What is new for treatment of stage 1 to 3 Osteoarthritis?

We are going to talk about Osteoarthritis.

Knee osteoarthritis (OA) is a common progressive joint disease, characterized by chronic pain and functional disability. The pooled global prevalence of knee OA in the year 2020 was 16.0% in individuals above 15 years of age and 22.9% in those aged 40 years and over The prevalence and incidence of knee OA increases with age and is higher in women than in men. It represents a substantial and increasing health burden with considerable personal, economic, and societal toll.

OA is characterized by the degradation of articular cartilage and bone matrix components. The aim of treatment is to preserve joints in order to improve pain, restore activity, and delay arthroplasty. Bone marrow stimulation techniques, cartilaginous or chondrogenic tissue repair, osteochondrogenic autologous transplantation, and autologous chondrocyte implantation are the most widely used options for treating OA. In addition, injection of corticosteroids, hyaluronic acid into the intra-articular region, and subchondral injections of platelet-rich plasma are other widely used techniques in OA patients. However, none of the aforementioned treatment options effectively arrest structural deterioration of cartilage and bone or successfully reverse existing structural defects . They also do not enable regeneration of the articular tissue with its distinct

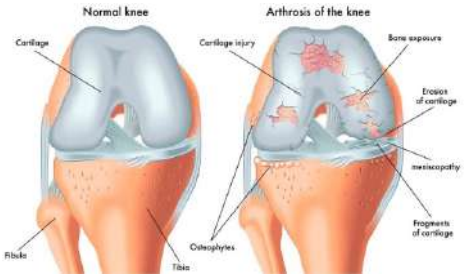
Although osteoarthritis can damage any joint, the disorder most commonly affects joints in your hands, knees, hips and spine.

Osteoarthritis symptoms can usually be managed, although the damage to joints can't be reversed. Staying active, maintaining a healthy weight and receiving certain treatments might slow progression of the disease and help improve pain and joint function.

Osteoarthritis symptoms often develop slowly and worsen over time. Signs and symptoms of osteoarthritis include:

- **Pain.** Affected joints might hurt during or after movement.
- **Stiffness.** Joint stiffness might be most noticeable upon awakening or after being inactive.
- **Tenderness.** Your joint might feel tender when you apply light pressure to or near it.

- **Loss of flexibility.** You might not be able to move your joint through its full range of motion.
- **Grating sensation.** You might feel a grating sensation when you use the joint, and you might hear popping or crackling.
- **Bone spurs.** These extra bits of bone, which feel like hard lumps, can form around the affected joint.
- **Swelling.** This might be caused by soft tissue inflammation around the joint.



- ***<u>What are the treatment choose?</u>***

Osteoarthritis can't be reversed, but treatments can reduce pain and help you move better.
Medications

Medications that can help relieve osteoarthritis symptoms, primarily pain, include:

- **Acetaminophen.** Acetaminophen can reduce mild to moderate pain. Taking more than the recommended dose of acetaminophen can cause liver damage.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), NSAIDs can cause stomach upset, cardiovascular problems, bleeding problems, and liver and kidney damage. NSAIDs as gels, applied to the skin over the affected joint, have fewer side effects and may relieve pain just as well.

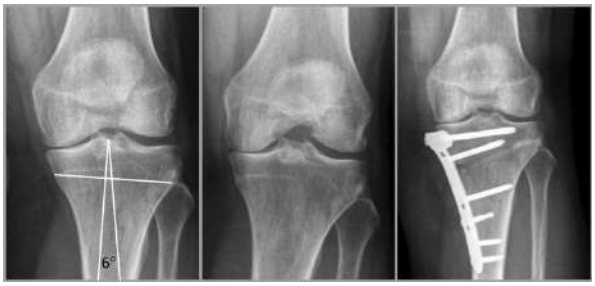
- **Duloxetine (Cymbalta).** Normally used as an antidepressant, this medication is also approved to treat chronic pain, including osteoarthritis pain

- **Physical therapy.** A physical therapist can show you exercises to strengthen the muscles around your joint, increase your flexibility and reduce pain. Regular gentle exercise that you do on your own, such as swimming or walking, can be equally effective.

