be visible, magnetization of the bound pool will partially exchange with the surrounding free water. Degrading the local free water signal in proximity to macromolecules, as shown by the dashed line. This exchange between pools of magnetization allows for the indirect study of the bound protons, and thus the density and stability of macromolecular content of a given imaging voxel. This technique is often reported as the magnetization transfer ratio or MTR, the signal change in free water due to magnetization exchange

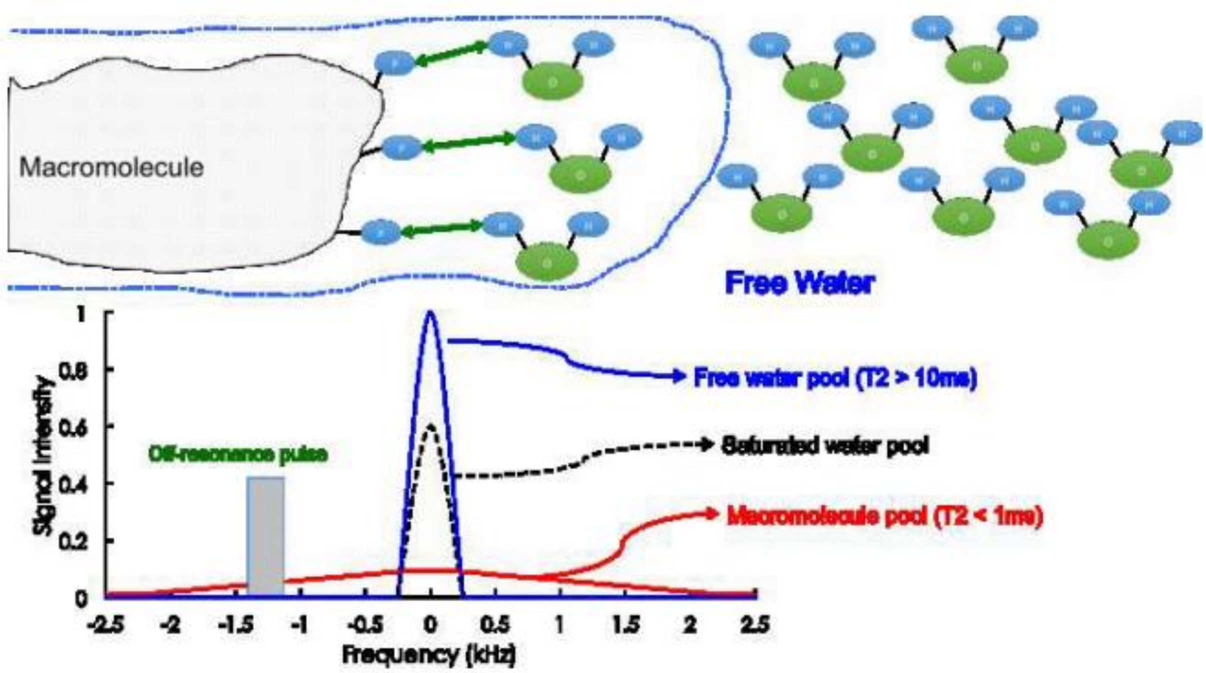

Figure 2 - A) A native sagittal T_2-weighted image of a participant with spinal cord injury. B) Native axial T_2-weighted images through the spinal cord lesion. C) The lesion filled image was then straightened along the spinal cord and registered to the MNI-Poly-AMU spinal cord template. The mean and standard deviation (SD) of the voxel intensities were then calculated within a non-

lesioned 1 cm axial cross-section of the spinal cord immediately superior to the lesion. The maximum intensity projection image was then thresholded at two standard deviations above the mean to define the lesion. D) The extent of spinal cord damage was then quantified in the axial plane as the ratio of the spinal cord that was lesioned across the total cord and within the right and left lateral corticospinal tracts (LCST) and gracile fasciculi (GF). One representative participant is shown. The right and left LCST and GF are shown in green and light blue, respectively.