Acta Biomed 2022; Vol. 93, N. 1: e2022135 DOI: 10.23750/abm.v93i1.11102

Review

Minimally manipulated adipose derived mesenchymal stromal cells and osteoarthritis: A narrative review

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Abstract. Human mesenchymal stromal cells (MSCs) have increasingly been used to treat osteoarthritis (OA) related pain and dysfunction, due to their capacity for regeneration and anti-inflammatory effects. Adipose-derived MSCs are characterized by their abundance, ease of access, easy isolation procedures, high lipoaspirate stromal cell production, quicker multiplication of cells, and less pain and morbidity during harvesting. These cells are typically enzymatically derived from adipose tissue but this technique has complicated regulatory problems. To address this problem, a new technique has been created to extract and process adipose tissue without expansion and the use of enzymes to produce autologous minimally manipulated adipose-derived MSCs. Recent studies have confirmed that this treatment is an effective and promising method for treating pain and improving joint function in patients affected by OA with a very low percentage of complications at short to mid-term follow-up. (www.actabiomedica.it)

Key words: Adipose-derived mesenchymal stromal cells, knee osteoarthritis; hip osteoarthritis, shoulder osteoarthritis;, degenerative meniscal tears, talus osteochondral lesions, pain

Introduction

Osteoarthritis (OA) is a degenerative joint disease that is the most frequent cause of persistent joint pain (1). There is no definitive approach to avoid OA development. Nonetheless, some conservative therapies are available to alleviate pain and enhance function: weight loss, orthotics, physical therapy, analgesics, topical and oral non-steroidal anti-inflammatory medications, chondroprotectors and intra-articular injections of corticosteroids, hyaluronic acid, platelets rich plasma, and oxygen-ozone (2, 3). Due to their capacity of regeneration and anti-inflammatory effects, human mesenchymal stromal cells (MSCs) have recently been applied to improve pain and function associated with OA with promising preliminary clinical results (3). Human MSCs are isolated from a number of tissues, including bone marrow, dental pulp, placenta and adipose tissue (4). Autologous bone marrow and adipose tissue are the two common sources of human MSCs used in orthopaedics (3). Bone marrow MSCs were originally used to treat cartilage injuries in humans. However, there were many difficulties with bone marrow MSCs including poor stromal cell yield, reduced viability and differentiation capacity with increased donor age, and possibile morbidity during bone marrow aspiration. Alternatively, adipose-derived MSCs may be more clinically appropriate due to their abundance (the frequency of MSCs in bone marrow is between 1 in 25,000 and 1 in 100,000 cells, while adipose-derived MSCs account for about 2% of lipoaspirate cells), easy access, simple isolation procedure, high yield of lipoaspirate stromal cells, faster proliferation of cells, and less pain during the harvesting procedure (4-6).

Adipose-derived MSCs exert their influence through two potential mechanisms. Firstly, these cells differentiate into chondrocytes, while secondly,

chondrocytes are activated by adipose-derived MSCs through the secretion of bioactive factors (7). These molecules promote angiogenic, antifibrotic, antiapoptotic, and immunomodulatory responses in target tissue in a paracrine mode (4). Adipose-derived MSCs are typically obtained enzymatically from fat lipoaspirates as a stromal vascular fraction and can undergo prolonged ex vivo expansion, with significant senescence and decreased multipotential. Moreover, the process has complex regulatory issues (4). To solve this problem, a new approach have been established for the harvesting and processing of adipose tissue without expansion and/or enzymatic treatment to generate autologous minimally manipulated adipose-derived MSCs retained with an intact stromal vascular niche ready for injection into patients or eventually cryopreserved for future use (4, 8). The purpose of this narrative review is to show the clinical utility of autologous minimally manipulated adipose-derived MSCs for the treatment of pain and dysfunction associated with OA.