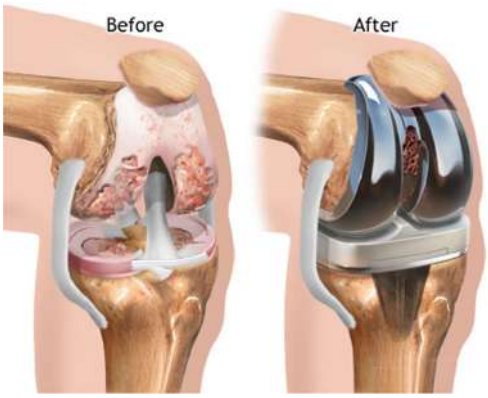
Surgical and other procedures

If conservative treatments don't help, you might want to consider procedures such as:

- **Cortisone injections.** Injections of a corticosteroid into your joint might relieve pain for a few weeks. The number of cortisone injections you can receive each year is generally limited to three or four, because the medication can worsen joint damage over time.
- **Lubrication injections.** Injections of hyaluronic acid might relieve pain by providing some cushioning in your knee, though some research suggests that these injections offer no more relief than a placebo. Hyaluronic acid is similar to a component normally found in your joint fluid.
- **Realigning bones.** If osteoarthritis has damaged one side of your knee more than the other, an osteotomy might be helpful. In a knee osteotomy, a surgeon cuts across the bone either above or below the knee, and then removes or adds a wedge of bone. This shifts your body weight away from the worn-out part of your knee



- **Joint replacement.** In joint replacement surgery, your surgeon removes your damaged joint surfaces and replaces them with plastic and metal parts. Surgical risks include infections and blood clots. Artificial joints can wear out or come loose and might eventually need to be replaced.



Now we are going to talk about what is new Non Surgical Treatment for Arthritis and other orthopaedic condition

We are going to talk about Micro-graftic and PRP use in Osteoarthritis and other Orthopaedic conditions

A) Micro-grafting, innovation technology on Orthopaedics

simple and effective regenerative procedure, capable of obtaining autologous micro-grafts from any body tissue. Through a simple process, without risks to the patient and great therapeutic potential, in a single session, the patient is a donor and recipient of autologous micro-grafts, allowing the recipient area to benefit from the regenerative activity of the progenitor cells and growth factors extracted from the donor's site.

The percentage success for regenerative medicine is closely related to the biological sources used, such as stem cells, scaffolds, growth factors, and grafts.

The main role of regenerative medicine is to replace damaged tissue while maintaining its original function or, alternatively, to stimulate regeneration of the tissue itself, respecting the original histological hierarchy.

The aim of stem cell therapy is to replace a damaged or aged tissue, restoring healthy, functioning cells. In practice, stem cell therapies are based mainly on the use of mesenchymal stem cells (MSCs), which are multipotent cells with unique biological properties.

The micro-grafting technique was conceived by Cicero Parker Meek at the University of South Carolina Aiken in 1958. Micro-grafting is based on the concept that by increasing the superficial

area of a skin graft by cutting the graft into smaller “micro-grafts,” it is possible to cover a wound larger than the original donor site. Micro-grafting was first applied to the treatment of burns because of a lack of available donor sites for skin grafting. The original Meek technique was complex because the micro-grafts were placed with the dermal side down to achieve optimal survival. Because this requirement of dermal orientation was impracticable, especially with very small graft fragments, the technique did not gain widespread clinical application, and it was eclipsed in 1964 after the introduction of mesh skin grafts by Tanner et al. Subsequently, several modifications were made to overcome the limitations; in 1993

Prospective Observational Study of a Non-Arthroscopic Autologous Cartilage Micrografting Technology for Knee Osteoarthritis, for Knee Chondropathy and Osteochondral Lesions.

