INTRODUCTION

The homeostasis of the intervertebral disc (IVD) is regulated by a delicate balance between catabolic and anabolic cellular processes. Unbalanced metabolic activity leads to the degeneration of the IVD tissue [1]. Several growth factors are known to up-regulate the anabolic activity of disc cells (e.g., TGF-β, IGF, BMPs, etc.) [1]. In particular, it has been reported that IGF-1 stimulates the production of proteoglycans (PG) composing the extracellular matrix (ECM) of IVD [2,3]. Therefore, the exogenous administration of IGF-1 has been proposed as a therapy for disc regeneration [2]. Since cell response to IGF-1 stimulation is dose-dependent [3], knowledge and control of the distribution of this molecule in IVD is crucial for the success of the therapy. However, molecular transport in IVD is very complex and involves a series of coupled mechano-electrochemical events. In particular, transport of IGF-1 is characterized by reversible binding reactions with binding sites (mainly IGFBP-3) present on the ECM of cartilaginous tissues [4,5].

The complexity of this problem requires the aid of a numerical tool. The objective of this study was to investigate on therapeutic treatments for disc degeneration by quantitatively analyzing protocols of exogenous administration of IGF-1 to IVD via intradiscal injections. This was accomplished by developing a numerical model able to predict the time-dependent distribution of IGF-1 in IVD during and after intradiscal infusions.

METHODS

The numerical model developed in this study was based on the mixture theory [6-8]. The IVD tissue was considered as a mixture of: (1) an elastic, porous, permeable, negatively charged solid phase with binding sites (IGFBP-3); (2) an interstitial fluid phase; (3) an electrolyte phase (NaCl); (4) a solute (IGF-1) able to reversibly bind to IGFBP-3. Reversible binding of IGF-1 to IGFBP-3 was described by the Langmuir binding model [9]. Human lumbar IVD was schematized as a 2D axisymmetric object consisting of two anatomical regions, the nucleus pulposus (NP) and the annulus fibrosus (AF), with dimensions and properties similar to those reported in a previous study [10] (Figure 1a). Due to the lack of experimental data, IGF-1 transport parameters in the disc were assumed to be similar to those reported for articular cartilage [5,11]. In the simulations, a saline solution containing 1 μg/ml IGF-1 was injected, from the center of the NP, via a 22 gauge needle. A total of 8 μl of solution were injected, with flow rates (Q) varying from 0.8 to 0.02 μl/min. Clearance of IGF-1 occurred through the vascular network surrounding the disc at the cartilage endplates (CEPs), and around the perianular surface of the disc. In vitro studies indicated that the enhancement of PG production occurs when IGF-1 concentration is above the threshold value of 1 ng/ml [3]. The percentage volume of NP characterized by free (i.e., unbound) IGF-1 concentration higher than 1 ng/ml (Effective Volume) was evaluated over a time-frame of 24 weeks, at several concentrations of IGFBP-3 in the NP (varying from 1.5 to 15 nM). The implicit solver of COMSOL® (Comsol 3.2, Comsol, Inc., Framingham, MA) was used for the simulations.

RESULTS

During infusion, the intradiscal fluid pressure at the cavity of injection was calculated. It was found that the value of intradiscal pressure increased with the rate of infusion (Q), varying from ~10 psi (for Q = 0.02 μl/min) to 45 psi (for Q = 0.8 μl/min), Figure 1b.

For all the infusion rates investigated, the distributions of IGF-1 in the disc were similar after less than a week from injection. The effect of IGFBP-3 concentration (Cbp) on the Effective Volume is reported in Figure 1c. Data were compared to the case of free diffusion (i.e., no binding interactions of IGF-1). The Effective Volume of NP affected by IGF-1 was inversely related to IGFBP-3 concentration. However, the duration of the therapeutic level of IGF-1 in NP increased with Cbp. The largest Effective Volume (more than 80% after 4 weeks), obtained at the lowest value of Cbp (green line), was sustained for a period of 8-12 weeks. In contrast, at higher Cbp (red line), the Effective Volume was smaller (still >40%), but sustained for a much longer time (> 24 weeks).

DISCUSSION

The objective of this study was to quantitatively analyze therapeutic protocols of IGF-1 injection in IVD. A finite element model, based on the mixture theory for charged hydrated soft tissues, was used to describe the coupled diffusive-reactive IGF-1 transport and electromechanical behavior of the disc.

The analysis performed in this study indicates that binding reactions significantly affect the time-dependent distribution of IGF-1 in IVD. The binding reactions reduce the amount of available (i.e., free) IGF-1 to disc cells, and slow down its clearance from IVD. Therefore, in order to optimize the dosage and the time sequence of IGF-1 administration in IVD, binding phenomena must be taken into account.

For all the cases investigated in this study (injected with the same volume of IGF-1 solution), the infusion rate (Q) did not significantly affect IGF-1 distribution within the disc. However, it was found that the intradiscal fluid pressure increased with the infusion rate, reaching a value of 45 psi for Q = 0.02 μl/min. The effective aggregate modulus of degenerated human lumbar NP (H1/12) is ~63 psi [12]. In designing a protocol for IGF-1 injection in IVD, the infusion rate must be carefully chosen to guarantee a value of intradiscal pressure sufficiently lower than H1/12. Uncontrolled intradiscal fluid pressure may generate pain and possibly result in tissue or cellular damage.

REFERENCES


ACKNOWLEDGEMENTS: This study was supported by grants from NIH (AR050609, AR056101, and EB008653).