Review Article

Human placental extract: a potential therapeutic in treating osteoarthritis

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Abstract: Osteoarthritis (OA) is a degenerative joint disease marked by cartilage degradation and loss of function. Recently, there have been increased efforts to attenuate and reverse OA by stimulating cartilage regeneration and preventing cartilage degradation. Human placental extract (HPE) may be an option due to its anti-inflammatory, antioxidant, and growth stimulatory properties. These properties are useful in preventing cell death and senescence, which may optimize *in-situ* cartilage regeneration. In this review, we discuss the anatomy and physiology of the placenta, as well as explore *in vivo* and *in vitro* studies assessing its effects on tissue regeneration. Finally, we assess the potential role of HPE in cartilage regenerative medicine and OA. The Medline database was utilized for all studies that involved the use of HPE or human placenta hydrolysate. Exclusion criteria included articles not written in English, conference reviews, editorials, letters to the editor, surveys, case reports, and case series. HPE had significant anti-inflammatory and regenerative properties *in vitro* and *in vivo*. Furthermore, HPE had a role in attenuating cellular senescence and cell apoptosis via reduction of reactive oxidative species both *in vitro* and *in vivo*. One study explored the effects of HPE in OA and demonstrated reduction in cartilage catabolic gene expression, indicating HPE's effect in attenuating OA. HPE houses favorable properties that can attenuate and reverse tissue damage. This may be a beneficial therapeutic in OA as it creates a more favorable environment for *in-situ* cartilage regeneration. More well designed *in-vitro* and *in-vivo* studies are needed to define the role of HPE in treating OA.

Keywords: Placental extract; osteoarthritis (OA); therapy; *in vitro*; *in vivo*

Submitted Sep 11, 2019. Accepted for publication Sep 29, 2019. Published online Oct 16, 2019.
doi: 10.21037/atm.2019.10.20
View this article at: http://dx.doi.org/10.21037/atm.2019.10.20

Introduction

Osteoarthritis (OA) is one the most prevalent musculoskeletal maladies with a global age-adjusted prevalence of 25.4% and 19.6% for knee and hip OA respectively (1). It is associated with significant disability and costs, as it ranks 11th in disability adjusted life years lost and costs over 300 billion dollars annually in the United States (2). Of this, wages lost due to symptomatic OA comprises the major portion of the burden imposed on the economy (3). As such, preventing and treating OA is essential for optimizing population health and world economies. The pathology of OA can be characterized radiographically by progressive cartilage degeneration, formation of subchondral bone cysts, reactionary osteophyte formation, and end-stage joint space narrowing and collapse. Yet, there is discordance between symptomatic and radiographic OA as symptoms often do not correlate with radiographic severity (4). As such, treatment is centered on symptom severity.

Historically, OA has been described as a disease of "wear-and-tear" characterized by joint degeneration. OA

was thought to be irreversible due to the poor healing capability of articular cartilage. The limited healing capacity of articular cartilage was largely attributed to its poor vascularity and low cell turnover (5). However, increasing insight unto the cellular processes of OA has created a clearer picture. A growing body of evidence now suggests the poor regenerative capability of cartilage regeneration to be due to chondrocyte senescence (6-9) and apoptosis that occurs during chronic inflammation. This phenomenon tips the balance of normal homeostatic processes that occur in the joint towards a catabolic state (10).

Conventional treatment options focus on joint stabilization and symptom relief. These treatment modalities include rest, ice, physical therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) for mild OA to intra-articular steroid injection and eventual joint replacement for severely symptomatic OA. Unfortunately, these modalities function to diminish symptoms and do little to regenerate joint tissue damage. Newer insight stemmed from advances in the biological sciences suggest potential for cartilage regeneration and a reversal of OA (11). This is now the target of newer modalities such as platelet rich plasma (PRP), amnion derived stem cells (AMSCs), and mesenchymal stem cell (MSC) therapy, which focus on regenerating articular cartilage and reversing OA progression.

