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Tissue engineering and its application in veterinary medicine: A review

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Abstract
Tissue engineering is an amalgam of principles and techniques of various disciplines which aims at assembling biological substitutes to aid either in growth of new tissues or to restore the structure and function of affected tissue. It involves construction of a three dimensional matrix which mimics the natural tissue in all aspects viz, functionally, structurally and mechanically by use of four key materials (i.e, scaffold, growth factor, extracellular matrix and cells). Although various types of cells are used in tissue engineering but autologous cells (stem cells) are preferred the most. Tissue engineering is an expanding field where in efforts are being made to include all tissue and organs of humans and animal body. The added advantage of tissue engineering is that it probably has the ability to correct various incurable defects as well as replacement of any damaged structure. Therefore it can be considered as a viable therapeutic option for replacement and regeneration of tissue. Although, the results are far more promising but it demands a lot of effort in future to be a successful tool in animal medicine

Keywords: Tissue engineering, stem cells, veterinary medicine.

Introduction
Tissue engineering is an interdisciplinary field that applies the principles and methods of bioengineering, material science, and life sciences towards the assembly of biologic substitutes that mimic the natural extracellular matrix to help guide the growth of new functional tissue *in vitro* or *in vivo* to restore, maintain and improve tissue functions following damage either by disease or traumatic processes (Knight, 2004) [20]. In 1990s, the term regenerative medicine was used interchangeably with tissue engineering. The general principles of tissue engineering involve combining living cells with a natural/synthetic support or scaffold to build a three dimensional living construct that is functionally, structurally and mechanically equal to or better than the tissue that is to be replaced (Stock, 2001) [35]. The development of such a construct involves successful interaction between four key materials i.e, scaffold, growth factors, extracellular matrix and cells (Fuchs, 2001, Shieh, 2005 and Naughton, 2002) [15, 30, 24].

Scaffolds
Scaffold materials are three-dimensional tissue structures that guide the organization, growth and differentiation of cells. Scaffolds must be biocompatible and designed to meet both nutritional and biological needs for the specific cell population (Vats, 2003) [37]. The main properties of biocompatible scaffolds (synthetic or natural) include optimal fluid transport, delivery of bioactive molecules, material degradation, cell-recognizable surface chemistries, mechanical integrity and the ability to induce signal transduction (Shin, 2003)[31]. Natural biomaterials (Alginate, cellulose, chitosan, collagen, fibrinogen, hyaluronic acid, silk fibroin, glycosaminoglycans (GAGs), hydroxyapatite (HA) etc.,) used for stem cell cultivation have an advantage of being bioactive, biocompatible with similar mechanical properties as native tissue (Chung, 2008) [9].

Growth factors and Extracellular matrix
Growth factors are soluble peptides capable of binding cellular receptors and producing either a permissive or preventive cellular response toward differentiation and/or proliferation of tissue (Whitaker, 2001) [41]. Extra cellular matrix (ECM) must be capable of providing the optimal conditions for cell adhesion, growth and differentiation within the construct by creating a system capable of controlling environmental factors such as pH, temperature, oxygen tension and mechanical forces (Naughton, 2002) [24].

These conditions are determined by particular cell lines and the properties of the scaffold (Naughton, 2002) [24].

