Original article

International Journal of Musculoskeletal Pain prevention

Volume 1, Number 3, Summer 2016

Transplantation of Autologous Adipose Derived Mesenchymal Stem Cells for Improvement of Quality of Life in Osteoarthritis Patients

Hajar Shafaei[1, 2*], Hassan Bagernezhad[2, 3], Hossein Soliemanlou[4], Masoud Poureisa[5]

1. Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
2. Bonyan Cellule Kosar Company, East Azarbaijan Science and Technology Park, Tabriz, Iran.
3. Radiology ward, Sina Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.
4. Orthopedic ward, Shahid Mahallati Hospital, Tabriz, Iran.
5. Department of Radiology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Background: Osteoarthritis (OA) has been recognized, as the most common inflammatory disease in the world. Adipose Stem Cells (ASCs), as a new feasible source with high numbers of stem cells and proliferative capacity have been used for regenerative medicine. Based immunomodulatory and chondrogenic properties of ASCs, this study aimed to assess intra articular injection of ASC effect on improvement of osteoarthritis signs.

Methods and Materials: Adipose tissue samples were obtained from subcutaneous of abdomen. ASCs were isolated and cultured for at least three passages in culture media containing autologous serum and expanded them to 15-20 × 10^6 cell. The morphology and proliferative potency of ASCs were determined. Immuno phenotype characteristics of ASCs were analyzed by flow-cytometry. Then cell suspensions were injected into knee articular spaces. After 6 months the function of knee was assessed by WOMAC, KOOS, Lysholm and Lequesne indexes.

Results: The results of this study showed that homogenous spindle-shape ASCs expanded rapidly with low doubling time. The low expression of CD14 and CD45 indicated that ASCs are non hematopoietic cells and expressed high percentages of CD44, CD105 and CD90. Our results showed that injected ASCs were effective in improvement of OA by scoring systems for evaluation of pain, joint movements and daily physical activities were significantly changed due to injection of stem cells. Osteoarthritis severity indexes means of WOMAC and Lequesne were decreased from 53 to 12.3 and 15.1 to 2.1 respectively. Also osteoarthritis improvement indexes Lysholm & KOOS means were significantly increased from 35 to 15.1 and 70 to 126.7 respectively. In six months follow up of intra articular injection of ASCs, we observed no local or systemic side effect. After ASCs injection, walking distance considerably increased. The flexion angle of knee improved by 20-30 degrees compares to before of treatment.

Conclusion: Autologous ASCs injection could be resulted in increasing of knee function, alleviated of pain and quality of life improvement.

Keywords: ASC, Osteoarthritis, Stem cell therapy, Alleviation of pain

Introduction

Among rheumatoid disease, Osteoarthritis (OA) of the knee is the most common health problem in worldwide (Shi, 2012) and fourth leading cause of disability (Fransen et al., 2011). In the United States in 2003, the costs of arthritis treatments were $128 billion (Yelin et al., 2007). The main therapeutic options at present are analgesics, anti-inflammatory drugs and surgical treatments such as arthroscopy, micro fracture and total joint replacement. Lack of actual cure of OA and its high economic consequences resulted in that investigators look for non invasive, inexpensive and effective methods for treatment of OA. Stem cell therapy is a promising strategy for treatment of diseases (Liang & Sun, 2015).

Corresponding author: No: 01, Department of Anatomical Sciences, Faculty of Medical Sciences, Tarbiat Modares University, P. O. Box: 5155668474, Tel: 00989147811605; Fax: 00989147811605: E-mail: shafaei49@gmail.com

Access this article online	
Website: ijmpp.modares.ac.ir	
DOI:	

