Umbilical Cord-Derived Wharton's Jelly in Orthopedic Regenerative Medicine

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Wharton's jelly (WJ) is an allogenic tissue comprised of connective tissue located within the umbilical cord. Wharton's jelly resists torsional and compressive stresses during fetal development levied upon the umbilical vessels. The primitive mesenchymal stem cells reside within the UC-derived WJ [15]. These perinatal MSCs resemble embryonic stem cells (ESCs) but exhibit many properties of adult MSCs. Wharton's jelly-derived mesenchymal stem cells (WJSCs) exhibit lower expression levels of pluripotent markers compared to ESCs, indicating multipotency rather than pluripotency [16,17]. Wharton's jelly contains the highest concentration of MSCs/mL compared to other tissue types.

umbilical cord | Wharton's jelly | regenerative medicine | mesenchymal stem cells | mesenchymal stromal cells | Wharton's jelly mesenchymal stem cells

1. Introduction

Orthopedic musculoskeletal ailments involve inflammatory and/or degenerative conditions in muscles, tendons, ligaments, nerves, and bones. These conditions are estimated to affect one in four people in developed countries, thus representing a significant burden on healthcare [1]. Traditionally, musculoskeletal injuries are handled with activity modification, physical therapy, immobilization, pharmacological drugs, and surgical management once conservative treatments are exhausted. These treatment modalities are imperfect, often attempting to limit pain instead of focusing on the underlying pathology [2][3].

The field of regenerative medicine has undergone a tremendous growth as of late, especially the field of orthopedic surgery [4]. Mesenchymal stem cells (MSCs) offer regenerative potential, aiming to slow or halt chronic disease as well as improve function and patient satisfaction [5][6][7]. MSCs can be harvested from autologous bone marrow concentrate (BMC), adipose tissue, and allogenic umbilical cord-derived Wharton's jelly (UC derived-WJ) [8][9][10][11]. Given the increased patient awareness and recent advances in MSC therapy, these biologic approaches are becoming more common in orthopedic practice [4].

BMC and adipose-derived stem cells (ADSCs) are clinically available and have a long history of being used with robust clinical data, in comparison to other sources [12]. However, both stem cell sources pose limitations. BMC is associated with surgical site morbidity from the aspiration procedure, a limited number of MSCs within the aspirated bone marrow concentrate, and signs of early senescence [13]. Adipose-derived stem cells exhibit

promising short-term clinical results, but research on this is minimal with limited randomized controlled trials and a lack of adequate long-term follow-up. Adipose-derived stem cells are also associated with donor site morbidity from the extraction procedure [14].

Wharton's jelly is easily accessible and available in comparison to autogenic tissues. The UC, and the Wharton's jelly within it, is an after-birth tissue, and is normally discarded after every birth, presenting ample opportunity for harvest [15]. The ease of collection offers several benefits over the existing BMSC and ADSC harvest, both of which may present donor site morbidity. This factor, in addition to the multipotency of WJSCs, makes Wharton's jelly a likely source of MSCs for regenerative medicine applications in the field of orthopedic surgery [16].

2. Umbilical Cord-Derived Wharton's Jelly in Orthopedic Regenerative Medicine

2.1. Degenerative Disc Disease

Han et al. analyzed the effect of Wharton's jelly cells on degenerative nucleus pulposus cells isolated from a degenerative intervertebral disc. Wharton's jelly cells were co-cultured in vitro with nucleus pulposus cells for seven days with and without direct cell-to-cell contact. Gene expression was quantified using a polymerase chain reaction (PCR) analysis. Compared to a Wharton's jelly cell control and a degenerative nucleus pulposus cell control, the expression of type II collagen, aggrecan, and SOX-9 were significantly elevated for Wharton's jelly and the nucleus pulposus co-culture. The gene expression was at its highest with direct cell-to-cell contact using a ratio of 75:25 Wharton's jelly cells to nucleus pulposus cells. The polymerase chain reaction gene expression of the co-cultured Wharton's jelly cells and degenerative nucleus pulposus cells differed from each individual control. Human Wharton's jelly cells could be induced to differentiate toward nucleus pulposus-like cells when co-cultured with degenerative nucleus pulposus cells [17].

