Scientific Research Publishing

Open Journal of Regenerative Medicine, 2023, 12, 85-96
https://www.scirp.org/journal/ojrm
ISSN Online: 2169-2521
ISSN Print: 2169-2513

Clinical and Magnetic Resonance Image Changes of Platelet-Rich Plasma Therapy in Combination with Human Mesenchymal Stem Cells from Autologous Adipose Tissue for Knee Osteoarthritis Treatment

Truong Sinh Cao, Thanh Huyen Le Thi

Vinh Medical University Hospital, Vinh City, Vietnam
Email: caotruongsinh@gmail.com, lehuyenvinh@gmail.com

How to cite this paper: Cao, T.S. and Le Thi, T.H. (2023) Clinical and Magnetic Resonance Image Changes of Platelet-Rich Plasma Therapy in Combination with Human Mesenchymal Stem Cells from Autologous Adipose Tissue for Knee Osteoarthritis Treatment. *Open Journal of Regenerative Medicine*, **12**, 85-96.
https://doi.org/10.4236/ojrm.2023.122006

Received: April 29, 2023
Accepted: June 22, 2023
Published: June 25, 2023

Abstract

Objective: To evaluate the efficacy based on clinical symptom and on magnetic resonance image of platelet-rich plasma therapy in combination with mesenchymal stem cells from autologous adipose tissue for knee osteoarthritis treatment. **Patients and Method:** 30 patients including 26 females and 4 males; correspondingly, 60 knee joints were diagnosed with osteoarthritis with stages II - III of Kellgren and Lawrence, their mean age was 58.63 ± 11.11. All were injected with autologous platelet-rich plasma that was extracted by PRP set, APC 30 PRP PRCEDURE PRAK and autologously extracted mesenchymal stem cells from abdominal adipose tissue using the ADI-25-01 ADIPOSEPRCEDURE PRAK of USA. **Results**: After 12 months: the pain level according to VAS score at the right knee joint was decreased from 6.0 ± 1.28 before treatment to 1.9 ± 0.3; VAS score at the left knee joint was decreased from 6.43 ± 1.19 to 2.25 ± 0.43. Total Lequene score at right knee joint was decreased from 16.04 ± 1.57 before treatment to 4.31 ± 1.04, at left knee joint was decreased from 17.52 ± 1.74 before treatment to 5.15 ± 1.48. Total WOMAC score at right knee joint was decreased from 55.93 ± 5.56 to 10.37 ± 1.56; at left knee joint was decreased from 53.97 ± 5.57 to 10.07 ± 1.59. There were 86.77% joints with cartilage thickness change and the patellar cartilage thickness was increased from 1.56 ± 0.09 mm before treatment to 1.65 ± 0.09 mm. **Conclusion**: The treatment of knee osteoarthritis by platelet-rich plasma therapyin combination with mesenchymal stem cells from autologous adipose tissue is effective in reducing pain, improving patient's mobility and walking function, reforming articular cartilage thickness on mag-

netic resonance image.

Keywords

Platelet-Rich Plasma, Mesenchymal Stem Cells, Autologous Adipose Tissue, Knee Osteoarthritis

1. Introduction

Osteoarthritis of the knee is a degenerative disease that can be classified into primary and secondary knee osteoarthritis. Primary knee osteoarthritis is a disease of unknown cause which is mainly related to the aging process. Secondary knee osteoarthritis with identifiable etiology includes endocrine disorders, anatomical abnormalities, post-traumatic arthritis, and septic arthritis [1]. Currently, the treatment of knee osteoarthritis is limited. There are several conventional therapies for knee osteoarthritis which include physical therapies, non-steroidal anti-inflammatory pain relievers, drugs which slow down the degenerative process such as glucosamine, joint lubricant supplements such as hyaluronic acid, platelet-rich plasma (PRP) or intra-articular corticosteroid injections, traditional medicine measures and arthroscopic knee surgery [2] [3]. All of the above-mentioned treatments can only relieve symptoms which do not restore articular cartilage. When degeneration is more severe, total knee replacement surgery is required [2] [3].