Mesenchymal Stem Cells (MSCs) have an ability to proliferate and differentiate toward mature tissues in specific microenvironments. These intrinsic characteristics of MSCs make them very attractive cell source for regenerative medicine. MSCs are found in numerous tissues of body (Via et al., 2012). However adipose tissue derived stem cells (ASCs) are accessible and abundant in each gram of this tissue and they are more than Bone Marrow Stem Cells (BMSCs)(Pittenger et al., 1999, Sen et al., 2001). Other properties of ASCs including their characteristics, differentiation potential, genetic stability, toxicity and tumorigenicity have widely been investigated. We previously showed that chondrogenic potential of ASCs (Shafaei & Baghernezhad, 2015, Shafaei et al., 2013). Karyotyping analysis showed that ASCs are genetically stable after expansion (Meza-Zepeda et al., 2008). Injection of ASCs in mice had no adverse effects in toxicity test (Meza-Zepeda et al., 2008). There is fundamental data for safety of collagenase isolated adipose-derived stem cells (Chang et al., 2013). Tumorigenic studies of ASCs revealed that no abnormal finding (Meza-Zepeda et al., 2008). Although previously (Bernardo et al., 2007) have reported BMSCs were not susceptible to malignant transformation as well (Bernardo et al., 2007). Another interesting characteristic of ASCs is their immunomodulatory potential (Blazquez et al., 2014). Pervious findings indicated that ASCs greatly up-regulate immunomodulatory cytokines and down-regulate inflammatory cytokines (Mohammadzadeh et al., 2014). In experimental OA, intra-articular injection of ASCs had protective effects on synovial membrane (Schelbergen et al., 2014). These cells can suppress inflammatory process by chemotactic ability and migration to inflammation sites (Markides et al., 2013). Vast majority of studies confirm MSCs to inhibit the immune response (Nauta et al., 2006). There has been a significant interest for therapeutic use of ASC due to immunomodulatory potency of ASC (Pittenger et al., 1999).

OA is an complex inflammatory disease due to released cytokines by cartilage, bone and synovium (Berenbaum, 2013). In arthritic patients, significant improvement has been shown using anti-TNFα treatment (Chou, 2012). It has been shown that mesenchymal stem cells of synovial fluid increase in joint injuries (Nakagawa et al., 2015). Findings of previous research indicate that intra articular injection of ASC in induced OA inhibits synovial thickening and cartilage destruction (ter Huurne et al., 2012). Although Autologous Chondrocyte Implantations (ACI) has positive outcome in repairing of articular joint injuries (Nauta et al., 2006). Therefore, in comparison with MSCs, implanted chondrocytes probably do not have anti inflammatory and immune modulating properties effect on injury site (Chang et al., 2011; Singer & Caplan, 2011). Many of MSC transplantation studies on osteoarthritis of knee in animals and humans have been done and they reported significant improvement (Vega et al., 2015; Davatchi et al., 2011). One year follow up by Magnetic Resonance Imaging (MRI) scans showed significantly better functional scores for the MSC recipient group (Wong et al., 2013). In 5 years follow up, MSC treated patients showed improvement better results than untreated knee (better knee of patient at day treatment has been kept as control with any MSC and control knee became the worse knee at 5 years (Davatchi et al., 2015). Intra articular injection of autologous ASCs for osteoarthritic knee resulted in decrease of the cartilage defect size by arthroscopic evaluation (Jo et al., 2014). Expanded and non-expanded MSC transplantation resulted in positive outcomes in clinical studies and formation of hyaline like cartilage based on arthroscopic, histologic and imaging evaluations (Buda et al., 2013, Buda et al., 2010). In this study we used expanded autologous ASCs of patients for treatment of OA and evaluated the improving of knee joint function by WOMAC, KOOS, Lysholm and Lequesne indexes.

Methods

This research is caring out on human subjects by ethical approval committee of the Tabriz University of Medical Sciences, Tabriz Iran, through ID number: 9368. Here we reported preliminary results of this study for three middle aged woman who had suffered OA. The procedure was done in Tabriz academic center for education, culture and research center.

Inclusion criteria for this study were woman suffering OA and aged between 45 and 60 year old with Body Mass Index (BMI) greater than 30kg/m2 and classification of cartilage joint Lesions by Kellgren-Lawrence scale greater or equal to 2. Exclusion criteria were osteoarthritis with grade greater than 2, previous chondral surgery, patients with diabetes mellitus, alzheimer, systemic lupus erythematosus, hepatitis, HIV, malignancy, addiction to opioids, treatment with growth factors during one month prior to entering into the study, patients with a history of septicemia, viral or fungal infection, history of radiotherapy, patients with long term contact with poisonous compounds.

The eligible patients had OA about grade 2 based on plain radiographic images (table 1) (Park et al., 2013). After fully explanation about the procedure of the study, they signed informed consent and filled WOMAC, KOOS, Lysholm and Lequesne indexes forms before MSC transplantation. Then blood sample and adipose tissue of the participated patients were collected if they had all inclusion criteria.

Table 1. Grading of the osteoarthritis of the knee joint by Kellgren-Lawrence.

