EUROPEAN PATENTED RIGENERA TECHNOLOGY

THE ONLY PROVEN AUTOLOGOUS MICROGRAFTING PROCEDURE

mytocel MSK

MOST FREQUENT ASKED QUESTIONS

ABOUT MYTOCEL MSK

ADVANCED REGENERATIVE MEDICINE
FOR MUSKOLOSKELETAL HEALTH

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01 What is Mytocel MSK and why should I have it in my clinic?

Mytocel MSK is an orthobiologic procedure based on autologous micrograft technology (AMT®) using Rigenera® Technology. Rigenera® Technology and autologous micrografting is a widely used medical technology in different therapeutic areas, such as dermatology, odontology, wound healing, cardiology and orthopaedics.

Mytocel MSK uses autologous biopsies from auricular cartilage (pinna auricular). The procedure is designed to be minimally manipulated regarding the biological material and minimally invasive for the patient. The final product obtained (a micrografting suspension or AMT® suspension) is infiltrated into the target and affected by osteoarthritis joint. Therefore, Mytocel MSK would be classified as a cell-based and as a PoC (Point of Care) procedure, according to ESSKA Consensus Project – Injectable Orthobiologics in Knee OA – Part 2, CBT (de Girolamo & Laver, 2024).

The components of Mytocel MSK are Sicurdrill® 2.0, Sicurstick, Sicurlid and Rigeneracons® RS. Rigeneracons® RS are disposable medical devices class IIa.

02 Which is the innovative concept and what are the unique features of Mytocel MSK?

Mytocel MSK represents an innovative advancement in regenerative medicine, especially in orthobiologics by adopting a comprehensive approach to joint treatment, recognizing the joint as a complex organ composed of multiple interconnected structures, including cartilage, ligaments, meniscus, and subchondral bone. Unlike other orthobiologics that target isolated components, Mytocel MSK is designed to create an optimal microenvironment within the joint, fostering a regenerative response that supports tissue repair and homeostasis.

At the core of this technology is micrografting, a process that enables the preparation of a tissue-specific micrograft suspension at the point of care, reducing the tissue collection to 200 times. This suspension contains the perfect regenerative combination of biological components essential for regeneration, including genes involved in chondrogenesis, multiple cell populations, a bioactive secretome, and extracellular matrix (ECM) components. Mytocel MSK lies in its ability to preserve these elements in their native state, ensuring that their biological activity remains intact without any artificial modifications or enzymatic alterations (Astarita *et al.*, 2020).

By maintaining the natural structure and function of the regenerative components, Mytocel MSK promotes a dynamic, self-sustaining healing process within the joint. This approach not only supports the repair of damaged cartilage but also modulates inflammatory responses and enhances the overall biomechanical integrity of the joint. Consequently, Mytocel MSK represents the latest generation, autologous, tissue-specific and minimally invasive orthobiologic solution for mild to moderate osteoarthritis leveraging the body's intrinsic regenerative potential to achieve long-term therapeutic benefits.

03 What is the indication of Mytocel MSK?

Mytocel MSK is indicated for patients diagnosed with mild to moderate osteoarthritis, up to grade III (Marcarelli *et al.*, 2021)(Tsoukas *et al.*, 2023)(Helito *et al.*, 2024).

04 How long do the clinical results last after the session of Mytocel MSK?

Clinical follow-ups and studies have shown that the effects of Mytocel MSK can last for at least three years after the procedure.

05 Does Mytocel MSK work for OA grade IV?

Currently, Mytocel MSK is indicated for mild to moderate osteoarthritis (OA). In advanced OA (grade III advanced and grade IV), there is insufficient clinical evidence to establish it as a standard indication. However, some clinical cases of grade IV OA have reported benefits, including pain relief, improved mobility, and reduced joint stiffness. These effects tend to be shorter-lasting, typically up to one year (Tsoukas *et al.*, 2023).

06 Are there specific contraindications for the use of Mytocel MSK for OA?

Contraindications due to local problems in the injection area: any contraindication for knee injections, such as infection, skin problems, others.

Contraindications due to systemic problems (they can be grouped in 4 main groups):

Infections: besides the well-known reasons not to perform a knee injection in a patient with active systemic infections, systemic infections also affect negatively the AMT® solution because it contains pro-inflammatory cytokines and cells that might be more reactive and with altered functions.

Donor site comorbidities: if the patient has auricular cartilage that is unsuitable for the Mytocel MSK protocol, the procedure may not be performed. Conditions that may affect the suitability of the donor site include ear deformities, trauma, fibrocartilage formation, or "cauliflower ear."

