Reviewer’s report

**Title:** Observations on morphologic changes in the aging and degenerating human disc: Secondary collagen alterations

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**Reviewer:** Dr Jeffrey Lotz

**Level of interest:** A paper whose findings are important to those with closely related research interests

**Advice on publication:** Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Manuscript Review

**Title:** Observations on morphologic changes in the aging and degenerating human disc: secondary collagen alterations

Gruber and Hanley

**General Comments**

This study reports observations on collagen structure made on specimens of human annulus fibrosus. Overall, the results are interesting and raise questions regarding how the biomechanical response of degenerated discs may be compromised. The study would be strengthened by clarifying how pervasive the noted changes are. Since EM and histology provide information on only a small region, it is unclear from the data presented how much of the annulus demonstrates collagenous alterations. Also, it is unclear to what degree the histologic alterations change the tissues biomechanical properties. In the future, biomechanical correlations would greatly improve our understanding of how disc degeneration enhances injury risk. Finally, This reader was interested to know how, if any, the tissues from the 'control' donors differed from patients. These differences may shed some light on why patients experience pain.

**Specific Comments:**

**Abstract**

Page 2, para 1. This reader is confused by the number of specimens. In the first paragraph 29 controls and 49 patients were stated, while in the second sentence 40 control and 53 surgical specimens are stated. It would be clearer to state 40 annular specimens from 29 control donors and 53 annular specimens from 49 patients. How are the 'controls' different from the patients? What is being controlled for?

Page 2, para 3. The results as stated are somewhat confusing. 'encircling layers of unusual matrix...' at this point, it is unclear what these layers are encircling. Also, if the collagen was absent then clearly the crimp pattern would be altered. Do the authors mean that the crimp pattern is altered adjacent to regions with reduced or absent collagen?
Background

Materials and Methods
Page 5, para 1. For the EM studies, how was the orientation of the specimens maintained? When analyzing the crimp pattern, it would be important to know the plane of sectioning relative to the lamellar architecture.

Page 5, para 2. It is not clear what 'three-dimensional intensity graphical presentation' is. What is being measured/quantified with this technique?

Results
Page 5, para 3. What does 'opportune sectioning planes' mean?

Page 6, para 1. Can the histologic data be used to clarify what the 'unusual extracellular matrix' is? Is it proteoglycan or collagen?

Page 6. Ninety-three specimens were analyzed. How common are the findings presented in Figures 2-4? Are there differences between inner and outer annulus? How are the 'controls' different from the surgical specimens? Can the authors provided information as to how common the noted changes are? The volume of annulus that is altered would be important to understand while reconciling the overall influence on disc biomechanics.

Are there quantitative data resulting from the image analyses of the crimping patterns presented in figure 4? If so, can these data be used to more broadly characterize their specimen population?

Discussion
While the observations the authors present are interesting, their role in the biomechanical function of the disc are unknown since no biomechanical tests were performed. Also, it is not clear how extensive the noted changes were in the disc tissues harvested. Both the nature of the tissue alterations, and their extent would contribute to the overall disc biomechanical function.

Page 8, para 2. How do the authors reconcile the previous observations of disc biochemistry and aging (cited from the literature) with their present data? Do the previous studies they cite support their results?

Competing interests:

None declared.