	Kellgren-Lawrence Grading Scale
Grade 0	No narrowing of joint space and no osteophytic
Grade 1	Doubtful narrowing of joint space and possible osteophytic
Grade 2	Definite osteophytes, definite narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

To preparing serum, 30 ml of autologous blood was collected in falcon tubes without any anti-coagulants and the blood samples were kept at 4^{o}C for 4 hours and clot centrifuged at 4000 rpm for 10 minutes, and the pure serum were stored at -20 ^{o}C until use.

Isolation and culture of ASCs: Ten gram of adipose tissues were obtained from abdominal subcutaneous adipose tissue by minimum incision on abdominal skin and transferred to lab. Isolation of ASCs were done by collagenase A (Worthington-CSLAFA) according to Zuk protocol (Zuk et al., 2002). Briefly, these stem cells were cultured at 37 ^{o}C, 5% CO2 in low glucose DMEM (Gibco, UK) and 10% autologous serum. After 24 hours, the culture media was replaced. The cells were trypsinized (0.25% trypsin/0.2% EDTA; Sigma, USA) and the harvested cell suspension was used for later passages or evaluation by flow cytometry. The culture medium being changed every 2–3 days. The morphology and proliferative potency of ASCs were determined. Immunophenotype characteristics of ASCs were analyzed by flow-cytometry. Then cell suspensions (15-20 x10^{6}) at passage 3 were injected into knee articular spaces. After 6 month the function of knee was assessed by WOMAC, KOOS, Lysholm and Lequesne indexes.

Results

The results of this study showed that ASCs were rapidly growing cells and spindle-shape at passage 3 before full confluency with appropriate doubling time (Fig. 1). Doubling time of ASCs in three cases is not statistically different. Forward scatter and side scatter dot plot confirmed that ASCs were homogenous small cells with low granularity. The low expression of CD14 and CD45 indicated that ASCs are non hematopoietic and they expressed high percentages of CD44, CD105 and CD90 (Fig 2). Our results showed that injected ASCs were effective in improvement of OA since scoring systems for evaluation of pain, joint movements and daily physical activities were significantly changed due to injection of stem cells. Osteoarthritis severity indexes means of WOMAC and Lequesne were decreased from 53 to 12.3 ($P < 0.002$) and 15.1 to 2.1 ($P = 0.002$) respectively (Fig 3A). Also osteoarthritis improvement indexes Lysholm and KOOS means were significantly increased from 35 to 15.1 ($P = 0.0083$) and 70 to 126.7 ($P = 0.0082$) respectively (Fig 3B). In six months follow up, we observed no local or systemic side effect from intra-articular injection. After stem cell injection walking distance considerably increased. The flexion angle of knee improved by 20-30 degree relation to before of treatment.

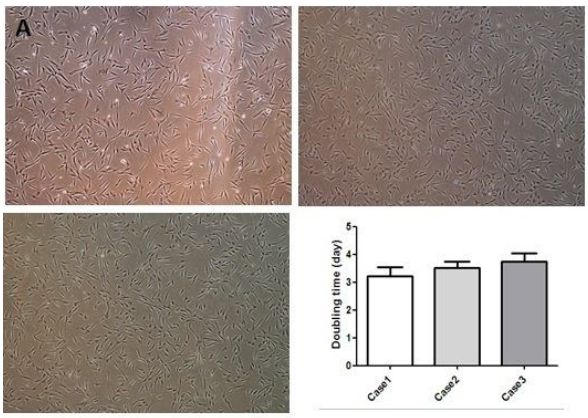

Figure 1. Morphology and growth rate of ASCs. A) Spindle shape cell ASCs at passage 3 before confluency in case 1. B) Spindle shape cell ASCs at passage 3 before confluency in case 2. C) Spindle shape cell ASC at passage 3 before full confluency in case 3. D) Doubling time of ASCs in three cases is not different.

