Author's response to reviews

Title: MRI signal distribution within the intervertebral disc as a biomarker of adolescent idiopathic scoliosis and spondylolisthesis

Authors:

Julien Gervais (julien-2.gervais@polymtl.ca)
Delphine Perie (delphine.perie@polymtl.ca)
Carl-Eric Aubin (carl-eric.aubin@polymtl.ca)
Stefan Parent (stefan.parent@umontreal.ca)
Hubert Labelle (hubert.labelle@recherche-ste-justine.qc.ca)

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Author's response to reviews: see over
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Editor in Chief, BMC Musculoskeletal Disorders

Please find enclosed the revisions of our article untitled «MRI signal distribution within the intervertebral disc as a biomarker of spinal deformities» for submission to your journal «BMC Musculoskeletal Disorders».

This letter includes the responses to the reviewers on a point-by-point basis. The revisions are highlighted in yellow in the manuscript.

All the co-authors, Julien Gervais, Delphine Périé, Stefan Parent, Hubert Labelle and Carl-Eric Aubin provided approval for the content of the revised manuscript and for its submission to «BMC Musculoskeletal Disorders».

Thank you for your consideration.
Yours truly.
Delphine Périé

Mechanical Engineering Department
Ecole Polytechnique, Montréal, Canada
Tel: 1-514-340-4711 ext. 4437
Email: delphine.perie@polymtl.ca
Responses to Reviewer 1

*Title: I would suggest to focus the title on scoliosis and spondylolisthesis, as ‘spine deformities’ may be misleading also to different congenital deformities. Also, the population of the study is essentially made by young subjects. Consider adding this detail to title and abstract.

The title was replaced by: MRI signal distribution within the intervertebral disc as a biomarker of adolescent idiopathic scoliosis and spondylolisthesis.

Abstract, Introduction: I would focus the attention on scoliosis and spondylolisthesis and not on spine deformities in general.

“Spine deformities” was replaced by “scoliosis and spondylolisthesis” in both abstract introduction and conclusion.

Abstract, Results: Authors describe ‘indices’ that are not clearly defined in the m/m section. Also the m/m do not include a clear indication of the fact that data were normalized in regard to CSF.

These informations were added in the abstract method section. The number of indices in the abstract result section was removed because this incomplete information was not relevant.

Abstract, Conclusion: authors state that variation in IVD signal intensity are not currently performed in clinics. The sentence should be rephrased, as the meaning is not retained compared to what reported in the discussion of the manuscript. Also, I would emphasize the clinical implications of the results.

The first sentence of the abstract conclusion was rephrased: “This study proved for the first time that changes in the intervertebral disc, non visible to the naked eye on sagittal T2-weighted MR images of the spine, can be detected from specific indices describing the distribution of the MR signal intensity”. The clinical implications of the results were added.

Main text, Introduction, second paragraph: MR spectroscopy has been used to assess IVD degeneration. Authors used reference #9 in the introduction. I would suggest to introduce briefly the topic and later discuss briefly the results in relationship to the

In the second paragraph of the introduction, we presented the use of MRI sequences available in clinical routine, more precisely T2-weighted images, to assess IVD degeneration. The reference 9 is just for T2-weighted images, and not for spectroscopy or multi-parametric MRI that are out of scope in this clinical context. We modified this paragraph of the Introduction section for more clarity. However, the reference you proposed was added and discussed in the Discussion section.

**Main text, Methods: Is it correct that all subjects provided explicit informed consent also for a retrospective study?**

As long as we use clinical images from patients to perform new analysis involving new parameters, we need the informed consent of the patients. Thus, at the hospital Ste-Justine, an informed consent form is presented to each patient for the potential use of their clinical data for research studies. This information was added in the text.

**Main text, Methods: How long does it take to analyze data of one patient? This may be useful to know for clinical practice.**

This information was given in the Method section – IVD selection and segmentation: “This segmentation was realized for three zones (Figure 1): IVD, nucleus pulposus (NP) and annulus fibrosus (AF) and took about ten minutes per disc”. The segmentation is the longer process in the data analysis as it requires a manual intervention of the operator. Once the segmentation is done, the data processing is fully automated and takes several seconds. This point was further discussed in the limits of the study.

**Main text, Results: absolute values of data are not reported neither in results or tables. Consider the opportunity of adding these data.**

We did not present the absolute values for the descriptive statistics of the normalized histograms by the cerebrospinal fluid signal or the normalized histograms by the bone signal because they don’t have direct clinical meanings. We did not see the pertinence of these absolute values as compared to the ANOVA results presented in Table 2. However, the
absolute values for the weighted centers and volume ratios were presented in Table 3 and Table 4.

**Main text, Discussion:** I would emphasize the clinical application of these results: how they can modify clinical practice? How the results can improve diagnosis?

A paragraph on the clinical application of our method was added at the end of the Discussion section.

**Main text, Discussion:** I would separate limitations in a specific paragraph.

The Discussion section was reorganized to group the limitations in a specific paragraph. Subtitles were added in the Discussion section for more clarity.

**Main text, Discussion:** Another limitation is that this analysis was applied in an ideal situation, with patients affected by a single pathology. In clinical practice, however, this condition occurs rarely. Thus, the application of this system in clinical practice may be more difficult. Also, I would emphasize that these results are obtained in young subject. Thus, application of this system in elderly subjects may produce dissimilar results.

Adolescent patients with a single pathology are not rare as we found easily 64 patients corresponding to this criterion and could find a lot more if we did not consider restrictions on the MR parameters (echo time of 121-126 ms and repetition time of 3200-3690 ms). Moreover, only few patients with scoliosis or spondylolisthesis at the CHU Ste-Justine had a MRI acquisition. We added comments on the application of our method to elderly subjects in the last paragraph of the Discussion section.
Responses to Reviewer 2

p5: "The selected cases presented ... no treatments prior to the MRI acquisition". What does no treatments mean? No surgical treatment? no physiotherapy? No pain medication? Please specify.
The patients did not have brace or surgical treatment. We did not have the information for physiotherapy or pain medication. This information was added.

"Siemens Medical Solutions" is now called "Siemens Healthcare".
This error was corrected.

"MR images were performed on a 1.5T system". On a single 1.5T system? or multiple scanners? which type of scanner?
All the acquisitions were performed at the hospital Ste-Justine of Montreal on a single scanner: Sonata system. This information was added.

As I understand the L4/L5 or L2/L3 was selected. I think the signal histograms obtained from different discs can be different because of different shape and different size of the disc. I think this is problematic and a limitation of this study, that should be mentioned.
How many discs in which level were included in which group? please provide in a table.
The normalization process took into account the different shape and sizes between discs. This was explained in the Method section – Data normalization: “First, each voxel was set to a fraction of the IVD’s volume to normalize the count of voxels between patients’ histograms due to the variable disc sizes and image resolution between subjects”. Thus this is not a limitation of the study.

Please label the axis in Figure 3.
This information was added in the Legend of the Figure.

"Figure 4: Segmented IVDs for control (a), scoliosis (b) and spondylolisthesis (c)."
Figure 4b shows a cupid's bow contour, which is not necessarily associated with scoliosis, but is also common in normal IVDs. Figure 4 suggests that this shape is caused
by scolios. Or do the authors have data suggesting this is more common in scoliosis? See Schmorl nodes of the thoracic and lumbar spine: radiographic-pathologic study of prevalence, characterization, and correlation with degenerative changes of 1,650 spinal levels in 100 cadavers. Pfirrmann CW, Resnick D. Radiology. 2001 May;219(2):368-74.

We did not suggest that this shape is caused by scoliosis. We removed Figure 4 as it was not referenced in the text neither discussed. Moreover, it avoids the confusion.

P.6. "the mean cancellous bone intensity of the above vertebra" was used for normalization of signal intensity. Did the authors make sure, there are no abnormal findings in cancellous bone signal like Modic type changes?

We did not see changes in the signal of the adjacent vertebral body. However, we previously measured changes in the bone density distribution from CT scans [Périé et al., Clinical Biomechanics 2002]. We recognize that, when using the bone signal to normalize the IVD signal, we take into account the bone health added to the disc health, as specified in both the Discussion section and the Conclusion. We added this reference.

p.8. "the mean CSF intensity was highly influenced by both the pathology (p=0.02) and the severity (p=0.04)." Should the CSF signal intensity not be constant, when normalized to CSF? Please explain this clearly in the manuscript. If the normalization to bone is unreliable why did you use it in your manuscript?

The CSF is constant between subjects. If the MR signal changes, it is only due to the gain of the MR system between acquisitions. The normalization to bone is not unreliable but different from the normalization to CSF as normalization to bone includes two phenomenons (MR system gain and bone changes with pathology) while the normalization to CSF includes only one phenomenon (MR system gain). This was further explained in the Results section - Mean bone and CSF intensities.

p.11. "a reproducibility study proved that intra-operator variability was negligible" Do the authors have data on that? Please mention numbers if available.

A sensitivity study was done on our method. We added the reference to the manuscript and summarized the most relevant results.
p.12. Are the Figures included in the manuscript the result of the described "automatic segmentation processes"? Otherwise please provide such examples.

Our segmentation process is not automatic but semi-automatic as it uses a snake algorithm followed by a manual intervention. The figures result from our semi-automatic segmentation process.

Table 1: please provide data on time of the day, age and BMI for each subgroup, maybe in a separate table. Where the group characteristics comparable?

We mentioned in the Method section – Subjects’ selection that “there were no significant differences in the distribution of the morphological parameters (Table 1) between each group, providing randomization”. Thus we thought not pertinent to present the patients’ age, height, weight, body mass index and MRI acquisition time of the day for each of the five groups.

There are some typos.
We corrected some typos.

General comments: The authors present a sound scientific paper, however, the clinical relevance of the used methodology has to be shown in future studies. The methodology should be explained more clearly.

The clinical applications were further discussed in the last paragraph of the Discussion section. Details were added to the Methodology section.