Methods

A review was conducted of PubMed articles from January 1, 2000 to Dicember 12, 2020 using a combination of the following keywords: hip, knee, shoulder, ankle, autologous minimally manipulated adipose derived mesenchymal stromal cells, and osteoarthritis. Randomized controlled trials (RCTs) and case series investigating the clinical efficacy of autologous minimally manipulated adipose-derived MSCs without expansion or enzymatic treatment for treating OA associated pain and dysfunction were reviewed. Additional studies have been found by examining the reference lists of the above articles. Excluded studies included: case report studies, in vitro studies, animal studies, autologous minimally manipulated adipose derived MSC with expansion or enzymatic treatment.

Results

A total of 13 papers (1, 3, 5, 7, 9-17) that reported clinical data on the use of autologous minimally manipulated adipose-derived MSCs for the treatment of pain and dysfunction associated with OA were included in the present narrative review. All the papers were case series (Level of Evidence IV) except one (15) that was a RCT (Level of Evidence I). Four papers (7, 14-16) were prospective and nine papers (1, 3, 5, 9-13, 17) were retrospective (Table 1.). All Clinical scores, except LEAS, improved significantly at latest followup compared to baseline ($p<0.05$). Results are summarized in Table 2 and 3.

Table 1. Demographic data. Abbreviations: n.s, not specified.

Author	Type of study	Patient (joint)	Mean age, years	Latest followup, years
Russo et al 2017 (10)	Retrospective	30 (30)	43	1
Russo et al. 2018 (3)	Retrospective	22 (22)	45	3
Panchal et al. 2018 (5)	Retrospective	17 (26)	68	1
Cattaneo et al. 2018 (11)	Retrospective	35 (35)	54	1
D'Ambrosi et al. 2018 (17)	Retrospective	4 (4)	n.s	0,5
Mautner et al. 2019 (1)	Retrospective	35 (48)	63	1,09
Hudetz et al. 2019 (7)	Prospective	20 (16)	n.s	1
Schiavone Panni et al. 2019 (12)	Retrospective	52 (52)	67	2
Dall'Oca et al. 2019 (13)	Retrospective	6 (6)	52	0,5
Bisicchia et al. 2019 (15)	Prospective	20 (20)	50	1
Heidari et al. 2020 (9)	Retrospective	110 (110)	n.s	1
Vinet-Jones et al. 2020 (14)	Prospective	25 (25)	n.s	1
Malanga et al. 2020 (16)	Prospective	20 (23)	60	1

Table 2. Clinical scores of autologous minimally manipulated adipose-derived MSCs for knee OA . Values are reported as mean.

Author	Year	KOOS		KOOS-S		KOOS-P		KOOS-ADLs		KOOS-Sp		KOOS-QOL		WOMAC		EQOL		VAS		IKDC		TLK		KSS		LEAS		OKS		EQ-5D		IKS	
		B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU
Russo et al. (10)**	2017	/	20	/	21	/	19	/	17	/	15	/	13						2,4		20		31											
Russo et al. (3) ****	2018	/	64															/	55	/	55	/	41										
Panchal et al. (5)	2018																	5,7	4,3					74	82	37	42						
Cattaneo et al. (11)***	2018			/	23	/	24	/	27	/	38	/	40	/	26																		
Mautner et al. (1)	2019			55	68	51	70	57	76	21	46	29	48			0,67	0,77	4,3	2,8														
Hudetz et al. (7)	2019			48	70	39	65	40	64	16	35	13	37	55	32			4	0,7														
Schiavone Panni et al. (12)	2019																	8,5	5,1													47	73
Bisicchia et al. (15)	2019													55	18			6,2	2,6									26	45	17	73		
Heidari et al. (9)*	2020																	7	3									25	34	0,62	0,69		

* Median values; ** Average median improvement related to baseline; *** Average mean improvement related to baseline; **** Improvement in percentage related to baseline.

