STEM CELLS AND DEVELOPMENT
Volume 30, Number 13, 2021

DOI: 10.1089/scd.2021.0053

ORIGINAL RESEARCH REPORTS

A Prospective Study Comparing Leukocyte-Poor Platelet-Rich Plasma Combined with Hyaluronic Acid and Autologous Microfragmented Adipose Tissue in Patients with Early Knee Osteoarthritis

Ignacio Dallo,[1,i] Dawid Szwedowski,[1,ii] Ali Mobasheri,[2–6,iii] Eleonora Irlandini,[1] and Alberto Gobbi[1,iv]

The objective of this study was to compare the clinical efficacy of repeated doses of leucocyte-poor platelet-rich plasma (LP-PRP) plus hyaluronic acid (HA) to a single dose of autologous microfragmented adipose tissue (AMAT) injections in patients with early osteoarthritis (OA) symptoms. Eighty knees in 50 patients (mean age: 61.3 years) were randomly allocated into two equal groups in a nonblinded design and prospectively followed for 12 months. Group 1 received three intra-articular injections (1 month apart) using autologous LP-PRP+HA. Group 2 received a single dose of AMAT injection. Outcomes were measured by PROMs Tegner, Marx, visual analog scale, and Knee Injury and Osteoarthritis Outcome Score (KOOS) at 6 and 12 months. Both groups had significant clinical and functional improvement at 6 and 12 months. The differences between groups were statistically significant in Tegner score and KOOS symptoms (both $P < 0.05$) at 6 months in group 2. The test with statistically significant differences ($P < 0.05$) at 12 months was Tegner ($P < 0.001$), with group 2 having a higher median than group 1. LP-PRP+HA and AMAT lead to clinical and functional improvement at 6 and 12 months. AMAT showed better clinical results in Tegner and KOOS symptoms at 6 months and Tegner at 12 months. Understanding which therapy offers the most benefits with the least risk can significantly improve the quality of life for millions of people affected by OA. Long-term randomized controlled studies are needed to verify differences in efficacy.

Keywords: AMAT, PRP, osteoarthritis, knee, clinical outcomes, cartilage

Introduction

Osteoarthritis (OA) is one of the most common forms of joint disease worldwide, causing pain and significant disability, and knee OA represents the major burden disease in the elderly population [1]. Nowadays, the incidence of OA is also rapidly increasing in younger and middle-aged individuals. Since OA has such a strong social impact, understanding which therapy offers the most benefits with the least risk can significantly improve the quality of life (QOL) for millions of people affected by OA. Even though various conservative therapies (Nonsteroidal anti-inflammatory drugs, topical anti-inflammatory gels, and corticosteroids) for the management of early knee OA, these treatments provide short-term benefits that can have lasting local and systemic side effects [2].

Early OA is defined by combining at least two pain episodes for >10 days in the previous year and structural changes on standard radiographs and magnetic resonance imaging (MRI) findings [3]. One of OA treatment research's primary foci in the last decade has been regenerative cellular therapy, primarily medicinal signaling cells (MSCs) and growth factors [4,5]. Several studies propose these therapies to provide symptomatic relief and create an anti-inflammatory and proanabolic microenvironment conducive

[1]O.A.S.I. Bioresearch Foundation, Gobbi NPO, Milano, Italy.
[2]Research Unit of Medical Imaging, Physics and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland.
[3]Department of Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania.
Departments of [4]Orthopedics and [5]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.
[6]Department of Joint Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China.
[i]ORCID ID (https://orcid.org/0000-0003-2744-8342).
[ii]ORCID ID (https://orcid.org/0000-0002-7027-0626).
[iii]ORCID ID (https://orcid.org/0000-0001-6261-1286).
[iv]ORCID ID (https://orcid.org/0000-0002-4868-0119).

to repair the joint [6–8]. Platelet-rich plasma (PRP) has been shown to have an anti-inflammatory effect and the capacity to counteract catabolic activity within the joint [9–11]. Similarly, studies have shown that hyaluronic acid (HA) provides proanabolic and anti-inflammatory effects [12,13].

As an alternative, experimental animal studies have shown that autologous microfragmented adipose tissue (AMAT) can also stimulate cartilage regeneration and improve the symptoms in degenerative cartilage diseases [14,15]. Following these animal studies, some clinical in vivo human studies were performed, which have shown encouraging results in the treatment of OA [8,16–18]. Given that both modalities are potentially promising, the purpose of this study was to compare the clinical efficacy of repeated doses of leucocyte-poor PRP (LP-PRP) combined with HA against a single dose of AMAT in the treatment of early symptomatic knee OA. It was hypothesized that one AMAT knee infiltration could be superior to LP-PRP+HA injections to treat early knee OA at 12 months follow-up.