Autologous intra-articular platelet-rich plasma (PRP) injection is a new method in the treatment of osteoarthritis. Platelet-rich plasma has been shown to contain growth factors, in which, TGF-β (Transforming Growth Factor-β) plays an important role to increase the base for chondrocytes' growth, the proliferation of chondrocytes and the regulation of proteoglycan synthesis [4].

In the world, in the past few years, many studies have shown that autologous intra-articular PRP injection is an effective therapy in the treatment of knee osteoarthritis [5]. This has been proven by many studies around the world.

Mesenchymal stem cells (MSCs) have the potential for self-renewal and multidirectional differentiation [6] which can exert therapeutic effects on various diseases through directed differentiation [7], regulate immune system [8], anti-inflammatory, progenitor [9], improve microenvironment [10] and promote regeneration [10]. MSCs have been used in the treatment of various diseases [11], such as ovarian failure, Parkinson's disease, nervous system damage and amyotrophic lateral sclerosis (ALS). MSCs therapy can be applied in the treatment of knee osteoarthritis and has shown encouraging results [7] [11].

Recent researches have shown the presence of stem cells in adipose tissues which are known as adipose-derived stem cells (ADSCs). These cells are referred to as mesenchymal stem cells (MSCs) that expose a number of special characteristics. They participate in the fibroblast-like surface formation and differentiate

into osteoblasts, cartilage, and adipocytes [12]. Many researchers have been conducted over the last few years which include preclinical and clinical trials to perform the treatment of cartilage injuries and knee osteoarthritis.

Stem cell therapy is a milestone in regenerative medicine for the treatment of knee osteoarthritis. MSCs have not been widely adopted because of cell source problems and expensive cell cultures. Furthermore, its efficacy and safety are being explored [13].

Therefore, the combination therapy of platelet-rich plasma with mesenchymal stem cells from autologous adipose tissue will promote both types of effects: 1) TGF-β plays the roleincreasing the substrate for chondrocyte's growth, proliferation of chondrocytes, regulation of proteoglycan synthesis; 2) mesenchymal stem cells increase cartilage regeneration, repair the organization of damaged cartilage, regenerate subchondral bone to heal joints.

Therefore, the aim of this study was to evaluate the efficacy of platelet-rich plasma therapy combined with autologous adipose tissue mesenchymal stem cells in the treatment of knee osteoarthritis.

2. Patients and Method

2.1. Study Setting and Design

The research is a randomized clinical trial design which evaluates the results by comparing those before and after treatment 1 week, 1 month, 3 months, 6 months and 12 months according to clinical rating scales and changes of cartilage thickness on magnetic resonance images.

The study was implemented at Vinh Medical University Hospital, from June 2020 to February 2021.

2.2. Study Population

In the study, there are selected 30 patients including 26 females and 4 males; correspondingly, 60 knee joints were diagnosed with osteoarthritis according to the American College of Rheumatology (ACR) [14] who are at the mean age of 58.63 ± 11.11, disease duration is from 5.3 ± 4.6 years which.

The inclusion criteria:

- Patients were diagnosed the osteoarthritis at stages II - III according to the classification standard of Kellgren and Lawrence.
- The platelet count of patients was normal (≥150,000/mm^3).

The exclusion criteria: the patients were at stage I, stage IV of knee osteoarthritis; have severe anemia and platelets < 150,000/mm^3, have secondary knee osteoarthritis, post-traumatic, infectious degeneration, cancer or have contraindications to surgery.

Patients received ultrasound and magnetic resonance imaging to evaluate input data before injecting platelet-rich plasma in combination with mesenchymal stem cells from autologous adipose tissue.

2.3. Study Materials

Autologous platelet-rich plasma was extracted from 30 ml of peripheral blood according to the process of PRP set, APC 30 PRP PRCEDURE PRAK and the Harvest smart extraction system of TERUMO BCT-USA, following an 8-step process with a count of 5 ml (platelet count is up to 1.5 million/ml). This 5ml platelet-rich plasma was contained in a clean, sterile cup that had ready the activating agent.