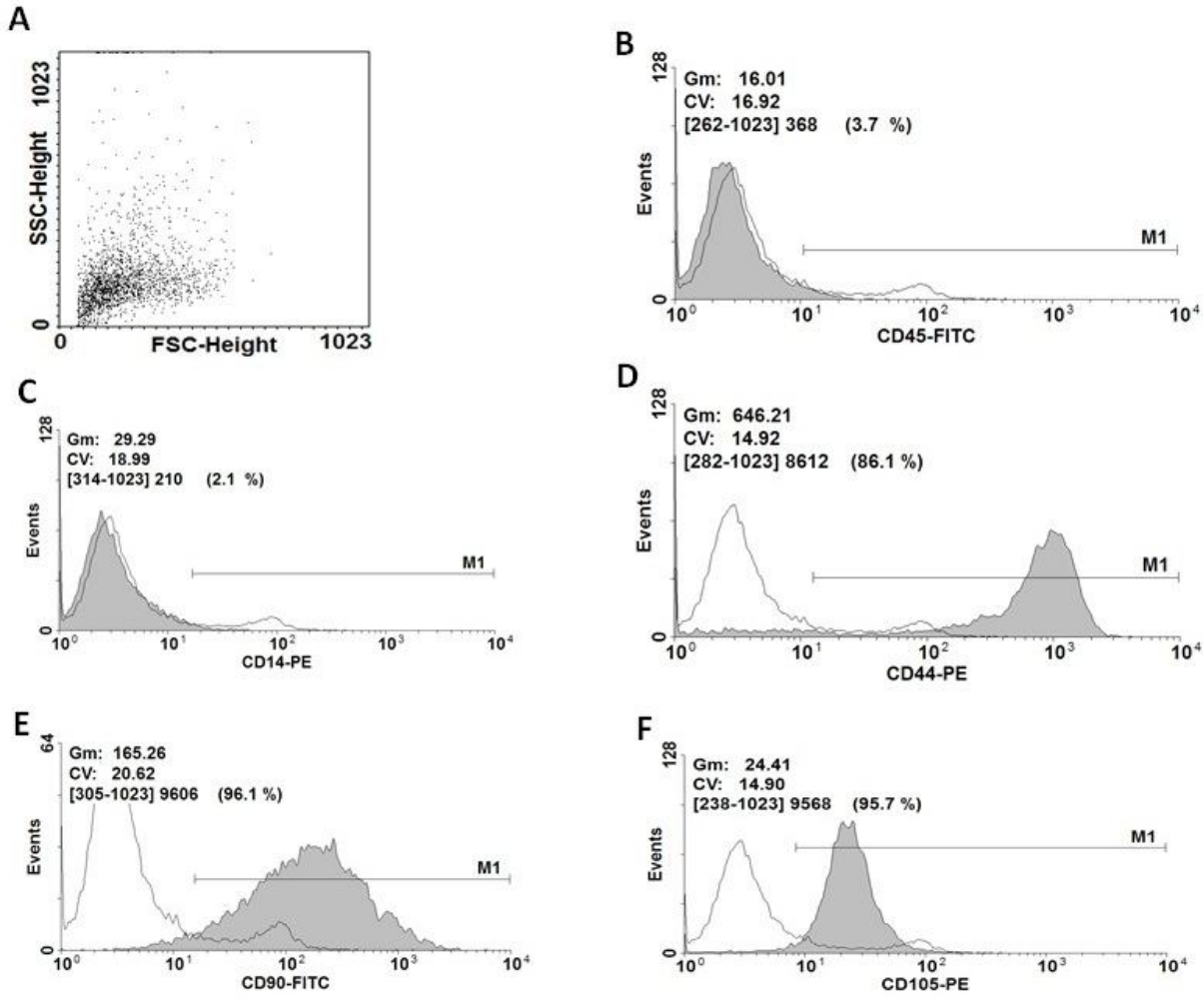

Figure 2. Flow cytometric analysis of ASCs. A) Forward and side scatter of ASC dot plot indicates small and homogenous cells with low granules. B)Surface marker expression of CD45, C) Expression of CD14, D) Expression of CD44, E) Expression of CD90 and F) Expression of CD105 on ASCs.

