



Human placental extract: the feasibility of translation from basic science into clinical practice

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Provenance and Peer Review: This article was commissioned by the Editorial Office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Comment on: Gwam C, Ohanele C, Hamby J, et al. Human placental extract: a potential therapeutic in treating osteoarthritis. *Ann Transl Med* 2020. doi: 10.21037/atm.2019.10.20.

Submitted Dec 23, 2019. Accepted for publication Jan 03, 2020.

doi: 10.21037/atm.2020.01.50

View this article at: <http://dx.doi.org/10.21037/atm.2020.01.50>

Osteoarthritis (OA) is one of the most prevalent disorders of the musculoskeletal system with a profound impact on patients' quality of life. An estimated loss of 0.5 quality-adjusted life-year (QALY) per person and a total of 7.5 million QALY is attributed to OA, owing to the associated pain and limited activity (1). While joint arthroplasty provides effective symptomatic relief (2), it is reserved for patients once non-operative treatment fails. In addition, as with any surgical treatment, it is inevitably associated with potential perioperative complications, infection, and the potential need for revision (3,4). Therefore, there has been increasing interest in the non-operative treatment modalities aiming at improving outcomes and providing symptom relief (5). The current absence of interventions that modify OA structural progression has prompted an increase in the interest and use of novel orthobiologic therapies. Although current available orthobiologic therapies have not been shown to halt disease progression, there have been promising early results in regards to symptoms modification. Nonetheless, the uses of these therapies surpass the quality of the available evidence supporting its effectiveness. Systematic reviews evaluating the application of orthobiologic therapeutics, such as newer agents as human placental extract (HPE), require scrutiny in evaluating the potential for clinical application. We commend Gwam *et al.* (6) on their comprehensive review of the current literature describing the effects of HPE *in vitro* and *in vivo*, in addition to its potential use as a therapeutic agent in OA. The current commentary discusses challenges facing constituent standardization, extrapolation to human

subjects, and evidence-based application of HPE in clinical practice. Lessons learned from previous experiences with other orthobiologics and cell-based therapies are also outlined.

Constituents of HPE

Human placentae are a rich source of multipotent cells and growth factors (7). Placental extracts, cord blood cells, stem and progenitor cells, amniotic, and chorionic membrane patches, in addition to entire placental tissue fragments, have been proposed for various clinical applications (8). Post-partum human placentae undergo variable alterations in the form of sterilization and decellularization before qualifying for regenerative experimentation. The variability in the mode of extraction can alter the final composition and growth factor concentration (9,10). Multiple decellularization protocols have been described involving the use of sodium dodecyl sulfate, ethylenediaminetetraacetic acid, trypsin, DNase-I, and the non-ionic agent Triton X-100 in variable concentrations and thermal conditions, therefore, yielding dissimilar levels of decellularization (11). The extraction methodology is poorly described in the majority of available literature. While the overall process of extraction involves cellular hydrolysis of the post-partum placental tissue, the mechanism of sterilization, hydrolysis, and purification is inadequately described. Moreover, the type and concentration of these growth factors are contingent upon the age of the placenta, with the late gestation placentae demonstrating the highest

levels of growth factors (8). Notably, cellular hydrolysis obviates any direct cell-mediated effect of the placental mesenchymal stem cells (pMSC) while preserving the biomolecules of the extracellular matrix (ECM) including HPE cytokines, chemokines, hormones, nucleotides, small peptides, glycosaminoglycans, glycoproteins and fatty acids which persist in the medium even after cellular lysis. Since the constituents of HPE heavily depend on the decellularization process, a description of the specific extraction method, the age of the source placenta and the immunohistochemical analysis of the yielded extract, is crucial for an adequate characterization and the subsequent standardization of HPE constituents. Notably, a significant number of the commercially available HPE is advertised as a “stem cell treatment” despite its known lack viable cells (e.g., stem cells).

The paucity of high-quality evidence

To our knowledge, there are no randomized controlled trials investigating the effect of HPE in osteoarthritic patients within the currently available literature. Indeed, most studies have been limited to *in vitro* observations or mouse model experiments whose results have not yet been validated or translated into human subjects.