Materials and Methods

In this level 2 prospective therapeutic study, patients were recruited from November of 2016 to December of 2017. Inclusion and exclusion criteria for patients presented with at least one early OA symptomatic knee are shown in Table 1. Seventeen patients were excluded, 4 had severe knee OA, 2 with previous cartilage transplantation, 1 had hepatitis, 2 with infection, 1 had intra-articular corticosteroids in the 3 months before the treatment, 4 smokers, 2 with inflammatory arthritis, and 1 had severe cardiovascular disease. Pretreatment radiographic images were taken to be evaluated according to the Kellgren–Lawrence OA classification. The evaluation included a standing anteroposterior (AP) long-leg radiograph (with hips and ankles), standing AP and lateral views of the knees, skyline patellofemoral, and standing 45° flexion knee views. MRI was also performed for patients to be graded according to WORMS and BLOKS criteria. Early knee OA of a patient was classified based on clinical and imaging findings and should fulfil the following three criteria: knee pain, Kellgren–Lawrence grade 0 to 2 (osteophytes only), and MRI findings of at least two of the following: Cartilage morphology WORMS 3–6, Cartilage BLOKS grades 2 and 3, Meniscus BLOKS grades 3 and 4, and Bone marrow lesions WORMS 2 and 3 [3,19]. A hematology report was run before testing, including a complete blood count and coagulation profile to detect blood diseases or infection.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria:
1. Symptomatic knee osteoarthritic (Kellgren–Lawrence Grade 1–2 cartilage lesions on radiographs or early osteoarthritis on magnetic resonance imaging)
2. Older than the age of 40 years with BMI <30 kg/m^2
3. Pain without relief with oral anti-inflammatory agents >3 months
4. Patients with stable knees without malalignment
5. Patients who consented to either treatment modality as per the protocol.
6. Normal blood results and coagulation profile (platelets between 150,000 and 450,000/μL)
7. Patients who had not undergone any surgery on the affected knee in the 2 years before enrollment into the study.
Exclusion criteria:
1. Tricompartmental osteoarthritis, rheumatoid arthritis, or concomitant severe hip osteoarthritis
2. Previous high tibial osteotomy or cartilage transplantation
3. Patients with blood diseases, systemic metabolic disorders, immunodeficiency, hepatitis B or C, HIV-positive status, local or systemic infection.
4. Ingestion of antiplatelet medications within 7 days before the treatment, or intra-articular or oral corticosteroids in the 3 months before initiating therapy.
5. Smokers
6. Inflammatory arthritis
7. Severe cardiovascular disease

Fifty patients (30 with bilateral OA) were accepted for the study, resulting in 80 total knees. Patients were randomly allocated in nonblinded manner into two groups using the simple randomization method of a coin flip [20,21]. Each group consisted of 25 subjects consisting of an equal number of unilateral and bilateral OA, with a total of 40 knees in each group (Fig. 1). The mean and standard deviation of anthropometrics and demographics and the count and percentage of OA severity are reported in Table 2 and *P* values between group parameters and knee OA severity. There were no significant differences detected between groups for gender, side of the knee, diagnosis severity, age, height, weight, or body mass index (BMI) (Table 2).

LP-PRP combined with HA

Group 1 received one LP-PRP cycle combined with HA intra-articular injection into the affected knee (Cellular Matrix; Regen Lab, Switzerland). A cycle consisted of three injections, given 1 month apart. Six milliliters of blood from the cubital vein was obtained and centrifuged for 5 min at 1,500*g* relative centrifugal field and 3,500 revolutions per minute as per the manufacturer's recommendations [22]. A mix was prepared of PRP with HA at a concentration of 3 mL of PRP for every 2 mL of HA. The PRP prepared was LP according to Dohan Ehrenfest et al. classification [23]. As per the PAW classification system, PRP obtained was classified as P2 Bβ. Total leukocyte concentration was below the normal level-specific granulocyte depletion >95% (mostly mononuclear cells being recovered 75% lymphocytes; 50% monocytes) in 4 mL of PRP. The system provides a 1.6–1.8 fold increase in platelets [22,24,25]. The PRP was aspirated into a syringe, and a topical anesthetic skin refrigerant was applied locally before intra-articular infiltration by a suprapatellar approach using sterile aseptic precautions. The PRP was not activated before injection.

AMAT preparation and application

Group 2 received one dose of AMAT (Lipogems, Italy) via a suprapatellar approach. Under aseptic conditions and local anesthesia, adipose tissue was harvested using an abdominal lipoharvest procedure. Using a lateral abdominal approach, the subcutaneous fat was infiltrated with up to 300 mL of tumescent fluid (composed of 30 mL of 2% lidocaine, 1 mL of 1:1,000 adrenaline, and 1 mL of 8.4% bicarbonate suspended in a standard saline solution for a total of 1,000 mL). Following this, up to 60 mL of adipose tissue

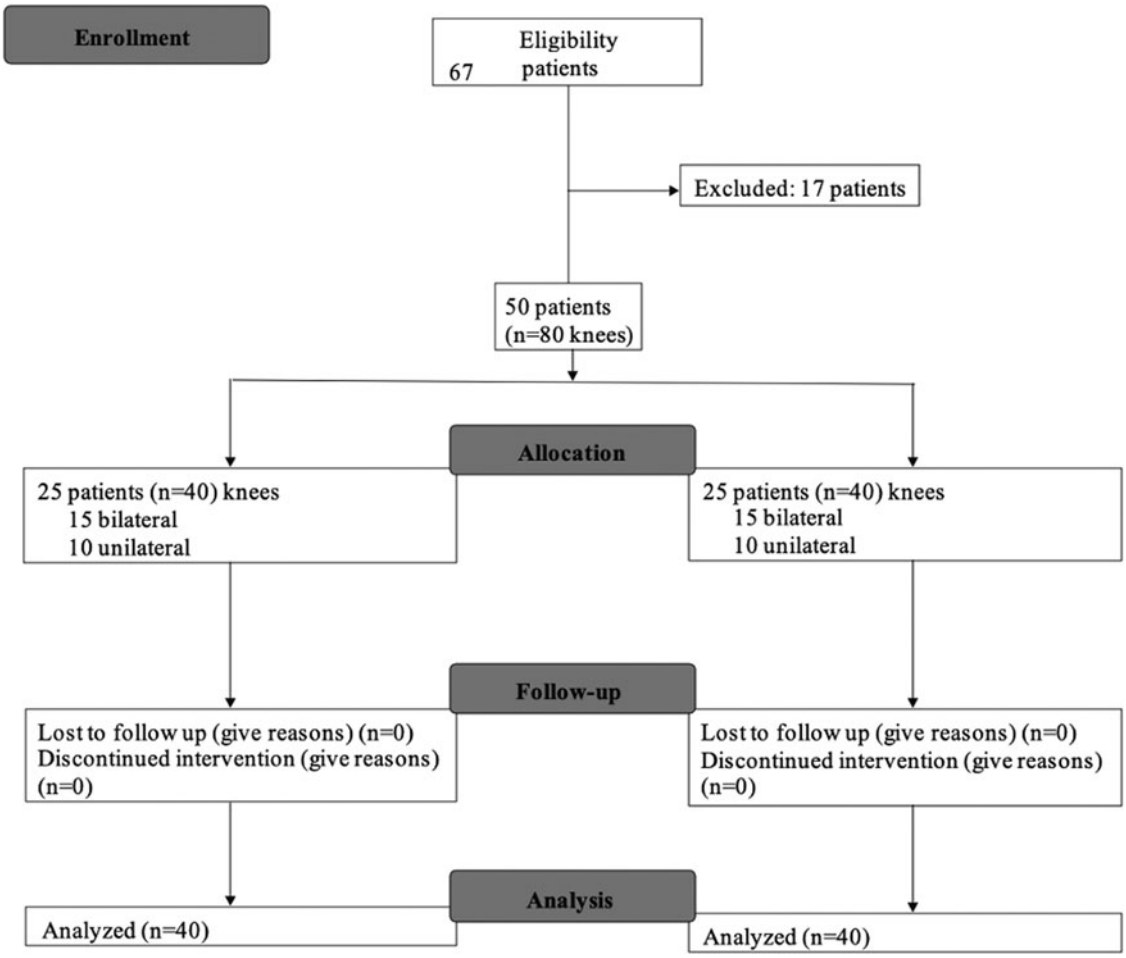

FIG. 1. CONSORT flow diagram showing the patients assessed for eligibility, excluded, enrolled, and analyzed in the study.

and tumescent fluid was aspirated through a 4 mm lipoaspirate cannula and collected within a sterile medical grade single use Shippert Tissu-Trans Collection filter (Shippert Medical, CO) [26]. The lipoaspirate was transferred directly to a Lipogems device. It is a closed, full-immersion, low-pressure cylindrical system to obtain fluid with a concentrated population of pericytes/MSCs [4,26]. A homologous use and only a minor change during the preparation of the adipose fraction were produced throughout the mini-manipulated procedure. The processed fat is subjected to minimal manipulation, only slight mechanical forces, with no detrimental effects on the stromal vascular cells' integrity, and the final preparation was injected into the knee using the suprapatellar approach. The final product created by this process is quite consistent, characterization of the AMAT injectate has been described in the recent publication by Gobbi et al. [27]. In 2017, the FDA finalized its rules, guiding the use of human cellular and tissue products. The agency reaffirmed that the AMAT (Lipogems system) meets the new guideline's criteria for minimal manipulation of the tissue and intended for homologous use.

After treatment, patients in both groups were allowed weight-bearing, and local ice application was recommended for 20 min every 2 to 3 h for 24 h. Vigorous activities of the knee were discouraged for at least 48 h. Single infiltration of AMAT for early knee OA has been studied in various clinical studies, which encouraged us to follow the same protocol [28,29]. The primary outcomes of the studies were pain, symptoms, and activity level. No patient from either group had adverse effects on the injection or final follow-up. The outcome of treatment was assessed through the following patient-reported outcome measure scores (PROMS); Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS) (0 = no pain to 10 = worst possible pain), Marx Knee Measure, and Tegner scoring systems. KOOS consists of five subscales: pain, other symptoms, function in activities of daily living, function in sport and recreation (Sport/Rec), and knee-related QOL. The patients completed questionnaires, and all scores were tabulated before the commencement of treatment, at 6 and 12 months follow-up. Data entry and collection were performed by an independent investigator using SOCRATES©2012 Ortholink PTY Ltd.

This study was approved by the Institutional Review Board and Ethics Committee of our Foundation (20–2016/approval number: 14.12.867 area 4 bis) and conforms to the Declaration of Helsinki and Good Clinical Practice:

Table 2. Baseline Characteristics and Patient Demographics

			Study group		
			Group 1 (N = *40*)	*Group 2* (N = *40*)	P
Baseline characteristics ($N = 80$ knees)	Knee, *n* (%)	Left	20 (50%)	20 (50%)	0.823
		Right	20 (50%)	20 (50%)	
	Severity of diagnosis (Kellgren–Lawrence), *n* (%)	Grade 1	15 (38%)	18 (45%)	0.496
		Grade 2	25 (63%)	22 (55%)	
	Gender, *n* (%)	Male	14 (56%)	9 (36%)	0.201
		Female	11 (44%)	16 (64%)	
Patient demographics (50 patients)	Age at treatment (mean ± SD)		62.5 ± 11.3	61.5 ± 9.5	0.714
	Height (m) (mean ± SD)		1.7 ± 0.1	1.7 ± 0.1	0.789
	Weight (kg) (mean ± SD)		76.9 ± 11.3	75.0 ± 16.9	0.660
	BMI (kg/m^2) (mean ± SD)		26.3 ± 3.6	25.8 ± 5.1	0.660

Statistically significant, $P < 0.05$.
SD, standard deviation.

Consolidated Guideline (CPMP/ICH/135/95). All patients were provided with a specific written informed consent signed before treatment.

Statistical analysis

The statistical analysis was conducted using SPSS (24.0; IBM Corp., Armonk, NY) by an independent statistician blinded to the treatment received by each patient of the two groups. In the present study, a significance level of 5% ($P < 0.05$) was used and an effect size equal to 0.8 was considered, which determined that the sample size for each group had to be 40 knees to reach power $(1-\beta) = 80\%$. The general linear model for repeated measure test was performed to investigate within time variations for the continuous variables (KOOS, Marx, and VAS) for all patients and each evaluated subgroup. The factors being assessed were ''number of cycles,'' and the Greenhouse-Geisser *P* value is reported. Post hoc test with Bonferroni adjustment for pairwise comparisons within time was performed to investigate each variable's improvement and deterioration and between subgroups. The nonparametric Friedman test was performed to detect within time differences in the ordinal variable (Tegner). The nonparametric Wilcoxon rank test as post hoc was used with a Bonferroni adjustment of the significant level. The nonparametric Mann–Whitney *U* test was performed to investigate the difference in improvement between the evaluated subgroups. The modified intention to treat analysis was performed on the originally randomized treatment groups to rule out bias due to crossover.