Cells

Finally, the development of a viable construct involves a suitable supply of cells that are ideally non immunogenic, highly proliferative, easy to harvest and have the ability to differentiate into a variety of cell types with specialized functions (Koh, 2004)[21]. Stem cells have the potential to divide and differentiate into various specialized cell types and can self-renew to produce more stem cells (Crovace, 2010) [10]. Stem cells can be divided based on their self-renewal and potency (Crovace, 2010) [10]. Self-renewal of stem cells is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state while other property of stem cells is potency which is the capacity to differentiate into specialized cell types (Nourissat, 2010) [25]. Based on the potency, stem cells can be divided into totipotent stem cells (Chen, 2012) [6] which can differentiate into embryonic and extraembryonic cell types (Nourissat, 2010) [25] and have the ability to construct a complete, viable organism (Guest, 2010) [16]. Potency of these cells is highest among other stem cell types (Nourissat, 2010) [25]. The second type is the pluripotent stem cells (Okamoto, 2010) [26]. These cells are the progenies of totipotent cells and can differentiate into almost all cells (e.g, cells derived from any of the three germ layers) (Ai, 2012) [1]. The third type is the multipotent stem cells (Chen, 2012) [6] which can differentiate into a number of cells, but only those of a closely related family of cells (Zscharnack, 2010) [48]. The potency of these cells is much lower than the totipotent stem cells and lower than pluripotent stem cells. The fourth type is the oligopotent stem cells. These cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells (Yao, 2012) [45]. Finally, the fifth group is the unipotent cells (Ter, 2012) [36] and the potency of these cells is extremely low so they can produce only one cell type, their own. They have the property of self-renewal, which distinguishes them from non-stem cells (Ter, 2012) [36]. Therefore, all types of stem cells have the ability of self-renewal but their potency is different and depends on the source that they have arisen from (Zscharnack, 2010) [48]. Current approaches to tissue engineering can be stratified into substitutive, histioconductive, and histioinductive (Knight, 2004) [20]. Substitutive approaches (ex vivo) are essentially whole organ replacement, whereas histioconductive approaches (ex vivo) involve the replacement of missing or damaged parts of an organ tissue with ex-vivo constructs. In contrast, histioinductive approaches facilitate self-repair and may involve gene therapy using DNA delivery via plasmid vectors or growth factors.

Techniques of Tissue engineering

When cells are used for tissue engineering, a small piece of donor tissue is dissociated into individual cells. In case of *in vivo* tissue engineering, patient acts as a bioreactor for cell differentiation and in case of *in vitro* tissue engineering, bioreactor is used for cell differentiation. These cells are either implanted directly into the host (invivo) or are expanded in culture (invitro), attached to a support matrix, and then reimplanted into the host after expansion. The source of donor tissue can be heterologous, allogeneic (same species, different individual), or autologous. Ideally, both structural and functional tissue replacements will occur with minimal complications. The most preferred cells to use are autologous cells, where a biopsy of tissue is obtained from the host, the cells are dissociated and expanded in culture, and the expanded cells are implanted into the same host. The use of autologous cells avoids rejection, and thus the deleterious side effects of immunosuppressive medications can be avoided.

Bioreactors

A bioreactor is a device that attempts to simulate a physiological environment in order to promote cell or tissue growth *in vitro***.** It is used to aid in the *in vitro* development of new tissue by providing a better physiological environment including temperature and oxygen or carbon dioxide concentration and extend to all kinds of biological, chemical or mechanical stimuli (Plunkett, 2011)[28]. The bioreactors used for 3D cell cultures are small plastic cylindrical chambers. l with regulated internal humidity and moisture. This humidity is important to achieve maximum cell growth and function. The bioreactor uses bioactive synthetic materials such as polyethylene terephthalate membranes to surround the spheroid cells in an environment that maintains high levels of nutrients. The bioreactor chamber is part of a larger device that rotates to ensure equal cell growth in each direction across three dimensions.

Applications of tissue engineering in veterinary medicine

Role of tissue engineering in tendon defects

Tissue engineering has been introduced to improve the outcome of incorporation of the tissue engineered grafts and improve the healing processes of injured tendons. A major advancement in tendon tissue engineering is related to the scaffolds. The first step in tendon regenerative medicine is to design a suitable environment for cell migration, proliferation, remodelling and maturation (Moshiri, 2013)[22]. Therefore, there are several factors that have an impact on the effectiveness of the scaffold including the basic material of the scaffold, architecture of the scaffold, diameter and orientation of the fibres, their biological characteristics and the amount of free spaces and pore size (Shearn, 2011 and Whitlock, 2012) [29,42]. Other issues that should be considered in manufacturing a scaffold (Chen, 2009) [7] is a suitable scaffold for tendon tissue engineering i.e, it should be cytocompatible *in vitro* and biocompatible and biodegradable *in vivo* (Shearn, 2011)[29].Unfortunately, most of the exogenous based biomaterials for tendon repair have serious limitations, such as lower capacity for inducing cell proliferation and differentiation (tenoinductivity), poor biocompatibility and remodelling potential (tenoconductivity) (Whitlock, 2012) [42].Basic material of the scaffold can generally be divided into three major groups including biological (natural), synthetic and hybrid materials (Chen, 2009) [7].Biological materials such as collagen, elastin, gelatin, chitosan, albumin, alginate, fibrin and chondroitin sulphate have been shown to be effective in tendon healing (Whitlock, 2007) [43]. Their toxicity is low and has some beneficial biological role after implantation in the injured area (Wotton, 2009) [44]. Mature tendons are composed of more than 90% type 1 collagen. Elastin is also present in tendons in a much less proportion (about 1%) and its major application in tissue engineering is to produce vascular scaffolds (Chen, 2009) [7]. Chitosan is a natural polysaccharide obtained from insects. There are also some nonbiodegradable biological materials such as silk and carbon fibres (Naughton, 2002) [24]. The usage of carbon fibre did not continue because of its high