Furthermore, a notable discrepancy can be discerned between the common pathogenesis of OA in human subjects and that induced in the mouse models currently used to quantify the benefit of HPE (12). In addition to the direct effect of wear and tear, the subsequent generation of proinflammatory cytokines promotes aging at the cellular level, which is implicated as one of the most common pathways leading to OA (13). Senescent cells demonstrate elevated levels of oxidative stress, thereby activating p38 MAPK and PI3K/Akt signaling pathways heavily involved in chondrocyte apoptosis in addition to promoting the cycle of inflammatory response (14). Kim *et al.* used a rat model to investigate the effect of HPE in monoiodoacetate (MIA)-induced OA (15). Notably, MIA disrupts chondrocyte glycolysis via the inhibition of glyceraldehyde-3-phosphatase dehydrogenase with consequent chondrocyte damage that was evident within their 28-day interval of experimentation. The acute insult instigated within this mouse model of OA is closer to that of acute inflammatory cartilaginous injury rather than the chronic process of cellular senescence (13). This instills doubts as to the reproducibility of similar effects in human subjects. The authors found that treatment with HPE fourteen days after

MIA injection leads to a significant attenuation of limping, roentgenographic and histologic OA changes in addition to lower matrix metalloprotein-2 and matrix metalloprotein-9 levels at 28 days post-MIA injection.

Extrapolation from *in vitro* and *in vivo* animal models

In vitro studies have shown HPE to possess anti-inflammatory, analgesic (8), antioxidant (16,17), radioprotective, cytoprotective (18), anti-allergic, regenerative and anti-senescent effects (8,19). However, these findings are a result of experimentation on a myriad of tissue types, and the assumption that HPE exerts the same particular effects on chondrocytes has not been established. Furthermore, *in vitro* effects of stem-cell-based therapies often fail to translate to *in vivo* findings (20). Even in the setting of remarkable *in vivo* animal model observations, similar findings in human subjects are not necessarily predictable. Altered joint biomechanics, the discrepancy in joint size and cartilage thickness in addition to the inherent variability in regenerative rates between humans and different animal models hinders the extrapolation of observed effects on human subjects (12). Therefore, the suggestion of a potential benefit that is solely based on *in vivo* observations in animal models could prove unreliable.

Learning from previous experience

The use of cell-based therapies for various ailments has experienced rapid inflation (5). Reported clinical benefits ranged from the prevention of hair loss and alleviating menopausal symptoms to the treatment of retinopathy in addition to a myriad of heterogeneous musculoskeletal disorders (21,22). The misrepresentation of inadequately characterized and minimally altered “stem cell therapy” lead to a surge in the clinical application of unproven biologic agents (23). In its aftermath, professional societies sought clear guidelines to define the indications and expectations of stem-cell-based therapeutic agents (24). While still in its early stages of experimentation, proposing HPE as a potential therapeutic agent in the treatment of OA requires conceptual validation in the form of (I) a thorough description of the mechanism of extraction; (II) describing a standardized composition of the utilized HPE; (III) conducting randomized controlled trials to test for the safety and efficacy of HPE; and (IV) the identification of specific target populations that would potentially benefit

from the use of HPE for OA. These elements are critical in outlining the potential for clinical applications of HPE.

