O Papel da Medicina Regenerativa no Tratamento e Reabilitação de Lesões Desportivas

The role of Regenerative Medicine in Sports Lesions Treatment and Rehabilitation

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Resumo

Tradicionalmente, o papel do cirurgião na reparação de lesões do foro ortopédico, prende-se com a restituição da função perdida recorrendo à otimização do ambiente biomecânico da lesão. No entanto, sabe-se que algumas das lesões observadas nesta área apresentam um fraco potencial de recuperação espontânea e que as técnicas disponíveis até há algum tempo acabavam por resultar em défices irrecuperáveis ou cuja recuperação era demasiado longa. A abordagem e o tratamento das lesões desportivas têm vindo a melhorar substancialmente nas últimas duas décadas graças à evolução das técnicas minimamente invasivas e de programas de reabilitação mais dirigidos. Este novo conhecimento veio abrir portas a novas terapias biológicas, especialmente o plasma rico em plaquetas e as células estaminais.

Foi realizada uma revisão da literatura publicada na base de dados PubMed, pesquisando pelo termo MeSH "*sports medicine*", considerado mais adequado e abrangente tendo em conta a informação disponível na literatura estrangeira. Foram selecionados os artigos disponíveis até dezembro de 2020, cuja pertinência para esta revisão foi posteriormente analisada.

O plasma rico em plaquetas parece representar uma opção segura para o tratamento e regeneração de alguns tecidos no contexto das lesões desportivas. Trata-se de uma terapia promissora e com baixo potencial para provocar efeitos secundários, já que utiliza tecido autólogo. As células estaminais terão um papel inquestionável no futuro do tratamento de lesões desportivas. Reconhece-se que têm tido efeitos promissores comprovados pela investigação dita de bancada e até pela progressão desta investigação para modelos animais. Até à data, os dados disponíveis permitem-nos assumir que a utilização de células estaminais mesenquimatosas será segura a curto prazo.

Embora os resultados sejam bastante promissores, ainda é precoce afirmar em que situações o plasma rico em plaquetas e as células estaminais possam ser utilizados com benefício comprovado, pelo que é imperativo que se realizem ensaios clínicos com o objetivo de estudar esta possibilidade, aliada a uma adequada reabilitação adaptada à lesão em si e às condições inerentes ao doente.

Palavras-chave: Células Estaminais; Medicina Desportiva; Medicina Regenerativa; Plasma Rico em Plaquetas; Terapia Biológica; Transplante de Células-Tronco Mesenquimais

Abstract

The surgeon's role in orthopedic lesions repair has been traditionally associated with restoring lost function through the optimization of the lesion's biomechanical environment. It is known, however, that the observed lesions in this particular field display a weak spontaneous recovery potential and that the available techniques until recently ended up resulting in irrecoverable deficits or

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lengthy recovery periods. Significant improvements over the past two decades in sports lesions' approach and treatment can be attributed to the development of minimally invasive techniques and more guided rehabilitation programs. All this new knowledge has provided a gateway for new biological therapies, notably platelet-rich plasma and stem cells.

A review of published papers in PubMed's database was performed using the MeSH term "sports medicine" as query, since this was considered the most adequate and broad term available according to foreign published papers. Through this method all articles available up to December 2020 were selected their relevance for this review was assessed.

Platelet-rich plasma seems to be a safe therapeutic option for some tissue treatment and healing in sports lesions. This is a promising therapy with a low potential for adverse reactions since it uses autologous tissue. Stem cells will undoubtedly play an important role in the future of sports lesions treatment. It is known that, thus far, it has produced promising effects that have been confirmed by laboratory research and even by the natural progression of this investigation onto animal models. Hitherto, the available data allows us to assume that the use of mesenchymatous stem cells will prove to be a safe option in the foreseeable future.

Albeit the promising results that they report it is still too early to ascertain with full confidence in what situations platelet-rich plasma and stem cells can be used with a proven benefit. Thenceforth it is imperative that clinical trials aimed at studying this possibility are performed, coupled with an adequate rehabilitation that is adapted not only to the lesion but to the overall patient's condition.