Regenerative medicine is currently considered a promising therapy for the treatment of OA in humans. This innovative method involves the use of biological sources such as stem cells and grafts that allow the regeneration and replacement of cells, tissues or organs in order to restore the original structure and physiological functions . Autologous micro-grafting technology involves the use of autologous micro-grafts to enhance regeneration of an impaired or damaged tissue. The key strengths of AMT are a good safety profile, non-rejection of the injected micro-grafts, and specificity to recover normal functioning of tissues through specific singling pathways . Use of autologous micro- grafts can overcome some of the current limitations of other therapeutic approaches, like invasiveness, donor site morbidity, cell death, and allogeneic response . The AMT procedure is not considered an advanced therapy medicinal product as it falls under the category of non-substantially manipulated cells or tissues used for the same essential function, which means that the cells when removed from their original environment in the human body are used to maintain the original function(s) in the same anatomical or histological environment under allogeneic or autologous conditions.

The Rigenera technology (Regenera Activa Worldwide S.L., Barcelona, Spain, and Human Brain Wave SRL, Torino, Italy) is a novel strategy for tissue mechanical disaggregation, which allows obtaining autologous micro-grafts enriched in progenitor cells expressing MSC-like markers and having strong regenerative potential . The AMT procedure using Rigenera technology has been

used worldwide for more than ten years since its development in 2012 to stimulate and enhance self-regenerative processes for multiple conditions. It has shown clinical efficacy in the management of complex wounds, for the regeneration of the bone in periodontal surgeries , for pinched nose deformity, for improving hair density in patients affected by androgenetic alopecia , for treatment of scars, for treatment of osteochondral lesions of the knee , and for the treatment of knee chondropathy. The procedure has also shown promise for treatment of osteochondral defects in a preclinical study.

The aim of this study was to determine the clinical effect and outcomes of the AMT procedure in patients with early stages of knee OA.

AMT Procedure

The tools used in the AMT procedure are Rigeneracons , Sicurdrill 2.0, Sicurlid and Sicurstick (Regenera Activa Worldwide S.L., Figure 1a–d).

<u>The Rigeneracons SRT</u>

is a sterile disposable container a medical device designed to mechanically disaggregate solid human tissue to obtain soluble autologous micro-grafts, which are injectable (the AMT solution).

Rigeneracons SRT comprises a grid with 100 hexagonal holes, each containing 6 calibrated microblades; a helix that rotates through an internal metal ring at a constant 80 revolutions per minute to disaggregate tissues with a cut off of 80 μm without causing cellular disruption and maintaining cell viability; and 3 arms.

<u>The Sicurdrill 2.0</u>

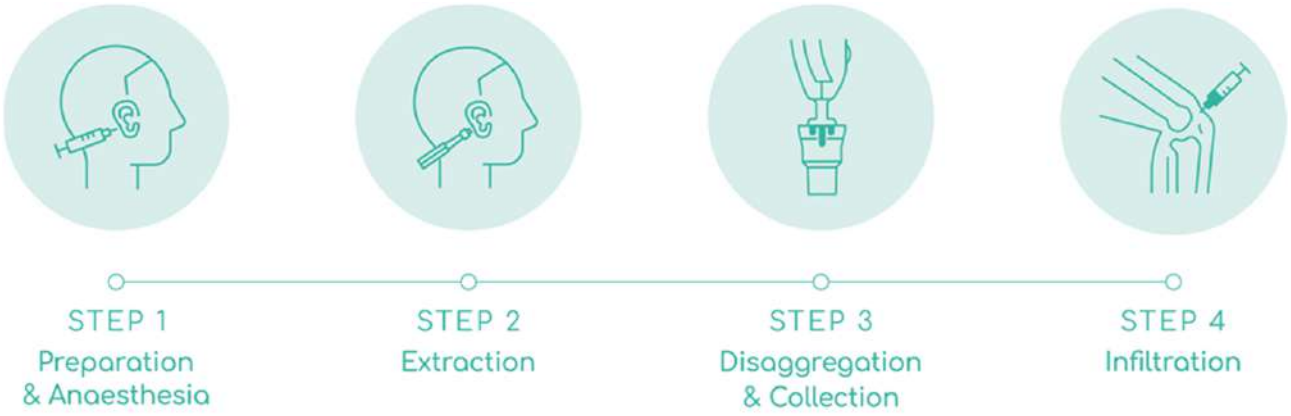
is a class I medical device with a motor that provides the electromechanical impulse to rotate the helix of the Rigeneracons SRT. The Sicurdrill 2.0 operates in 1-min cycles, each cycle started by pressing the frontal button. It is specially designed to be easily transportable. The Sicurlid and Sicurstick are specific adapters to secure the Rigeneracons SRT to the Sicurdrill 2.0. The procedure is shown in Figure 1.