Autologous mesenchymal stem cells were obtained from the patient's abdominal adipose tissue and was extracted by a set of ADI-25-01 ADIPOSEPRCEDURE PRAK (2 syringes, 25 ml in each syringe) and by the Harvest Smart Stem Cell Extractor of TERUMO BCT-USA company according to the 13-step process, the obtained count is 10 ml with 1.6 million cells.

Two products with the platelet-rich plasma and the mesenchymal stem cells were mixed together in a clean, sterile cup (15 ml including: 5 ml of the platelet-rich plasma and 10 ml of the mesenchymal stem cells) and then were equally divided into 2 single-use syringes, each 7.5ml syringe was injected into a knee joint.

All procedures are carried out in the operating room, extraction room, and sterile injection room.

2.4. Criteria for Evaluating Treatment Results

1) Evaluation of improvement in pain symptoms and knee function: before treatment, in the first week, in 1 month, 3 months, 6 months and 12 months after injection.

Using the rating scale: VAS (Visual Analog Scale); LEQUESNE; WOMAC (Western Ontario and McMaster Universities Osteoarthritis).

+ VAS scale is with 4 pain levels, in which from 1 to 3 is mild pain, from 4 to 6 is moderate pain, from 7 to 9 is severe pain (very painful), 10 is unbearable pain.

+ LEQUESNE scale has totally 24 points: Severe ≥ 14 points; Very heavy 11-13 points; Heavy: 8-10 points; Average 5 - 7 points; Mild: 0 - 4 points.

+ WOMAC scale includes general WOMAC, pain WOMAC, stiffness WOMAC, mobility WOMAC. The maximum score of WOMAC scale is 96 points, in which pain WOMAC is 20, stiffness WOMAC is 8, mobility WOMAC is 68.

2) Evaluation of the results on magnetic resonance image aftertreatment12 months versus before treatment.

- There are a number of patients with changes in cartilage thickness on magnetic resonance image.
- The cartilage thickness is changed after treatment: the thickness of articular cartilage is measured at the positions of internal condyle, external condyle of the femur, intercondylar, medial tibial plateau, lateral tibial plateau, middle tibial plateau, patella.

2.5. Statistical Analysis

The data was processed using SPSS 20.0 software; qualitative variables are expressed as frequency and proportions, quantitative variables are expressed as mean ± standard deviation. The Chi^2 test was used to compare the 2 proportions and the T test was to compare the 2 means. The difference was statistically significant when $p < 0.05$.

3. Results

3.1. Baseline Characteristics

In our study sample, the number of male patients including 4 people accounted for 13.3%. The number of female patients accounted for 86.7% and the number of knee osteoarthritis with stage II was 20% and stage III damage accounted for 80%. Baseline characteristics of patients were summarized in Table 1.

3.2. Evaluation of Treatment Results

3.2.1. Evaluation of Treatment Results through the VAS Scale

The average VAS pain score of right knee before treatment was 6 ± 1.28 which decreased to 2.70 ± 0.46 after 6 months of treatment and to 1.90 ± 0.30 after 12 months of treatment. This improvement was statistically significant with $p < 0.001$.The mean VAS pain score of the left knee joint before treatment was 6.43 ± 1.19, which decreased to 3.5 ± 0.51 after 6 months of treatment and to 2.25 ± 0.43 after 12 months of treatment. This improvement was statistically significant with $p < 0.001$.The results were presented in Table 2.

Table 1. Baseline characteristics.