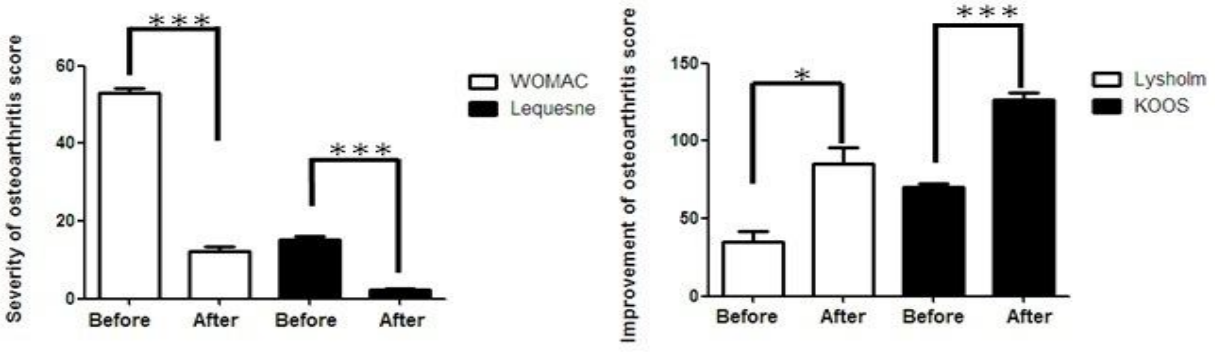

Figure 3. Comparison of knee function before and after intra-articular injection of autologous ASCs in osteoarthritic joint. A) Severity of osteoarthritis score by WOMAC and Lequesne indexes. B) Improvement of osteoarthritis signs by Lysholm and KOOS indexes.

Discussion

This study showed that ASC transplantation on osteoarthritic joint decreases symptoms of patients who suffer from osteoarthritis. In six months follow up, we observed no side effect from intra-articular injection except pain during first 24-48h after injection. Our results showed that ASCs at passage three had characteristics of

MSCs such as small and spindle shape cells and ASCs are non hematopoietic cells due to lack of CD14 and CD45 on cell surface. Presence of positive antigens (CD44, CD90 and CD105) on ASCs indicates that injected ASCs have features of stem cell. These results reported for short term follow up and these limitations will improve by enrolling more patients and continuing follow ups in longer periods in this study.

Heterogeneity of MSCs is major problem in cartilage tissue engineering (Tuan, 2006; Colter et al., 2002) confirmed that small and spindle shape cells are rapidly growing subpopulation of MSCs and they can expand up to as many as 50 population doublings (Sekiya et al., 2002; Colter et al., 2001; Colter et al., 2000). In this study we used homogenous ASCs by their morphologic appearance and forward scatter results. Previous studies demonstrated that MSCs from different tissues expresses above mentioned surface antigens. International Society for Cellular Therapy defines an MSC as expressing cell surface phenotype CD34-, CD45-, CD73+, CD90+, CD105+, HLA-DR- (Dominici et al., 2006). Our pervious findings showed that ASCs do not express CD31 and HLA-DR (Shafaei et al., 2011). This significant issue is necessary for cell therapy.

ASCs could modulate the therapeutic activities on transplanted knee joint. Improvement functional parameters of the knee could be regeneration properties and also because of anti-inflammatory properties of ASCs. Anti inflammatory effects of ASCs has been shown in rabbits (Singer & Caplan, 2011). It has been shown that positive outcome of intra-articular injection of stem cells in reducing of osteoarthritis symptoms (Emadedin et al., 2015; Davatchi et al., 2015; Delling et al., 2015). In comparison, BMSC harvesting is a painful procedure with donor site morbidity versus ASCs (Mazor et al., 2014). Hence, ASCs have been considered as abundant and accessible cells.

For evaluation of treatment effects on knee, WOMAC is responsive index (Angst et al., 2001). but we used four scoring systems due to possible mistranslation of forms to patient language. Also MRI is useful method in evaluation of treatment and imaging results properly correlate with clinical symptoms (Raynauld et al., 2004).

Recently it has shown that intra articular injection of MSCs in OA affected joints is safe and promising therapeutically data support of the use of these stem cell for hyaline cartilage regeneration with better results in treated knee than untreated knee and control knee became worse at 5 years (Black et al., 2008; Davatchi et al., 2015; Delling et al., 2015; Emadedin et al., 2015; Guercio et al., 2012; Noth et al., 2008). In agreement with our results no adverse effects or evidence of tumor or neoplastic changes were reported in ASCs transplantation in previous study (Emadedin et al., 2015) treated with MSCs had better arthroscopic and histologic scores (Wakitani et al., 2002). The possible regenerative effect of injected MSCs may be by homing of MSC in injury site and then local signal lead to differentiation of ASCs into chondrocyte. Injected GFP-labeled MSCs into knee of rat were mobilized to the injured sites (Agung et al., 2006). However in clinical studies following of homing is not feasible. The other possible therapeutic effect may be because of immune-modulatory effects of ASCs on inflammation rather than their chondrogenic potential. This paracrine effect of MSCs was reported by others that is more important than the differentiation potential of the cells (Wu et al., 2011).

Conclusion

Autologous adipose mesenchymal stem cell injection might be resulted in increasing of knee function, alleviated of pain and improveement of physical activities in OA patients.

Conflicts of Interest

There is no conflict of interest In this study.