PRP is a supra-physiological filtrate of platelet and cytokines, derived from patient plasma, that functions to catalyze anabolic processes in the joint. AMSCs utilize pluripotent cells from human amnion to stimulate chondrocyte differentiation in order to regenerate articular cartilage. Similarly, autologous MSCs differentiate along the chondrogenic pathway in order to stimulate cartilage repair (12). Despite a plethora of *in-vitro* studies supporting the use of PRPs (13), AMSCs, and MSCs, the regenerative potential of these therapies has not been demonstrated in humans. Varying explanations exists for the lack of results with the use of these modalities. PRP, while effective *in vitro*, experiences a significant drop in efficacy once injected in a joint. This has been attributed to a highly variable quality of derived platelets (14), platelet inactivation, and external patient factors such as the use of NSAIDs (15). Stem cell therapy has not yet demonstrated regenerative capability of articular cartilage in human studies and may be proinflammatory. This is because of senescent chondrocyte (snCho) activity, which are found accumulated in OA, that acts to suppress exogeneous stem cells (16).

Human placental extract (HPE; also known as human placenta hydrolysate) is a potential treatment option for attenuating and reversing OA progression. The formulation is derived from a post-delivery placenta that subsequently undergoes cellular hydrolysis. The resulting extract houses high levels of growth factors, anabolic cytokines, nucleic acids, and essential amino acids that may stimulate tissue regeneration and anti-inflammatory proteins that attenuate inflammation. HPE has a strong history in oriental regions and has shown to be effective in a myriad of pathologies. In this review, we covered the anatomy and physiology of the placenta, its immunomodulatory properties, and the formulation and rationale behind HPE use. We also explored *in-vitro* and *in-vivo* studies to uncover the properties and efficacy of HPE as a treatment modality. Finally, we assessed the potential role of HPE in cartilage regenerative medicine and OA.

Methods

An electronic systematic review of the literature was conducted using the Medline database. Studies published in the field were identified using various keyword combinations and Boolean operators. The search was performed in April 2019. The following strings were used for the search:

"Placental Extracts"[Majr], "Placental Extracts/therapeutic use"[Mesh], "Placental Extracts"[Mesh], OR "placenta extract"/exp OR "placenta extract", "Placental Extracts/therapeutic use"[Mesh] AND "osteoarthritis"[Mesh], ("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]) AND ("placenta"[MeSH Terms] OR "placenta"[All Fields]) AND hydrolysate[All Fields].

The exclusion criteria were as follows: articles not written in English, conference reviews, editorials, letters to the editor, surveys, case reports, and case series.

Results

The placenta

Structure

The placenta is a temporary organ that ensures the coexistence of a developing fetus and the maternal body. It functions to maintain blood supply to the fetus as well as the removal of metabolic waste and preventing immune rejection (17,18). The post-delivery placenta is typically 16 to 20 cm in diameter and on average weighs 500 g. It

can be divided into the fetal placenta which is developed from blastocysts, and the maternal placenta, which develops from maternal uterine tissue. The fetal part of the placenta includes the amnion, umbilical cord and the chorionic plate. The chorionic plate is comprised of fibroblasts and trophoblasts which functions to provide structure and nutrients to the placenta. The amnion contains pluripotent stem cells that are involved in the development of the fetus. Finally, the umbilical cord is involved in providing nutrients and blood as well as waste removal for the fetus. In it contains two arteries and one vein all immersed in fluid rich with hyaluronic acid and fibroblast cells.