Variable	Male	Female	Total
Number of patients	4 (13.3%)	26 (86.7%)	30 (100%)
Number of joints	8 (13.3)	52 (86.7)	60 (100%)
Age	54.25 ± 9.57	59.31 ± 11.34	58.63 ± 11.11
Disease duration	3.00 ± 1.15	5.69 ± 4.88	5.3 ± 4.6
Height	1.63 ± 0.03	1.55 ± 0.05	1.56 ± 0.05
Weight	64.25 ± 7.27	53.5 ± 7.2	54.93 ± 8.00
BMI (kg/m^2)	24.0 ± 2.33	22.1 ± 2,2	22.3 ± 2.28
Obesity	0	2 (6.7%)	2 (6.7%)
Diabetes	1 (3.3%)	2 (6.7%)	3 (10%)
Hypertension	2 (6.7%)	4 (13.3%)	6 (20%)
Degenerative stage according to Kellgren and Lawrence classification			
Stage II	2 (3.3%)	10 (16.7%)	12 (20%)
Stage III	6 (10%)	42(70%)	48 (80%)
Platelet count	220.25 ± 53.7	275.23 ± 90.44	267.9 ± 87.81

Table 2. Evaluation of treatment results of bilateral knee joints through the VAS scale.

Variable	Before treatment	After treatment					p(b-a)
		1 week	1 month	3 months	6 months	12 months	
Knee joint R	6.0 ± 1.28	6.37 ± 1.16	5.5 ± 0.68	4.1 ± 0.48	2.7 ± 0.46	1.9 ± 0.3	0.00
Knee joint L	6.43 ± 1.19	6.73 ± 0.58	5.9 ± 0.55	4.4 ± 0.62	3.5 ± 0.51	2.25 ± 0.43	0.00

p(b-a): p value of before and after treatment.

3.2.2. Evaluation of Treatment Results Using the Lequesne Scale

After 12 months of treatment, the mean LEQUESNE scale of right knee joint was improved, decreasing from 16.04 ± 1.57 to 4.31 ± 1.04 with statistical significance with $p < 0.001$. After 12 months of treatment, the average LEQUESNE scale of the left knee joint was improved, decreasing from 17.52 ± 1.74 to 5.15 ± 1.48 with statistical significance with $p < 0.001$.

The changes Lequesne scale after treatment 12 months versus before treatment were showed in Table 3.

3.2.3. Evaluation of Treatment Results by WOMAC Scale

Overall WOMAC scale of right knee joint was decreased from 55.93 ± 5.56 to 10.37 ± 1.56 after 12 months of treatment. There was a remarkable improvement in the scales of pain WOMAC, mobility WOMAC, and stiffness WOMAC after the treatment. Results were presented in Table 4.

Overall WOMAC scale of left knee joint was decreased from 53.97 ± 5.57 to 10.07 ± 1.56 after 12 months of treatment. There was a remarkable improvement in the scales of pain WOMAC, mobility WOMAC, and stiffness WOMAC after the treatment. Results were showed in Table 5.

3.2.4. Evaluation of the Results Based on the Change of Cartilage Thickness on Magnetic Resonance Image

The surface of articular cartilage on magnetic resonance in the above mentioned positions were improved after 12 months of treatment, the difference was statistically significant. The changes of cartilage thickness on magnetic resonance were showed in Table 6.

After 12 months of treatment, there were 8 joints (13.33%) that did not change the total thickness of cartilage at the measured locations (lower end of femur, upper end of tibial, patella joint), found in degenerative joints of stage III. Results were presented in Table 7.

4. Discussion

4.1. Evaluation of Treatment Results

Clinical Evaluation of Treatment Results

After 12 months of treatment with a mixture of platelet-rich plasma in combination with mesenchymal stem cells from autologous adipose tissue, we found that the patients had reduced pain, improved motor function, and improved signs of knee stiffness which was as follows.

Table 3. Evaluation of treatment results of knee joints by Lequesne scale.

Variable	Before treatment	After treatment					p(b-a)
		1 week	1 month	3 months	6 months	12 months	
Knee joint R	16.04 ± 1.57	17.03 ± 0.73	15.51 ± 1.64	12.53 ± 2.17	6.0 ± 1.38	4.31 ± 1.04	0.00
Knee joint L	17.52 ± 1.74	18.13 ± 2.02	16.35 ± 1.81	13.55 ± 1.95	7.02 ± 1.27	5.15 ± 1.48	0.00

Table 4. Evaluation of treatment results of the right knee joint through the WOMAC scale.