Cancer: in terms of malignancies, current literature has not demonstrated a clear link between AMT® contents and the risk of tumor proliferation, either locally or remotely. However, due to the theoretical risk that the content of AMT® may contribute to tumor growth promotion in situations where either a benign or malignant tumor exists in the knee joint, in these cases it is a contraindication to perform Mytocel MSK. Due to similar concerns and until further evidence is available, this recommendation should also apply to tumors with or without metastasis located in other locations, outside/even remote from the knee, although consultation should be made with the managing oncologist/physician in specific cases.

Autoimmune disorders: patients with active autoimmune disorders undergoing immunosuppressive treatment or suffering from immune deficiency.

07 Which is the standard Mytocel MSK protocol?

Mytocel MSK procedure consists of 4 steps:

- Anesthesia of the donor site – auricular pinna with Lidocaine 2%.
- Extraction of 3 biopsies of 2,5 mm.
- Mechanical disaggregation with Rigenera Technology for 6 minutes.
- Infiltration into the joint.

Please, watch the video for more details: Mytocel MSK procedure

08 Do I need a surgery room to perform Mytocel MSK?

A surgery room is not required to perform Mytocel MSK; however, it is strongly recommended to ensure maximum hygiene and conduct the procedure in a sterile field. If the healthcare professional (HCP) prefers to use a surgery room, there are no restrictions on doing so.

09 If a doctor wants to treat 2 knees with AMT®, what is the protocol?

They must take 5-6 punches of 2.5 mm, the biopsies can be extracted from the same ear if the cartilage allows it, and/or from the other ear.

10 How long does a session of Mytocel MSK last?

Usually, the procedure for 1 joint (for example knee) could last 30 minutes. The time can vary depending on HCP and joint.

11 Which is the recommended posology for Mytocel MSK procedure?

The clinical experience up to date shows that 1 session of Mytocel MSK is enough for mild to moderate OA.

12 Is other additional equipment needed besides the Sicurdrill® and the Rigeneracons® RS?

Yes, you also need 2% aqueous chlorhexidine, 2% lidocaine without vasoconstrictor, adrenaline (just in case the bleeding of donor area does not stop), injectable physiological saline solution, Nobecutan®, 3ml and 5ml syringes, 30G x ½ 0.3 x 12mm needle, 21G x ½ 0.8 x 40mm needle, 2.5mm dermal punch, sterile Adson tweezers, round sticking plasters, sterile gloves and surgical drapes.

13 When does the patient experience improvement?

Patients typically experience clinical improvement—including pain relief, reduced stiffness, and improved mobility—between 2 and 6 weeks after the procedure.

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14 How many times can a patient receive Mytocel MSK?

There is no specific limit to the number of Mytocel MSK procedures a patient can receive. Typically, one infiltration is sufficient to relieve OA symptoms. However, the availability of donor cartilage may be a limiting factor. If the auricular cartilage does not provide enough tissue for at least three punches of 2.5 mm, additional procedures may not be feasible.

15 Is a repeated use of Mytocel MSK recommended following a previous successful Mytocel MSK treatment for knee OA upon the re-emergence of symptoms?

Mytocel MSK is typically recommended as a one-time treatment following the standard protocol. However, there is no specific limit to the number of procedures a patient can receive. The primary limitation is the availability of sufficient donor cartilage from the ear. If symptoms re-emerge, Mytocel MSK can be repeated based on the physician's clinical judgment and the feasibility of obtaining adequate donor tissue.

16 Have you used Mytocel MSK for other articulations, apart from the knee?

AMT® can be used for various joints diagnosed with osteoarthritis (OA). While most treated cases involve gonarthrosis (knee OA), AMT® has also been applied in cases of shoulder, ankle, hip, and rizarthrosis (thumb OA).

17 Can Mytocel MSK be used in healthy knees as a preventive treatment?

Currently, there is not enough clinical evidence addressing this question, and therefore it cannot be stated that the application of Mytocel MSK in asymptomatic osteoarthritis prevents its progression. However, there are no known contraindications for its use.

18 For what age range is Mytocel MSK recommended?

Mytocel MSK has been studied in patients with a mean age range of 37 to 84 years. However, there is no strict age limitation for its use. The recommendation should be based on multiple factors beyond chronological age, including OA grade, chronic inflammation, biomechanics, and overall patient condition. The decision to proceed with Mytocel MSK should be made on an individual basis by the treating physician.

19 Is there any special recommended post procedure care?

- Mild joint inflammation may occur in 10% of cases within the first 24-48 hours.
- Analgesics are recommended, but NSAIDs should be avoided.
- Maintain resting positions for at least 7 days post-procedure.
- After this period, gentle exercise and physiotherapy are encouraged.
- Hygiene of the donor site (ear) must be carefully maintained.
- Avoid washing the ear wound for the first 24 hours to prevent infection.