Acknowledgment

The authors would like to thank East Azerbaijan Science and Technology Park for financial support.

Author contribution

H. B; Study implementation, Data collection and analysis, writing the first draft of Paper.

H. SH, H. B: Study design and data analysis, editing and confirming the final draft of the paper.

H. SH, H. B, H. S, M. P: Study design, confirming the final draft of the paper .

Funding/Support

We would also like to express our gratitude to East Azerbaijan Science and Technology Park for financially supporting this research.

References

Agung, M., Ochi, M., Yanada, S., Adachi, N., Izuta, Y., Yamasaki, T. et al., (2006) Mobilization of bone marrow-derived mesenchymal stem cells into the injured tissues after intraarticular injection and their contribution to tissue regeneration. *Knee Surgery. Sports Traumatology, Arthroscopy*. *14* (12), 1307-1314.

Angst, F., Aeschlimann, A., Steiner, W. & Stucki, G. (2001) Responsiveness of the WOMAC osteoarthritis index as compared with the SF-36 in patients with osteoarthritis of the legs undergoing a comprehensive rehabilitation intervention. *Annals of the rheumatic diseases*. *60* (9), 834-840.

Berenbaum, F. (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and Cartilage*. *21* (1), 16-21.

Bernardo, M. E., Zaffaroni, N., Novara, F., Cometa, A. M., Avanzini, M. A., Moretta, A., et al. (2007) Human bone marrow–derived mesenchymal stem cells do not undergo transformation after long-term in vitro culture and do not exhibit telomere maintenance mechanisms. *Cancer Research*. *67* (19), 9142-9149.

Black, L. L., Gaynor, J., Adams, C., Dhupa, S., Sams, A. E., Taylor, R., et al. (2007) 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: Research in Applied Veterinary Medicine*. *9* (3), 192-200.

Blazquez, R., Sanchez-Margallo, F. M., de la Rosa, O., Dalemans, W., Álvarez, V., Tarazona, R., et al. (2014) Immunomodulatory potential of human adipose mesenchymal stem cells derived exosomes on in vitro stimulated T cells. *Frontiers in Immunology*, *5*, 556, DoI:10.3389/fimmu.2014.00556, Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220146/[Acessed on 4th July, 2017].

Buda, R., Vannini, F., Cavallo, M., Baldassarri, M., Luciani, D., Mazzotti, A., et al. (2013) One-step arthroscopic technique for the treatment of osteochondral lesions of the knee with bone-marrow-derived cells: three years results. *Musculoskeletal Surgery*. *97* (2), 145-151.

Buda, R., Vannini, F., Cavallo, M., Grigolo, B., Cenacchi, A. & Giannini, S. (2010) Osteochondral lesions of the knee: a new one-step repair technique with bone-marrow-derived cells. The *Journal of Bone and Joint Surgury*. *92* (Supplement 2), 2-11.

Chang, H., Do, B. R., Che, J. H., Kang, B. C., Kim, J. H., Kwon, E., et al. (2013) Safety of adipose-derived stem cells and collagenase in fat tissue preparation. *Aesthetic Plastic surgery*. *37* (4), 802-808.

Chang, J. W., Hung, S. P., Wu, H. H., Wu, W. M., Yang, A. H., Tsai, H. L., et al., (2011) Therapeutic effects of umbilical cord blood-derived mesenchymal stem cell transplantation in experimental lupus nephritis. *Cell Transplantation*. *20* (2), 245-257.

Chou, C. T. (2012) Why is biologic therapy useful in spondyloarthritis? knowledge from synovial immunopathologic studies of spondyloarthritis. *International Journal of Rrheumatic Diseases*. *15* (6), 507-511.

Colter, D. C., Class, R., DiGirolamo, C. M. & Prockop, D. J. (2000) Rapid expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow. *Proceedings of the National Academy of Sciences*.*97* (7), 3213-3218.

Colter, D. C., Sekiya, I. & Prockop, D. J. (2001) Identification of a subpopulation of rapidly self-renewing and multipotential adult stem cells in colonies of human marrow stromal cells. *Proceedings of the National Academy of Sciences*. *98* (14), 7841-7845.

Davatchi, F., Sadeghi Abdollahi, B., Mohyeddin, M. & Nikbin, B. (2015) Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients. *International journal of rheumatic diseases*. 19 (3), 219-225.