Keywords: Biological Therapy; Mesenchymal Stem Cell Transplantation; Platelet-Rich Plasma; Regenerative Medicine; Sports Medicine; Stem Cells

Introduction

Regenerative Medicine is a field of Medicine that studies and applies regenerative techniques to tissues in order to restore their function.[1] Its role in treating sports lesions has grown, currently taking on a central role in research for new and better knowledge, which led to this period of great investment and advances in research involving this field of Medicine. The scope of techniques applied in this field of Medicine is vast and from this array of interventions we must consider, such as tissue engineering, genetic engineering and the usage of biomolecules to stimulate tissue regeneration.[1] This last procedure has been used in several contexts but it currently refers specifically to the use of biological therapies in order to replace, repair or promote damaged tissue's regeneration.[2] According to the Food and Drug Administration (FDA), biologicals include an extended array of products, such as vaccines, blood and its components, cells, tissues, proteins, *inter alia*. These products' isolation can be performed from human tissue, animal sources or microorganisms.[3,4]

Traditionally, the surgeon's role in orthopedic lesions' repair is concerned with restoring loss function through biomechanical environment optimization (tendon repair, fracture stabilization, replacement of damaged tissue) and preventing lesion's extension to other tissues.[5] It is well established that some of the lesions observed in this field, namely tendon and ligament, present a low potential for spontaneous recovery and that the available techniques up until some time ago ended up leading to irrecoverable deficits or ones were the recovery period was too long.[6] Furthermore, patient's comorbidities further impair recovery especially when pathologies that affect tissue vascularization and/or oxygenation are involved. The knowledge of each phase and the players involved in tissue regrowth has allowed the identification of key points that need improvement in this field, further guiding research into biological drugs' field. Thus it is possible, in strict coordination with proper rehabilitation under the scope of Physical and Rehabilitation Medicine, to maximize non-surgical treatments usage thereby minimizing patients' risks.[7]

Sports' lesions approach and treatment has improved substantially for the past two decades thanks to the development of minimally invasive techniques and sophisticated rehabilitation programs. These improvements are the result of an exponential growth in knowledge of biomechanical and tissue engineering fields.[8] There is a clear focus on the study of pathophysiological features of each lesion, either on a cellular or even a molecular level, in order to further understand how to approach them so as to obtain the best possible outcome in the shortest time span.[8] All this new knowledge has opened the gates for new biological therapies, notably platelet-rich plasma (PRP) and stem cells.

It was soon acknowledged that lesions related to sports practice are remarkably different from others, since they occur in a mainly younger, healthier and more sports-oriented population.[9,10] Due to their singular nature, it is paramount to implement targeted therapeutical strategies taking into account patients' young age and therefore the need for a specially quick and side effects and long-term consequences free rehabilitation. Thenceforth, the scope of this review is to summarize platelet-rich plasma and stem cells use breakthrough in sports' lesions management up until this moment.

Methods

A literature review was performed for published papers in PubMed's database with the consequent identification of all available articles up until December 2020. Using EndNote, a search

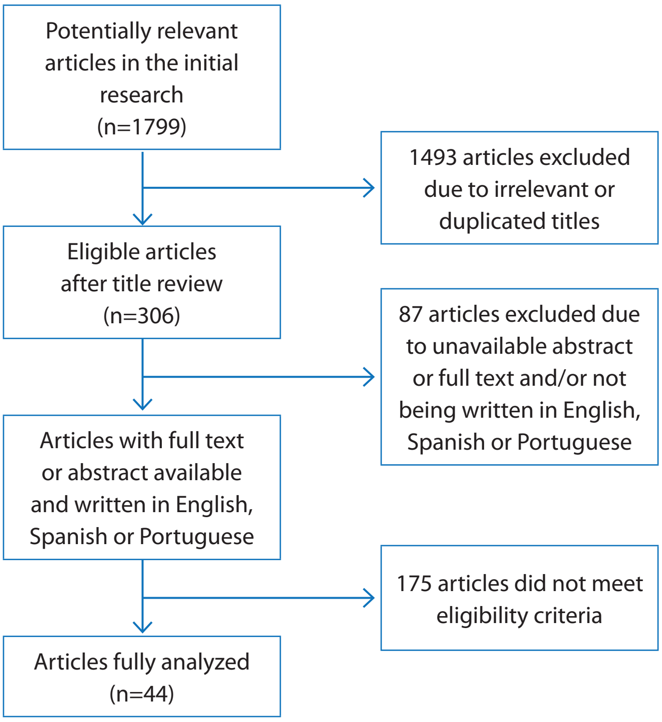

Figure 1. Flow diagram of literature selection process.