20 Does Mytocel MSK regenerate cartilage?

Mytocel MSK has been shown to improve mobility, reduce stiffness, and alleviate pain, as demonstrated in three clinical studies. In one study by Dr. Marcarelli, MRI assessments indicated structural changes in treated patients, with manual measurements comparing pre- and post-treatment MRIs revealing modifications in cartilage structure.

However, current data is not yet conclusive in proving in vivo cartilage regeneration or the formation of new cartilage. Ongoing animal model research is being conducted to further investigate cartilage generation mechanisms, the extent of regeneration, and the type of cartilage formed (Marcarelli *et al.*, 2021).

21 Biopsies for Mytocel MSK are taken from auricular cartilage (elastic cartilage), while the joints consist of hyaline cartilage.

What are the key differences between these two types of cartilage, and is there any risk associated with using elastic cartilage-derived micrografts in hyaline cartilage repair?

Elastic and hyaline cartilage differ in their composition as the elastic one contains more quantity of elastic fibers than the hyaline. This is the reason why elastic cartilage is found in places that require mobility and resistance while hyaline provides structural support. However, it is known that elastic cartilage contains cells with higher regenerative potential than hyaline cartilage. In a structure called perichondrium, there are found chondroprogenitor cells that, under certain conditions, can integrate and functionally adapt to the joint environment. A study conducted on rabbits demonstrated that perichondral progenitor cells promote the proliferation and chondrogenesis of mature chondrocytes, as well as contribute to their rejuvenation (Ho *et al.*, 2022).

Moreover, research has identified the presence of mesenchymal stem cells (MSCs) in micrograft solutions. These cells, through the secretion of bioactive molecules such as growth factors and cytokines, facilitate tissue repair by modulating inflammation, stimulating the activity of surrounding cells, and promoting both healing and chondrogenesis (Shi *et al.*, 2018)(Klimczak & Kozlowska, 2016).

Additionally, cells derived from the head and neck region exhibit greater regenerative potential than those from the extremities. This difference is attributed to their mixed embryonic origin, as they come from mesodermal and ectodermal layer. Ectodermic-derived cells have been shown to have better regenerative properties than only mesoderm-derived cells alone (Li *et al.*, 2020).

All these properties of elastic cartilage have already been used in other therapeutic areas such as plastic surgery and otorhinolaryngology. In a study conducted with patients who underwent revision rhinoplasty with auricular cartilage grafts, histologic and biochemical changes were observed, proving the ability of elastic cartilage to integrate into hyaline cartilage (Wu *et al.*, 2023).

22 Why don't you take hyaline articular cartilage, instead of auricular cartilage?

Auricular cartilage, composed of elastic cartilage, is surrounded by the perichondrium, a dense connective tissue membrane that plays a crucial role in protection, nourishment, growth, and cartilage repair. Unlike hyaline cartilage in joints, which lacks this vascularized structure, auricular cartilage is utilized due to the presence of the perichondrium. Additionally, its anatomical location is more accessible compared to other sites containing perichondrium, such as the eustachian tube, epiglottis and larynx.

23 Within which timeframe should the micrograft solution be injected back into the body?

It is recommended to inject it as promptly as possible to preserve the viability of the biological components, maximum within 1 hour.

24 Are there any factors that can affect the quality of the micrograft suspension?

Yes, it is strongly recommended to follow the protocol to ensure optimal results. Several factors can influence the quality of the micrograft suspension and, consequently, the outcome of the procedure, including:

- Proper use of the technology
- High-quality biopsy collection (ensuring adequate and viable tissue samples)
- Precise disaggregation time (to optimize cell and tissue component extraction)
- Strict sterility maintenance throughout the process
- Accurate infiltration technique to ensure proper distribution in the target joint

25 Is Mytocel MSK a safe device for the patient?

The Sicurdrill® is a class I medical device and the Rigeneracons® are sterile disposable class IIa medical devices approved and certified by EMA (CE), AEMPS (CE), PMDA (Japan) and FDA listed*.

*Does not mean approved.

26 Is Mytocel MSK considered an advanced Advanced Therapeutical Medicinal Product(ATMP)?

No, Mytocel MSK is not considered an ATMP as micrografts are not manipulated before the injection.