Delling, U., Brehm, W., Ludewig, E., Winter, K. & Jülke, H. (2015) Longitudinal Evaluation of Effects of Intra-Articular Mesenchymal Stromal Cell Administration for the Treatment of Osteoarthritis in an Ovine Model. *Cell transplantation*. *24* (11), 2391-2407.

Dominici, M. L. B. K., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F. C., Krause, D. S., et al. (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. *8* (4), 315-317.

Fransen, M., Bridgett, L., March, L., Hoy, D., Penserga, E. & Brooks, P. (2011) The epidemiology of osteoarthritis in Asia. *International Journal of Rheumatic Diseases*. *14* (2), 113-121.

Guercio, A., Marco, P., Casella, S., Cannella, V., Russotto, L., Purpari, G., et al., (2012) Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. *Cell Biology International*. *36* (2), 189-194.

Jo, C. H., Lee, Y. G., Shin, W. H., Kim, H., Chai, J. W., Jeong, E. C., et al. (2014) Intra-Articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells*. 32 (5), 1254-1266.

Liang, J. & Sun, L. (2015) Mesenchymal stem cells transplantation for systemic lupus erythematosus. *International Journal of Rheumatic Diseases*. *18* (2), 164-171.

Markides, H., Kehoe, O., Morris, R. H. & El Haj, A. J. (2013) Whole body tracking of superparamagnetic iron oxide nanoparticle-labelled cells–a rheumatoid arthritis mouse model. *Stem cell research & therapy*. *4* (5), 126: DOI 10.1186/scrt337, Available from https://www.ncbi.nlm.nih.gov/pubmed/24406201 [Accessed on 4 th July, 2017].

Mazor, M., Lespessailles, E., Coursier, R., Daniellou, R., Best, T. M. & Toumi, H. (2014) Mesenchymal stem-cell potential in cartilage repair: an update. *Journal of Cellular and Molecular Medicine*. 18 (12), 2340-2350.

Meza-Zepeda, L. A., Noer, A., Dahl, J. A., Micci, F., Myklebost, O. & Collas, P. (2008) High-resolution analysis of genetic stability of human adipose tissue stem cells cultured to senescence. *Journal of Cellular and Molecular Medicine*. 12 (2), 553-563.

Mohammadzadeh, A., Pourfathollah, A. A., Shahrokhi, S., Hashemi, S. M., Moradi, S. L. A. & Soleimani, M. (2014) Immunomodulatory effects of adipose-derived mesenchymal stem cells on the gene expression of major transcription factors of T cell subsets. *International Immunopharmacology*, *20* (2), 316-321.

Nakagawa, Y., Muneta, T., Kondo, S., Mizuno, M., Takakuda, K., Ichinose, S., et al. (2015) Synovial mesenchymal stem cells promote healing after meniscal repair in microminipigs. *Osteoarthritis and Cartilage*. *23* (6), 1007-1017.

Nauta, A. J., Westerhuis, G., Kruisselbrink, A. B., Lurvink, E. G., Willemze, R. & Fibbe, W. E. (2006) Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting. *Blood*, *108* (6), 2114-2120.

Park, H. J., Kim, S. S., Lee, S. Y., Park, N. H., Park, J. Y., Choi, Y. J.,et al. (2013) A practical MRI grading system for osteoarthritis of the knee: association with Kellgren–Lawrence radiographic scores. *European Journal of Radiology*. *82* (1), 112-117.

Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D.,et al. (1999) Multilineage potential of adult human mesenchymal stem cells.*Science*. *284* (5411), 143-147.

Raynauld, P., Martel-Pelletier, J., Berthiaume, M. J., Labonté, F., Beaudoin, G., de Guise, J. A., et al. (2004) Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis & Rheumatism*. *50* (2), 476-487.

Schelbergen, R. F., van Dalen, S., Ter Huurne, M., Roth, J., Vogl, T., Noel, D., et al. (2014) Treatment efficacy of adipose-derived stem cells in experimental osteoarthritis is driven by high synovial activation and reflected by S100A8/A9 serum levels. Osteoarthritis and Cartilage. 22 (8), 1158-1166.

Sekiya, I., Vuoristo, J. T., Larson, B. L. & Prockop, D. J. (2002) In vitro cartilage formation by human adult stem cells from bone marrow stroma defines the sequence of cellular and molecular events during chondrogenesis. *Proceedings of the National Academy of Sciences*. *99* (7), 4397-4402.