Variable		Before treatment	After treatment					p(b-a)
			1 week	1 month	3 months	6 months	12 months	
General WOMAC	$\overline{X}$	55.93	54.00	43.93	30.53	25.67	10.37	0.00
	SD	5.56	5.60	4.64	3.39	3.44	1.56	
Pain WOMAC	$\overline{X}$	12.47	12.17	10.03	6.30	4.20	2.17	0.00
	SD	2.47	2.90	2.70	2.17	1.52	0.95	
Mobility WOMAC	$\overline{X}$	40.00	38.37	31.70	23.17	20.57	7.33	0.00
	SD	3.86	3.99	2.72	2.27	2.40	0.99	
Stiffness WOMAC	$\overline{X}$	3.47	3.47	2.20	1.07	0.90	0.87	0.00
	SD	1.14	1.14	0.61	0.45	0.40	0.34	

Table 5. Evaluation of treatment results of the left knee joint through the WOMAC scale.

Variable		Before treatment	After treatment					p(b-a)
			1 week	1 month	3 months	6 months	12 months	
General WOMAC	$\overline{X}$	53.97	55.00	42.93	33.90	19.43	10.07	0.00
	SD	5.57	5.60	4.64	4.51	3.51	1.59	
Pain WOMAC	$\overline{X}$	12.17	12.17	11.03	9.30	4.20	3.17	0.00
	SD	2.90	2.90	2.70	2.16	1.51	0.95	
Mobility WOMAC	$\overline{X}$	38.33	39.37	29.70	23.53	14.57	6.33	0.00
	SD	3.95	3.99	2.73	3.44	2.40	0.99	
Stiffness WOMAC	$\overline{X}$	3.47	3.47	2.20	1.07	0.67	0.57	0.00
	SD	1.14	1.14	0.61	0.45	0.55	0.50	

Table 6. Change in thickness of articular cartilage on MRI.

Position	Time	Measurement position (mm)					
		External condyle	p(b-a)	Internal condyle	p(b-a)	Intercondylar	p(b-a)
Lower end of femur	Before treatment	1.40 ± 0.10	0.00	1.35 ± 0.16	0.00	1.57 ± 0.11	0.00
	After treatment	1.46 ± 0.11		1.42 ± 0.15		1.64 ± 0.12	
Upper end of femur	Before treatment	1.39 ± 0.10	0.00	1.35 ± 0.16	0.00	1.56 ± 0.12	0.00
	After treatment	1.45 ± 0.12		1.43 ± 0.16		1.63 ± 0.12	
Patellofemoral joint	Before treatment	1.56 ± 0.09					0.00
	After treatment	1.65 ± 0.09					

p(b-a): p-value before and after treatment.

Table 7. Number of joints with changes in cartilage thickness on MRI.

Variabilities	Stage II		Stage III		Overall	
	n	%	n	%	n	%
Unchanged joints	0	0	8	100	8	13.33
Changed joints	12	23.07	40	76.92	52	86.77

The patient's joint pain relief was shown by the mean of VAS score at the right knee, the left knee joint decreased significantly compared to before treatment. This improvement started after 1 month, 6 months and was most pronounced after 12 months.

Patients improved signs of stiffness, the ability to walk, go up and down stairs, squat as shown by the mean of LEQUESNE score of the right knee and the left knee all decreased significantly compared to before treatment with $p < 0.001$.

The WOMAC score of both right and left knee decreased significantly after 12 months of treatment. In which, there was a significant improvement in the WOMAC pain scale, WOMAC movement score, and WOMAC joint stiffness score after the treatment.

In this regard, some studies also showed similar results.

In the study by Bui *et al.* (2014) on 21 patients with stage II-III knee osteoarthritis treated with adipose tissue stem cell therapy combined with platelet-rich plasma. The results showed that all patients had improved knee function after 8.5 months of treatment. The VAS score of pain decreased from 7.6 ± 0.5 to 3.5 ± 0.7 after 3 months and 1.5 ± 0.5 score after 6 months [15].