<u>Tools used in Autologous Micrografting Procedure.</u>

Preparation and anesthesia: The auricular concha of the ear was disinfected with chlorhexidine and the area for biopsy extraction was marked with a dermal marker. The area was anesthetized with 2.5 mL of 2% lidocaine without vasoconstrictors; 0.5 mL in the retroauricular nerve to anesthetize and

the rest on both sides of the auricular concha to hydro separate the skin from the cartilage. Adrenaline was used if the bleeding did not stop after applying 5 min of hemostatic pressure.

Extraction: Three biopsy punches were made in the marked area with a 2.5 mm dermal punch. The three biopsies were placed on the grid of the Rigeneracons SRT, and manually rotated to cover them under the helix. The donor area in the ear was covered with a band-aid.



Disaggregation and collection: Approximately 4.0 mL of saline solution was added through the extraction hole of the Rigeneracons SRT with a Luer Slip syringe, until the biopsies were slightly embedded in the solution. Then the cap was closed, the Sicurstick inserted in the Rigeneracons SRT and placed into the Sicurlid. The device was then attached to the Sicurdrill 2.0. The frontal button on the Sicurdrill was pressed to start the tissue disaggregation, which was indicated by the yellow flashing LED on the Sicurdrill. The Sicurdrill was operated for six consecutive cycles, each cycle of 1-min duration. At the end of six cycles, 4.0 mL of the AMT® solution was collected with a Luer Slip syringe.

Infiltration:

The external femorotibial compartment area of the affected knee disinfected with chlorhexidine. The 4.0 mL of AMT solution was injected with a 21G 0.8 × 40 mm needle into the external femorotibial compartment. The joint was mobilized to distribute the injected AMT solution evenly across the treated area.

All steps were carried out under sterile conditions and the full Rigeneracons SRT kit which is intended for single use was safely disposed of after use in accordance with local guidelines.

Joint inflammation, if any, in the first 24–72 h post-procedure was treated with anal- gesics (other than nonsteroidal anti-inflammatory drugs which may interfere with the effectiveness of the micrograft. Patients were advised to rest in positions that do not overstrain the treated joint for at least 7 days post-procedure. To ensure healing of the biopsy site in the ear, patients were advised to not shower or have a sauna bath in the first 24–48 h post-procedure, to change the dressing of the biopsy site after 24 h and to keep the biopsy site clean and dry.

Figure 1. Use of the Rigeneracons medical device to generate autologous cartilage micrografts: (**A**) The autologous cartilage sample is collected with a punch; (**B**) Size of the autologous cartilage micrografts after collection; (**C**) The tissue, along with sterile saline solution, is inserted in the Rigeneracons device, which is activated by its motor; (**D**) After the cartilage fragmentation, the micrografts suspension is directly collected; (**E**) The cartilage micrografts suspension is directly injected into the knee of the patient with a syringe.

Eligibility Criteria

Patients included in the study were at the age between 35 and 75 those diagnosed with OA grade 2–3 (except for two patients with OA grade 3–4) on Kellgren and Lawrence scale , meaning that the joint preserved at least part of the articular cartilage.

Patients excluded

were those with any autoimmune diseases including rheumatoid arthritis; those with any concomitant uncontrolled metabolic diseases; patients undergoing systemic and/or local corticosteroids treatment; hyaluronic acid infiltration within the previous six months; as well as those with grade 4 advanced OA.