Abbreviations: KOOS, Knee Osteoarthritis and Injury Outcome Score, S, Symptoms subscale, P, Pain subscale, ADLs, Activities of Daily Living subscale, Sp, Sports subscale, QOL, Quality Of Life subscale; WOMAC, Western Ontario and Mc Master University; EQOL, Emory Quality of Life ; VAS, Visual Analog Scale; IKDC, International knee documentation committee; TLK, Tegner Lysholm Knee; KSS, Knee Society Score; LEAS, Lower Extremity Activity Scale; OKS, Oxford Knee Score; EQ-5D, EuroQol 5D; IKS, International Knee Society score; B, Basline; FU, FollowUp.

Table 3. Clinical outcomes of autologous minimally manipulated adipose-derived MSCs for other joints OA.

Author	Year	KOOS-S		KOOS-P		KOOS-ADLs		KOOS-Sp		KOOS-QOL		WOMAC		VAS		AOFAS		HSS		DASH	
		B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU	B	FU
D'Ambrosi et al. (17)	2018													8	2,2	47	84				
Dall'oca et al. (13)	2019											36	20	4,6	1,5			67	85		
Vinet-Jones et al. (14)*	2020													/	84					/	59
Malanga et al. (16)	2020	58	78	62	80	67	84	34	62	33	59			5,4	2,2						

Values are reported as mean. * Values reported as improvement in percentage related to baseline. Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; HSS, Harris Hip Score; DASH, Disabilities of the Arm, Shoulder and Hand.

Autologous minimally manipulated adipose-derived MSCs and knee OA

In vitro and in vivo studies, adipose-derived MSCs have shown to be able to synthesize cartilage matrix proteins such as collagen type II, VI, and chondroitin 4-sulfate (18). Furthermore, in two prospective non-randomized studies (19, 20), it has been observed that a single intra-articular injection of autologous minimally manipulated adipose-derived MSCs in patients with knee OA (Kellgren Lawrence stage III-IV (21)) lead to increased glycosaminoglycan content of the cartilage extracellular matrix as assessed by delayed gadolinium-enhanced magnetic resonance imaging of cartilage 12 and 24 months after treatment respectively which is in line with the observed improved pain scores and clinical results.

Many studies have reported encouraging preliminary clinical results of using autologous minimally manipulated adipose-derived MSCs alone or in combination with surgery in patients with mild, moderate and severe knee OA (1, 3, 5, 7, 9-12).

In a recent observational retrospective study, Heidari et al. (9) reported a statistically significant improvements in pain, function, and quality of life of 110 knees at twelve months after a single ultrasound-guided intra-articular injection of autologous minimally manipulated adipose-derived MSCs for the treatment of knee OA (KL grade I-IV). Similarly, in a study (1) of 35 patients (48 knees) affected by knee OA (KL grade I-IV) who underwent the same procedure, the authors observed a significant improvement of pain and function of these patients at a mean followup of 1.09 +/- 0.49 years.

Autologous minimally manipulated adipose-derived MSCs have been used by many authors as an adjuvant for the surgical treatment (3, 10-12).

Russo et al. (10) performed a retrospective analysis evaluating the 1-year efficacy and outcome of a single intra-articular injection of autologous minimally manipulated adipose-derived MSCs associated with ACL/LCL reconstruction, high tibial osteotomy, meniscectomy or arthroscopy alone in 30 patients with degenerative knee condropathy (KL grade < 4). At 12 months of follow-up, all clinical scores increased statistically, no patients deteriorated clinically related to pre-operative status thus concluding that this treatment is effective and secure for diffuse degenerative knee chondropathy. The same group (3) analyzed the findings of the same patient population at a 3-year follow-up. They found that the results of patients reported at 1 year were preserved without a patient woresened relative to the pre-operative status concluding that this treatment is effective and safe for the management of diffuse degenerative knee chondropathy also in the mid-term followup.