As Gwam *et al.* (6) highlighted in their conclusion, well designed *in vitro* and *in vivo* studies are required to thoroughly investigate the potential of HPE in the management of OA. While HPE certainly holds potential, a definitive benefit cannot be established based on the currently available literature. However, valuable reviews of literature as the one provided by Gwam *et al.* are of utmost importance in highlighting the current gaps of knowledge.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: NS PiuZZi has the following disclosures: ISCT: Board or committee member; Orthopaedic Research Society: Board or committee member; Zimmer: Research support. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Losina E, Silva GS, Smith KC, et al. Quality-Adjusted Life-Years Lost Due to Physical Inactivity in the United States Osteoarthritis Population. *Arthritis Care Res (Hoboken)* 2019. [Epub ahead of print].
2. Li W, Ayers DC, Lewis CG, et al. Functional Gain and Pain Relief After Total Joint Replacement According to Obesity Status. *J Bone Joint Surg Am* 2017;99:1183-9.
3. Healy WL, Della Valle CJ, Iorio R, et al. Complications of total knee arthroplasty: Standardized list and definitions of the knee society knee. *Clin Orthop Relat Res* 2013;471:215-20.
4. Healy WL, Iorio R, Clair AJ, et al. Complications of Total Hip Arthroplasty: Standardized List, Definitions, and Stratification Developed by The Hip Society. *Clin Orthop Relat Res* 2016;474:357-64.
5. PiuZZi NS, Dominici M, Long M, et al. Proceedings of the signature series symposium "cellular therapies for orthopaedics and musculoskeletal disease proven and unproven therapies-promise, facts and fantasy," international society for cellular therapies, montreal, canada, may 2, 2018. *Cytotherapy* 2018;20:1381-400.
6. Gwam C, Ohanele C, Hamby J, et al. Human placental extract: a potential therapeutic in treating osteoarthritis. *Ann Transl Med* 2020. doi: 10.21037/atm.2019.10.20.
7. Silini AR, Cargnoni A, Magatti M, et al. The Long Path of Human Placenta, and Its Derivatives, in Regenerative Medicine. *Front Bioeng Biotechnol* 2015;3:162.
8. Pogozhykh O, Prokopyuk V, Figueiredo C, et al. Placenta and Placental Derivatives in Regenerative Therapies: Experimental Studies, History, and Prospects. *Stem Cells Int* 2018;2018:4837930.
9. Shakouri-Motlagh A, Khanabdali R, Heath DE, et al. The application of decellularized human term fetal membranes in tissue engineering and regenerative medicine (TERM). *Placenta* 2017;59:124-30.
10. Keane TJ, Swinehart IT, Badylak SF. Methods of tissue decellularization used for preparation of biologic scaffolds and in vivo relevance. *Methods* 2015;84:25-34.
11. Leonel LCPC, Miranda CMFC, Coelho TM, et al. Decellularization of placentas: establishing a protocol. *Braz J Med Biol Res* 2017;51:e6382.
12. Kuyinu EL, Narayanan G, Nair LS, Laurencin CT. Animal models of osteoarthritis: classification, update, and measurement of outcomes. *J Orthop Surg Res* 2016;11:19.
13. McCulloch K, Litherland GJ, Rai TS. Cellular senescence in osteoarthritis pathology. *Aging Cell* 2017;16:210-8.
14. Jeon OH, David N, Campisi J, et al. Senescent cells and osteoarthritis: a painful connection. *J Clin Invest* 2018;128:1229-37.
15. Kim JK, Kim TH, Park SW, et al. Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis. *Biol Pharm Bull* 2010;33:1004-10.
16. Choi HY, Kim SW, Kim B, et al. Alpha-fetoprotein, identified as a novel marker for the antioxidant effect of placental extract, exhibits synergistic antioxidant activity in

- the presence of estradiol. *PLoS One* 2014;9:e99421.
17. Han NR, Park CL, Kim NR, et al. Protective effect of porcine placenta in a menopausal ovariectomized mouse. *Reproduction* 2015;150:173-81.
 18. Kawakatsu M, Urata Y, Goto S, et al. Placental extract protects bone marrow-derived stem/progenitor cells against radiation injury through anti-inflammatory activity. *J Radiat Res* 2013;54:268-76.
 19. Vakharia RM, Roche MW, Alcerro JC, et al. The Current Status of Cell-Based Therapies for Primary Knee Osteoarthritis. *Orthop Clin North Am* 2019;50:415-23.
 20. O'Brien T, Creane M, Windebank AJ, et al. Translating stem cell research to the clinic: a primer on translational considerations for your first stem cell protocol. *Stem Cell Res Ther* 2015;6:146.
 21. Piuze NS, Ng M, Chughtai M, et al. The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. *J Knee Surg* 2018;31:551-6.
 22. Lee KK, Choi WS, Yum KS, et al. Efficacy and safety of human placental extract solution on fatigue: a double-blind, randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2012;2012:130875.
 23. Chu CR, Rodeo S, Bhutani N, et al. Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference. *J Am Acad Orthop Surg* 2019;27:e50-63.
 24. Piuze NS, Khlopas A, Sodhi N, et al. Cellular Therapies in Orthopedics: Where Are We? *Surg Technol Int* 2017;31:359-64.

Cite this article as: Emara AK, Anis H, Piuze NS. Human placental extract: the feasibility of translation from basic science into clinical practice. *Ann Transl Med* 2020;8(5):156. doi: 10.21037/atm.2020.01.50