Assessments

Magnetic resonance imaging (MRI) and X-ray were performed pre-procedure. The Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire recommended by the International Knee Documentation Committee was used for assessing pain, stiffness, and function pre-procedure and at 1- and 6-months post-procedure. The KOOS is a self- reported outcome measure assessing the patient's opinion about the health, symptoms, and functionality of their knee. It is a 42-item questionnaire, including 5 sub scales symptoms (seven items), pain (nine items), function in daily living (ADLs [17 items]), sports and recreation function (five items), and quality of life (four items). Each item has five possible answer options scored from 0 (No Problems) to 4 (Extreme Problems) and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems. An aggregate score of all subs cales is not calculated since it is regarded desirable to analyze and interpret the five dimensions separately.

Results

The study included 10 patients, 4 men and 6 women; all except one patient were aged 53 years and above (Table 1). Patients reported pain in their affected knee for the past

<1 year to 10 years prior to start of study.

Table 1. Patients' baseline demographics and disease characteristics.

Patient Number	Age (Years)	Sex	BMI (kg/m^2)	Diagnosis Based on KL Scale	Clinical History	Past Medications	Past Procedures
1	63	Male	25	OA grade 3; chondropathy in left knee	Pain for the past 4 years and stiffness which became worse around a month before enrollment into study. Medial meniscus posterior horn tear 10 years prior to study enrollment which was not treated	None	None
2	84	Female	23	OA grade 3–4	Pain in right knee from past 10 years	None	None
3	64	Female	22	OA grade 3–4	Left knee pain for 8 years, worsening over time. Gonarthrosis for 8 years	NSAIDs	PRP injections in 2020 and 2021
4	37	Male	25	Chondropathy grade 3	Gonarthrosis	NSAIDs and paracetamol	Physiotherapy and PRP
5	74	Female	23	OA grade 3	Gonarthrosis. Pain in affected right knee for the past 10 years that became worse after an accident nearly 7 months prior to study enrolment	None	None
6	73	Female	22	OA grade 2	Pain for past 2 years	NSAIDs for 3 months	Physiotherapy
7	73	Female	22	OA grade 1-early 2	Very mild pain for the past less than 1 year	None	None
8	64	Female	23	OA grade 1 early 2	Pain for the past one year. Fibromyalgia and depression	None	None
9	53	Male	31	OA grade 1 early 2	Pain, reduced mobility and grinding sensation (crackling)	NSAIDs, education about weight control	Physiotherapy
10	53	Male	31	OA grade 3 symptomatic	Mild pain and reduced mobility	None	None

MRI and X-ray Findings

MRI at baseline revealed subchondral bone edema, chondropathy patella, and medial compartment narrowing; Baker cyst was noted in one patient (Table 2). X-ray revealed presence of osteophytes and medial compartment narrowing (Table 2).

Table 2. Magnetic resonance imaging and X-ray findings pre-procedure.

Table 2. Magnetic resonance imaging and X-ray findings pre-procedure.

Patient Number	MRI Findings	X-ray Findings
1	Subchondral bone edema medial femoral condyle with small cartilage lesion, medial meniscus degenerative tear. Chondropathy patella grade III.	Standing X-ray: medial compartment narrowing
2	Chondropathy patella II–III and medial femoral condyle grade III–IV.	Osteoarthritis KL scale grade 3–early 4
3	Medial compartment narrowing with chondropathy both condyles.Baker cyst 4 cm × 9 cm	Osteophytes present; KL scale grade 3 to 4 of osteoarthritis with medial compartment narrowing
4	Patella alta 3rd degree chondropathy patella and cartilage wear 1.7 cm × 1.5 cm at the femoral trochlea	Patella alta
5	Chondropathy with diffuse cartilage defects	Osteoarthritis grade 3
6	Chondropathy patella grade III with cartilage defects	Osteoarthritis grade 2
7	Diffuse cartilage wear Outerbridge grade II	Osteoarthritis grade 1–2
8	Three-plane study of the left knee. Internal meniscus of preserved morphology and signal. External meniscus with increased horizontal signal that also extended to the lower articular surface compatible with meniscal tear and associated with the presence of small loculated cystic images that extended anteriorly with a larger component that crossed the lateral retinaculum which might correspond to the palpable swelling, compatible with parameniscal cyst. Conclusion: Rupture of the external meniscus body with parameniscal cyst extending anteriorly, crossing the lateral retinaculum. Slight decrease in the thickness of the patellar cartilage in its superior and central portion.	Osteoarthritis KL grade 1–2
9	Chondropathy wear lateral tibial condyle	Osteoarthritis of the femorotibial joint left knee KL grade 1–2
10	Cartilage wear medial femoral condyle Outerbridge grade 2 and medial tibial condyle grade 2–3.	Osteoarthritis KL grade 3