2.2. Osteoporotic Vertebral Compression Fracture

Shim et al. presented the results of a randomized, open-label, phase I/IIa study examining the safety and effectiveness of managing osteoporotic vertebral compression fractures with WJSCs and teriparatide. Twenty subjects were followed for 12 months. All subjects received a daily subcutaneous injection of 20 mg teriparatide and 20 mg oral bazedoxifene daily for 6 months. The subjects in the experimental group underwent an injection of WJSCs intramedullarily on day 0 and intraveniously on day 7. Three subjects from the control group dropped out because of an adverse reaction to teriparatide. Four subjects in the experimental group experienced an adverse event. Three patients chose to drop out of the study: one secondary to a urinary tract infection shortly after WJSC injection, another secondary to a pulmonary embolus discovered 30 days after WJSC injection on chest CT, and the third secondary to a diagnosis of pancreatic cancer discovered on CT. The clinical outcome scores exhibited statistically significant improvements in VAS, ODI, and SF-36 after 12 months versus the baseline. The pain score in the VAS, as well as the ODI and SF-36 scores, for the experimental group were statistically significant when compared to the control group at 12 months. Bone turnover markers measured did not demonstrate a statistical

significance between the control and experimental groups. Bone mineral density improved significantly for both the control and experimental groups, but there was no statistically significant difference between the two groups. CT analysis demonstrated an improved microarchitecture for the experimental group compared to the control group at 12 months [18].

2.3. Peripheral Nerve Injury

Shalaby et al. examined the effect of Wharton's jelly cells added to a nerve conduit on the functional recovery of a 10 mm sciatic nerve deficit. At 12 weeks, the Functional Recovery Index was −5.2 ± 2.1 in the uninjured control group, −55.3 ± 12.3 in the injured control group, −23.8 ± 5.6 in the injured group treated with nerve conduit alone, and −9.8 ± 2.5 in the injured group treated with nerve conduit and Wharton's jelly cells. There was a greater significant improvement in the Wharton's jelly group. For the pin prick-functional analysis, there was a statistically significant improvement in the treated groups, but no significance for the nerve conduit group and the group treated with Wharton's jelly. Histologic analysis of the surgically treated nerve exhibited more normally appearing nerve fibers and axons with thin a myelin sheath than nerve conduit and control groups. The real-time PCR showed a significant increase in innetrin-1, ninjurin, the glial cell-line-derived neurotrophic factor (GDNF), the brain-derived neurotrophic factor (BDNF), the vascular endothelin growth factor (VEGF), and angiopoitin-1 gene expression versus the other three groups [19].

2.4. Osteoarthritis

Sofia et al. conducted a basic science study observing the matrix metalloproteinase-13 (MMP-13) gene expression of synoviocytes isolated prior to a total knee arthroplasty versus those cells combined with Wharton's jelly cells. This study analyzed the gene expression of two pro-inflammatory markers: MMP-13 and RELA. The addition of Wharton's jelly to synoviocytes isolated from human knees with grade IV osteoarthritis reduced the expression of MMP-13 and RELA. The findings were statistically significant compared to the synoviocyte control [20].

2.5. Osteochondral Defect

Zhang and colleagues seeded Wharton's jelly cells to an acellular cartilage extracellular matrix scaffold. The seeded scaffold was then tested against a microfracture for the restoration of a 6.5 mm diameter, femoral condyle osteochondral defect in a caprine model. At nine months, the Wharton's jelly group demonstrated more abundant glycosaminoglycans and type II collagen with highly organized fibers compared to that of the microfracture group. The modulus of elasticity was 2.9 ± 9 MPa for the Wharton's jelly group compared to 2.2 ± 5 MPa for the microfracture group. An MRI analysis of the treated osteochondral defect demonstrated an appearance that was similar to the native articular cartilage than the microfracture group. Of note, two knees of goats from the microfracture group were deemed to have a meniscus tear at the time of euthanasia [21].

3. Summary

The Wharton's jelly extracellular matrix is partly comprised of glycosaminoglycans and collagen, similar to cartilage [22][23][24]. This relationship makes Wharton's jelly cells an excellent source for cartilage tissue engineering [25][26][27][28]. Chondrocytes and human Wharton's jelly cells also express aggrecan, type II collagen, and hyaluronic acid [22]. These similarities in the relationship and property between chondrocytes and Wharton's jelly, as well as their regenerative ability, make WJSCs an excellent source for cartilage regeneration purposes.

Aging negatively affects stem cells. This makes stem cells cultured from the umbilical cord or placenta advantageous over stem cells cultured from adipose tissue, bone marrow, or other autogenic adult cell sources. Birth-derived products have shown potential for use in the orthopedic sector. Multiple companies now have a flowable placental allograft formulation that is under consideration for approval by the US FDA as Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) for eventual clinical use. While there is growing interest from companies, consumers, and healthcare providers, a lack of insurance reimbursement and limited safety and efficacy studies limit the development and use of these products. Additionally, to our knowledge the current commercial products on the market do not offer living cells [29].

Similar to placental tissue, Wharton's jelly is obtained after birth. This alleviates the controversial aspects of harvesting embryonic cells. Unique to WJSCs, the process used to extract WJSCs can be performed without the use of digestive enzymes, cryoprotectants, or the in vitro expansion of cells [1]. All reviewed publications showed a certain degree of effectiveness in handling orthopedic injuries when compared with the controls. Only one study included a placebo control, and none of the studies compared the effectiveness of WJSCs to different stem cell types. Of the three studies related to intervertebral disc injury, one of the studies examined peripheral nerve injury, and the remaining two studies focused on osteochondral injury. Given the limited number of published preclinical studies, the variability between the animal models used, the specific injury model, and route of administration, it was not feasible to perform a comparative analysis. However, another review may be completed in the near future with an emphasis on preclinical models as the data seem to be positive in several studies [30][31].