Results

The two treated groups were homogeneous in terms of age, gender, BMI, and severity of OA measured on the K-L scale. The mean age was 62.5 ± 11.3 years among those who underwent LP-PRP+HA treatment and 61.5 ± 9.5 years for those who received AMAT injection ($P = 0.714$). The mean BMI was 26.3 ± 3.6 kg/m^2 among those in group LP-PRP+HA and 25.8 ± 5.1 for those in the AMAT group ($P = 0.660$). Demographic data are described in Table 2. Fifty patients (80 knees) were available at final follow-up: 25 patients (40 knees) in the LP-PRP+HA group, and 25 patients (40 knees) in the AMAT group. No patient was lost to follow-up or was excluded. There was an improvement in all scores (KOOS, VAS, Tegner, and Marx) at each follow-up. (Fig. 2). When comparing the effect of these two methods, at 6 months, both groups showed a similar tendency to improve all scores. However, the differences between the groups were statistically significant only in Tegner score and KOOS Symptoms ($P < 0.05$) at 6 months with better functionality in the AMAT group for both test scores. The only test with statistically significant differences between the groups ($P < 0.05$) at 12 months was Tegner, with the AMAT group having a higher median than the LP-PRP+HA group (Table 3). At 1-year follow-up, the scores had increased from the 6-month value in both the groups in Tegner and KOOS Sport and QOL subscales. In turn, the KOOS Pain subscale and VAS declined from the 6-month value at the last follow-up visit. The mean value in both groups remained above the pretreatment value at 6- and 12-month follow-up. The patients in the AMAT group had higher mean values for all the scores despite the Marx scale. The variations of all the test scores for both groups at different time intervals are presented graphically in Fig. 2. No serious adverse events were recorded at the time of surgery or throughout follow-up, and no complications were identified.

Discussion

The primary finding of this study was that, while AMAT is favored to LP-PRP according to Tegner and KOOS symptoms tests at 6 months and Tegner at 12 months of follow-up, both treatments offered significant improvements in the treatment of patients with early knee OA symptoms. The OARSI guidelines considered structured land-based exercise programs, dietary weight management in combination with exercise, and mind-body exercise (such as Tai Chi and Yoga) for the nonsurgical management of knee, hip, and polyarticular OA to be effective and safe for all patients with Knee OA, regardless of comorbidity. These treatments are recommended for use alone or with interventions of any recommendation level, as deemed appropriate for the individual [30].

Both PRP and HA treatments have been shown to result in decreased joint tissue catabolic activity [13,31]. However, PRP treatment has also been shown to significantly reduce