KL: Kellgren–Lawrence; MRI: magnetic resonance imaging; NA: not available.

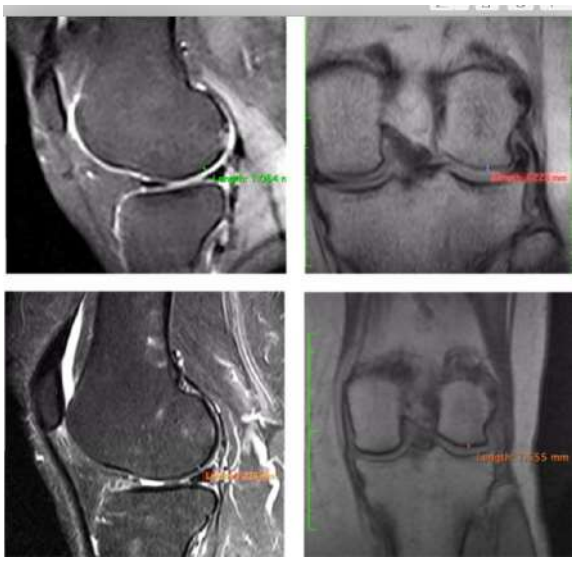


Table 3. Clinical outcomes within 12 months following AMT® procedure.

Patient Number	Description of Clinical Condition
1	No pain and good mobility at 10 months post-procedure
2	Lateral pain and good mobility as early as 3 weeks post-procedure
3	Less pain and better mobility as early as 3 weeks post-procedure
4	Impressive improvement in mobility and pain reduction from within 2 months post-procedure. The patient started bicycling post-procedure, which was stopped earlier due to pain
5	Improvement in clinical outcomes as early as 6 weeks post-procedure The patient started running at 2 months and playing basketball at low intensity at 3 months
6	Able to do daily activities without any pain. Clinical improvement observed was maintained even after 11 months post-procedure
7	No pain while carrying out daily activities, while pre-procedure the patient could not be on foot for more than 2 h The patient was able to walk for longer periods and was also able to take the stairs instead of the elevator Clinical improvement observed was maintained even after 1-year post-procedure
8	No pain and good mobility which was maintained even after 10 months post-procedure
9	Reduced pain and ability to walk long distances of more than 10 km with only minimal pain The patient lost some weight, but not sufficient to significantly help with the overall body inflammation and biomechanics in the joint
10	Reduced pain and improved mobility

AMT: autologous micrografting technology.

AMT Procedure Outcomes

In all patients, the wound in the ear completely healed within one week without any need for stitches. None of the patients needed adrenaline to stop the bleeding from the biopsied area in the ear. There were no cases of infection or signs of anormal healing of the donor area like "cauliflower ear". The patients strictly followed physician's aftercare recommendations for the healing of the donor area.

The AMT procedure was successful in all 10 patients. Pain resolution and good recovery of daily activities was seen in all 10 patients, with improvement in mobility being observed as early as 3 weeks post-procedure in 2 patients (Table 3).

Physical examination at 1- month and 6-months post-AMT® procedure demonstrated a steady improvement in all patients in knee instability, pain, swelling, mechanical locking, stair climbing and squatting.

