Reviewer's report

Title: Biochemical characterization of osteochondritis dissecans in the ankle

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Reviewer: Laura Creemers

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The current manuscript aims to demonstrate a correlation between biochemical parameters of the synovial fluid and progression of OCD. Several growth factors previously described by mainly the same authors as being associated with joint pathology were measured in a group of 28 patients whose joint fluid was aspirated prior to surgery. In particular IGF-1 and IGF-IR are found to be negatively correlated to the stage of OCD, whereas several proteins in the BMP signalling pathways did not show such association.

Major Compulsory Revision
The main concern I have is that the major conclusion, i.e. that loss of IGF-1/IGF-1R signalling is related to progression of OCD, is not supported by the data, due to the set up of the study. As OCD stage is also clearly correlated to ageing, the association of IGF-1 with OCD may merely reflect the association with IGF-1 with ageing. Therefore, only a study including age-matched control subjects without cartilage pathology or maybe even with other pathology, can show such correlation. Alternatively, the authors may want to look for IGF-1 levels in synovial fluid in other studies, to disprove an intrinsic correlation of IGF-I with age as such.

Minor essential revisions
What is the role of soluble IGF-1R in synovial fluid and how does it get there, being a transmembrane receptor? Synthetic soluble receptors are being used to inhibit IGF signalling, suggesting that the IGF-1R may even have inhibited IGF-mediated effects, although at a molar basis IGF-1 was present at a 350 fold excess. Please discuss.

It is unclear which synovial fluid samples were used for direct measurement by ELISA and which ones after lavage. When were they taken?

The AOSS scoring system should be described in a table rather than fully written in the text.

The number of patients is very limited, as the authors already pointed out. Did the authors statistically correct for the fact that they carried out multiple correlation analyses, thereby increasing the chance of finding one with a $P<0.05$?

The disclosure statement suggests that all author have financial relations to disclose, but I think they mean otherwise.
alternated should be "altered"

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests