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Novel P.A.S.T.A. Technique Combining PRP and MSCs from SVF Shows Improved Outcomes at Short-/Long-Term Follow-Up for Osteoarthritis and Chondropathy

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Keywords: Osteoarthritis; Chondropathy; Mesenchymal stem cells; Platelet-rich plasma; Stromal vascular fraction; Orthobiologics.

Abstract

Purpose: The aim of this study is to evaluate the outcomes of a novel technique to treat osteoarthritis and chondropathy, termed "P.A.S.T.A." for **P**latelets **A**dipose **S**tromal **T**reatment for **A**rthritis. This technique utilizes the combination of platelet-rich plasma (PRP) derived from peripheral blood and mesenchymal stem cells (MSCs) derived from stromal vascular fraction (SVF) sourced from microfragmented adipose tissue. We hypothesized that with this new technique, we could take advantage of mesenchymal stem cell's ability to stimulate cartilage regeneration and improve joint symptoms as well as act synergistically with growth factors and cytokines in platelet-rich plasma, further enhancing the healing process.

Methods: This is a prospective, single-center, cohort study encompassing 131 participants with osteoarthritis or chondropathy undergoing our P.A.S.T.A. procedure; we evaluated the quality of life, functional, and clinical outcomes of patients receiving a single dose of combined PRP and MSCs derived from adipose tissue processed into SVF. The primary outcome measure was the Knee Injury and Osteoarthritis Outcome Score (KOOS), however with any occurrences of adverse effects, the Visual Analogue Scale (VAS), and the European Quality of Life (EQL) surveys were also collected during follow-up. Outcomes and patient factors were compared preoperatively, at 6-month, 1-year, 2-year, and 4-year follow-ups. Statistical models were used to assess KOOS, VAS, and EQLs.

Results: Treatment with the novel P.A.S.T.A. technique for the treatment of osteoarthritis and chondropathy had significantly improved KOOS scores, VAS scores, and EQL at 6-months, 1-year, 2-years, and 4-years postoperatively.

Conclusion: This study shows combining PRP and MSCs derived from SVF in our novel P.A.S.T.A. technique leads to improved quality of life, functional, and clinical outcomes in the short- and long-term follow-up. This demonstrates that this technique could be a safe and effective non-surgical alternative, preventing or delaying the need for surgeries such as cartilage reconstruction or arthroplasty.

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Introduction

In the current age, characterized by significant advancements in both physiological and pathological insights and technological developments in orthobiologics, platelet-rich plasma (PRP), hyaluronic acid (HA), and mesenchymal stem cells (MSCs), now termed "medicinal signaling cells," have emerged as important tools in a clinician's arsenal in the non-surgical treatment of osteoarthritis and chondropathy. Their simplicity in production, preparation, storage, and administration has made them valuable in the treatment of a variety of musculoskeletal disorders, particularly in cases of osteoarthritis and chondropathy.

PRP has gained significant recognition as a valuable therapeutic approach within the field of orthopaedics. Among the various orthobiologics available, PRP is particularly notable for its widespread application in addressing joint disorders and injuries involving cartilage, tendons, muscles, ligaments, and menisci. PRP is produced from plasma obtained through the centrifugation of autologous blood, resulting in a concentration of platelets that surpasses the normal baseline levels [1]. After the activation of platelets (endogenous or exogenous), a variety of molecules are released from their distinct granules, which are essential for processes such as hemostasis, immune function, inflammation, and regenerative mechanisms. Three key granules play a crucial role in defining the functionality of platelets: α-granules, dense granules, and lysosomes. However, the α-granules exhibit the primary role in regeneration, being rich in a diverse array of cytokines and growth factors (Table 1). These bioactive substances contained in α-granules are essential for facilitating tissue repair by promoting processes like angiogenesis and neovascularization as well as cell proliferation, chemotaxis, and differentiation [2-7]. By effectively isolating and concentrating these critical cytokines and growth factors, the application of PRP to injury sites can markedly enhance the healing process, particularly in cases of chondral defects and osteoarthritis [8].

Table 1: Platelet granules and contents.

α-granules	Dense Granules	Lysosomes
Adhesion Proteins (ie: Fibrinogen, von Willebrand factor)	Bioactive Amines (ie: 5-HT, Histamine)	Acid Proteases (ie: Carboxypeptidases, Cathepsins, Acid Phosphatase, Collagenase)
Angiogenic Factors (ie: EGF, ECGF, TGFβ, IGF-1 and -2, FGF, PDGF, VEGF)	Cations (ie: Ca^{2+}, Mg^{2+}, K^{+})	Glycohydrolases (ie: Heparinase, β-glucuronidase, β-galactosidase, α-D- glucosidase)
Chemokines (ie: CCL2, CCL3, CCL5, CXCL4, CXCL12)	Nucleotides (ie: ADP, ATP)	
Coagulant/Anticoagulant and Fibrinolytic Proteins (Factor V, Factor IX, Factor XIII, Plasminogen)	Polyphosphates	
Immune Mediators (ie: IgG, complement precursors)		
Integral Membrane Proteins (ie: P-selectins, GPIbα)		

MSCs are typically sourced from bone marrow aspirate (BMA) bone marrow aspirate concentrate (BMAC) and microfragmented adipose tissue and play a crucial role as trophic mediators rather than merely serving as progenitor cells, representing a notable advancement in regenerative medicine. These cells significantly influence the local cellular environment through the secretion of bioactive molecules. This expanded understanding brings to light the paracrine roles of MSCs, which include immune modulation, anti-inflammatory actions, facilitation of angiogenesis, and activation of local repair processes. This understanding of MSCs as trophic mediators highlights their capacity to foster an optimal microenvironment conducive to healing and regeneration, thereby reinforcing their significance in the treatment of various musculoskeletal disorders. The benefits of utilizing microfragmented adipose tissue as a source of MSCs are particularly evident due to its straightforward collection process, minimal invasiveness, and high cell yield. Furthermore, the combination of BMA and adipose-derived MSCs, whether used independently or alongside other cartilage repair techniques such as debridement, microfracture, and biologic scaffolds, has been shown to enhance functional outcomes, clinical efficacy, and pain alleviation.

Gobbi et al. were some of the first investigators to investigate the role of autologous microfragmented adipose tissue in the treatment of cartilage defects and osteoarthritis [8,9]. This technique utilized a product that was initially intended for plastic surgery and reconstruction, namely the Lipogems® system (Lipogems International SpA, Milan, Italy), in which MSCs were obtained through volumetric reduction through microfracturing of adipose tissue through a series of filtration and manual shaking. Through international investigation, this treatment of utilizing MSCs to treat osteoarthritis was shown to be effective in improving both clinical and functional outcomes.

During this time, the use of biologic injectables for orthopaedic treatments was still in its infant stages, as PRP was not yet a household name, lacking the scientific guidelines, consensus and immense scientific research that we see today. After publishing their results on microfragmented adipose tissue, along with their successes on treating osteoarthritis and chondropathy using various matrices and scaffolds combined with MSCs derived from BMAC [10,11], Dr. Gobbi wanted to investigate the regenerative and clinical potential of combining the effects of both PRP and MSCs. Starting from the mid-2010s to the present, Dr. Gobbi had proposed his novel technique combining both adipose-derived MSCs and PRP, termed "P.A.S.T.A." for **P**latelets **A**dipose **S**tromal **T**reatment for **A**rthritis [12], in many international congresses, such as the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS), European Society of Sports Traumatology, Knee Surgery & Arthroscopy (ESSKA), International Cartilage Regeneration and Joint Preservation Society (ICRS), Joint Preservation Congress, International Sports Medicine Fellows Conferences, and Annual Conferences of Indian Arthroscopy Society. Here, he had hoped to introduce a new idea that the growth factors and cytokines found in PRP may act synergistically with the regenerative potential of MSCs in the treatment of cartilage diseases.

The aim of this study is to evaluate the outcomes of the novel P.A.S.T.A. technique and its use in the treatment of joint arthritis and chondral pathologies. This novel technique utilizes the combination of autologous leukocyte-poor PRP derived from peripheral blood and MSCs derived from SVF sourced from microfragmented adipose tissue harvested from the ab-

domen or supra-gluteal area. We hypothesized that with this new technique we take advantage of MSCs' ability to stimulate cartilage regeneration and improve joint symptoms, as well as act synergistically with growth factors and cytokines in PRP, further enhancing the healing process, improving quality of life, functional, and clinical outcomes.