toxic effect and serious inflammatory reactions. However, investigations into silk are still in progress, as that have low value in translational medicine (Chen, 2009) [7]. Synthetic materials such polycaprolactone (absorbable), polydioxanone (absorbable), polygalactin 910 (absorbable) and nylon (non-absorbable) are other options with invaluable results (Hakimi, 2012) [17]. Several types of scaffolds with different technologies have been introduced. Tendon and ligament injuries are a frequently occurring problem not only in human but also in equine athletes. Successful therapy is challenging because of high re-injury rates following conventional treatment regimes and poor regeneration capacities of tendon tissue (Dowling, 2000 and Chong, 2009)[12,8]. Treatment of tendon injuries is challenging with major limitations of peritendinous adhesions because of proliferation of fibroblasts in a haphazard fashion (Moshiri, 2011) [23]. With the result, migration of fibroblast in the defect area is reduced followed by reduction in the amount of collagen production. Continuity of the defect area in such a tendon injury may not be established (Chalmers, 2000) [5]. Tendon transplantation is the only available option when the injured tendons are having-large tendon deficits (Zhang, 2012) [47]. Mesenchymal stem cells (MSCs) represent an attractive tool for tendon tissue repair in equines and bone marrow mesenchymal cells possess the best capability of differentiating into tenocytes (Stefania, 2009) [34].

Role of tissue engineering in bone regeneration and healing

Bone healing has its own limitations and complications. In large massive bone defects, such as osteosarcoma, gunshot fractures, severe trauma, burn, etc, proper graft both in size and quality is needed for bone transplantation; however it may not be available for such cases. Therefore, there is a need to accelerate bone healing by increasing the amount of the newly regenerated callus in the defect area. Stem cells may have a role to aid bone formation in this regard. Musculoskeletal disorders represent a major part of all cases, especially in horses and dogs which represent a high proportion of the orthopaedic case load in veterinary clinical practice and prognosis for patients suffering from musculoskeletal disorders such as tendon or joint injuries is always poor, therefore it is not surprising that they are currently taking a leading role in mesenchymal stromal cells (MSC) therapies. The focus of attention in veterinary science is currently drawn to mesenchymal stromal cells (MSC) and their potential in regenerative medicine (Walter, 2012) [40]. Several therapies utilizing MSC for animal patients are being developed and some, like the treatment of equine tendinopathies (Smith, 2003andSmith 2008) [33, 32] or cartilage degeneration in dogs (Black, 2007and 2008) [4, 3]. The stromal compartment of bone marrow was the first source reported to contain multipotent progenitor cells (Fortier, 1998) [13]. For this reason, bone marrow is currently the best investigated origin of MSC. Bone marrow collection from the sternum is probably favored for cell-based therapies in equine regenerative medicine. This is due to the reliable isolation success of bone marrow-derived MSC in horses following an easy preparation procedure and separation of MSC via plastic adherence and cell culture (Vidal, 2006) [38]. The major disadvantage of bone marrow-derived MSC is the invasive collection procedure associated with the risk of complications such as hemorrhage, infection, pneumothorax, or pneumopericardium(Vidal, 2007) [39]. Similar to human beings, various forms of joint disease occur, including developmental diseases (i.e. osteochondrosis), acute accidental injuries (i.e. focal cartilage defect) and chronic acquired diseases. The ultimate result is often osteoarthritis (OA), a joint disease characterized by a progressing loss of functional cartilage matrix, synovitis and variable subchondral bone reaction. Horses suffering from OA induced by experimental osteochondral fragmentation were treated with bone marrow-derived MSC or the stromal-vascular fraction from adipose tissue (Frisbie, 2009) [14]. Dogs suffering from elbow and hip joint OA were injected with the stromal-vascular cell fraction from adipose tissue and an improvement of clinical parameters was observed (Black, 2007 and 2008) [4, 3]. Therefore, tissue engineering and the use of stem cells are important in situations where bone healing is delayed, where an arthrodesis needs to be supported, or in cases where bone loss is too important to be repaired without intervention (Walter, 2012)[40].