Immunomodulatory properties

The placenta protects the developing fetus from the maternal immune system thus serving as a model for an in-situ organ allograft (19). In doing so, the placenta plays a critical immunomodulatory role in order to prepare and maintain an environment conducive to fetal development. Integral to this role is stem cell [placental mesenchymal stem cells (pMSCs)] activity on the maternal immune system. pMSCs express the membrane bound human leukocyte antigen (HLA)-G which is known to inhibit T cell function and proliferation (20-22). Specifically, pMSCs prevent proliferation and release of cytokines by T helper-1 (Th1) cells while inducing the expression and secretion of T helper-2 (Th2) cytokines (23). Furthermore, pMSCs induce the differentiation of T regulatory lymphocytes, Th2 polarization [associated with increased levels of interleukin (IL)-4 and IL-10], and Th17 induction (produce high concentrations of IL-6 and IL-7). This is achieved through direct pMSC contact with T cells and the secretion of soluble cytokines and anti-inflammatory mediators (24) which serve to attenuate T cell activity. This same anti-inflammatory effect has been observed on other cell types including B cells (25), macrophages (26), and dendritic cells (27). pMSCs have been explored clinically in patients with knee arthritis. In their pilot study, Khalifeh Soltani *et al*. revealed intra-articular injection of pMSCs is safe and provided pain improvement for patients with OA, suggesting that single or multiple injections may improve and prolong the efficacy of MSC therapy (28).

Rationale for the use of acellular placenta preparation

Despite pMSCs immunomodulatory processes, its use in an osteoarthritic joint has not been demonstrated to be effective, with some studies suggesting worsening of OA. This may be due to early onset inactivation by snChos found accumulated in an osteoarthritic joint. This inhibitory effect on transplanted stem cells by snChos was demonstrated in a study conducted by Cao *et al*. (16). The authors reported snChos-mediated-apoptosis of bone marrow-derived mesenchymal stem cells (BMSCs) after 21 days of co-culture that was reduced after the administration of ABT-263 (an antisenescence agent) (29). Furthermore, the authors reported promotion of BMSC senescence by native snChos. This apoptotic and senescent effect was bidirectional, as the implanted BMSCs increased the rate of apoptosis and senescence of healthy chondrocytes, in addition to stimulating an increased expression of IL-6, IL-1b, matrix metalloproteinase (MMP)-1, and MMP-13. Another study conducted by Endrinaldi *et al*. (30) revealed increased levels of IL-4 and MMP-1 after injection of pMSCs in osteoarthritic rat knees suggesting increased degradation of cartilage extracellular matrix after pMSC administration.

Nutrient content and properties of placental extract

The placenta is capable of retaining nutrients and growth factors necessary after delivery (31). Placenta extract is formulated by the hydrolyzation of placental cells. The resulting extract contains collagen, elastin, laminin, vitamins, trace elements, nucleic acids, amino acids, peptides, cytokines and growth factors (32-35). Polydeoxyribonucleotide (PRDN), an active component, composed of different lengths of deoxyribonucleotide polymers extracted from the placenta, activates the salvage pathway for biosynthesis of nucleosides, nucleotides, and nucleic acids (32,36). It has shown efficacy in augmenting healing for scars, ulcers, and wounds (35,37,38). Similarly, placental extract contains supraphysiologic levels of essential and non-essential amino acids such as alanine, aspartic acid, histidine, arginine, phenylalanine, proline, tryptophan, lysine, tyrosine, leucine, and valine (32,39-41). This has been shown to stimulate fibroblast proliferation and collagen production *in vitro* (41). Vitamins B_1, B_2, B_5, B_6, B_7, B_9, and B_{12} are found in high concentrations in HPE formulation and play a role in cell metabolism and energy protection (42). Furthermore, studies have demonstrated a high concentrate of cytokines and growth factors housed by the post-delivery placenta. These factors include granulocyte colony-stimulating factor (G-SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin growth factor (IGF), platelet-derived growth factor (PDGF),

Table 1 Summary of studies exploring the anti-inflammatory properties of HPE

Author and year	Experiment	Results
Parida *et al.* 2019 (47)	HPE on mitigating the effects of B[a]P neuronal damage in hippocampi of Wistar pups	HPE mediate reduction in inflammatory markers NF-κB, TNF-alpha, and IL-2
Yamauchi *et al.* 2017 (48)	HPE in preventing non-alcoholic steatohepatitis in wild-type C57BL/6J mice	Less fibrosis, decrease in TNF-alpha, decrease in MMP-9, and less oxidative stress in the perivascular hepatic regions
Samiei *et al.* 2016 (49)	HPE in preventing amiodarone induced pulmonary fibrosis in Sprague-Dawley rats	28% percent reduction in alveolar septum thickness and less lung inflammation in groups treated with HPE

HPE, human placental extract; B[a]P, Benzo(alpha)Pyrene; NF-κB, nuclear factor-kappa B; TNF-alpha, tumor necrosis factor-alpha; IL-2, interleukin-2; MMP, matrix metalloproteinase.

transforming growth factor (TGF), and vascular endothelial growth factor (VEGF), all of which have demonstrated anti-inflammatory and regenerative properties (43-46).