Materials and methods

This is a prospective, single-center, cohort study encompassing 131 participants with osteoarthritis or chondropathy undergoing our P.A.S.T.A. procedure, receiving a single dose of PRP and MSCs derived from adipose tissue processed into SVF was conducted with the highest respect for the individual participants. The present study is conducted in accordance with the ethical considerations and principles outlined in applicable guidelines, including the Declaration of Helsinki, the WHO guidelines, and the International Conference on Harmonization's Good Clinical Practice. Before the beginning of any study-related activities, each study participant signed informed consent.

The inclusion criteria are as follows: 18 years old or older, knee osteoarthritis Kellgren-Lawrence grade II to IV, single chondral lesions Outerbridge grade II to IV, history of chronic (≥6 months) pain or knee swelling, and limitation of daily activities or sport. Exclusion criteria are the following: previous surgeries or procedures in the involved knee, associated injuries of the menisci and ligaments around the knee, use of corticosteroids or use of non-steroidal anti-inflammatory drugs (NSAIDs) at least 1 month prior to treatment, previous injections of PRP, HA, or other orthobiologics, varus/valgus joint malalignment greater than 8 degrees, and cutaneous infections in the area to be injected.

Standard standing, weight-bearing, anterior-posterior radiographs of the lower extremity and knees were performed to determine the osteoarthritis grade and joint alignment, while standard plain (non-contrast) magnetic resonance imaging was performed to determine the Outerbridge grade. All patients were treated at the O.A.S.I. Medical Center under a single surgeon, abiding by a standardized surgical technique, following the same inclusion criteria, and were prospectively evaluated preoperatively and at 6-month, 1-year, 2-year, and 4-year follow-up visits.

Surgical technique

For adipose tissue collection, the participants were placed in supine position (abdominal collection) or prone position (supra-gluteal collection) and local anesthesia (Klein Solution) was administered at the incision sites before the procedure. The subcutaneous fat from the abdominal area was infiltrated with up to 300 mL of tumescent fluid (comprised of 30 mL of 2% lidocaine, 1 mL of 1:1000 adrenaline, and 1 mL of 8.4% bicarbonate suspended in a normal saline solution for a total of 1000 mL) (Figure 1A). Following infiltration, approximately 15 minutes were allowed to ensure the solution takes effect. Once the adipose tissue was properly anesthetized, aspiration of adipose tissue commenced with the use of a 3 mm lipoaspirate harvesting cannula connected to a 50 mL syringe (Figure 1B). It is important to allow proper separation of the adipose tissue from the other elements aspirated by positioning each syringe in an upright position (Figure 1C). Once proper separation is achieved and adipose tissue has settled and collected at the top of the syringe, the remaining dependent fluid and tissue elements were discarded (Figure 1D).

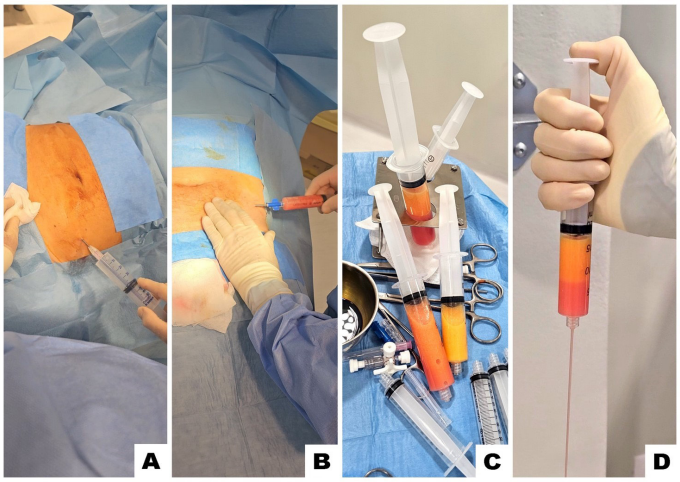

Figure 1: **(A)** Administration of Klein solution into the abdomen. **(B)** Lipoaspiration of abdominal adipose tissue. **(C)** Three syringes showing newly aspirated lipoaspirate, settling of lipoaspirate from other elements, and isolated fatty-rich lipoaspirate tissue. **(D)** Once fatty-rich lipoaspirate tissue has settled to the top, discard the remaining fluid and tissue elements.

A total of 30 to 60 mL (30 mL for single knee infiltration, 60 mL for bilateral knee infiltration) of fatty-rich lipoaspirate tissue is collected and transferred to Arthrex ACP® Double-Syringe Systems (Arthrex GmbH, Munich, Germany) (Figure 2A) using a three-way valve connector plug, where they undergo the first round of centrifugation for 4 minutes at 2,500 rpm. This allows separation of the different fractions by gravitational force. Once centrifugation is completed, there should be 3 distinct layers (Figure 2B) within the Arthrex ACP® Double-Syringe System: (from top to bottom) 1) oil from ruptured adipocytes, 2) condensed fatty-rich lipoaspirate, and 3) aqueous fraction. Through the use of the double syringe system, we utilize the smaller inner syringe to aspirate the topmost layer of oil from ruptured adipocytes (Figure 2C). While the inner syringe is out, the red stopper is removed to allow for the aqueous solution to drain out spontaneously by gravitational force (Figure 2D). After the oil and aqueous layers are discarded, the middle layer of condensed lipoaspirate is transferred and divided equally into two appropriately sized syringes (typically 20 – 30 mL).

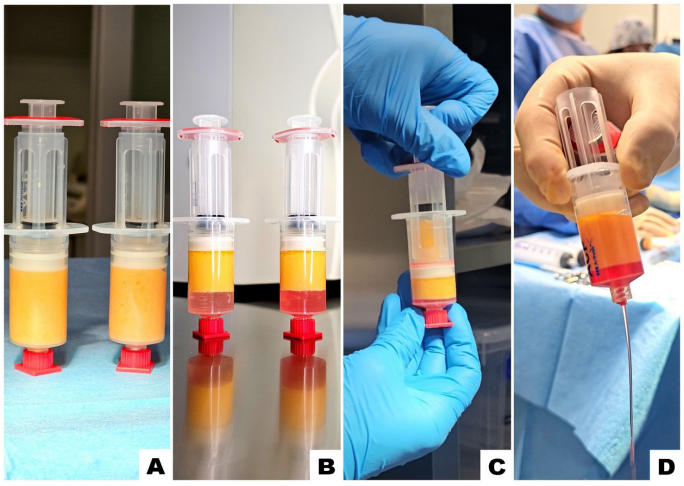

Figure 2: **(A)** Condensed fatty-rich lipoaspirate tissue is collected and transferred to Arthrex ACP Double-Syringe Systems. **(B)** After 1st centrifugation. Amount and distribution of layers may vary from case to case. **(C)** Aspirate the oil layer using the inner syringe. **(D)** After removing the red stopper, allow the aqueous solution to drain out spontaneously.

The two syringes containing the condensed lipoaspirate are then connected using a 1.4 mm female luer lock connector. The lipoaspirate is then passed from one syringe to the other 30 times through the 1.4 mm female luer lock connector to allow microfragmentation of the condensed fatty-rich lipoaspirate (Figure 3A). Once microfragmentation of the condensed fatty-rich lipoaspirate is complete, the newly microfragmented condensed lipoaspirate is then divided equally into two Arthrex ACP Double-Syringe Systems, where they will undergo a 2nd round of centrifugation, again, for 4 minutes at 2,500 rpm. After the 2nd round of centrifugation, there should be 3 distinct layers (Figure 3B) within the Arthrex ACP Double-Syringe System (from top to bottom): 1) oil from ruptured adipocytes from microfragmentation, 2) SVF, and 3) aqueous fraction. The SVF is then isolated by aspirating the topmost layer of oil using the inner syringe (Figure 3C).

Towards the concluding stages of the SVF processing, PRP is processed starting with the collection of 15 mL of peripheral blood from the upper extremity of the patient, typically from the basilic vein, median cubital vein, or cephalic vein located in the cubital fossa using a 20-gauge or 21-gauge butterfly needle set, directly into an Arthrex ACP® Double-Syringe System. In cases of bilateral knee treatment, a total of 30mL of peripheral blood is collected into two Arthrex ACP® Double-Syringe Systems. The remaining blood contained within the butterfly needle set is then analyzed using an in-house hematology analyzer (Horiba ABX Micros ES 60), where red blood cells, white blood cells, and platelet values were analyzed. An important note about our technique is that we do not add anticoagulant to our Arthrex ACP® Double-Syringe System as we centrifuge the Arthrex ACP® Double-Syringe System immediately after collection. We typically do not add anticoagulant as we have noticed decreased amounts of platelet concentration when adding anticoagulant prior to peripheral blood collection. Once the appropriate amount of peripheral blood is collected into the Arthrex ACP® Double-Syringe System(s), we centrifuge for 5 minutes at 1,500 rpm. After centrifugation, the PRP layer is then collected (Figure 3D) using the inner syringe and analyzed again using our hematology analyzer.

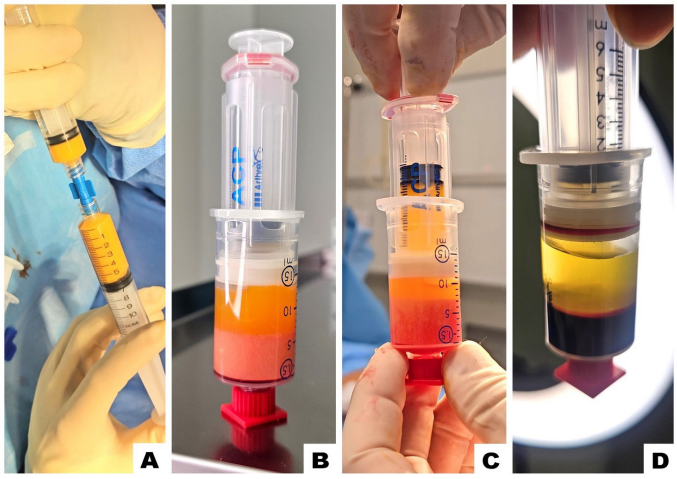

Figure 3: **(A)** Microfragmentation step. **(B)** After 2nd centrifugation. Three distinct layers will be seen. **(C)** Aspirate the oil layer using the inner syringe. **(D)** Prepared PRP from peripheral blood using the Arthrex ACP® Double-Syringe System.

The PRP solution and the isolated SVF are then mixed together, passing the mixture from one syringe to another 10 times (Figure 4A/4B). After mixing the PRP and SVF solutions, this single mixture is then administered into the appropriate knee using the lateral suprapatellar intra-articular approach (Figure 4C).

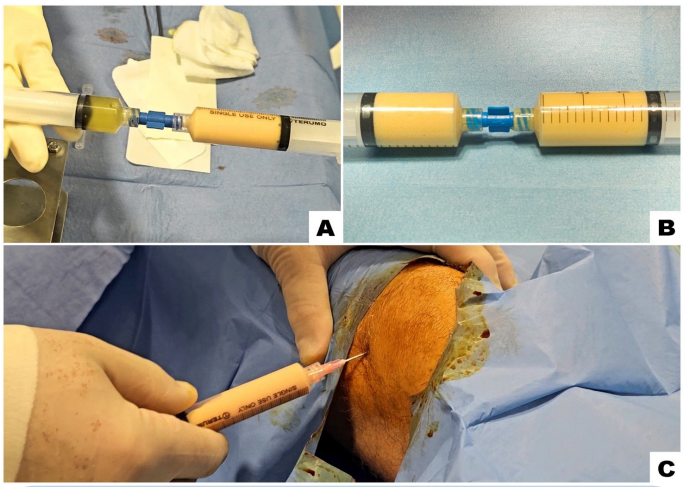

Figure 4: **(A)** Mixing of PRP with SVF. **(B)** Final product prior to injection. **(C)** PRP and SVF mixture injected using the lateral suprapatellar intra-articular approach.

Postoperatively, we applied an abdominal binder and compression sleeves over the abdomen (in participants who had undergone abdominal collection) and injected knees, respectively, to prevent any possible hematoma formation and swelling (Figure 5). No functional limitations or precautions were advised postoperatively and patients were allowed to ambulate without any assistive device after the procedure. Patients were advised on proper hygiene and wound care procedures to prevent any post-treatment infections. Paracetamol was given on an "as needed" basis in the event the patient experienced immediate postoperative pain. Anti-inflammatories or NSAIDs were not advised.

Figure 5: Abdominal binder and compression sleeves over the abdomen and injected knees.

Statistical analysis

The primary outcome measure was the Knee Injury and Osteoarthritis Outcome Score (KOOS); however, any occurrence of adverse events, Visual Analogue Scale (VAS), and European Quality of Life (EQL) surveys were also collected prior to undergoing the P.A.S.T.A. procedure and at 6-month, 1-year, 2-year, and 4-year follow-up visits. Data encoding was done using Microsoft Excel for ease of encoding. Completeness, consistency, and errors were checked. All data sets were encoded and analyzed using STATA15. Descriptive statistics such as mean and standard deviation were used to present data on the demographic and clinical profile of the included patients. Frequency and percentages were used to present categorical data. Graphi-

cal presentation was also utilized in presenting the data. Differences in the characteristics were compared using Student's T-test for continuous variables and the Chi-Square Test for categorical variables. The outcomes of interest were presented as mean and standard deviation. Differences in the outcomes of interest between timepoints and other variables were determined using repeated-measures ANOVA, which was followed by post-hoc analysis using Tukey HSD for pairwise comparison to determine which timepoints have significant differences. *P*-values <0.05 were considered statistically significant. Sample size was calculated to achieve a power of 0.80.

Results

Amongst the 131 participants in our study, the mean age of all participants was 63.58 years old (45–83 years old). There was no significant variation between the chondropathy and osteoarthritis groups in terms of gender and laterality. The majority of patients in the osteoarthritis group had Kellgren-Lawrence grades of II and III, with only 12 participants (17.4%) with grade IV osteoarthritis. Amongst the chondropathy group, 18 participants (29.0%) had lesions of Outerbridge grade II, 25 participants (40.3%) with Outerbridge grade III, and 19 participants (30.7%) with Outerbridge grade IV (Table 2).

Table 2: Demographic, clinical profile, and diagnosis of the participants.

	Total n=131	Chondropathy n=62	Osteoarthritis n=69	*P*-values
Age	63.58 ± 9.76	57.89 ± 10.23	68.70 ± 5.73	<0.0001[a]
Gender				
Female	74 (56.5)	32 (51.6)	42 (60.9)	0.536[b]
Male	57 (43.5)	30 (48.4)	27 (39.1)	
Laterality				
Left	55 (42.0)	23 (37.1)	32 (46.4)	0.462[b]
Right	76 (58.0)	39 (62.9)	37 (53.6)	
Kellgren-Lawrence Type (Osteoarthritis)				
II			27 (39.1)	
III			30 (43.5)	
IV			12 (17.4)	
Outerbridge Grade (Chondropathy)				
II		18 (29.0)		
III		25 (40.3)		
IV		19 (30.7)		

Presented as Mean±SD; Frequently (%)
[a]Student's T-test
[b]Chi-square Test

Table 3: Comparison of EQL, VAS, and KOOS preoperatively and on follow-up.

	PREOP	6 months	1 year	2 year	4 year	P-value
EQL VAS	30.98 ± 13.05	69.20 ± 19.60	73.00 ± 24.41	73.75 ± 22.58	79.57 ± 14.21	<0.0001
Mobility	3.57 ± 0.60	1.98 ± 0.74	1.88 ± 0.89	1.71 ± 0.93	1.57 ± 0.73	<0.0001
Self-Care	3.54 ± 0.66	2.02 ± 0.72	1.90 ± 0.88	1.76 ± 0.92	1.74 ± 1.01	<0.0001
Usual Activities	3.70 ± 0.57	2.05 ± 0.74	1.84 ± 0.95	1.68 ± 0.99	1.74 ± 1.10	<0.0001
Pain/Discomfort	3.73 ± 0.55	2.09 ± 0.71	1.90 ± 0.92	1.76 ± 0.97	1.83 ± 1.07	<0.0001
Anxiety/Depression	1.12 ± 0.47	1.05 ± 0.23	1.04 ± 0.20	1.00 ± 0.00	1.00 ± 0.00	0.0665
VAS	6.74 ± 2.00	2.88 ± 1.83	2.53 ± 2.07	2.59 ± 2.16	2.35 ± 1.34	<0.0001
TOTAL KOOS	39.79 ± 18.68	77.35 ± 18.04	79.40 ± 18.04	81.29 ± 21.82	82.49 ± 21.09	<0.0001
Symptoms/Stiffness	47.24 ± 23.15	81.03 ± 17.35	82.39 ± 19.24	84.74 ± 20.59	85.53 ± 18.48	<0.0001
Pain	42.60 ± 23.33	78.57 ± 18.46	79.27 ± 19.94	82.18 ± 21.84	81.15 ± 23.59	<0.0001
Activities of Daily Living	45.74 ± 23.64	81.84 ± 19.53	82.99 ± 18.41	84.15 ± 20.64	82.42 ± 22.26	<0.0001
Sports and Recreational Activities	31.58 ± 16.93	70.53 ± 21.60	74.51 ± 23.20	77.80 ± 27.98	82.39 ± 21.47	<0.0001
Quality of Life	31.80 ± 18.61	74.78 ± 21.19	77.82 ± 21.37	77.59 ± 25.27	80.98 ± 23.12	<0.0001

When comparing all participants as a whole, there were significant improvements in all outcome parameters: KOOS, VAS, and EQL. The EQL subcategory of anxiety and depression had no significant change, as the mean anxiety and depression score was already at the lowest possible score of 1.12 preoperatively. This signifies that the participants did not experience a significant amount of depression or anxiety as a result of their pathology, be it chondropathy or osteoarthritis. From 6 months to 4 years postoperatively, there was a steady improvement in anxiety and depression scores, reaching the lowest value; however, as their preoperative scores were already at the best functional value, statistically, there was no significant change (Table 3).

There was an increase of 44.54% in the EQL mobility score at the 6-month follow-up compared to preoperative scores and increased to 56.02% at the 4-year follow-up. For EQL self-care, we appreciate an increase of 42.94% at the 6-month follow-up with a continued increasing trend to 50.85% at the 4-year follow-up. EQL usual activities showed an initial improvement of 44.59% at the 6-month follow-up with consistent improvement to 52.97% at the 4-year follow-up. For EQL pain and discomfort, we appreciate an increase of 43.97% at 6-month follow-up with a steady increase to 50.94% at the 4-year follow-up. The EQL anxiety and depression score had an improvement of 6.25% and settled at a score improvement of 10.71% at the 2-year and 4-year follow-ups.

VAS pain scores decreased by 57.27% at 6 months, while at the 4-year follow-up there was still continued decrease in pain by 65.13% (Figure 6).

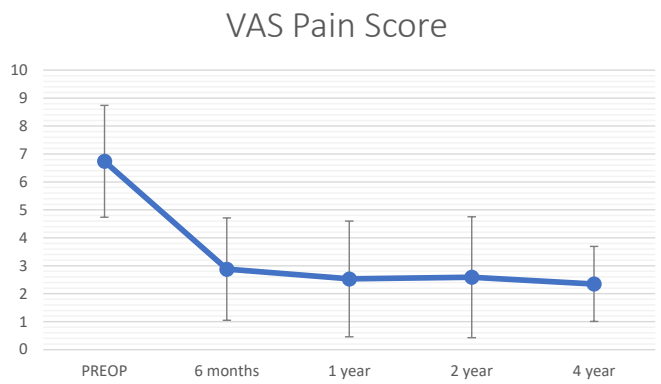

Figure 6: Consistent and sustained improvement in VAS pain scores from 6 months to 4 years.

Upon comparing the improvements of the KOOS categories at 6-month and 4-year follow-ups (Figure 7), the total KOOS score showed an increase of 48.56% and 51.76%, respectively; KOOS symptoms and stiffness by 41.70% and 44.77%; KOOS pain of 45.78% and 47.50%; KOOS activities of daily living by 44.11% and 44.50%; KOOS sports and recreational activities by 55.22% and 61.67%; and KOOS quality of life by 57.48% and 60.73%.

When stratifying chondropathy and osteoarthritis groups separately, there were still significant improvements in all outcome parameters: at 6-months, 1-year, 2-years, and 4-years follow-up visits compared to preoperative scores. In patients with chondropathy, there was continuous improvement in all outcome scores from 6 months to 4 years postoperatively; however, in the osteoarthritis group, no outcome parameter showed a consistent improvement as time went on, with some outcome measures showing a non-significant slight decline from the 1-year to 2-year follow-up or 2-year to 4-year follow-up (Table 4).

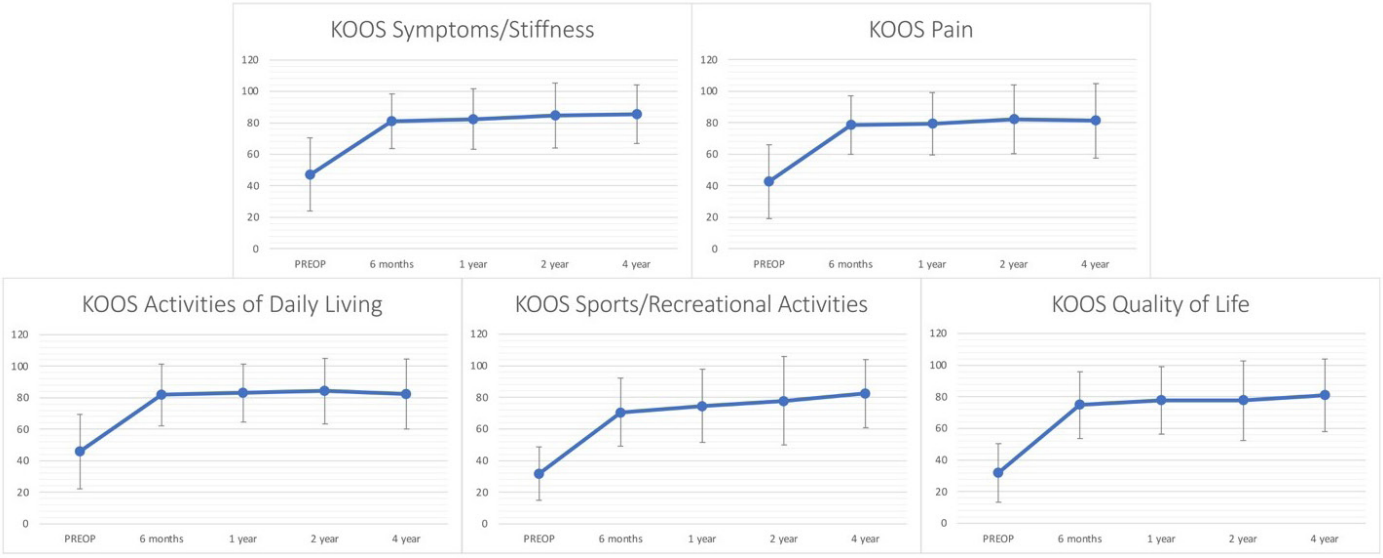

Figure 7: Consistent and sustained improvement in KOOS subscales from 6 months to 4 years.

Table 4: Comparison of EQL, VAS, and KOOS preoperatively and on follow-up by pathology.

	PREOP	6 months	1 year	2 year	4 year	*P*-value
EQL VAS						
Osteoarthritis	32.0 ± 9.6	64.8 ± 22.6	68.3 ± 28.4	67.4 ± 25.8	70.8 ± 13.6	<0.0001
Chondropathy	29.8 ± 16.3	74.2 ± 14.2	80.0 ± 14.9	82.4 ± 13.9	89.1 ± 7.0	<0.0001
VAS						
Osteoarthritis	6.7 ± 1.5	3.2 ± 2.0	2.7 ± 2.4	2.9 ± 2.5	2.8 ± 1.5	<0.0001
Chondropathy	6.8 ± 2.4	2.6 ± 1.6	2.3 ± 1.6	2.2 ± 1.6	1.8 ± 0.9	<0.0001
TOTAL KOOS						
Osteoarthritis	42.2 ± 12.6	76.1 ± 20.9	77.1 ± 22.3	78.5 ± 26.0	74.6 ± 24.9	<0.0001
Chondropathy	37.1 ± 23.7	78.8 ± 14.5	82.7 ± 13.4	84.9 ± 14.9	91.1 ± 11.8	<0.0001
Symptoms/Stiffness						
Osteoarthritis	53.2 ± 18.5	82.1 ± 18.8	82.6 ± 20.4	83.4 ± 23.8	80.1 ± 21.7	<0.0001
Chondropathy	40.6 ± 26.2	79.9 ± 15.8	82.1 ± 17.9	85.9 ± 16.1	91.5 ± 12.6	<0.0001
Pain						
Osteoarthritis	45.5 ± 16.4	77.1 ± 20.5	77.1 ± 22.5	79.5 ± 25.3	71.4 ± 27.6	<0.0001
Chondropathy	39.4 ± 29.6	80.2 ± 16.2	82.4 ± 15.7	85.6 ± 16.4	91.8 ± 12.1	<0.0001
Activities of Daily Living						
Osteoarthritis	47.1 ± 18.2	80.8 ± 21.7	80.0 ± 21.4	79.8 ± 24.8	72.8 ± 25.5	<0.0001
Chondropathy	44.2 ± 28.8	83.0 ± 17.2	87.3 ± 12.4	89.7 ± 12.3	92.9 ± 12.0	<0.0001

Sports and Recreational Activities						
Osteoarthritis	31.5 ± 12.1	67.3 ± 25.5	71.3 ± 26.5	75.4 ± 28.8	75.0 ± 25.5	<0.0001
Chondropathy	31.7 ± 21.3	74.1 ± 16.0	79.0 ± 17.1	80.8 ± 19.3	90.4 ± 12.7	<0.0001
Quality of Life						
Osteoarthritis	33.8 ± 13.1	72.9 ± 24.9	74.6 ± 25.2	73.9 ± 30.2	74.0 ± 28.3	<0.0001
Chondropathy	29.6 ± 23.4	76.9 ± 16.4	82.4 ± 13.6	82.3 ± 16.6	88.6 ± 13.4	<0.0001

Table 5: Number of osteoarthritis participants needing arthroplasty.

	n	No	Yes	*P*-values
Kellgren Lawrence Type (Osteoarthritis)				
II	18	18 (100.0)	0	0.011
III	25	19 (76.0)	6 (24.0)	
IV	19	10 (52.6)	9 (47.4)	

The most common adverse event after performing the P.A.S.T.A. procedure was postoperative donor site pain requiring paracetamol lasting for a mean time of 3.7 days in 82 participants (62.5%). The second most common adverse event was postoperative swelling and inflammation at the administration site for a mean time of 5.8 days in 45 patients (34.3%). There were no serious adverse effects such as infection or allergic reactions requiring intervention or need for antibiotics after performing the P.A.S.T.A. procedure in any of the participants; however, there was a total of 15 participants who eventually underwent arthroplasty. All 15 participants were in the osteoarthritis group and underwent arthroplasty under a different surgeon after the 4-year follow-up due to recurrence of pain. No patient in the osteoarthritis group with Kellgren-Lawrence Grade II underwent arthroplasty, but 6 out of 25 participants with Kellgren-Lawrence Grade III and 9 out of 19 participants with Kellgren-Lawrence Grade IV eventually underwent total knee arthroplasty. There was a significant increase in the incidence of total knee arthroplasty in those who underwent the P.A.S.T.A. procedure with increasing Kellgren-Lawrence grade (Table 4). There was only 1 participant in the chondropathy group who had surgery on the affected knee in the postoperative period. This patient eventually had arthroscopy and cartilage repair using a 1-stage technique of a hyaluronic acid-based scaffold with activated bone marrow aspirate concentrate (HA-BMAC) after the 4-year follow-up due to recurrence of pain.

Discussion

Articular cartilage plays a crucial role within the complex architecture of the knee joint. Its primary function is to create a low-friction surface that facilitates movement while also serving as a cushion to effectively distribute forces. However, the cartilage is deprived of a rich supply of nutrients and progenitor cells, which makes it particularly susceptible to injury. The presence of isolated chondral lesions is linked to the initiation and progression of osteoarthritis. Cartilage injuries in the knee are prevalent, impacting more than one-third of athletes, in contrast to less than one-fifth of the general population [13]. Cartilage injuries may arise from an acute trauma, such as a chondral fracture caused by shear and/or compression forces, or they can develop as a consequence of repetitive microtrauma associated with athletic activities [14-17]. These injuries can lead to considerable morbidity and often result in the end of athletic careers. Furthermore, focal cartilage defects have been identified in 60-67% of patients undergoing knee arthroscopy [18]. Traumatic damage to the cartilage can trigger a series of pathological events within the joint environment, ultimately leading to joint degeneration [19].

Osteoarthritis is estimated to impact over 7.6% of the global population, with prevalence higher in women than in men. Age is an important factor in the prevalence of osteoarthritis, where it increases by 132.2% in individuals over 30 years with an expected rise of 60 to 100% by 2050. In fact, in ages older than 70 years old, osteoarthritis ranks 7th worldwide in the leading causes of disability. However, osteoarthritis is not simply a disease of the old, as more than half of new cases of early-onset osteoarthritis are seen before 55 years of age. This incidence and prevalence of early-onset osteoarthritis has doubled in the last 30 years [20].

With the knee being the most common joint affected by osteoarthritis [21], focus has shifted towards conservative management strategies to tackle early and moderate stages of the disease, especially in the young [22]. The use of orthobiologics has become the front-runner in addressing this problem. Orthobiologic products, such as PRP, HA, and MSCs, with their relative ease associated with their production, preparation, storage, and administration, have become vital components in the therapeutic strategies for numerous musculoskeletal ailments, particularly in the context of chondral injuries and arthritis [8-12,23-51].

The concept of MSCs was introduced by Arnold Caplan in 1991. Initially, it was posited that MSCs are not limited to embryonic stages but are also present in adult tissues. These autologous MSCs, with their remarkable self-repair abilities, could potentially form the basis for innovative regenerative medicine approaches through cell-based technologies. MSCs are recognized as multipotent stem cells, with the capacity to differentiate into a variety of mesodermal tissues, such as bone, muscle, adipose tissue, tendons, ligaments, and cartilage. This multipotency, allowing for differentiation into diverse tissue lineages, was the key reason Caplan initially referred to these cells as "stem cells" [52].

Caplan recognized the potential of MSCs in the repair of bone and cartilage. He noted that a specific subset of osteochondral progenitor cells, upon commitment to a particular lineage, could differentiate into these types of tissues. Caplan's significant insights into the role of MSCs in the body were substantially enhanced by the research conducted by Crisan et al. [53], which elucidated the relationship between MSCs and perivascular cells, subsequently termed "pericytes." Due to their perivascular origin, MSCs function through two primary mechanisms: immunomodulation and trophic support [54].

Following tissue injury, disease, or inflammation, MSCs are known to secrete bioactive molecules that facilitate immunomodulatory and trophic processes. These molecules effectively inhibit T-cell interactions with antigens and restrict the proliferation of T-cell progenitors. This action serves to protect the injured area from the body's immune system, thereby reducing

the likelihood of autoimmune reactions. Furthermore, activated MSCs play a significant role in dampening chronic inflammatory responses, preventing apoptosis, especially in ischemic scenarios, suppressing the formation of myofibroblasts to avert scar tissue development, stimulating the proliferation of intrinsic tissue progenitors for repair, and promoting angiogenesis and vessel stabilization through their pericyte-like activities [53,55,56]. The secretion of bioactive substances can generate a unique regenerative microenvironment that encourages the repair of injured tissues. MSCs serve as a comprehensive reservoir of therapeutic agents (Table 6), functioning similarly to a "drugstore" to promote and facilitate natural tissue regeneration, prompting Caplan to adopt the new name for MSCs as "medicinal signaling cells" [57]. Interactions between prostaglandin E2 and the EP4 receptor on stimulated M1 macrophages can lead to a suppression of pro-inflammatory cytokine secretion, notably Tumor Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β). This process is accompanied by an upregulation of anti-inflammatory mediators, particularly Interleukin-10 (IL-10) produced by M2 macrophages. Such mechanisms facilitate the transition from pro-inflammatory M1 macrophages to their anti-inflammatory M2 counterparts [58].

For many years, bone marrow has been the predominant source of MSCs utilized in orthopaedic therapies, primarily due to the advantages associated with donor-recipient compatibility. Nevertheless, the proportion of nucleated cells classified as MSCs in bone marrow aspirate is exceedingly low, ranging from 0.01% to 0.0001%. In contrast, adipose tissue has emerged as a dependable reservoir for these nucleated cells. A notable limitation in the application of MSCs is their susceptibility to age-related factors. However, the decline in the capacity of MSCs to proliferate and differentiate is markedly less pronounced in adipose tissue than in bone marrow, potentially attributable to its rich and stable vascular network. Subcutaneous adipose tissue contains a high density of mature adipocytes along with an array of blood vessels, leukocytes, fibroblasts, macrophages, and pre-adipocytes, collectively referred to as the Stromal Vascular Fraction (SVF). Each adipocyte is supported by its own network of capillaries, which may explain the significantly higher concentration of MSCs found in adipose tissue compared to bone marrow [59-66].

Specifically for adipose-derived mesenchymal stem cells, it has been demonstrated that they possess surface markers that promote chondrogenesis, such as CD73, CD90, CD105, and CD106 [67-69]. The systematic review and meta-analysis conducted by Anil et al. and Aletto et al. demonstrated that the application of adipose-derived mesenchymal stem cells can lead to significant improvements in clinical outcomes, particularly in terms of pain management and functional capacity, for patients with knee osteoarthritis. Additionally, their study found that these stem cells are most closely linked to achieving the best clinical and functional results when compared to other intra-articular injections such as corticosteroids, PRP, and HA [70,71].

Table 6: MSCs secrete various cytokines, growth factors, processes of innate tissue repair and other molecules that and immunomodulation play a crucial role in the [42].

