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CORR Insights

CORR Insights®: Prolotherapy Induces an Inflammatory Response in Human Tenocytes In Vitro

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Where Are We Now?

The current study by Ekwueme and colleagues addresses a critical first step in understanding the response of two types of human tenocytes in vitro to two different prolotherapy agents. Briefly, the authors found that dextrose and a combination of phenol, glucose, and glycerin (P2G) decreased the metabolic activity of the cultured tenocytes, upregulated a focused panel of proinflammatory markers, and decreased cell migration by tenocytes, with P2G generally demonstrating stronger or more pronounced measured effects than dextrose. These findings provide important initial insights into how prolotherapy might work; however, the investigators really examined the in vitro effects of two common prolotherapy agents, rather than prolotherapy itself. As a result, we know that prolotherapy is commonly used by some practitioners in clinical practice [2], and that it likely does induce cell death and an accompanying subsequent local inflammatory response [1].

Where Do We Need To Go?

We still need to determine the ideal local inflammatory response for any delivered irritant, osmotic, or chemotactic. In the current study, P2G generally exhibited stronger apparent effects than dextrose in vitro. Is P2G then a preferable agent to dextrose? We do not know. It is possible to envision either an injection inducing too much tissue necrosis, ultimately resulting in tendon weakening or incompetence or, alternatively, not enough inflammation to induce the desired eventual healing response. Sometimes more is more—but sometimes more is too much.

This CORR Insights® *is a commentary on the article* "Prolotherapy Induces an Inflammatory Response in Human Tenocytes In Vitro" *by Ekwueme and colleagues available at:* DOI: 10.1007/s11999-017-5370-1.

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Concurrently, and most importantly, we need to determine if prolotherapy actually works in patients. As Ekwueme and colleagues note, prolotherapy, in general, remains controversial, and convincing evidence of efficacy of any formulation, for any indication, is lacking [4, 7, 8].

How Do We Get There?

First, we need to investigate the local effects of a variety of prolotherapy agents in vivo in an animal model(s) of tendinopathy and/or ligament injury. Several such models already exist, in both small and large animals, for multiple diagnoses [3], so we need not reinvent the wheel. These animal studies should provide an improved understanding of how prolotherapy could work in humans, and demonstrate measurable findings beyond mere quantification of local inflammatory response, such as ultimate healing architecture and tendon or ligament strength. These findings can, in turn, help guide eventual human trials to definitively answer the question as to whether or not prolotherapy is effective, while concurrently providing baseline data to which new or existing, repurposed agents could be measured.

Second, we need high-quality human studies of prolotherapy to determine if this modality is actually effective at all. The refrain demanding additional, high-quality studies is tired only because it is so often true. Particularly given that I have written in *CORR*® on the dubious clinical benefit of platelet rich plasma injections (itself arguably a chemotactic form of prolotherapy) [6], why would I suggest high-quality studies of an intervention with a similar track record? Because providers and therapists are performing prolotherapy anyway, and we owe it to our patients and ourselves to answer the question one way or the other. We can then either definitively adopt (effective) prolotherapy into our clinical armamentarium, or discard (ineffective) prolotherapy onto the heap of abandoned treatments [5]. The first recommendation for in vivo animal testing can certainly inform the ideal design of clinical trials for the second, but given the ubiquity of prolotherapy and associated interventions in some circles, these two routes of advancement need not proceed sequentially.

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