However, the novelty in our study versus the study by Bui *et al.* were that we used the USA Harvest smart extraction system to separate the platelet-rich plasma and the mesenchymal stem cells with amount of platelet about 1.5 million/1ml and 1.6 million mesenchymal stem cells/10ml.

Similarly, Tran *et al.* (2016) evaluated the effect of autologous adipose stem cell therapy on 42 patients with stage I-II knee osteoarthritis compared with the control group treated with intramuscular hyaluronic acid, the results showed that the intervention group had lower VAS and WOMAC scores than the control group. After 12 months of follow-up, VAS score decreased from 6.16 ± 1.06 to 2.26 ± 1.04 and WOMAC decreased from 54.26 ± 10.61 to 16.7 ± 9.47 points with $p < 0.05$ [16].

Another study treated knee osteoarthritis with autologous adipose tissue stem cell therapy by Pham (2017) showing that before treatment all the patients had pain when climbing stairs (100%). Then, after 6 months of treatment, the rate of knee pain when climbing stairs was 69.4% and reduced to 48.6% after 1 year of treatment. Furthermore, before treatment 83.3% of patients felt pain of their knees when standing for more than 30 minutes, but after 1 year of treatment, there were no cases of pain when standing [17].

Recent meta-analysis by Yancheng Song and colleagues (2020) in China for

the treatment of knee osteoarthritis with mesenchymal stem cells. The study based on the results of 15 controlled clinical trials, 2 longitudinal follow-up studies, and 2 cohort studies with a total of 484 joints. The results showed that stem cell therapy for knee osteoarthritis significantly reduced the VAS score after 12 months of treatment and the WOMAC score significantly decreased after 6 months [13].

4.2. Evaluation of Treatment Outcomes Based on MRI

The results of our study depicted that all positions of the surface of articular cartilage on MRI has improved. Specially, the lateral condyle of the lower femoral increased from 1.40 ± 0.10 mm before treatment to 1.46 ± 0.11 mm after 12 months of treatment. The surface of articular cartilage of the medial condyle in the lower femoral bone increased from 1.35 ± 0.16 to 1.42 ± 0.15 and the surface of the condyle in the head of the tibia increased from 1.35 ± 0.16 to 1.43 ± 0, 16 after 1 year of treatment. The surface of inferior femoral condylar increased from 1.57 ± 0.11 to 1.64 ± 0.12 after 1 year of treatment. The surface of supracondylar on the tibia increased from 1.56 ± 0.12 to 1.63 ± 0.12 after 1 year of treatment. All 3 measurement positions of the kneecap, there was an improvement from 1.56 ± 0.09 to 1.65 ± 0.09 after 1 year of treatment (**Table 6**). After 12 months of treatment, remaining 8 stage-III knees (13.33%) had no change in total cartilage thickness at measurement sites at the lower head of femoral, the upper tibia and the patellar joint (**Table 3**).

Several studies have used parameters on MRI such as the change of cartilage thickness to evaluate the effectiveness of autologous adipose tissue stem cell therapy or platelet-rich plasma therapy in the treatment of knee osteoarthritis.

Study by Tran *et al.* (2016) showed that there was an improvement in articular cartilage thickness on MRIat 4 positions which were medial tibial plateau, lateral tibial plateau, medial condyle, and lateral condyle of the femur at the time of 6 months and 1 year follow-up but there was no statistical significance ($p > 0.05$). This may be because the majority of study subjects are mild knee osteoarthritis (stage I-II), so the difference was not significant [17].

Another study by Pham (2017) on treatment of primary osteoarthritis with autologous adipose stem cell therapy, the findings depicted that: the thickness of articular cartilage at the femoral condyle increased from 1.52 ± 0.57 mm before treatment to 1.61 ± 0.59 mm after 6 months and to 1.65 ± 0.56 mm after 1 year. The thickess of articular cartilage at the tibial plateau from 1.59 ± 0.59 mm before treatment to 1.68 ± 0.59 mm after 6 months and to 1.75 ± 0.57 mm after 1 year [16].