27 Are exosomes present in the AMT® solution obtained with Mytocel MSK?

The mechanism of action of Mytocel MSK is primarily driven by paracrine effects and immunomodulation. In these processes, the secretome plays a crucial role in mediating cell-to-cell communication. The secretome consists of extracellular vesicles, including exosomes, whose release is influenced by various factors such as health status, age, tissue condition, and the presence of chronic diseases (Swami *et al.*, 2024).

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28 What is the difference between Mytocel MSK and Platelet-Rich-Plasma?

Mytocel MSK utilizes autologous, tissue-specific micrografts derived from auricular cartilage, whereas PRP, though also autologous, consists of blood-derived elements. The tissue specificity of Mytocel MSK preserves the original microenvironment, maintaining regenerative cells, cytokines, and growth factors that promote healing and cartilage regeneration. A key distinction between the two is Mytocel MSK's cellular component, which contributes to its longer-lasting effects. Unlike PRP, which contains no cells and typically requires 3-4 infiltrations, Mytocel MSK requires only 1 session, as micrograft's cells (expressing MSCs markers) act as biological "drugstores", continuously supporting tissue repair and regeneration in vivo (Justicz *et al.*, 2020) (Caplan *et al.*, 2011).

29 Is there any risk of carcinogenesis when AMT® suspension is applied to the patient?

No, there is no evidence of carcinogenesis associated with Mytocel MSK. Since Mytocel MSK utilizes autologous tissue containing already differentiated adult and near-adult cells, there is no risk of cancer development. Furthermore, the cells remain within their natural environment without genetic manipulation or **in vitro** processing after tissue disaggregation, ensuring their biological integrity and safety.

30 Can Mytocel MSK be performed on a patient with autoimmune disease?

It is not recommended to use Mytocel MSK in patients with autoimmune disease. Autoimmune diseases are a diverse group of conditions characterized by aberrant B cell and T cell reactivity to normal constituents of the host. Among these diseases, the most prominent immunological manifestation is the production of autoantibodies. Performing autografts could be risky in the presence of an autoimmune disease, as the effects of autoantibodies and autoreactive cells inside the joint cavity are not well understood (Pisetsky, 2023).

31 Could Mytocel MSK be used for knee OA during the inflammatory phase when joint effusion is present (following effusion aspiration)?

Evidence regarding the injection of Mytocel MSK during the inflammatory phase in knee OA, as well as with regards to effusion aspiration prior to Mytocel MSK injection, is lacking. However, pre-clinical and clinical studies have demonstrated the presence of MSCs in the autologous micrograft solutions. MSCs can regulate inflammatory processes, and they can orchestrate local and systemic innate and adaptive immune responses through the release of various mediators, including immunosuppressive molecules, growth factors, exosomes, chemokines, complement components and various metabolites. These proven anti-inflammatory properties could support the rational for its use during the inflammatory phase (Shi *et al.*, 2018).

There is no clear evidence on the best timing for injecting Mytocel MSK in knee osteoarthritis when there is joint effusion. However, it is recommended that if effusion is present, it should first be drained before administration of Mytocel MSK. Draining the effusion can help prevent the dilution of Mytocel MSK after injection, improve pain relief, and enhance mobility recovery.

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32 Is Mytocel MSK suitable for patients with chronic inflammatory diseases?

The presence of local or systemic inflammatory diseases, such as Crohn's disease, is not a contraindication for Mytocel MSK. However, it must be considered that the nature of these diseases can lead to general inflammation of the tissues and Mytocel MSK is an autologous procedure using patient's own tissue.

33 Is Mytocel MSK able to repair meniscus?

Mytocel MSK has not yet been studied for the treatment of degenerative meniscus lesions. As a result, there is currently no clinical evidence to confirm its effectiveness in meniscus repair.

34 Is Mytocel MSK a clinically better injectable option than hyaluronic acid for the treatment of knee OA?

Hyaluronic acid (HA) is a negatively charged polysaccharide with strong hydrophilic properties, which allows it to be present in areas of the body exposed to compression forces, such as joints. It is one of the many substances that form the extracellular matrix. Mytocel MSK contains tissue-specific cells, cytokines, growth factors and other molecules from the ECM that promote the healing microenvironment within the joint (Abatangelo *et al.*, 2020). If Mytocel MSK is regarded as a cell-based procedure there are several high-level studies comparing the effectiveness of cell-based procedures to HA for knee OA, with the majority favouring these procedures in terms of overall clinical improvement and a longer-lasting effect documented to last up to 12 months (Goncars *et al.*, 2017).

35 What kind of sports related injuries can we treat with Mytocel MSK®?

A thorough history of prior injuries, treatments and procedures should be conducted. Locking, catching, clicking, or popping are common complaints from the knee and are suggestive of concomitant pathology. Mytocel MSK could be particularly beneficial in post-traumatic sports injuries in athletes, triggering osteoarthritis in the future. Moreover, the protocol could be extended to other articulations besides the knee joint, such as the hip, shoulder and ankle.