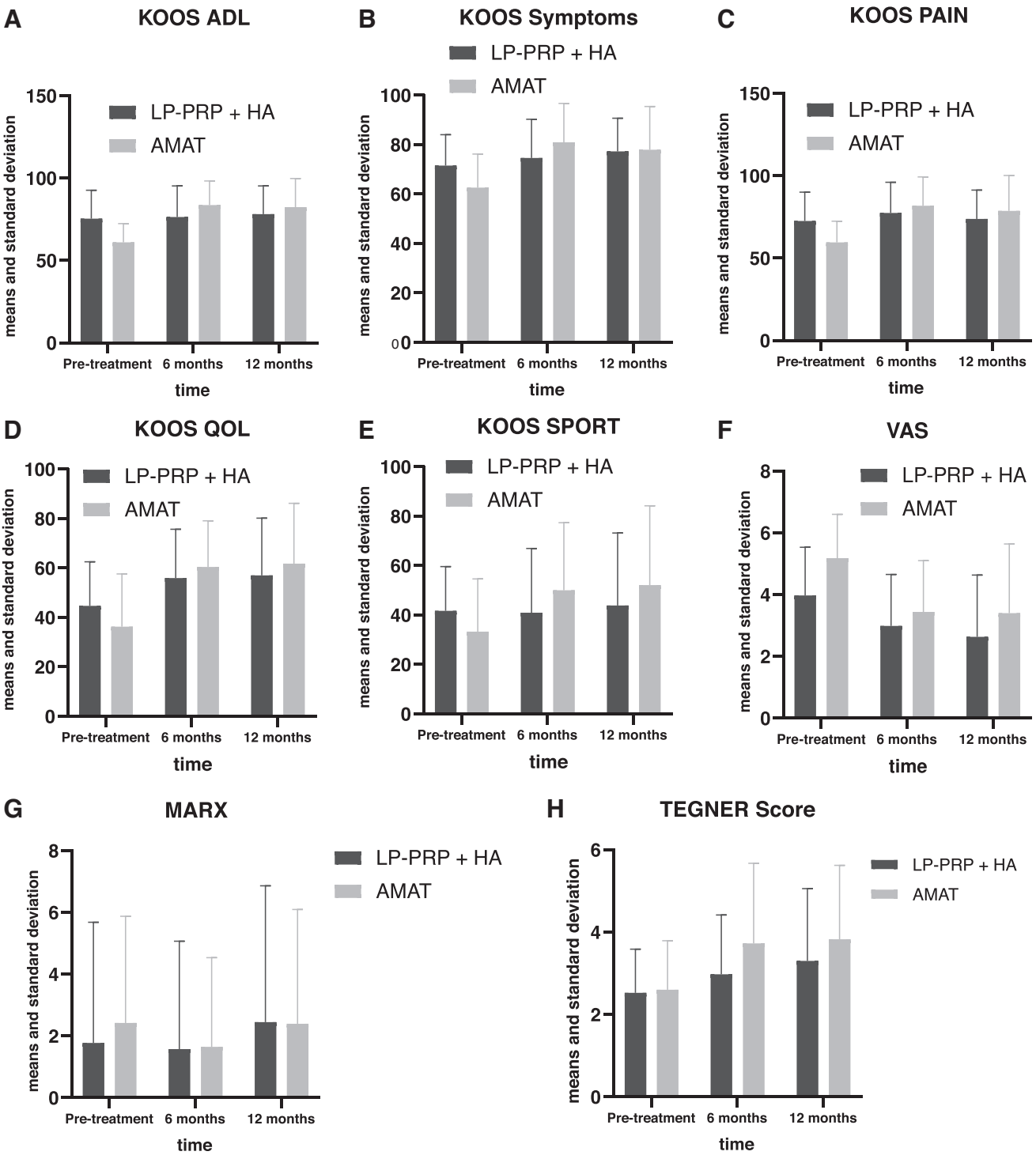

FIG. 2. Means and standard deviations at pretreatment, 6 and 12 months comparing LP-PRP+HA, (group 1) and AMAT, (group 2) using different PROMs. **(A)** Mean of KOOS ADL demonstrating no statistical differences between treatments. **(B)** Means of KOOS Symptoms showing statistically significant improvement in favor of group 2 at 6 months ($P < 0.05$). **(C)** Mean of KOOS Pain demonstrating no statistical differences between treatments. **(D)** Mean of KOOS QOL demonstrating no statistical differences between treatments. **(E)** Mean of KOOS SPORTS demonstrating no statistical differences between treatments. **(F)** Mean of VAS demonstrating no statistical differences between treatments. **(G)** Mean of MARX demonstrating no statistical differences between treatments. **(H)** Mean of Tegner showing statistically significant improvement in favor of group 2 at 6 months ($P < 0.05$), and 12 months ($P < 0.05$). An improvement in all scores is evident in the 6 and 12 months in both groups, comparing with pretreatment for all patients in the study. ADL, the activity of daily living; AMAT, autologous microfragmented adipose tissue; HA, hyaluronic acid; KOOS, knee osteoarthritis outcomes score; LP-PRP, leucocyte-poor platelet-rich plasma; PROMS, patient-reported outcome measure scores; QOL, the quality of life; VAS, visual analog scale.

TABLE 3. COMPARISON OF CLINICAL OUTCOME SCORES BETWEEN EACH GROUP (1-LP-PRP+HA, 2-AMAT)

Score	*Group*	*Pretreatment*	*6 months*	P	*12 months*	P
VAS	1	3.97 ± 1.56	3.20 ± 2.09	0.289	2.64 ± 2.00	0.176
	2	5.18 ± 1.42	3.44 ± 1.66		3.40 ± 2.24	
Marx	1	1.78 ± 3.86	1.58 ± 3.49	0.624	2.45 ± 4.36	0.623
	2	2.42 ± 3.45	1.65 ± 2.89		2.40 ± 3.69	
KOOS symptoms	1	71.58 ± 12.47	74.62 ± 15.62	**≤0.05**	77.30 ± 13.41	0.696
	2	62.6 ± 13.63	80.97 ± 15.76		77.97 ± 17.47	
KOOS pain	1	72.57 ± 17.44	77.40 ± 18.63	0.237	73.78 ± 17.49	0.133
	2	59.50 ± 12.89	81.78 ± 17.48		78.63 ± 21.62	
KOOS ADL	1	75.38 ± 17.35	76.45 ± 18.82	0.066	78.15 ± 17.19	0.144
	2	65.05 ± 11.36	83.62 ± 14.73		82.38 ± 17.49	
KOOS SPORT	1	41.73 ± 17.87	40.95 ± 26.01	0.46	48.87 ± 29.29	0.304
	2	33.30 ± 21.31	50.00 ± 27.36		52.13 ± 32.06	
KOOS QOL	1	44.70 ± 17.84	55.98 ± 19.76	0.308	57.00 ± 23.25	0.434
	2	36.25 ± 21.34	60.43 ± 18.7		61.80 ± 24.40	
TEGNER	1	2.56 ± 1.06	2.98 ± 1.44	**≤0.05**	3.30 ± 1.78	**≤0.05**
	2	2.60 ± 1.19	3.73 ± 1.95		3.83 ± 1.79	

The nonparametric Mann–Whitney *U* test was performed to investigate the difference in improvement between the evaluated subgroups. The nonparametric Friedman test was performed to detect within time differences in the ordinal variable (Tegner). The nonparametric Wilcoxon rank test as post hoc was used with a Bonferroni adjustment of the significant level. The scores with a statistically significant differences are in bold.

ADL, activities of daily living; AMAT, autologous microfragmented adipose tissue; HA, hyaluronic acid; KOOS, Knee Injury and Osteoarthritis Outcome Score; LP-PRP, leucocyte-poor platelet-rich plasma; QOL, quality of life; VAS, visual analog scale.