In 2012, Yong-Gon Koh and colleagues evaluated the clinical and imaging results in 18 patients with knee osteoarthritis treated with autologous adipose tissue stem cells at the lower-kneecap. The authors evaluated the improvement of articular cartilage by the WORMS (whole organ magnetic resonance imaging score) scale, the findings showed that the WORMS score decreased from 60.0 to 48.3 points ($p < 0.01$). In particular, this study also showed that there was a posi-

tive correlation between the improvement of clinical symptoms and images of knee osteoarthritis with the amount of injected stem cells. The authors concluded that adipose tissue stem cells were a valuable source of cells in the treatment of articular cartilage damage [18] [19].

In 2016, a study by Liang-jing Lu and colleagues on 18 patients with bilateral knee osteoarthritis who were treated with adipose tissue stem cell therapy with 3 injections: before treatment, after 3 weeks and after 48 weeks, the results showed that the volume of articular cartilage of the femur, tibia and patella increased steadily during the entire follow-up period, which was statistically significant after 6 months, 12 months and 18 months [20].

In summary, all above researches have depicted that the adipose tissue stem cells was effective in repairing cartilage damage.

5. Conclusion

The treatment of knee osteoarthritis by platelet-rich plasma therapy in combination with mesenchymal stem cells from autologous adipose tissue was effective in reducing pain, improving patient's mobility and walking function through scale reductions of VAS, LEQUENE, WOMAC comparing with before treatment, improving significantly the thickness of articular cartilage on magnetic resonance image.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Koh, Y.G. and Choi, Y.J. (2012) Infrapatellar Adipose Pad-Derived Mesenchymal Stem Cell Therapy for Knee Osteoarthritis. *The Knee*, **19**, 902-907. https://doi.org/10.1016/j.knee.2012.04.001

[2] Freitag, J., Bates, D., Boyd, R., Shah, K., Barnard, A., Huguenin, L., *et al.* (2016) Mesenchymal Stem Cell Therapy in the Treatment of Osteoarthritis: Reparative Pathways, Safety and Efficacy—A Review. *BMC Musculoskeletal Disorders*, **17**, Article No. 230. https://doi.org/10.1186/s12891-016-1085-9

[3] Jones, I.A., Togashi, R., Wilson, M.L., Heckmann, N. and Vangsness, C.T. (2019) Intra-Articular Treatment Options for Knee Osteoarthritis. *Nature Reviews Rheumatology*, **15**, 77-90. https://doi.org/10.1038/s41584-018-0123-4

[4] El-Sharkawy, H., Kantarci, A., Deady, J., Hasturk, H., *et al.* (2007) Platelet-Rich Plasma: Growth Factors and Pro- and Anti-Iflammatory Properties. *Journal of Periodontology*, **78**, 661-669. https://doi.org/10.1902/jop.2007.060302

[5] Sampson, S., Reed, M., Silvers, H., Meng, M. and Mandelbaum, B. (2010) Injection of Platelet-Rich Plasma in Patients with Primary and Secondary Knee Osteoarthritis: A Pilot Study. *American Journal of Physical Medicine & Rehabilitation*, **89**, 961-969. https://doi.org/10.1097/PHM.0b013e3181fc7edf

[6] Coulson-Thomas, V.J., Coulson-Thomas, Y.M., Gesteira, T.F. and Kao, W.Y. (2016) Extrinsic and Intrinsic Mechanisms by Which Mesenchymal Stem Cells Suppress

the Immune System. *The Ocular Surface*, **14**, 121-134. https://doi.org/10.1016/j.jtos.2015.11.004

[7] Ryu, J.S., Jung, Y.H., Cho, M.Y., Yeo, J.E., Choi, Y.J., Kim, Y.I. and Koh, Y.G. (2014) Co-Culture with Human Synovium-Derived Mesenchymal Stem Cells Inhibits Inflammatory Activity and Increases Cell Proliferation of Sodium Nitroprusside-Stimulated Chondrocytes. *Biochemical and Biophysical Research Communications*, **447**, 715-720. https://doi.org/10.1016/j.bbrc.2014.04.077