The benefits of WJSCs for cartilage restoration seem to be the most promising, given the similarities between chondrocytes and Wharton's jelly cells and the cellular matrix of cartilage and Wharton's jelly. Further well-designed and appropriately powered, prospective, non-randomized and randomized studies evaluating the safety and efficacy of WJSCs in a human model are warranted to justify their clinical use.

References

1. Koyuncu, N.; Karcioglu, O. Musculoskeletal complaints in health care personnel in hospital: An interdepartmental, cross-sectional comparison. Medicine 2018, 97, e12597.
2. Gupta, A.; El-Armin, S.F., 3rd; Levy, H.J.; Sze-Tu, R.; Ibim, S.E.; Maffulli, N. Umbilical cord-derived Wharton's jelly for regenerative medicine applications. J. Orthop. Surg. Res. 2020, 15, 49.
3. Gupta, A.; Rodriguez, H.C.; Potty, A.G.; Levy, H.J.; El-Amin, S.F., III. Treatment of Knee Osteoarthritis with Intraarticular Umbilical Cord-Derived Wharton's Jelly: A Case Report.

Pharmaceuticals 2021, 14, 883.

4. Lamplot, J.D.; Rodeo, S.A.; Brophy, R.H. A Practical Guide for the Current Use of Biologic Therapies in Sports Medicine. Am. J. Sports Med. 2019, 48, 488–503.
5. Caplan, A.I. Mesenchymal stem cells. J. Orthop. Res. 1991, 9, 641–650.
6. Minguell, J.J.; Erices, A.; Conget, P. Mesenchymal Stem Cells. Exp. Biol. Med. 2001, 226, 507–520.
7. Andia, I.; Maffulli, N. New biotechnologies for musculoskeletal injuries. Surgeon 2019, 17, 244–255.
8. Patel, J.M.; Saleh, K.S.; Burdick, J.A.; Mauck, R.L. Bioactive factors for cartilage repair and regeneration: Improving delivery, retention, and activity. Acta Biomater. 2019, 93, 222–238.
9. Sezgin, E.A.; Atik, O.S. Are orthobiologics the next chapter in clinical orthopedics? A literature review. Eklem. Hastalik. Cerrahisi 2018, 29, 110–116.
10. Duerr, R.A.; Ackermann, J.; Gomoll, A.H. Amniotic-Derived Treatments and Formulations. Clin. Sports Med. 2019, 38, 45–59.
11. Chirichella, P.S.; Jow, S.; Iacono, S.; Wey, H.E.; Malanga, G.A. Treatment of Knee Meniscus Pathology: Rehabilitation, Surgery, and Orthobiologics. PMR 2019, 11, 292–308.
12. Salem, H.S.; Thiemermann, C. Mesenchymal stromal cells: Current understanding and clinical status. Stem Cells 2010, 28, 585–596.
13. Mohamed-Ahmed, S.; Fristad, I.; Lie, S.A.; Suliman, S.; Mustafa, K.; Vindenes, H.; Idris, S.B. Adipose-derived and bone marrow mesenchymal stem cells: A donor-matched comparison. Stem Cell Res. Ther. 2018, 9, 1–15.
14. Usuelli, F.G.; D’Ambrosi, R.; Maccario, C.; Indino, C.; Manzi, L.; Maffulli, N. Adipose-derived stem cells in orthopaedic pathologies. Br. Med. Bull. 2017, 124, 1–24.
15. Rodriguez, H.C.; Gupta, M.; Cavazos-Escobar, E.; El-Amin, S.F., 3rd; Gupta, A. Umbilical cord: An allogenic tissue for potential treatment of COVID-19. Hum. Cell 2021, 34, 1–13.
16. Schugar, R.C.; Chirieleison, S.M.; Wescoe, K.E.; Schmidt, B.T.; Askew, Y.; Nance, J.J.; Evron, J.M.; Péault, B.; Deasy, B.M. High Harvest Yield, High Expansion, and Phenotype Stability of CD146 Mesenchymal Stromal Cells from Whole Primitive Human Umbilical Cord Tissue. J. Biomed. Biotechnol. 2009, 2009, 789526.
17. Han, Z.; Zhang, Y.; Gao, L.; Jiang, S.; Ruan, D. Human Wharton’s Jelly Cells Activate Degenerative Nucleus Pulposus Cells In Vitro. Tissue Eng. Part A 2018, 24, 1035–1043.
18. Shim, J.H.; Kim, K.T.; Kim, K.G.; Choi, U.Y.; Kyung, J.W.; Sohn, S.; Lim, S.H.; Choi, H.; Ahn, T.K.; Choi, H.J.; et al. Safety and efficacy of Wharton’s jelly-derived mesenchymal stem cells with

teriparatide for osteoporotic vertebral fractures: A phase I/IIa study. Stem Cells Transl. Med. 2021, 10, 554–567.