KOOS Subscale Scores

All 10 patients completed the assessments at 1- and 6-months post-procedure. Significant improvements were seen in the mean scores of all five subscales of KOOS (KOOS symptoms, KOOS pain, KOOS ADL, KOOS sport and recreation, and KOOS quality-of-life) between pre-procedure and 1- and 6-month post-procedure (Figure 3, all $p \leq 0.05$). Between 1- and 6-months post-procedure, significant improvements were observed in the mean scores of the subscales of KOOS symptoms, KOOS pain, and KOOS ADL (all $p \leq 0.05$), while for the subscales of KOOS sport and recreation, and KOOS quality-of-life, the im- provements observed at 1-month were maintained at 6-months. Each one of the KOOS subscales was analyzed and passed the Bonferroni test.

Safety and Long-Term Follow-Up

Clinical evaluation at 12 months post-procedure showed that all 10 patients had continued good mobility and minimal or no pain in the affected knee.

The AMT procedure showed a good tolerability profile since none of the patients reported any adverse event during the study.

Use of biological strategies such as endogenous stem cells or tissue-specific progenitor cells to enable patient's own cartilage regeneration ability represents an important advance in the treatment of cartilage defects and OA

In this study, use of AMT procedure with auricular micrografts was found to be effective and safe in the treatment of early stage and moderate knee OA. Post-procedure, all patients reported minimal or no pain. Improvement in mobility was observed as early as 3 weeks post-procedure, which was maintained even after 12 months post-procedure, indicating early benefits maintained over the long-term. These observations were supported by the significant improvements observed in all five subscales of KOOS, a patient-reported outcome (PRO) measure, at 1- and 6-months post-procedure. PROs are increasingly recog- nized by regulators, clinicians, and patients as valuable tools to collect patient-centered data.

B. Platelet-rich plasma (PRP) Used Primarily for Chronic Conditions.

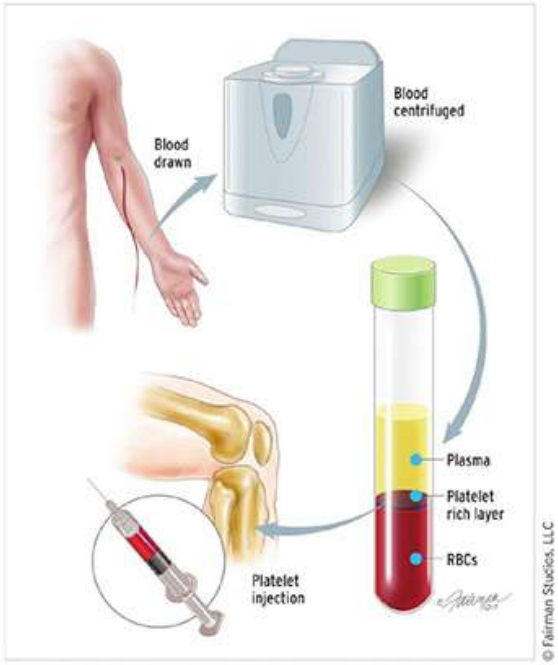
PRP treatments have been used for the past two decades to improve wound healing and bone grafting procedures by plastic and maxillofacial (mouth, jaw and neck) surgeons. It is only in recent years that orthopaedic surgeons and sports medicine specialists have utilized this technology.
PRP use in sports medicine primarily has been for the treatment of chronic tendon conditions, but also for acute muscle injuries and for the augmentation of tendon repair in the operating room. The most common applications include:

Conditions that Benefit from PRP

PRP has been used to treat chronic and acute injuries as well as degenerative joint changes. It can also be used during surgery to jump-start the healing process following the surgical procedure.
Some of the most common applications of PRP include treatment of:

- Shoulder pain and instability
- Hamstring and hip strains
- Knee, hip, and other joint osteoarthritis
- Rotator cuff injuries, including partial-thickness
- Hip joint arthritis
- Tennis and golfer's elbow
- Knee sprains and instability

- Patellar tendonitis
- Achilles tendonitis & plantar fasciitis
- Carpal Tunnel Syndrome
- Ankle sprains
- Knee and ankle arthritis
- Lumbar spine disc pain
- Shoulder arthritis



Preparation and administration of platelet-rich plasma