[8] Barry, F. and Murphy, M. (2013) Mesenchymal Stem Cells in Joint Disease and Repair. *Nature Reviews Rheumatology*, **9**, 584-594. https://doi.org/10.1038/nrrheum.2013.109

[9] Mamidi, M.K., Das, A.K., Zakaria, Z. and Bhonde, R. (2016) Mesenchymal Stromal Cells for Cartilage Repair in Osteoarthritis. *Osteoarthritis and Cartilage*, **24**, 1307-1316. https://doi.org/10.1016/j.joca.2016.03.003

[10] Caplan, A.I. (2013) Adult Mesenchymal Stem Cells for Tissue Engineering Versus Regenerative Medicine. *Journal of Cellular Physiology*, **213**, 341-347. https://doi.org/10.1002/jcp.21200

[11] Grässel, S. and Lorenz, J. (2014) Tissue-Engineering Strategies to Repair Chondral and Osteochondral Tissue in Osteoarthritis: Use of Mesenchymal Stem Cells. *Current Rheumatology Reports*, **16**, Article No. 452. https://doi.org/10.1007/s11926-014-0452-5

[12] Zuk, P.A., Zhu, M., Mizuno, H., Huang, J., Futrell, J.W., Katz, A.J., Benhaim, P., Lorenz, H.P. and Hedrick, M.H. (2001) Multilineage Cells from Human Adipose Tissue: Implications for Cell-Based Therapies. *Tissue Engineering*, **7**, 211-228. https://doi.org/10.1089/107632701300062859

[13] Song, Y., Zhang, J., Xu, H., Lin, Z., Chang, H., Liu, W. and Kong, L. (2020) Mesenchymal Stem Cell in Knee Osteoarthritis Treatment: A Sytematic Review and Meta-Analysis. *Journal of Orthopaedic Translation,* **24**, 121-130. https://doi.org/10.1016/j.jot.2020.03.015

[14] Srikulmontree, T. (2012) Osteoarthritis. The American College of Rheumatology, Georgia (U.S. State).

[15] Van Pham, P., Bui, K.H.T., Duong, T.D., Nguyen, N.T., Nguyen, T.D., Mai, V.T., *et al.* (2014) Symptomatic Knee Osteoarthritis Treatment Using Autologous Adipose Derived Stem Cells and Platelet-Rich Plasma: A Clinical Study. *Biomedical Research and Therapy*, **1**, Article No. 2. https://doi.org/10.7603/s40730-014-0002-9

[16] Hoai, T.P. (2017) Study on Treatment Results of Primary Knee Osteoarthritis with Autologous Adipose Tissue Stem Cell Therapy. Doctoral Thesis in Medicine, Hanoi Medical University, Hanoi.

[17] Viet, T.T., *et al.* (2015) Research on the Application of Autologous Stem Cells in the Treatment of Osteoarthritis. State-Level Independent Project, Military Medical Academy.

[18] Koh, Y.-G., Jo, S.-B., Kwon, O.-R., *et al.* (2012) Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis. *The Journal of Arthroscopic and Related Surgery*, **29**, 748-755. https://doi.org/10.1016/j.arthro.2012.11.017

[19] Koh, Y.-G., Choi, Y.-J., Kwon, S.-K., Kim, Y.-S. and Yeo, J.-E. (2013) Clinical Results and Second-Look Arthroscopic Findings after Treatment with Adipose-Derived Stem Cells for Knee Osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, **23**, 1308-1316. https://doi.org/10.1007/s00167-013-2807-2

[20] Lu, L.-J., *et al.* (2016) Treatment with Human Adipose-Derived Mesenchymal Stem

Cells for Knee Osteoarthritis. NCT 021626693. *The* 18*th Congress of Asia Pacific League of Association for Rheuatology* (*APLAR* 2016), Shanghai, 26-29 September, 2016.