HPE in attenuating inflammation and facilitating tissue regeneration

HPE has shown significant promise as a therapeutic through its anti-inflammatory and anti-oxidant properties. The following studies explore the effect of HPE on mitigating organ inflammation and facilitating recovery (see *Table 1*).

HPE in the reduction of tissue and organ damage

Parida *et al*. explored the role of HPE in mitigating the effects of Benzo(alpha)Pyrene {B[a]P} in the hippocampi of Wistar rat pups (47). B[a]P is a procarcinogen that is known to lead to neuronal damage via cytochrome P450 1A1 (CYP1A1)-mediated metabolism. In their study, the authors created two sets of experiments. The first set contained five experimental groups: normal control, vehicle control {buffer without B[a]P}, 0.25 µM B[a]P, 0.5 µM B[a]P; and 1.0 µM B[a]P. The second set contained four experimental groups: (I) a normal control; (II) minimal B[a]P concentration inducing inflammation; (III) HPE injection and; (IV) HPE injection followed by B[a]P treatment; (V) HPE followed by 0.25 µM B[a]P. The authors reported lower levels of the inflammatory marker nuclear factor-kappa B (NF-κB) in groups treated with HPE followed by 0.25 µM B[a]P when compared to B[a]P alone, and lower levels of both tumor necrosis factor-alpha (TNF-alpha) and IL-2 in HPE treated group when compared to the 0.25 µM B[a]P treated group.

Yamauchi *et al*. (48) explored the role of HPE on the prevention of non-alcoholic steatohepatitis (NASH) in wild-type C57BL/6J mice by utilizing a NASH-mouse model. The authors demonstrated less pronounced fibrosis and a decrease in TNF-alpha and MMP-9 expression in the HPE-treated mice. Additionally, the authors revealed lower levels of oxidative stress in the perivascular hepatic regions. Samiei *et al*. (49) assessed the role of HPE in preventing amiodarone induced pulmonary fibrosis in male Sprague-Dawley rats. Amiodarone is an antiarrhythmic therapeutic that has been implicated in multiple side effects such as pulmonary, ocular, thyroidal, and liver toxicity due to its formation of reactive oxygen species once metabolized (50,51). In their study, the first, second, and third groups received no treatment, amiodarone (100 mg/kg), and HPE (500 µL/kg; intraperitoneal injection), respectively. The fourth group was treated with amiodarone + HPE. The authors reported a decrease in total alveolar space in the amiodarone group that was not observed in the amiodarone + HPE group. Furthermore, there was 28% increase in alveolar septum thickness in the amiodarone group that was not observed in the amiodarone + HPE group. Finally, the authors reported a reduction in inflammation in the amiodarone + HPE group when compared to the amiodarone group.

HPE as an anti-apoptotic, promoting cell proliferation and tissue regeneration

Studies exist that highlight the proliferative and regenerative potential of HPE on organ cells (see *Table 2*). HPE contains supraphysiologic levels of anabolic factors that promote cellular proliferation that allows for tissue regeneration.