MicroRNAs	Immunomodulatory Molecules	Surface Markers and Cytokine Receptors	Secreted Growth Factors and Cytokines
miRNA-1224	LL37 antibac pep	SSEA-4	LIF
miRNA-486-5p	HO-1	SSEA-3	SCF
miRNA-451	Gal-9	HLA-G	GM-CSF inducible
miRNA-222-3p	Gal-1	(HLA Class II -inducible)	G-CSF
let-7a-5p	TSG-6	HLA Class I	M-CSF
miRNA-199	Inos	CD332 FGFR2	FLT-3 Ligand
miRNA-191-5p	IDO	CD331 FGFR1	FGF2
miRNA-146b	HLA-G	CD222 IGF2R	VEGF
miRNA-145	LIF	CD221 IGF1R	
miRNA-143-3p	IL10	CD166 IGF1R	
miRNA-133b	IL-6	CD146 MCAM	
miRNA-125b	IL-1RA	CD140b PDGFRB	
miRNA-29	PGE2 antibac too	CD120b TNFIIR	
miRNA-24	HGF	CD120a TNFIR	
miRNA-23b	TGF	CDw119 IFNγR	
miRNA-21		CD117 KIT	
miRNA-10b		CD106 VCAM-1	
miRNA-10a		CD105 Endoglin	**Integrins-positive**
miRNA-9-5p		CD90 Thy -1	CD104 β4
		CD73 Ectonucleotidase	CD61 β3
Hemato-negative	**Integrins-negative**	CD71 Transferrin Rec	CD29 β1
CD45	CD49d α4	CD62L L-Selectin	CD51 aα
CD34	CD18 Cβ2	CD58 LFA-3	CD49e αv
CD14	CD11a αL	CD54 ICAM-1	CD49c α3
CD11b		CD44 HA Rec	CD49b α2
CD4		CD9	CD49a α1

In the context of PRP, the significance of platelets and their constituents is paramount in facilitating the regenerative process. The primary constituent of platelets is their α-granules. These α-granules and their contained growth factors and cytokines play a crucial role in the recruitment and activation processes of immune cells, thus, promoting tissue regeneration [2-6].

By combining the benefits of both MSCs and PRP, we can boost anti-inflammatory processes, reduce cartilage degeneration, and promote greater tissue healing/regeneration through increased cell proliferation and differentiation into cartilage cells. This study shows significant improvement in all outcome measurements – KOOS, VAS, and EQL from 6 months and maintained beyond 4 years follow-up when treating osteoarthritis and chondropathy of the knee using our novel P.A.S.T.A. technique utilizing a combination of PRP and microfragmented adipose tissue. This therapy can significantly improve functional outcomes, quality of life, and reduce pain. Our study demonstrated that functional outcomes such as total KOOS score (51.76%, 4 years), KOOS activities of daily living (44.50%, 4 years), KOOS sports and recreational activities (55.22%, 4 years), EQL mobility (56.02%, 4 years), EQL self-care (50.85%, 4 years), and EQL usual activities (52.97%, 4 years) all had short-term (6 months) and long-term (4 years) improvement from pre-procedure condition.

Pain, being the most common complaint amongst patients with osteoarthritis and chondropathy, also had significant improvements at short-term and long-term follow-ups. VAS pain score and EQL pain both showed significant improvements with an improvement of 65.13% and 44.77%, respectively, at the 4-year follow-up.

As there is no present study regarding the Minimal Clinically Important Difference (MCID) for this combination treatment of PRP and MSCs for osteoarthritis and chondropathy, we would like to reference the study by Boffa et al. [72]. Here, they determined the MCID for patients with knee osteoarthritis treated with PRP injections for the KOOS subscales. With no significant difference in MCID at 6-month and 12-month follow-ups for KOOS subscale outcome measures, we used their MCID thresholds at 12 months: KOOS pain 9.1, KOOS symptoms 8.2, KOOS activities of daily living 9.2, KOOS sport and recreational activities 11.6, and KOOS quality of life 10.3. Using these MCID thresholds, all KOOS subscale scores at 1-year, 2-year, and 4-year follow-up showed clinical relevance.

The P.A.S.T.A. technique proved to have a positive effect on the development and progression of osteoarthritis and chondropathy symptoms, demonstrated by the KOOS symptom and stiffness subscale. At 6 months and 4 years follow-up, there was a mean increase of 33.79 (41.70%) and 38.29 (44.77%), respectively, which exceeded the MCID threshold of 8.2. This further showed that this treatment is an effective disease-modifying therapy for osteoarthritis and chondropathy.

The mean age of all participants was 63.58 years old (45–83 years old); however, we saw a significant variation in the mean age when comparing the osteoarthritis group to the chondropathy group. Moderate to end-stage osteoarthritis (Kellgren-Lawrence Types II-IV) are typically a result of degeneration of articular cartilage over time. This degenerative nature of osteoarthritis can account for the mean age of this group being older than those in the chondropathy group. Isolated chondral lesions are also typically encountered in younger patients, which is consistent with our data [73,74].

This study demonstrated a higher percentage of participants who eventually underwent knee arthroplasty were in the Kellgren-Lawrence grade IV group, compared to those with lower severity grades. Amongst the participants with Kellgren-Lawrence grade II, none underwent arthroplasty, additional procedures, or surgeries within or beyond the 4-year period; however, 24.0% of participants with Kellgren-Lawrence grade III and 47.4% of participants with Kellgren-Lawrence grade IV eventually underwent total arthroplasty beyond the 4-year follow-up.

In the chondropathy group, only 1 participant had surgery on the affected knee in the postoperative period. This patient had an Outerbridge grade III at the time of the P.A.S.T.A. procedure and had undergone arthroscopy, meniscal, and cartilage repair using a 1-stage technique of a hyaluronic acid-based scaffold with activated bone marrow aspirate concentrate (HA-BMAC) after the 4-year follow-up due to recurrence of pain. It was important to note that this patient remained very active in sports and motocross after undergoing P.A.S.T.A., which may be contributing factors to the recurrence of pain. The patient also presented with a newly encountered meniscal lesion, which may have also contributed or acted as a new source of knee pain. However, after the second procedure, there was no recurrence of pain and the patient was able to successfully return back to activities and sport.

Many of our patients with Kellgren-Lawrence grade III and IV or Outerbridge grade III or IV came to us with previous advise from other surgeons to undergo total knee arthroplasty due to their chronic and persistent pain despite undergoing other forms of conservative management. Many of these patients were reluctant to undergo surgery at that time. From our data, the majority of these patients found enough relief and improvement in symptoms to avoid or delay the need for arthroplasty, similar to the previous international multicenter study by Gobbi et al. involving autologous microfragmented adipose tissue alone using the Lipogems® system (Lipogems International SpA, Milan, Italy) [3]. This may indicate that the P.A.S.T.A. procedure, when used as a treatment option in moderate to severe grades of osteoarthritis and chrondropathy, can be effective in delaying or preventing the recurrence of symptoms, progression of osteoarthritis, and subsequently the need for total knee arthroplasty. At this point, due to lack of histological, arthroscopic, and imaging studies to document the effects of this procedure on cartilage, we can only report the improvement in quality of life, clinical, and functional outcomes. We plan to continue collecting data and investigating these aspects of the treatment for future publication.

The P.A.S.T.A. procedure can also be utilized in other pathologies rather than being limited to arthropathy of the knee. We have had great success in relieving symptoms in patients suffering from osteoarthritis and chondral lesions in the hip, ankle, elbow, and shoulder, as well as lesions secondary to impingement and malalignment. Due to lack of samples on these pathologies, we chose to exclude these patients from this study, but may be a topic for further investigation in the future.

Our study is not without its own limitations. We were unable to evaluate additional covariates, such as BMI, age, comorbidities, and smoking history which can help determine risk factors for identifying participants who had less pronounced or no effects, “non-responders,” compared to those who had significant improvements, “responders,” after receiving treatment. The identification of risk factors leading to less significant outcomes may be important for future research to determine

the ideal population for this technique. Diagnostic arthroscopies or post-treatment MRIs can also be done to further evaluate the efficacy of this treatment by evaluating the joint and cartilage. Through these investigations, it may be possible to demonstrate if the clinical and functional improvements were simply due to the anti-inflammatory effects, if there is evidence of cartilage healing and regeneration, or if there is a delay in cartilage degeneration compared to other treatment options or controls. This study demonstrates our P.A.S.T.A. technique is a safe and effective treatment for osteoarthritis and chondropathy and significantly improves clinical and functional outcomes, as well as quality of life. Following our demonstration of this treatment's safety and efficacy, we are in the process of organizing a randomized controlled trial to facilitate a more thorough comparison of this treatment with other recognized treatment modalities for osteoarthritis and chondropathy.