Furthermore, Cattaneo et al. (11) reported the results of 35 patients with symptomatic knee OA (KL grade I-III) treated with autologous minimally manipulated adipose-derived MSCs combined with

chondral shaving (alone or associated with meniscectomy), and showed that the pre-surgical clinical scores related to 1, 3, 6, and a 12-month follow-up were improved constantly. Additionally, 92% of patients improved clinically and 100% were satisfied with the treatment. Therefore they concluded that this treatment is safe and a useful adjuvant in the surgical treatment of degenerative knee chondropathy.

Similarly, Schiavone Panni et al. (12) conducted a retrospective analysis to report the clinical and functional results of 52 patients with early knee OA (KL grade <3) treated with intra-articular injection of autologous minimally manipulated adipose-derived MSCs associated with arthroscopic debridement (chondral shaving/abrasion and/or meniscal regularization). At 24 month followup, all scores improved significantly compared with pre-operative scores and 96.2% of patients reported good or excellent improvements in function and/or pain.

Autologous minimally manipulated adipose-derived MSCs has been shown to be effective also in severe knee OA (5, 7). In a prospective study, Hudetz et al. (7) evaluated the clinical and functional results of an intraarticular injection of autologous minimally manipulated adipose-derived MSCs in 20 patients with severe knee OA (KL grades: III and IV) 12 months after treatment and found that seventeen patients (85%) showed a significant enhancement in clinical scores, concluding that this treatment reduces clinical symptoms in patients with late stage knee OA. Similar findings were reported by Panchal et al. (5) who found substantial improvement in pain, quality of life and function in 17 subjects (26 knees) with severe knee OA at 12 months after autologous minimally manipulated adipose-derived MSCs were injected concluding that this treatment is safe and successful for patients with severe knee OA and may represent a non-surgical treatment alternative to postpone knee joint replacement in this cohort of patients.

Autologous minimally manipulated adipose-derived MSCs and other joints OA

Autologous minimally manipulated adipose-derived MSCs injection therapy has been shown to be a safe alternative also for the treatment of other joints OA, such as hip OA (13), and shoulder OA (14). Dall'oca et al. (13) conducted a retrospective analysis at 6 month follow-up to demonstrate the usefulness of injections with autologous minimally manipulated adipose-derived MSCs in 6 patients with hip OA (OA scored 0-2 on the Tonnis grading scale) and found that at latest follow-up all clinical scores increased compared with the pre-injection values. Therefore, the authors concluded that this treatment is a safe procedure with good clinical results for early phases of hip OA.

Vinet-Jones et al. (14) performed a prospective non randomized clinical study to determine the effectiveness of the use of autologous minimally manipulated adipose-derived MSCs for the treatment of pain and dysfunction in 25 patients with mild to moderate shoulder OA (KL grade II-III). At latest followup of 52 weeks, they observed that all patients reported significant improvement in clinical and functional outcome compared to pre-treatment. Moreover, a statistically significant increases in glenohumeral joint spacing following the treatment up to 1 year post-treatment have been shown on radiologic examination.

Autologous minimally manipulated adipose-derived MSCs and OA related lesions

Recent studies suggested that this treatment is effective as well in OA related lesions as knee focal chondral lesions (15), degenerative meniscal tears (16), and talus osteochondral lesions (17). Bisicchia et al. (15) assessed in a prospective RCT, the clinical outcomes at 12 month followup in 40 patients affected by symptomatic focal chondral lesions of the knee (KL <3 grade) and treated with autologous minimally manipulated adipose-derived MSCs with microfractures (experimental) relative to microfractures alone (control). No statistically significant variations in pain scores between groups or compared to pre-treatment were reported during the 1-month assessment, while, there was a significant increase in pain and functional scores compared to pre-treatment in both groups at 3, 6 and 12 month follow-up. Moreover, a signifiantly lower pain but not functional scores were seen in the experimental treatment group at 3 month follow-up, while, a significantly lower pain and functional scores were observed in the experimental group at 6 and 12 month followup.