MMP-13, an increase in HAS-2 expression in synoviocytes, and an increase in synthetic cartilage activity compared with HA [9,32]. These results indicate that PRP acts to stimulate endogenous HA. PRP has been shown to provide relief from pain and inflammation associated with OA, making it a viable treatment in OA management. Better outcomes have been reported in younger patients with mild to early OA without malalignment, smoking, or obesity [9,33]. Initial research suggests that LP-PRP results in improved functional outcome scores compared with leucocyte-rich PRP (LR-PRP) and placebo when used to treat knee OA [34]. LR-PRP resulted in significantly greater cell death and proinflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α), increasing cartilage degradation compared to LP-PRP based on the relevant findings of basic science study [35,36]. Some studies suggest that the combined application of PRP with HA could have a synergistic effect on treatment for OA [37]. A recent meta-analysis comprising 337 patients comparing HA-PRP injections and HA alone conclude that for symptomatic patients with knee OA, the combination of PRP and HA demonstrated more significant improvement in pain and function compared to patients who received HA injections only, as assessed by 3-, 6-, and 12-month VAS scores, and 12-month Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function and stiffness scores [38]. Lana et al., who treated 105 patients suffering from Kellgren and Lawrence I to III knee OA, found that the improvement in pain and physical function scores was significantly greater in patients treated with consecutive injections of HA and PRP, in comparison to each product administered separately [39]. In another clinical study, Abbassy et al. enrolled 25 patients injected with three doses of HA combined with PRP for a period of 2 weeks between each injection. All patients received standardized physiotherapy. The results showed that 68% of patients achieved >50% improvement in pain, stiffness, and function of the knee joints, and there were no adverse reactions [22]. In the PRP-HA group, a cycle consisting of three injections, each given at a monthly interval, was performed, and the positive effects of repeated intra-articular PRP injections on clinical outcomes of early knee OA have previously been published [40,41]. While these studies support the use of PRP for symptomatic knee OA, there remains important debate regarding its overall clinical efficacy. A recent meta-analysis of 78 randomized control trials comparing PRP to control found that PRP led to a reduction in knee OA pain but that the overall evidence for clinically significant efficacy was limited [42]. A call for standardization with a detailed description of the PRP preparation protocol is required to compare studies and provide reproducibility [43].

Microfragmented adipose tissue, also known as adipose stromal vascular fraction therapy, has gained recent popularity as a treatment. Compared to peripheral blood, adipose tissue has 25,000 times more reparative cells [44]. In the bone marrow, MSCs represent a small fraction (0.001%–0.01%) of nonhematopoietic, multipotent cells [45]. Adipose tissue has been reported to have larger quantities of progenitor cells [46]. The clinical results at 12 months follow-up in the AMAT group in our study are comparable to the studies in the recent literature. Koh et al. published a therapeutic case-control study of 50 patients with knee OA treated with 1 dose of 1.89×10^6 adipose-derived cells harvested from the infrapatellar fat pad after arthroscopic debridement and 3 doses of PRP, compared with 25 patients with 3 doses of PRP alone. They showed significant improvement in Lysholm, Tegner, and VAS scores in both groups with no significant difference at 1 year [16]. More recently, Koh et al. analyzed the group of adipose-derived cells at 2 years and reported that the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points ($P < 0.001$), particularly in cartilage which improved from 28.3 points to 21.7 points [8]. In another study of 30 patients with knee OA, Adriani et al. demonstrated significant

improvements in pain, QOL, and function at 12 months after ultrasound-guided injection of AMAT. Twelve males and 18 females; mean age of 63.3 years; mean BMI of 25.1; and without prior treatment over the last 12 months. The patients were evaluated at baseline and 1, 3, 6, and 12 months after treatment using the VAS and WOMAC. The average VAS was 7.7 at baseline and improved to 4.3 at a 3-month follow-up. However, a slight deterioration (VAS 5.0) was noted at 1 year. Total WOMAC score was 89.9 at baseline, 68.6 at 3 months, and 73.2 at 12-month follow-up [17]. Recently, Russo et al. showed that clinical improvement using AMAT to treat diffuse degenerative knee OA was maintained at 3 years of follow-up [18]. Garza et al. published a double-blinded prospective randomized controlled clinical trial. Thirty-nine patients with symptomatic knee OA were eligible. They reported significantly decreased knee OA symptoms and pain at 6 months and 1 year [47]. Finally, this year, Gobbi et al. in a multicentric international study show that a single-dose of microfragmented adipose tissue injection leads to clinical, functional, and QOL improvement at 2 years in 75 elderly patients, in KL grades 2 to 4 of knee OA [27].

An intriguing explanation for these results may come from the new vision of MSCs proposed by Caplan. According to this concept, MSCs, rather than participating in tissue formation, work as site-regulated ''drugstores'' in vivo by releasing trophic and immunomodulatory factors activated by local injury [4,5]. Although promising, these studies have provided insufficient evidence to support AMAT therapy's efficacy, making their adoption into standard clinical practice extremely challenging. It is recommended that the use of minimally manipulated cell products and tissue-derived cells be referred to as cell therapy, and the nature of these treatments be clearly understood. Clinicians and researchers must utilize the DOSES tool for describing cell therapies to improve transparency and to allow clinicians and patients to understand the characteristics of current and future cell preparations [48]. It is recommended that physicians and institutions offering biologic therapies establish patient registries for surveillance and quality assessments [49].

In addition to clinical outcomes, clinicians and patients should consider each therapy's convenience, comfort, and cost. PRP can be obtained from the patient on the same day that the injection is given and is processed through minimal steps, making it both cost-effective and convenient for treatment in patients with OA. A recent study analyzed cost-effectiveness based on evidence from level 1 randomized controlled trials. Bendich et al., concluded that for patients with symptomatic knee OA, PRP is cost-effective, from the payer perspective, at a total price (inclusive of clinic visits, procedure, and injectable) of less than €1,000 over 12 months, relative to HA and saline [50]. During this study, the cost of 1 kit to obtain the AMAT was €1,200, and the cost of 1 kit to obtain the LP-PRP+HA was €400. The final cost of both group's treatments was the same. However, adipose tissue harvesting was a more invasive and painful procedure, needing local anesthesia and being performed within a surgery center compared to simple blood aspiration in an outpatient facility. It is essential to know the cost-effectiveness of various intra-articular injectables in practicing resource-conscious, nonoperative care of knee OA. For patients who are faced with a self-pay proposition for PRP injections, having cost-effectiveness data about the relative value can help further inform treatment decisions.

