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## The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis: Response to Patel and Dhillon

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# The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis: Letter to the Editor

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## Dear Editor:

In the January 2014 issue of *The American Journal of Sports Medicine*, Sundman et al<sup>11</sup> published a controlled laboratory study ("The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis") wherein they studied the mechanism of action of platelet-rich plasma (PRP) and hyaluronic acid (HA) in relieving pain in knee osteoarthritis (OA) by noting the expression of anabolic and catabolic genes and on the secretion of nociceptive and inflammatory mediators from OA cartilage and synoviocytes. We want to congratulate the authors for conducting such a well-planned study.

Use of PRP has shown promising results in the treatment of early OA of the knee in various studies.<sup>3,5,6-10</sup> Spakova et al<sup>10</sup> and Kon et al<sup>5</sup> had compared PRP with HA and had shown better results in the PRP group. In 2013, we conducted a randomized controlled trial<sup>8</sup> wherein we found that clinical improvement of PRP in terms of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) are immediate and had a tendency to wane at the 6-month follow-up. Similar findings were noticed by Filardo et al.<sup>3</sup> We felt that it was more of an anti-inflammatory and antinociceptive mechanism rather than chondral remodeling or anabolism that was responsible for the early clinical gains. Sundman et al have used a co-culture, which is good as we expect interactions between both in real life as well.

Sundman and colleagues have found a positive role of PRP in synoviocyte response in terms of significant improvement in hyaluronan synthase (HAS)-2 expression and significant reduction of matrix metalloproteinase (MMP)-13 expression. Anitua et al<sup>1</sup> also noticed similar effects of PRP on increasing HA secretion within joints. In addition, they noticed a positive role in terms of cartilage synthetic activity compared with controls and HA, as indicated by the increase in cartilage aggrecan (ACAN) expression and collagen type I $\alpha$ 1 (COL1A1) expression. When looking more closely at Figure 3 of the article, there seems to be a very small difference in terms of increase in gene expression of ACAN and COL1A1; this brings into debate the significance of this small rise in value.

Despite a very well-planned study, we feel that the authors were biased in the interpretation of results, as evidenced by their support of the PRP group rather than the HA group. If evaluated carefully, it becomes clear that both

tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6 were decreased more in the HA group than in the PRP group (where IL-6 was increased). The authors have stated in the discussion that "the concentration of IL-6 appears to decrease with increasing severity of OA"<sup>11(p39)</sup> and cite the Brenner et al<sup>2</sup> study. However Brenner et al mentioned in their abstract that "apart from a correlation between PGE<sub>2</sub> and WOMAC-index ( $r = 0.36, P = 0.035$ ) no significant relationships could be found between the various inflammatory parameters and any of the assessed clinical signs."<sup>2(p469)</sup> The finding by Sundman and coauthors of decreased IL-6 and TNF- $\alpha$  in the HA group should actually be interpreted as more an anti-inflammatory and antinociceptive property of HA rather than any influence of PRP. No other inferences should be derived out of this specific finding.

IL-1 $\beta$  is a very important proinflammatory cytokine in controlling the degeneration of articular cartilage matrix, as evidenced in previous studies.<sup>4</sup> In spite of using high-sensitivity enzyme-linked immunosorbent assay (ELISA), IL-1 $\beta$  was not detectable in any of the samples in the study.

In the last paragraph of the article, the authors note the "positive effect of HA on cartilage matrix gene expression"<sup>11(p40)</sup> (although their results show that PRP has positive effects). Based on this statement, they have postulated that a combination of PRP and HA could be used and may be better for clinical gains. We feel that such conclusions should not be drawn from this study and that the results should be interpreted with caution.

Even though PRP results in a generalized stimulation of cartilage metabolism by increasing both aggrecan and collagen type I expression, as shown by a marginal increase in their expressions as compared with both controls and HA samples, the situation may be quite different in real life. For chondral remodeling and anabolism, there needs to be a continual supply of growth factors from PRP for a long duration of time. This may imply that there needs to be more frequent injections of PRP (depending on the half-life of growth factors), to ensure availability.

Our experience, as well as the published literature, suggests that there are still a lot of gray areas in our understanding of the mechanism of PRP action in knee OA; this area needs further research before such specific conclusions can be drawn.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

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the seminal work of Anitua et al<sup>1</sup> that platelet-rich plasma (PRP) has mechanisms of action beyond stimulating the synthesis of cartilage matrix molecules. We respectfully disagree that our interpretation of the data was biased. Robust statistical analyses were performed, and the authors did not interpret trends as being meaningful nor representative of statistical differences when comparing hyaluronic acid (HA) to PRP.

Interleukin-1 $\beta$  is clearly involved in the initiation of osteoarthritis (OA), but its role or presence in late-stage OA has not been reported. The tissues used for this study were from patients with end-stage OA and were retrieved during total knee arthroplasty. At this stage of disease, it is possible that downstream cytokines such as matrix metalloproteinase-13 are the major catabolic mediators.

We agree with the concept that results from an in vitro study should be interpreted with caution. As a subsequent investigation, we recently completed a prospective randomized double-blind clinical trial at Rush University Medical Center in Chicago comparing autogenous PRP to HA for the treatment of OA. Each patient had time zero and 4 synovial fluid aspirates following treatment, in which we have analyzed several anabolic and catabolic cytokines. This study should provide further insight into the mechanisms of action of PRP in OA joints.

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### Authors' Response:

We thank Drs Patel and Dhillon for their comments. As pointed out in their letter to the editor, our data support

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