Thank you for letting me review your work on the topic of fluoroquinolone induced tendinopathies. I enjoyed the read of this interesting basic sciences paper which in my opinion is decently written and overall well carried out.
I hope your work will bring more attention and clarification to his topic, which in my opinion and especially from a clinical standpoint, hasn't received the attention it should have until now. Attached find my comments, which hopefully will give you some hints, which points in my opinion could be addressed to make the paper more powerful and clear for the (clinical) reader.

Best regards,
Cyrill Suter

Line 34: treatment

Line 88: tissue (Riley 2008) – missing space.

Line 114: From how many equines did you get specimens, resp. how many specimens derived from the same equine? How where they distributed? Was there a way to ensure the specimens were distributed equally/by chance into the different treatment and control groups?

Line 125: Reasoning for 96 hours? According to Morales et al. (2018, Indications for Systemic Fluoroquinolone Therapy in Europe and Prevalence of Primary-Care Prescribing in France, Germany and the UK: Descriptive Population-Based Study) acute bronchitis, acute sinusitis and UTI's – for those indications treatment is at least a week. And can be up to several weeks i.e. in prostatitis. Therefore, it would be interesting to see if also a time dependent viability reduction/ PG synthesis reduction could have been shown in the different FQ groups.

Line 173: Were placed in RNA later at 4°C overnight - missing space (also missing spaces lines: 284, 285, 288, 291 295 296 299 etc.)

Line 234: biglyan

Line 302: Why transitory decrease? after 96 hours of treatment only versican (300µg/mL) was downregulated – 8 days after discontinuation Biglycan (10, and 100µg), Aggrecan (1, and 10µg/mL) and versican (1µg/mL) were decreased.

Line 303: Could you please elaborate. Maybe in one or two sentences how you replaced them? And in what context this stands in respect to this study?

Line 308: (concentrations >100µg/mL, as well as 1µg/mL)

Line 310-12: In order to support and/or understand this speculation, I believe it's crucial to know a bit more of the statistical power behind it. What's the absolute number of the 10µg/mL group? In this context, providing absolute numbers also for the other FQ groups would be helpful for more transparency, and therefore trustworthiness of the results.

Line 335: during...something is missing I assume …? To my understanding degradation of the various PG's mRNA was more dominant/clear 8 days after treatment discontinuation.

Line 343-45: Reducing viability of tendon is in my understanding a pretty straight forward tendon injury/pathological tissue change. Would you claim that as long as the tendon doesn't rupture without moving it, it isn't a primary pathological tissue change? What's the discrimination of primary and secondary in this context?

Figure 2: confidence level missing for ** - I would suggest to keep the confidence levels same throughout the study/figures and not change them for different outcomes.

Figure 3: Chondroitin sulfate levels – interpretation of it in the discussion?

Figure 6: For making interpretations of findings more easy, I would suggest to combine figures of the different expressions of mRNA's at time 0 and 8 days after FQ. Accordingly, combine figure 6 and 11, figure 7 and 12, etc.