The findings of this study have to be seen in light of some limitations. Nonetheless, these results must be interpreted with caution. The first is the difficulty to conduct a double-blind study for ethical and practical reasons as PRP does not require any anesthesia and liposuction like AMAT. The second limitation concerns the study's short-term clinical results, and a long follow-up will be necessary to confirm these results. Additional data on treatment failures such as medical comorbidity and more precise timing of failures are recommended for they can provide for long-term survivorship analyses of treatment. The doses used in the LP-PRP+HA group and AMAT group were different. The failure in controlling the doses would cause a misleading conclusion. Some patients were treated in both knees at the same time, so the symptoms of one knee could affect the outcome of the analysis of the other knee. The study did not include a placebo control group to compare results as it is not ethically acceptable by our Institutional Review Board and this would be the case in many other institutions. In addition, clinical definitions of treatment failure (eg, MCID, PASS) will help protect the results against biases such as regression to the mean. Techniques to deal with missing data, such as imputation, paired with sensitivity analysis should be considered in further analyses. We recommend more extensive research with long-term follow-ups. Biological outcomes such as synovial fluid biomarkers and histology of the joint's tissues are of great interest for future studies.

Conclusion

This study shows that both LP-PRP+HA and AMAT injections lead to clinical and functional improvement at 6 and 12 months. There was a statistically significant difference favoring AMAT for Tegner and KOOS symptoms at 6 months and Tegner at 12 months of follow-up. However, our findings can be of great clinical relevance because adipose tissue harvesting is a more invasive and painful procedure than simple blood aspiration. We need long-term randomized controlled studies with large sample numbers to understand the modalities of these two treatments' real efficacy and differences.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this study.

References

1. Vos T, AD Flaxman, M Naghavi, R Lozano, C Michaud, M Ezzati, K Shibuya, JA Salomon, S Abdalla, et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380: 2163–2196.
2. Jevsevar DS. (2013). Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 21:571–576.

3. Luyten FP, M Denti, G Filardo, E Kon and L Engebretsen. (2012). Definition and classification of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 20:401–406.
4. Caplan AI. (2017). Mesenchymal stem cells: time to change the name! Stem Cells Transl Med 6:1445–1451.
5. Caplan AI and D Correa. (2011). The MSC: an injury drugstore. Cell Stem Cell 9:11–15.
6. Cerza F, S Carni, A Carcangiu, I Di Vavo, V Schiavilla, A Pecora, G De Biasi and M Ciuffreda. (2012). Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 40:2822–2827.
7. Gobbi A, G Karnatzikos, V Mahajan and S Malchira. (2012). Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health 4:162–172.
8. Koh YG, SB Jo, OR Kwon, DS Suh, SW Lee, SH Park and YJ Choi. (2013). Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. Arthroscopy 29: 748–755.
9. Cole BJ, V Karas, K Hussey, K Pilz and LA Fortier. (2017). Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. Am J Sports Med 45:339–346.
10. Fortier LA, JU Barker, EJ Strauss, TM McCarrel and BJ Cole. (2011). The role of growth factors in cartilage repair. Clin Orthop Relat Res 469:2706–2715.
11. Sanchez M, E Anitua, D Delgado, P Sanchez, R Prado, JJ Goiriena, F Prosper, G Orive and S Padilla. (2016). A new strategy to tackle severe knee osteoarthritis: combination of intra-articular and intraosseous injections of Platelet Rich Plasma. Expert Opin Biol Ther 16:627–643.
12. Castellacci E and T Polieri. (2004). Antalgic effect and clinical tolerability of hyaluronic acid in patients with degenerative diseases of knee cartilage: an outpatient treatment survey. Drugs Exp Clin Res 30:67–73.
13. Moreland LW. (2003). Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 5:54–67.
14. Ude CC, SB Sulaiman, N Min-Hwei, C Hui-Cheng, J Ahmad, NM Yahaya, AB Saim and RB Idrus. (2014). Cartilage regeneration by chondrogenic induced adult stem cells in osteoarthritic sheep model. PLoS One 9:e98770.
15. Guercio A, P Di Marco, S Casella, V Cannella, L Russotto, G Purpari, S Di Bella and G Piccione. (2012). Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. Cell Biol Int 36:189–194.
16. Koh YG and YJ Choi. (2012). Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. Knee 19:902–907.
17. Adriani E, M Moio, B Di Paola, W Salustri, A Alfieri, P Parisi, M Ruggiero, Z Borab and B Carlesimo. (2017). Percutaneous fat transfer to treat knee osteoarthritis symptoms: preliminary results. Joints 5:89–92.
18. Russo A, D Screpis, SL Di Donato, S Bonetti, G Piovan and C Zorzi. (2018). Autologous micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis: an update at 3 year follow-up. J Exp Orthop 5:52.
19. Madry H, E Kon, V Condello, GM Peretti, M Steinwachs, R Seil, M Berruto, L Engebretsen, G Filardo and P Angele. (2016). Early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 24:1753–1762.
20. Suresh K. (2011). An overview of randomization techniques: an unbiased assessment of outcome in clinical research. J Hum Reprod Sci 4:8–11.
21. Altman DG and JM Bland. (1999). Statistics notes. Treatment allocation in controlled trials: why randomise? BMJ 318:1209.
22. Abbassy AA, S Trebinjac and N Kotb. (2020). The use of cellular matrix in symptomatic knee osteoarthritis. Bosn J Basic Med Sci 20:271–274.
23. Dohan Ehrenfest DM, L Rasmusson and T Albrektsson. (2009). Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 27:158–167.
24. Mazzucco L, V Balbo, E Cattana, R Guaschino and P Borzini. (2009). Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, Regen PRP-Kit, Plateltex and one manual procedure. Vox Sang 97:110–118.
25. Abate M, S Verna, C Schiavone, P Di Gregorio and V Salini. (2015). Efficacy and safety profile of a compound composed of platelet-rich plasma and hyaluronic acid in the treatment for knee osteoarthritis (preliminary results). Eur J Orthop Surg Traumatol 25:1321–1326.
26. Tremolada C, C Ricordi, AI Caplan and C Ventura. (2016). Mesenchymal stem cells in lipogems, a reverse story: from clinical practice to basic science. Methods Mol Biol 1416: 109–122.
27. Gobbi A, I Dallo, C Rogers, RD Striano, K Mautner, R Bowers, M Rozak, N Bilbool and WD Murrell. (2021). Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: a multi-centric, international study. Int Orthop 45:1179–1188.
28. Russo A, V Condello, V Madonna, M Guerriero and C Zorzi. (2017). Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. J Exp Orthop 4:33.
29. Panchal J, G Malanga and M Sheinkop. (2018). Safety and efficacy of percutaneous injection of lipogems microfractured adipose tissue for osteoarthritic knees. Am J Orthop (Belle Mead NJ) 47. DOI: 10.12788/ajo.2018.0098.
30. Bannuru RR, MC Osani, EE Vaysbrot, NK Arden, K Bennell, SMA Bierma-Zeinstra, VB Kraus, LS Lohmander, JH Abbott, et al. (2019). OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 27:1578–1589.
31. Sundman EA, BJ Cole, V Karas, C Della Valle, MW Tetreault, HO Mohammed and LA Fortier. (2014). The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med 42: 35–41.
32. Cook CS and PA Smith. (2018). Clinical update: Why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. Curr Rev Musculoskelet Med 11: 583–592.
33. Lin KY, CC Yang, CJ Hsu, ML Yeh and JH Renn. (2019). Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthroscopy 35:106–117.
34. Riboh JC, BM Saltzman, AB Yanke, L Fortier and BJ Cole. (2016). Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. Am J Sports Med 44:792–800.