Role of tissue engineering in cartilage healing

The incidence of cartilage injury is very high and has minimum healing capability like that of tendon (Davatchi, 2011 and Kasemkijwattana, 2011) [11, 18]. It has been suggested that MSCs therapy can increase the rate and quality of cartilage regeneration both in animals and humans (Zscharnack, 2010) [48] Platelet rich plasma (PRP) is reported to promote collagen synthesis and cell proliferation as well as enhance cartilage repair (Moshiri, 2013) [22].

Recent advances and future prospects

Recently, skin tissue engineering is considered to be the primary treatment for epidermal and dermal construct (Whitlock, 2012) [42]. Dermal fibroblasts are obtained from neonatal foreskin, expanded *in vitro*, seeded onto a scaffold of polylactic or polyglycolic acid before being cultured in a bioreactor system to generate a dermal layer (Kern, 2011) [19]. A bilaminate construct is produced by coating the dermal layer with multiple layers of keratinocytes (Bianco, 2001) [2]. Complexity and specialized conducting infrastructure of the heart and low proliferative potential of cardiomyocytes is a challenge for heart tissue engineering. Promising solution is embryonic stem cell lines. Engineered heart products include biocompatible, non-biodegradable but ineffective for longterm replacement. Nonetheless, the possibility of development of an engineered heart is exemplified by the successful manufacturing of tissue-engineered valves and myocardial infarct scar remodeling (Orlic, 2001) [27].

Tissue engineering has the ability to repair various defects which are otherwise incurable and it can be used to replace any of the damaged structure. The results thus far are very promising but a lot of effort still needs to be put to make it a viable therapeutic option for replacement and regeneration of tissue or organ in animal medicine.

Conclusion

Engineered tissues have progressively expanded clinical applicability in the future because they represent a viable therapeutic option for those who require tissue replacement or regeneration. Efforts for tissue engineering are currently underway for virtually every type of tissue and organ within the human or animal body. Various engineered tissues are at different stages of development, with some already being used clinically, a few in preclinical trials, and some in the discovery stage. More recently, major advances in the areas of

stem cell biology, tissue engineering, and nuclear transfer techniques have made it possible to combine these technologies to create the comprehensive scientific field of regenerative medicine.