Conclusion

This study demonstrates that the novel P.A.S.T.A. technique and its utilization of a combination of autologous leukocyte-poor PRP derived from peripheral blood and MSCs derived from SVF sourced from microfragmented adipose tissue harvested from the abdomen or supra-gluteal area is safe and effective in the treatment of low to moderate osteoarthritis and chondropathy with significant improvement in function, pain, and quality of life as early as 6 months and maintained through 4 years follow-up.

References

1. Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Romeo AA, Bradley JP, et al. Platelet-rich plasma differs according to preparation method and human variability. The Journal of bone and joint surgery. American. 2012; 94: 308–316.
2. Blair P, Flaumenhaft R. Platelet α–granules: Basic biology and clinical correlates. Blood Rev. 2009; 23: 177.
3. Sehgal S, Storrie B. Evidence that differential packaging of the major platelet granule proteins von Willebrand factor and fibrinogen can support their differential release. J Thromb Haemost. 2007; 5: 2009e2016.
4. Italiano JE, Battinelli EM. Selective sorting of alpha-granule proteins. J Thromb Haemost. 2009; 7: 173e176.
5. King SM, Reed GL. Development of platelet secretory granules. Semin Cell Dev Biol. 2002; 13: 293e302.
6. Sprugel KH, Mcpherson JM, Clowes AW, Ross R. Effects of Growth Factors in Vivo I. Cell Ingrowth Into Porous Subcutaneous Chambers. American Journal of Pathology. 1987: 129.
7. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. The American journal of sports medicine. 2009; 37: 2259–2272.
8. Gobbi A, Dallo I, Rogers C, Striano RD, Mautner K, Bowers R, et al. Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: a multi-centric, international study. International orthopaedics. 2021; 45: 1179–1188.
9. Dallo I, Szwedowski D, Mobasheri A, Irlandini E, Gobbi A. A Prospective Study Comparing Leukocyte-Poor Platelet-Rich Plasma Combined with Hyaluronic Acid and Autologous Microfragmented Adipose Tissue in Patients with Early Knee Osteoarthritis. Stem cells and development. 2021; 30: 651–659.
10. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-Step Cartilage Repair with Bone Marrow Aspirate Concentrated Cells and Collagen Matrix in Full-Thickness Knee Cartilage Lesions: Results at 2-Year Follow-up. Cartilage. 2011; 2: 286–299.
11. Gobbi A, Whyte GP. One-Stage Cartilage Repair Using a Hyaluronic Acid-Based Scaffold With Activated Bone Marrow-Derived Mesenchymal Stem Cells Compared With Microfracture: Five-Year Follow-up. The American journal of sports medicine. 2016; 44: 2846–2854.
12. Dallo, I., Morales, M., & Gobbi, A. (2021). Platelets and Adipose Stroma Combined for the Treatment of the Arthritic Knee. Arthroscopy techniques. 2021; 10: e2407–e2414.
13. Flanigan DC, Harris JD, Trinh TQ, Siston RA, Brophy RH. Prevalence of chondral defects in athletes' knees: a systematic review. Medicine and science in sports and exercise. 2010; 42: 1795–1801.
14. Herman K, Dallo I, Gobbi A. The Illustrative Marrow Stimulation Techniques for Cartilage Repair: The Microfracture Technique. In: Goyal, D.R. (eds) The Illustrative Book of Cartilage Repair. Springer, Cham. 2021.
15. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2014; 22: 1986–1996.
16. Gobbi A, Nunag P, Malinowski K. Treatment of full thickness chondral lesions of the knee with microfracture in a group of athletes. Knee surgery, sports traumatology, arthroscopy: official journal of the ESSKA. 2005; 13: 213–221.
17. Acosta M, Gobbi A. Articular Cartilage Reconstruction: Review of Concepts, Techniques, Complications, Risk Factors, and Bail Out/Salvage Strategies, Journal of Clinical Orthopaedics and Trauma. 2024; 2024: 102875.
18. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. The Knee. 2007; 14: 177–182.
19. Wilder FV, Hall BJ, Barrett JP, Lemrow NB. History of acute knee injury and osteoarthritis of the knee: a prospective epidemiological assessment. The Clearwater Osteoarthritis Study. Osteoarthritis and cartilage. 2002; 10: 611–616.
20. Courties A, Kouki I, Soliman N, Mathieu S, Sellam J. Osteoarthritis year in review 2024: Epidemiology and therapy. Osteoarthritis and cartilage. 2024; 32: 1397–1404.
21. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet (London, England). 2019; 393: 1745–1759.
22. Aggarwal VK, Goyal N, Deirmengian G, Rangavajulla A, Parvizi J, Austin MS. Revision total knee arthroplasty in the young patient: is there trouble on the horizon?. The Journal of bone and joint surgery. American volume. 2014; 96: 536–542.
23. Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM. One-step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2017; 25: 2494–2501.
24. Whyte GP, Bizzoco L, Gobbi A. One-Step Cartilage Repair of Full-Thickness Knee Chondral Lesions Using a Hyaluronic Acid-Based Scaffold Embedded With Bone Marrow Aspirate Concentrate: Long-term Outcomes After Mean Follow-up Duration of 14 Years. The American journal of sports medicine. 2024; 52: 3561–3568.

25. Whyte GP, Gobbi A. Biologic Knee Arthroplasty for Cartilage Injury and Early Osteoarthritis. In: Gobbi, A., Espregueira-Mendes, J., Lane, J., Karahan, M. (eds) Bio-orthopaedics. Springer, Berlin, Heidelberg. 2017.

26. Rogers C, Gobbi A. The Optimization of Natural Healing. In: Gobbi, A., Espregueira-Mendes, J., Lane, J., Karahan, M. (eds) Bio-orthopaedics. Springer, Berlin, Heidelberg. 2017.

27. Dallo I, Frank RM, Bradsell H, Piuzzi NS, Gobbi A. Overview of Orthobiologics and Joint Function. In: Gobbi, A., Lane, J.G., Longo, U.G., Dallo, I. (eds) Joint Function Preservation. Springer, Cham. 2022.

28. Gobbi A, Lad D, Karnatzikos G. New Techniques for Cartilage Repair of the Patella. In: Gobbi, A., Espregueira-Mendes, J., Nakamura, N. (eds) The Patellofemoral Joint. Springer, Berlin, Heidelberg. 2014.

29. Gobbi A. L'impiego delle cellule mesenchimali nel trattamento di ampi difetti osteocondrali. In Cartilagine: istruzioni per l'uso (1st ed., Vol. 1, pp. 117–125). essay, CIC edizioni internazionali. 2013; 1: 117-125.

30. Gobbi A, Karnatzikos G, Mahajan V. Biologic Arthroplasty. In Cartilage repair: clinical guidelines: decision making in cartilage repair - variables influencing the choice of treatment. 2012; 1: 271-282.

31. Gobbi A, Boldrini L, Espregueira-Mendes J. The Use of Platelet Rich Plasma for Cartilage Repair. In Cartilage repair: current concepts. essay, DJO Publications. 2010; 1: 119-126.

32. Gobbi A, Karnatzikos G, Malchira S, Kumar A. Platelet Rich Plasma (PRP) in Osteoarthritis. In: Lana, J., Andrade Santana, M., Dias Belangero, W., Malheiros Luzo, A. (eds) Platelet-Rich Plasma. Lecture Notes in Bioengineering. Springer, Berlin, Heidelberg. 2014.

33. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-Induced Autologous Chondrocyte Implantation versus Multipotent Stem Cells for the Treatment of Large Patellofemoral Chondral Lesions: A Nonrandomized Prospective Trial. Cartilage. 2015; 6: 82–97.

34. Gobbi A, Whyte GP. Long-term Clinical Outcomes of One-Stage Cartilage Repair in the Knee With Hyaluronic Acid-Based Scaffold Embedded With Mesenchymal Stem Cells Sourced From Bone Marrow Aspirate Concentrate. The American journal of sports medicine. 2019; 47: 1621–1628.

35. Gobbi A, Karnatzikos G, Sankineani SR. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. The American journal of sports medicine. 2014; 42: 648–657.

36. Sadlik B, Gobbi A, Puszkarz M, Klon W, Whyte GP. Biologic Inlay Osteochondral Reconstruction: Arthroscopic One-Step Osteochondral Lesion Repair in the Knee Using Morselized Bone Grafting and Hyaluronic Acid-Based Scaffold Embedded With Bone Marrow Aspirate Concentrate. Arthroscopy techniques. 2017; 6: e383–e389.

37. Whyte GP, Gobbi A, Sadlik B. Dry Arthroscopic Single-Stage Cartilage Repair of the Knee Using a Hyaluronic Acid-Based Scaffold With Activated Bone Marrow-Derived Mesenchymal Stem Cells. Arthroscopy techniques. 2016; 5: e913–e918.