35. Riboh JC, BM Saltzman, AB Yanke and BJ Cole. (2016). Human amniotic membrane-derived products in sports medicine: basic science, early results, and potential clinical applications. Am J Sports Med 44:2425–2434.
36. Braun HJ, HJ Kim, CR Chu and JL Dragoo. (2014). The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. Am J Sports Med 42:1204–1210.
37. Chen WH, WC Lo, WC Hsu, HJ Wei, HY Liu, CH Lee, SY Tina Chen, YH Shieh, DF Williams and WP Deng. (2014). Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. Biomaterials 35:9599–9607.
38. Karasavvidis T, T Totlis, R Gilat and BJ Cole. (2021). Platelet-rich plasma combined with hyaluronic acid improves pain and function compared with hyaluronic acid alone in knee osteoarthritis: a systematic review and meta-analysis. Arthroscopy 37:1277–1287.e1.
39. Lana JF, A Weglein, SE Sampson, EF Vicente, SC Huber, CV Souza, MA Ambach, H Vincent, A Urban-Paffaro, et al. (2016). Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. J Stem Cells Regen Med 12:69–78.
40. Gobbi A, D Lad and G Karnatzikos. (2015). The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 23:2170–2177.
41. Gormeli G, CA Gormeli, B Ataoglu, C Colak, O Aslanturk and K Ertem. (2017). Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 25:958–965.
42. Johal H, M Khan, SP Yung, MS Dhillon, FH Fu, A Bedi and M Bhandari. (2019). Impact of platelet-rich plasma use on pain in orthopaedic surgery: a systematic review and meta-analysis. Sports Health 11:355–366.
43. Chahla J, ME Cinque, NS Piuzzi, S Mannava, AG Geeslin, IR Murray, GJ Dornan, GF Muschler and RF LaPrade. (2017). A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. J Bone Joint Surg Am 99:1769–1779.
44. Murphy MB, K Moncivais and AI Caplan. (2013). Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 45:e54.
45. Madry H, L Gao, H Eichler, P Orth and M Cucchiarini. (2017). Bone marrow aspirate concentrate-enhanced marrow stimulation of chondral defects. Stem Cells Int 2017:1609685.
46. Lopa S, A Colombini, M Moretti and L de Girolamo. (2019). Injective mesenchymal stem cell-based treatments for knee osteoarthritis: from mechanisms of action to current clinical evidences. Knee Surg Sports Traumatol Arthrosc 27:2003–2020.
47. Garza JR, RE Campbell, FP Tjoumakaris, KB Freedman, LS Miller, D Santa Maria and BS Tucker. (2020). Clinical efficacy of intra-articular mesenchymal stromal cells for the treatment of knee osteoarthritis: a double-blinded prospective randomized controlled clinical trial. Am J Sports Med 48:588–598.
48. Murray IR, J Chahla, MR Safran, AJ Krych, DBF Saris, AI Caplan and RF LaPrade. (2019). International expert consensus on a cell therapy communication tool: DOSES. J Bone Joint Surg Am 101:904–911.
49. Chu CR, S Rodeo, N Bhutani, LR Goodrich, J Huard, J Irrgang, RF LaPrade, C Lattermann, Y Lu, et al. (2019). Optimizing clinical use of biologics in orthopaedic surgery: consensus recommendations from the 2018 AAOS/NIH U-13 conference. J Am Acad Orthop Surg 27:e50–e63.
50. Bendich I, WJ Rubenstein, BJ Cole, CB Ma, BT Feeley and DA Lansdown. (2020). What is the appropriate price for PRP injections for knee osteoarthritis? A cost-effectiveness analysis based on evidence from level 1 randomized controlled trials. Arthroscopy 36:1983–1991.e1.

Address correspondence to:
Dr. Ignacio Dallo
O.A.S.I. Bioresearch Foundation
Gobbi Onlus
20133 Milano
Italy

E-mail: doctorignaciodallo@gmail.com

Received for publication March 11, 2021
Accepted after revision April 19, 2021
Prepublished on Liebert Instant Online April 24, 2021