Sen, A., Lea-Currie, Y. R., Sujkowska, D., Franklin, D. M., Wilkison, W. O., Halvorsen, Y. D. C.,et al. (2001) Adipogenic potential of human adipose derived stromal cells from multiple donors is heterogeneous. *Journal of Cellular Biochemistry*. 81 (2), 312-319.

Shafaei, H. & Baghernezhad, H. (2016) Ultrasound Effect on Gene Expression of Sex Determining Region Y-box 9 (SOX9) and Transforming Growth Factor β Isoforms in Adipose Stem Cells. *Zahedan Journal of Research in Medical Sciences*. 18 (4), e6465. doi: 10.17795/zjrms-6465. Available from: http://zjrms.com/en/articles /6465.html [Accessed on 4 th July, 2017].

Shafaei, H., Esfandiari, E., Esmaeili, A., Razavi, S., Hashemibeni, B., Esfahani, M. H. N., et al. (2013) Optimizing a novel method for low intensity ultrasound in chondrogenesis induction. *Advanced Biomedical Research*. DOI: 30; 2: 79. doi: 10.4103/2277-9175, Avalable from: https://www.ncbi. nlm.nih.gov/pubmed/24520547 [Accessed on 4 th July, 2017].

Shafaei, H., Esmaeili, A., Mardani, M., Razavi, S., Hashemibeni, B., Nasr-Esfahani, M. H., et al. (2011) Effects of human placental serum on proliferation and morphology of human adipose tissue-derived stem cells. *Bone Marrow Transplantation*. *46* (11), 1464-1471.

Shi, C. (2012) Recent progress toward understanding the physiological function of bone marrow mesenchymal stem cells. *Immunology*. *136* (2), 133-138.

Singer, N. G. & Caplan, A. I. (2011) Mesenchymal stem cells: mechanisms of inflammation. *Annual Review of Pathology: Mechanisms of Disease*. *6*, 457-478.

ter Huurne, M., Schelbergen, R., Blattes, R., Blom, A., de Munter, W., Grevers, L. C., et al. (2012) Antiinflammatory and chondroprotective effects of intraarticular injection of adipose-derived stem cells in experimental osteoarthritis. *Arthritis & Rheumatism*. 64 (11), 3604-3613.

Tuan, R. S. (2006) Stemming cartilage degeneration: adult mesenchymal stem cells as a cell source for articular cartilage tissue engineering. *Arthritis & Rheumatism*. *54* (10), 3075-3078.

Vega, A., Martín-Ferrero, M. A., Del Canto, F., Alberca, M., García, V., Munar, A., et al. (2015) Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation*. *99* (8), 1681-1690.

Giai Via, A., Frizziero, A. & Oliva, F. (2012) Biological properties of mesenchymal Stem Cells from different sources. *MLTJ Muscles, Ligaments and Tendons Journal*. *2* (3), 154-162.

Wakitani, S., Imoto, K., Yamamoto, T., Saito, M., Murata, N. & Yoneda, M. (2002) Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis and Cartilage*. *10* (3), 199-206.

Wong, K. L., Lee, K. B. L., Tai, B. C., Law, P., Lee, E. H. & Hui, J. H. (2013) Injectable Cultured Bone Marrow–

Derived Mesenchymal Stem Cells in Varus Knees With Cartilage Defects Undergoing High Tibial Osteotomy: A Prospective, Randomized Controlled Clinical Trial With 2 Years' Follow-up. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. *29* (12), 2020-2028.

Wu, L., Leijten, J. C., Georgi, N., Post, J. N., van Blitterswijk, C. A. & Karperien, M. (2011) Trophic effects of mesenchymal stem cells increase chondrocyte proliferation and matrix formation. *Tissue Engineering Part A*. 17 (9-10), 1425-1436.

Yelin, E., Murphy, L., Cisternas, M. G., Foreman, A. J., Pasta, D. J. & Helmick, C. G. (2007) Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. *Arthritis & Rheumatism*. 56 (5), 1397-1407.

Zuk, P. A., Zhu, M., Ashjian, P., De Ugarte, D. A., Huang, J. I., Mizuno, H., et al. (2002) Human adipose tissue is a source of multipotent stem cells. *Molecular Biology of the Cell*. 13 (12), 4279-4295.

How to cite this article: Shafaei, H., Bagernezhad, H., Soliemanlou, H., Poureisa, M., Transplantation of Autologous Adipose Derived Mesenchymal Stem Cells for Improvement of Quality of Life in Osteoarthritis Patients. IJMPP. 2016; 1 (3): 109-116.