38. Gobbi A, Lane JG, Morales M, D'Ambrosi R. Articular cartilage delamination at eight years following cellular-based repair procedures: a case reports. J Exp Orthop. 2022; 9: 90.

39. Hurley ET, Sherman SL, Stokes DJ, Rodeo SA, Shapiro SA, Mautner K, et al. Experts Achieve Consensus on a Majority of Statements Regarding Platelet-Rich Plasma Treatments for Treatment of Musculoskeletal Pathology. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2024; 40: 470–477.e1.

40. Herman K, Gobbi A. Evidence-Based Approach to Orthobiologics for Osteoarthritis and Other Joint Disorders. Physical medicine and rehabilitation clinics of North America. 2023; 34: 71–81.

41. Gobbi A, Herman K, Bizzoco L, Avio G. Evaluation of Safety And Performance of Hyaluronic Acid Combined with Niacinamide Versus Standard Infiltrative Therapy in the Treatment of Joint Degenerative and Post- Traumatic Diseases. J Orthop Muscular Syst. 2023; 6: 1024.

42. Gobbi A, Herman K, Szwedowski D. Bio-Orthopedics: A New Approach to Osteoarthritis and Joint Disorders. IntechOpen. 2023.

43. Gobbi A, Morales M. Use of Hyaluronic Acid for Rotator Cuff Tendinopathy. Am J Biomed Sci & Res. 2021.

44. Gobbi A, Morales M, Avio G, D'Ambrosi R. Double-blinded prospective randomized clinical trial in knee joint osteoarthritis treatment: Safety assessment and performance of trehalose hyaluronic acid versus standard infiltrative therapy based on medium-weight sodium hyaluronate. Journal of Cartilage & Joint Preservation. 2022; 2: 100043.

45. Gobbi A, Dallo I, D'Ambrosi R. Autologous microfragmented adipose tissue and leukocyte-poor platelet-rich plasma combined with hyaluronic acid show comparable clinical outcomes for symptomatic early knee osteoarthritis over a two-year follow-up period: a prospective randomized clinical trial. European journal of orthopaedic surgery & traumatology : orthopedie traumatology. 2023; 33: 1895–1904.

46. Gobbi A, Herman K, Dallo I, Bizzoco L, Acosta M. Chapter 1 - Autologous blood: platelet-rich plasma and platelet-poor plasma. OrthoBiologics. 2025: 1-11.

47. Gobbi A, Acosta M, Boiocchi C. Regenerative Medicine: Fact or Fiction. Regenerative Medicine in Sports and Orthopaedics. Springer, Cham. 2025. https://doi.org/10.1007/978-3-031-84693-9_1

48. Gobbi A, Slynarski K, Acosta M, Caplan A. MSCs: A New Approach. Regenerative Medicine in Sports and Orthopaedics. Springer, Cham. 2025. https://doi.org/10.1007/978-3-031-84693-9_3

49. Acosta M, Bizzoco L, Boiocchi C, Gobbi A. Use of New Formulation in Hyaluronic Acid in Regenerative Medicine. Regenerative Medicine in Sports and Orthopaedics. Springer, Cham. 2025. https://doi.org/10.1007/978-3-031-84693-9_23

50. Acosta M, Sánchez M, Delgado D, Rehak L, Bizzoco L, Gobbi A. New Approach with Personalized Platelet-Rich Plasma. Regenerative Medicine in Sports and Orthopaedics. Springer, Cham. 2025. https://doi.org/10.1007/978-3-031-84693-9_21

51. Everts PA, Lane JF, Acosta MI, Pires L, van Domselaar A, Gobbi A, et al. Essential Considerations in Platelet-Rich Plasma Preparations with Emphasis on Platelet Dosing and Bioformulations: There Is No One-Size-Fits-All Method. Regenerative Medicine in Sports and Orthopaedics. Springer, Cham. 2025: 291-313.

52. Caplan AI. Mesenchymal stem cells. Journal of orthopaedic research: official publication of the Orthopaedic Research Society. 1991; 9: 641–650.

53. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell stem cell. 2008; 3: 301–313.

54. Krasnodembskaya A, Song Y, Fang X, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. STEM CELLS 2010;28:2229–2238.

55. Caplan AI. All MSCs are pericytes?. Cell stem cell. 2008; 3: 229–230.

56. da Silva Meirelles L, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. Stem cells (Dayton, Ohio). 2008; 26: 2287–2299.

57. Caplan AI, Correa D. The MSC: an injury drugstore. Cell stem cell. 2011; 9: 11–15.

58. Ylöstalo JH, Bartosh TJ, Coble K, Prockop DJ. Human mesenchymal stem/stromal cells cultured as spheroids are self-activated to produce prostaglandin E2 that directs stimulated macrophages into an anti-inflammatory phenotype. Stem cells (Dayton, Ohio). 2012; 30: 2283–2296.

59. Gobbi A, de Girolamo L, Whyte GP, Sciarretta FV. Clinical Applications of Adipose Tissue-Derived Stem Cells. In: Gobbi, A., Espregueira-Mendes, J., Lane, J., Karahan, M. (eds) Bio-orthopaedics. Springer, Berlin, Heidelberg. 2017.

60. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem cells (Dayton, Ohio). 2007; 25: 2739–2749.

61. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. Journal of cellular physiology. 2007; 213: 341–347.

62. Yoshimura K, Shigeura T, Matsumoto D, Sato T, Takaki Y, Aiba-Kojima E, et al. Characterization of freshly isolated and cultured cells derived from the fatty and fluid portions of liposuction aspirates. Journal of cellular physiology. 2006; 208: 64–76.

63. Tsuji W, Rubin JP, Marra KG. Adipose-derived stem cells: Implications in tissue regeneration. World journal of stem cells. 2014; 6: 312–321.

64. Crandall DL, Hausman GJ, Kral JG. A review of the microcirculation of adipose tissue: anatomic, metabolic, and angiogenic perspectives. Microcirculation (New York, N.Y. : 1994). 1997; 4: 211–232.

65. Strem BM, Hicok KC, Zhu M, Wulur I, Alfonso Z, Schreiber RE, et al. Multipotential differentiation of adipose tissue-derived stem cells. The Keio journal of medicine. 2005; 54: 132–141.

66. Brambilla L, Scotti C, Gobbi A, Peretti GM. Evolving Perspectives in Orthobiologic Approaches to Articular Cartilage Regeneration. In: Gobbi, A., Espregueira-Mendes, J., Lane, J., Karahan, M. (eds) Bio-orthopaedics. Springer, Berlin, Heidelberg. 2017.

67. Ragni E, Colombini A, Viganò M, Libonati F, Perucca Orfei C, Zagra L, et al. Cartilage Protective and Immunomodulatory Features of Osteoarthritis Synovial Fluid-Treated Adipose-Derived Mesenchymal Stem Cells Secreted Factors and Extracellular Vesicles-Embedded miRNAs. Cells. 2021; 10: 1072.

68. Ragni E, Perucca Orfei C, De Luca P, Colombini A, Viganò M, de Girolamo L. Secreted Factors and EV-miRNAs Orchestrate the Healing Capacity of Adipose Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis. International journal of molecular sciences. 2020; 21: 1582.

69. Jankowski M, Dompe C, Sibiak R, Wąsiatycz G, Mozdziak P, Jaśkowski JM, et al. In Vitro Cultures of Adipose-Derived Stem Cells: An Overview of Methods, Molecular Analyses, and Clinical Applications. Cells. 2020; 9: 1783.

70. Anil U, Markus DH, Hurley ET, Manjunath AK, Alaia MJ, Campbell KA, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. The Knee. 2021; 32: 173–182.

71. Aletto C, Oliva F, Maffulli N. Knee intra-articular administration of stromal vascular fraction obtained from adipose tissue: A systematic review. Journal of clinical orthopaedics and trauma. 2022; 25: 101773.

72. Boffa A, Andriolo L, Franceschini M, Martino AD, Asunis E, Grassi A, et al. Minimal Clinically Important Difference and Patient Acceptable Symptom State in Patients With Knee Osteoarthritis Treated With PRP Injection. Orthop J Sports Med. 2021; 9: 23259671211026242.

73. Robson K, Pope R, Orr R. Incidence and Risk Factors for Acute Articular Cartilage Tears in Military and Other Occupational Settings: A Systematic Review. Healthcare (Basel, Switzerland). 2024; 12: 595.

74. Wilk KE, Briem K, Reinold MM, Devine KM, Dugas J, Andrews JR. Rehabilitation of articular lesions in the athlete's knee. The Journal of orthopaedic and sports physical therapy. 2006; 36: 815–827.