Reference

1. Ai J, Ebrahimi S, Khoshzaban A, Jafarzadeh Kashi TS, Mehrabani D. Tissue engineering using human mineralized bone xenograft and bone marrow mesenchymal stem cells allograft in healing of tibial fracture of experimental rabbit model. Iran Red Crescent Medical Journal. 2012; 14(2):96-103.
2. Bianco P, Robey PG. Stem cells in tissue engineering. Nature 2001; 414:118-121.
3. Black LL, Gaynor J, Adams C, Dhupa S, Sams AE, Taylor R *et al*. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Veterinary Therapeutics. 2008; 9:192-200.
4. Black LL, Gaynor J, Gahring D, Adams C, Aron D, Harman S *et al*. Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. Veterinary Therapeutics. 2007; 8:272-284.
5. Chalmers J. Review article: Treatment of Achilles tendon ruptures. Journal of Orthopedic Surgery. 2000; 8(1):97-9.
6. Chen HS, Chen YL, Harn HJ, Lin JS, Lin SZ. Stem cell therapy for tendon injury. Cell Transplant. 2012.
7. Chen J, Xu J, Wang A, Zheng M. Scaffolds for tendon and ligament repair: review of the efficacy of commercial products. Expert Review of Medical Devices. 2009; 6(1):61-73.
8. Chong AK, Chang J, Go JC. Mesenchymal stem cells and tendon healing. Front Biosci. 2009; 14:4598-4605.
9. Chung C, Burdick JA. Engineering Cartilage Tissue. Advanced Drug. Delivery Reviews. 2008; 14:243-262.
10. Crovace A, Lacitignola L, Rossi G, Francioso E. Histological and immunohistochemical evaluation of autologous cultured bone marrow mesenchymal stem cells and bone marrow mononucleated cells in collagenaseinduced tendinitis of equine superficial digital flexor tendon. Veterinary Medicine International. 2010, 250978.
11. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. International Journal of Rheumatic Diseases. 2011; 14(2):211-5.
12. Dowling BA, Dart AJ, Hodgson DR, Smith RK. Superficial digital flexor tendonitis in the horse. Equine Veterinary Journal. 2000; 32:369-378.
13. Fortier LA, Nixon AJ, Williams J, Cable CS. Isolation and chondrocytic differentiation of equine bone marrow-derived mesenchymal stem cells. American Journal of Veterinary Research. 1998; 59:1182-1187.
14. Frisbie DD, Kisiday JD, Kawcak CE, Werpy NM, McIlwraith CW. Evaluation of adipose-derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. Journal of Orthopedic Research. 2009; 27:1675-1680.
15. Fuchs JR, Nasseri BA, Vacanti JP. Tissue engineering: a 21st century solution to surgical reconstruction. The Annals of Thoracic Surgery. 2001; 72:577-591.
16. Guest DJ, Smith MR, Allen WR. Equine embryonic stem-like cells and mesenchymal stromal cells have different survival rates and migration patterns following their injection into damaged superficial digital flexor tendon. Equine Veterinary Journal. 2010; 42(7):636-42.
17. Hakimi O, Murphy R, Stachewicz U, Hislop S, Carr AJ. An electrospun polydioxanone patch for the localisation of biological therapies during tendon repair. European Cells and Materials. 2012; 24:344-57.
18. Kasemkijwattana C, Hongeng S, Kesprayura S, Rungsinaporn V, Chaipinyo K, Chansiri K. Autologous bone marrow mesenchymal stem cells implantation for cartilage defects: two cases report. Journal of Medical Association of Thailand. 2011; 94(3):395-400.
19. Kern A, Liu K, Mansbridge J. Modification of fibroblast gamma-interferon responses by extracellular matrix. Journal of Investigative Dermatology 2001; 117:112-118.
20. Knight MA, Evans GR. Tissue engineering: progress and challenges. Plastic Reconstructive Surgery. 2004; 114:26E-37E.
21. Koh CJ, Atala A. Therapeutic cloning and tissue engineering. Current Topics in Developmental Biology. 2004; 60:1-15.
22. Moshiri A, Oryan A. Role of platelet rich plasma in soft and hard connective tissue healing: an evidence based review from basic to clinical application. Hard Tissue 2013; 2(1):6.
23. Moshiri A, Oryan A. Structural and functional modulation of early healing of full-thickness superficial digital flexor tendon rupture in rabbits by repeated subcutaneous administration of exogenous human recombinant basic fibroblast growth factor. The Journal of Foot and Ankle Surgery. 2011; 50(6):654-62.
24. Naughton GK. From lab bench to market: critical issues in tissue engineering. Annals of the New York Academy of Sciences. 2002; 961:372-385.
25. Nourissat G, Diop A, Maurel N, Salvat C, Dumont S, Pigenet A *et al*. Mesenchymal stem cell therapy regenerates the native bone-tendon junction after surgical repair in a degenerative rat model. Public Library of Sciences. 2010; 5(8):e12248.
26. Okamoto N, Kushida T, Oe K, Umeda M, Ikehara S, Iida H. Treating Achilles tendon rupture in rats with bone marrow- cell transplantation therapy. Journal of Bone and Joint Surgery American. 2010; 92(17):2776-84.
27. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B *et al*. Bone marrow cells regenerate infarcted myocardium. Nature. 2001; 410:701-705.
28. Plunkett N, O'Brien FJ. Bioreactors in tissue engineering. Technology Health Care. 2011; 19:55-69.
29. Shearn JT, Kinneberg KR, Dyment NA, Galloway MT, Kenter K, Wylie C *et al*. Tendon tissue engineering: progress, challenges, and translation to clinic. Journal of Musculoskeletal and Neuronal Interactions. 2011; 11(2):163-73.
30. Shieh SJ, Vacanti JP. State-of-the-art tissue engineering: from tissue engineering to organ building. Surgery. 2005; 137:1-7.
31. Shin H. Biomimetic materials for tissue engineering. Biomaterials. 2003; 24:4353-4364.
32. Smith RK. Mesenchymal stem cell therapy for equine tendinopathy. Disability and Rehabilitation. 2008; 30:1752-1758.