Kwon *et al*. (52) explored the role of HPE in preventing hair loss through its effects on the Wnt/β-catenin signaling pathway. The authors revealed that HPE mediated induction of β-catenin expression through the inhibition of glycogen synthase kinase 3β as well as induction of alkaline phosphatase expression in human dermal papilla cells. The authors also demonstrated that HPE was effective in inducing root hair elongation in rat vibrissa hair follicles. Hong *et al*. (53) explored the role of HPE in a wound

Table 2 Studies exploring the anti-apoptotic and tissue regenerative properties of HPE

Author and year	Experiment	Results
Kwon *et al*. 2015 (52)	HPE in preventing hair loss through the Wnt/β-catenin signaling pathway	Induction of β-catenin expression as well as induction of alkaline phosphatase in human dermal papilla cells
Hong *et al*. 2010 (53)	Role in HPE in a wound healing mouse model	Accelerated wound healing among mice treated with HPE. Higher levels of TGF-β and VEGF among mice treated with HPE

HPE, human placental extract; VEGF, vascular endothelial growth factor.

Table 3 HPE and its effect on reactive oxygen species

Author and year	Experiment	Results
Lee *et al.* 2019 (62)	HPE's role on liver regeneration in Sprague-Dawley rats	Upregulation of cellular antioxidants
Bak *et al.* 2018 (63)	HPE's role in preventing D-galactosamine induced liver toxicity	Induction of antioxidant enzymes and a reduction in reactive oxygen species
Bak *et al.* 2019 (64)	HPE's role in preventing hydrogen peroxide induced cell death in C2C12 mouse myoblasts	Reduction of cytosolic and mitochondrial ROS through NF-κB signaling

HPE, human placental extract; ROS, reactive oxygen species.

healing mouse model. The authors reported accelerated wound healing in the experimental group (received HPE treatment) compared to the control group. Additionally, the authors demonstrated a higher quantity of TGF-β and VEGF after wound analysis in the experiment group when compared to control.

HPE and reduction of reactive oxygen species

Reactive oxidation species (ROS) causes damage to cellular DNA which elicits irreversible growth arrest and apoptosis (54,55). Stress-induced premature senescence (SIPS) is cellular phenotype often induced by ROS and is characterized as an arrest of cellular replication and increased cellular release of inflammatory factors (7,56). Cellular mitochondria serve as the main source of ROS and is increased during surges in cellular metabolism (57,58). Enzymes, such as glutathione reductase (59), catalase (60), and superoxide dismutase (61) serve as cellular defenses against ROS. Studies exist demonstrating HPE's capability in reducing intracellular ROS (see *Table 3*) thereby preventing SIPS and premature cellular apoptosis.

Lee *et al*. (62) explored the role of HPE on hepatocyte proliferation and liver regeneration in Sprague-Dawley rats. They reported HPE to have significant radical scavenging activity and lipid peroxidation inhibitory effect in a dose dependent manner. Additionally, Lee and colleagues reported increased proliferation of hepatocytes and accelerated liver regeneration after partial hepatectomy in the experimental group (+ HPE). The authors also demonstrated a higher quantity of mitotically active cells (ki-67 positive) in the experimental group and an increase in glutathione peroxidase and superoxide dismutase, thereby suggesting evidence of less oxidative stress. Bak *et al*. (63) reported on the anti-apoptotic effects of HPE against hepatocyte toxicity *in vivo* and *in vitro*. Their study involved the use D-galactosamine (D-GalN)- and lipopolysaccharide (LPS)-induced hepatocyte apoptosis *in vivo* and *in vitro*. The treatment was defined as HPE administration. The authors found that pre-treatment with HPE led to improved cell viability, reduction in apoptosis protein expression, increase in proliferating cell nuclear antigen (PCEN), and induction of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. Furthermore, the authors reported HPE mediated reduction in reactive oxygen species and the reduction of damage-regulated autophagy modulator, p53, and C/EBP homologous protein. In a separate study, Bak *et al*. (64). demonstrated the antioxidant effect of HPE against oxidative stress on muscle atrophy. The authors reported HPE inhibition of hydrogen peroxide induced cell death in C2C12 cells, and reduction of cytosolic and mitochondrial ROS through myostatin gene expression via NF-κB signaling.