19. Shalaby, S.M.; El-Shal, A.S.; Ahmed, F.E.; Shaban, S.F.; Wahdan, R.A.; Kandel, W.A.; Senger, M.S. Combined Wharton’s jelly derived mesenchymal stem cells and nerve guidance conduit: A potential promising therapy for peripheral nerve injuries. Int. J. Biochem. Cell Biol. 2017, 86, 67–76.
20. Sofia, V.; Nasrul, E.; Manjas, M.; Revilla, G. The The Influence of Wharton Jelly Mesenchymal Stem Cell toward Matrix Metalloproteinase-13 and RELA Synoviocyte Gene Expression on Osteoarthritis. Open Access Maced. J. Med. Sci. 2019, 7, 701–706.
21. Zhang, Y.; Liu, S.; Guo, W.; Wang, M.; Hao, C.; Gao, S.; Zhang, X.; Li, X.; Chen, M.; Jing, X.; et al. Human umbilical cord Wharton’s jelly mesenchymal stem cells combined with an acellular cartilage extracellular matrix scaffold improve cartilage repair compared with microfracture in a caprine model. Osteoarthr. Cartil. 2018, 26, 954–965.
22. Valiyaveettil, M.; Achur, R.N.; Muthusamy, A.; Gowda, D.C. Characterization of chondroitin sulfate and dermatan sulfate proteoglycans of extracellular matrices of human umbilical cord blood vessels and Wharton’s jelly. Glycoconj. J. 2004, 21, 361.e75.
23. Franc, S.; Rousseau, J.-C.; Garrone, R.; van der Rest, M.; Moradi-Améli, M. Microfibrillar composition of umbilical cord matrix: Characterization of fibrillin, collagen VI and intact collagen V. Placenta 1998, 19, 95–104.
24. Pennati, G. Biomechanical properties of the human umbilical cord. Biorheology 2001, 38, 355–366.
25. Jadalannagari, S.; Converse, G.; McFall, C.; Buse, E.; Filla, M.; Villar, M.T.; Artigues, A.; Mellot, A.J.; Wang, J.; Detamore, M.S.; et al. Decellularized Wharton’s Jelly from human umbilical cord as a novel 3D scaffolding material for tissue engineering applications. PLoS ONE 2017, 12, e0172098.
26. Martinez, C.; Fernandez, C.; Prado, M.; Ozols, A.; Olmedo, D.G. Synthesis and characterization of a novel scaffold for bone tissue engineering based on Wharton’s jelly. J. Biomed. Mater. Res. A 2017, 105, 1034–1045.
27. Converse, G.L.; Li, D.; Buse, E.E.; Hopkins, R.A.; Aljitawi, O.S. Wharton’s Jelly Matrix Decellularization for Tissue Engineering Applications. Host-Fungus Interact. 2017, 1577, 25–33.
28. Penolazzi, L.; Pozzobon, M.; Bergamin, L.S.; D’Agostino, S.; Francescato, R.; Bonaccorsi, G.; De Bonis, P.; Cavallo, M.; Lambertini, E.; Piva, R. Extracellular Matrix from Decellularized Wharton’s Jelly Improves the Behavior of Cells from Degenerated Intervertebral Disc. Front. Bioeng. Biotechnol. 2020, 8, 262.

29. Berger, D.R.; Centeno, C.J.; Kisiday, J.D.; McIlwraith, C.W.; Steinmetz, N.J. Colony Forming Potential and Protein Composition of Commercial Umbilical Cord Allograft Products in Comparison With Autologous Orthobiologics. Am. J. Sports Med. 2021, 49, 3404–3413.
30. Ribitsch, I.; Baptista, P.M.; Lange-Consiglio, A.; Melotti, L.; Patruno, M.; Jenner, F.; Schnabl-Feichter, E.; Dutton, L.C.; Connolly, D.J.; van Steenbeek, F.G.; et al. Large Animal Models in Regenerative Medicine and Tissue Engineering: To Do or Not to Do. Front. Bioeng. Biotechnol. 2020, 8, 972.
31. Iacono, E.; Brunori, L.; Pirrone, A.; Pagliaro, P.P.; Ricci, F.; Tazzari, P.L.; Merlo, B. Isolation, characterization and differentiation of mesenchymal stem cells from amniotic fluid, umbilical cord blood and Wharton’s jelly in the horse. Reproduction 2012, 4, 455–468.