33. Smith RK, Korda M, Blunn GW, Goodship AE. Isolation and implantation of autologous equine mesenchymal stem cells from bone marrow into the superficial digital flexor tendon as a potential novel treatment. Equine Veterinary Journal. 2003; 35:99-102.
34. Stefania V, Paola R, Laura FP, Chiara G, Poala Mariani. Horse bone marrow mesenchymal stem cells express embroyo stem cell markers and show the abilityfor tenogenic differentiation by *in vitro* exposure to BMP-12. BMC cell biology. 2009; 10:29.
35. Stock UA, Vacanti JP. Tissue engineering: current state and prospects. Annual Review of Medicine. 2001; 52:443-451.
36. Huurne M, Schelbergen R, Blattes R, Blom A, de Munter W, Grevers LC *et al*. Antiinflammatory and chondroprotective effects of intraarticular injection of adipose-derived stem cells in experimental osteoarthritis. Arthritis Rheumatism. 2012; 64(11):3604-13.
37. Vats A, Tolley NS, Polak JM, Gough JE. Scaffolds and biomaterials for tissue engineering: a review of clinical applications. Clinical Otolaryngoogy and Allied Sciences. 2003; 28:165-172.
38. Vidal MA, Kilroy GE, Johnson JR, Lopez MJ, Moore RM, Gimble JM. Cell growth characteristics and differentiation frequency of adherent equine bone marrow-derived mesenchymal stromal cells: adipogenic and osteogenic capacity. Veterinary Surgery. 2006; 35:601-610.
39. Vidal MA, Kilroy GE, Lopez MJ, Johnson JR, Moore RM, Gimble JM. Characterization of equine adipose tissue-derived stromal cells: adipogenic and osteogenic capacity and comparison with bone marrow-derived mesenchymal stromal cells. Veterinary Surgery. 2007; 36:613-622.
40. Walter Brehm, Janina Burk, Uta Delling, Claudia Gittel, Iris Ribitsch. Stem cell-based tissue engineering in veterinary orthopaedics. Cell Tissue Research. 2012; 347:677-688.
41. Whitaker MJ, Quirk RA, Howdle SM, Shakesheff KM. Growth factor release from tissue engineering scaffolds. J Pharmacy and Pharmacology. 2001; 53:1427-1437.
42. Whitlock PW, Seyler TM, Parks GD, Ornelles DA, Smith TL, Van Dyke ME *et al*. A novel process for optimizing musculoskeletal allograft tissue to improve safety, ultrastructural properties, and cell infiltration. Journal of Bone and Joint Surgery American. 2012; 94(16):1458-67.
43. Whitlock PW, Smith TL, Poehling GG, Shilt JS, Van Dyke M. A naturally derived, cytocompatible, and architecturally optimized scaffold for tendon and ligament regeneration. Biomaterials. 2007; 28(29):4321-9.
44. Wotton FT, Akoh JA. Rejection of Permacolmesh used in abdominal wall repair: a case report. World Journal of Gastroenterology. 2009; 15(34):4331-3.
45. Yao J, Woon CY, Behn A, Korotkova T, Park DY, Gajendran V, Smith RL. The effect of suture coated with mesenchymal stem cells and bioactive substrate on tendon repair strength in a rat model. Journal of Hand Surgery. 2012; 37(8):1639-45.
46. Zhang Q, Cheng B. Tendon-derived stem cells as a new cell source for tendon tissue engineering. Front Biosciences. 2013; 18:756-64.
47. Zhang X, Bogdanowicz D, Erisken C, Lee NM, Lu HH. Biomimetic scaffold design for functional and integrative tendon repair. Journal of Shoulder and Elbow Surgery. 2012; 21(2):266-77.
48. Zscharnack M, Hepp P, Richter R, Aigner T, Schulz R, Somerson J *et al*. Repair of chronic osteochondral defects using predifferentiated mesenchymal stem cells in an ovine model. American Journal of Sports Medicine. 2010; 38(9):1857-69.