In conclusion, multiple studies demonstrate HPE's effectiveness in reducing inflammation, preventing cell damage and optimizing cell viability. The most critical

Table 4 Study explaining the therapeutic effects of HPE in osteoarthritis

Author and year	Experiment	Results
Kim *et al*. 2010 (82)	Effects of HPE on preventing monoiodoacetate induced osteoarthritis in rats	Dose dependent decrease in glycosaminoglycans. A reduction in MMP-2 and MMP-9

HPE, human placental extract; MMP, matrix metalloproteinase.

aspect of HPE may be its ability to reduce oxidative stress through reduction of ROS and induction of cellular-antioxidant enzymes. These properties are worth further exploration and maybe useful in chronic disease in tissues marked with low cell content and cell turnover

HPE as a potential therapeutic for OA

OA: ROS-mediated SIPS

OA is a disease characterized by articular cartilage degeneration, subchondral cysts, and synovial inflammatory response (65). Articular cartilage remains the critical target in attenuating OA progression (66). Previous therapies have aimed to stabilize articular cartilage to prevent further damage and degradation. However, growing evidence now suggests innate regenerative potential for articular cartilage that is stymied by ROS induced chondrocyte senescence. As previously stated, an excess amount of ROS causes to considerable DNA damage which elicits cellular growth arrest (56,67). Chondrocytes that withstand the chronic inflammation found in an OA joint will often transition into the irreversible SIPS phenotype (56). Potentiating the problem is the proinflammatory state chondrocytes attained once transitioned to the SIPS phenotype. These SIPS-chondrocytes secrete increased levels of IL-1 (68), IL-6, IL-7 (69) and metalloproteases and demonstrate a decreased response to anabolic growth factors (70-77). Stress induced senescence phenotype-chondrocyte may also be implicated in the observed subchondral edema, and osteophyte formation due to high secretion of VEGF (78,79). Furthermore, oxidative stress from increased ROS may contribute to chondrocyte senescence by promoting endoplasmic reticulum (ER) stress (69). ER stress has been shown to down-regulate expression of cartilage matrix proteins and aggrecans and increase chondrocyte apoptosis (80,81).

HPE in OA

HPE harbors antioxidant properties and may play a significant role in preventing chondrocyte transitioning to SIPS, thereby allowing a favorable environment for *in-situ* cartilage regeneration. While no study directly assesses HPE's potential in reduction of ROS mediated SIPS, one study exist that demonstrates reduction in cartilage degeneration after use of HPE (see *Table 4*).

Kim *et al*. (82) investigated the effect of HPE on cartilage degradation *in vitro* osteoblastic MG-63 cells, articular cartilage rabbit explants, and *in vivo* monoiodoacetate (MIA)-induced OA. MMP-2 activity was significantly decreased in a dose dependent manner for HPE-treated MG-63 cells when compared to the control (no HPE). Similarly, the authors revealed lower levels of glycosaminoglycans (GAG) release upon rhIL-1alpha stimulated explants when treated HPE. Furthermore, the authors demonstrated reduced severity of MIA-induced OA by radiographic and histopathological examination for rats treated with HPE. They also report *in-vivo* reduction in MMP-2 and MMP-9 expression in rats treated with HPE. Their study demonstrates the potential of HPE in mitigating OA progression. As such, more studies like these are necessary.

Conclusions

The human placenta is a temporary organ that contains immunomodulatory, growth stimulatory, and antioxidant properties to facilitate fetal development. These properties have been studied to assess HPE's potential to treat a variety of ailments. OA, which is marked by cartilage damage and degradation, may be one such malady. The regenerative and antioxidant capabilities of HPE may help mitigate the occurrence of SIPS-chondrocytes thereby optimizing *in-situ* articular cartilage regeneration. More well-designed *in-vitro* and *in-vivo* studies are needed to study the role of HPE in OA.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.

amegroups.com/article/view/10.21037/atm.2019.10.20/coif). The 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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Cite this article as: Gwam C, Ohanele C, Hamby J, Chughtai N, Mufti Z, Ma X. Human placental extract: a potential therapeutic in treating osteoarthritis. Ann Transl Med 2023;11(9):322. doi: 10.21037/atm.2019.10.20