These findings should be used to counsel patients that clinical improvement could not be seen until 3 months after treatment. A recent prospective pilot study (16), found a significant increase of clinical scores relative to baseline of 20 patients (23 knees) affected by degenerative meniscal tears with associated knee OA (MRI graded from none to severe) and treated by ultrasound guided percutaneous trephination of the meniscal tear and intra-meniscal and intra-articular autologous minimally manipulated adipose-derived MSCs injections at twelve months post-treatment representing a safe and potentially successful treatment option for patients suffering knee pain from degenerative meniscal tears with associated knee OA.

Lastly, D'ambrosi et al. (17) assessed the efficacy of the treatment with autologous minimally manipulated adipose-derived MSCs and arthroscopic microperforations of 4 patients affected by talus osteochondral lesions. Six months after treatment, they observed that all patients registered clinical improvement with no documented complications concluding that the results of this treatment are encouraging and indicating that the procedure provides significant pain relief in patients with talus osteochondral lesion.

Factors affecting the clinical outcome

Various factors have been reported which affect the final clinical results of patients treated with autologous minimally manipulated adipose-derived MSCs injections. Russo et al. (10) observed that patients with femoral condyle chondropathy had higher clinical scores than patients with chondropathy in any other compartment, whereas patients with patellofemoral chondropathy PF had lower scores than patients with chondropathy in any other compartment. In addition, patients with lesions in more than one compartment showed higher clinical scores compared to patients with lesions in one compartment only. Finally patients with low grade chondropathy improved slightly more in all grades relative to patients with high grade chondropathy. Likewise, Mautner et al. (1) reported that the chances of obtaining pain and function improvements were greater with earlier knee OA changes (KL grade I-II) compared to more advanced knee OA (KL grade III-IV), which is a valuable clinical observation that should be emphasized when informing patients on what they might obtain from orthobiological procedures, especially those with advanced knee OA trying to delay or avoid TKR. In contrast, Schiavone Panni et al. (12) found that knee OA grade did not significantly affect the improvement of clinical results. Lastly, Cattaneo et al. (11) observed less but nevertheless important differences in the associated autologous minimally manipulated adipose-derived MSCs and chondral shaving treatment compared to the associated autologous minimally manipulated adipose-derived MSCs and meniscectomy treatment (74% vs. 92%). In addition, women and patients under the age of 55 showed better improvements than men and elderly patients, respectively.

Complications

None of the literature studies documented any severe adverse effects related to treatment with autologous minimally manipulated adipose-derived MSCs but only minor complications such as discomfort and swelling at the injection or harvest site that resolved within a few days (10).

Limitations of the studies

There are several limitations of these studies. The absence of a control group (a placebo or other injections such as corticosteroid or hyaluronic acid), thus a placebo effect may play a role of results and no definitive conclusions can be drawn regarding efficacy of this treatment. The heterogeneity of the population and the associated surgical procedures such as: meniscectomy and chondral shaving or debridment (3, 10-12). It is however, widely acknowledged that arthroscopic debridement alone is unsuccessful in the management symptoms of OA. Moreover, the efficacy of meniscal regularization of degenerative meniscal tears remains somewhat controversial. The short mean follow-up (12-36 months). The fact that all studies except one (15) were case series and all studies except one (9) analyzed relatively small number of patients. Nevertheless, all studies showed encouraging preliminary results providing an important basis for the future RCTs with a larger number of patients at a longer followup.

Conclusions

Autologous minimally manipulated adipose-derived MSCs without expansion or enzymatic treatment are an effective and promising method for pain management and joint function improvement in patients with OA with a very low percentage of complications in the short-to mid-term follow-up. Based on our two years' clinical experience and the above findings, we recommend this treatment as a second resort, when conservative treatments are no longer effective for controlling symptoms in patients with early OA or in patients with advanced OA not willing to undergo TKA. In order to confirm the preliminary results, long term RCTs on a significant number of patients at a long term followup are required.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 13 December 2020
Accepted: 12 January 2021
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