36 Can Mytocel MSK be performed in patients which have received previously corticosteroids, PRP, and/or HA?

Corticosteroids have been shown to have detrimental effects on chondrocytes and can lead to accelerated cartilage degeneration, especially with multiple/repeated injections, although corticosteroids are strong anti-inflammatory agents and can provide short term relief in knee OA (mainly less than 3 months). Orthobiologics injections have been shown to have the potential for a longer effect in comparison to the shorter-term effect of corticosteroids injections. They also seem to provide a safer use profile with less potential related complications compared to corticosteroids, especially when considering the

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potential need for repeated injections in knee OA patients, more so in younger patients. Therefore, Mytocel MSK can be performed 2 months after local injection of corticosteroids or 2 months after interrupting systemic corticosteroids treatment.

Platelet-Rich-Plasma (PRP) is an autologous orthobiologic blood-derived product. It is NOT a cell-based product. Usually, the protocol of treatment consists of 3-4 infiltrations in 1-2 months' time. Mytocel MSK can be performed 2 months after the last injection of PRP or 2 months before first injection of PRP.

Hyaluronic Acid (HA) is an orthobiologic product mainly used for its viscosupplementation properties in joints treatments. Mytocel MSK can be performed after 6 months post high molecular weight HA infiltration and after 3 months post low molecular weight HA infiltration. If Mytocel MSK is performed before HA infiltration, a minimum interval of 3 months is recommended between the two procedures.

37 Can Mytocel MSK be followed by electrostimulation (TENS) for the chronic pain management present in OA?

Mytocel MSK can be followed by TENS for chronic pain management in OA. However, it is recommended to delay electrostimulation in the initial phase of tissue regeneration to avoid potential interference with the inflammatory response and cellular repair. TENS can be introduced in the later stages to enhance pain relief and mobility, under professional supervision.

38 Can Mytocel MSK be performed at the same session with other orthobiologic procedures?

No, Mytocel MSK should not be performed in the same session with other orthobiologic treatments. The AMT® suspension has a unique composition, and the introduction of other biological components could alter its inherent properties, potentially compromising its effectiveness.

39 Can I combine Mytocel MSK with other orthobiologic procedures/products?

There are no contraindications for its combination with other orthobiologic procedures, if the combination is carefully planned to optimize outcomes and avoid potential interactions. It is important to consider patient-specific needs and perform always under medical supervision. Check question number 36.

40 Should intra-articular local anaesthesia be used when infiltrating Mytocel MSK?

Currently no clinical studies exist regarding the effect of local anaesthesia with Mytocel MSK. However, in vitro studies have shown that anesthetic drugs interfere with cells integrity and functionality as well as diminish the positive effects on cell proliferation. Therefore, it is not recommended the use of intra-articular local anaesthetics when injecting Mytocel MSK.

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41 Are fasting or dietary restrictions recommended before Mytocel MSK? Any other patients' behaviour could affect the treatment?

There is not enough evidence to recommend a specific diet or fasting regimen before undergoing Mytocel MSK. However, emerging studies suggest that lifestyle and dietary habits may influence the effectiveness of regenerative medicine-based treatments.

For example, alcohol and tobacco consumption have been associated with an inflammatory profile that may negatively impact the activity of mesenchymal stem cells (MSCs) in our tissues. While not a mandatory recommendation, avoiding these inflammatory substances before the procedure could potentially enhance the efficacy of Mytocel MSK, considering that it is an autologous treatment (Zhu *et al.*, 2021)(Di Rocco *et al.*, 2019).

42 Is antibiotics administration recommended after or before Mytocel MSK procedure?

Like other injectable products for the knee joint, autologous preparation process involves tissue harvesting and therefore some degree of infectious risk should be taken into consideration. To reduce the infectious risk, we recommend strictly to follow the protocol recommendations regarding sterile field. HCPs should apply their medical judgement to determine whether an antibiotic prophylaxis is needed when performing Mytocel MSK.

43 Is Mytocel MSK reimbursed by the public and private health insurance in any country?

Today, Mytocel MSK is not reimbursed by any private health insurance company. However, in some countries, AMT® has been proposed and used in the public health system as a grafting technique. All aspects regarding the legislation of orthobiologic treatments and medical devices, as well as market access and regulatory compliance, are entirely market-dependent for each country. We are collaborating with partners in most countries to simplify and enhance patient and doctor access to Mytocel MSK.

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