for the MESH term "sports medicine" was conducted, since this term was the better suited and most comprehensive term considering the available information in foreign literature, and all relevant articles were selected through title's analysis. As eligibility criteria, it was previously determined that, in a first stage, articles that addressed specifically the use of biological therapies for the treatment of sports' lesions would be included. Of the 1799 results obtained with this search, 44 articles were obtained, read, and analyzed in their entirety for the purpose of this review, as summarized in the flow diagram of literature selection process (Fig. 1).

Platelet-Rich Plasma (PRP)

Platelet-rich plasma has been used in Maxillofacial and Plastic Surgery since the nineties.[11-13] In Sports Traumatology, this technique has been used coupled with bone grafts to improve fracture consolidation with a growth in interest for its use in muscular and tendon lesions recovery.[11] In 2003, began its application in treatment of cartilaginous injuries albeit the very weak scientific evidence to support said use.[14] In 2008, the International Olympic Committee (IOC) published a consensus that predicted a great increase in the application of growth factors for the treatment of musculoskeletal injuries resulting from high intensity sports activity.[14] It seems that the use of these techniques allows for better results regarding the reported pain by patients and, therefore, in the intensity and need of analgesia in post-operative.[14]

PRP consists of plasma with a platelet count above base level.[11,12,14,15] Platelets are the smaller cellular component of peripheral blood with a diameter of 2-3 µm and an irregular shape, enucleated but with several organelles, with a need to highlight alfa-granules, that possess over 30 bioactive proteins many of which possess an important role in hemostasis and tissue regrowth (although their functions are not fully known).[14] The role of platelets in regenerative processes is associated with the secretion of growth factors and cytokines that lead to the recruitment of other cell types.[11] As soon as they are activated, platelets release the contents of their granules in supraphysiological amounts, enhancing the natural abilities for tissue regrowth.[16] The release of these products begins in 10 minutes with 95% of the products released by the end of 1 hour.[14] During the following days, platelets will continue to synthesize and release more growth factors. This process will draw mesenchymal stem cells (MSC), macrophages and fibroblasts, promoting the removal of damaged and necrotic tissues while stimulating the process of tissue regeneration.[16] The process of PRP extraction is summarized in Fig. 2.

There is not a consensus on the usefulness of platelet activation before its administration in the site of interest nor on the timing of said activation.[14] Recent studies suggest that the environment of the area where the PRP is injected may already include the necessary components for PRP activation.[17]

Due to the different extraction methods that exist to obtain PRP, as shown in summary in Fig. 2, there can be leucocytes in the concentrate that will be injected. The effect of the presence of these cells in PRP is controversial.[11] *In vitro* studies showed that the presence of neutrophiles in PRP can unleash a response that worsens pre-existent tissue damage.[11] Besides the benefits related to regeneration, PRP appears to possess antibacterial properties with potential clinical benefits.[12,14] Both platelets and leucocytes possess this role for their chemotactic and oxidative effects and due to the release of antibacterial peptides with bactericide properties.[14] There are also *in vitro* studies that support these antibacterial abilities, capable of affecting both methicillin resistant and sensitive *Staphylococcus aureus*.[14]

In vitro research performed so far has shown an increase in collagen and extracellular matrix production genes expression as well as the increase in the production of vascular growth factors in tenocytes exposed to PRP, although similar results have been observed in comparison with platelet-poor plasma.[11,14] These results suggest that PRP can be especially beneficial when applied in tendon lesions albeit animal models have demonstrated that this improvement will only be observed if mechanical stimuli are maintained, thus rendering no effect in immobilized joints.[14] It also suggests that a larger concentration of platelets does not correlate necessarily to a better outcome.[7]

Several *in vivo* studies have demonstrated the benefits of using PRP for injury recovery, especially in tendons, in both surgical and non-surgical approaches.[11,14] In a case-control study that

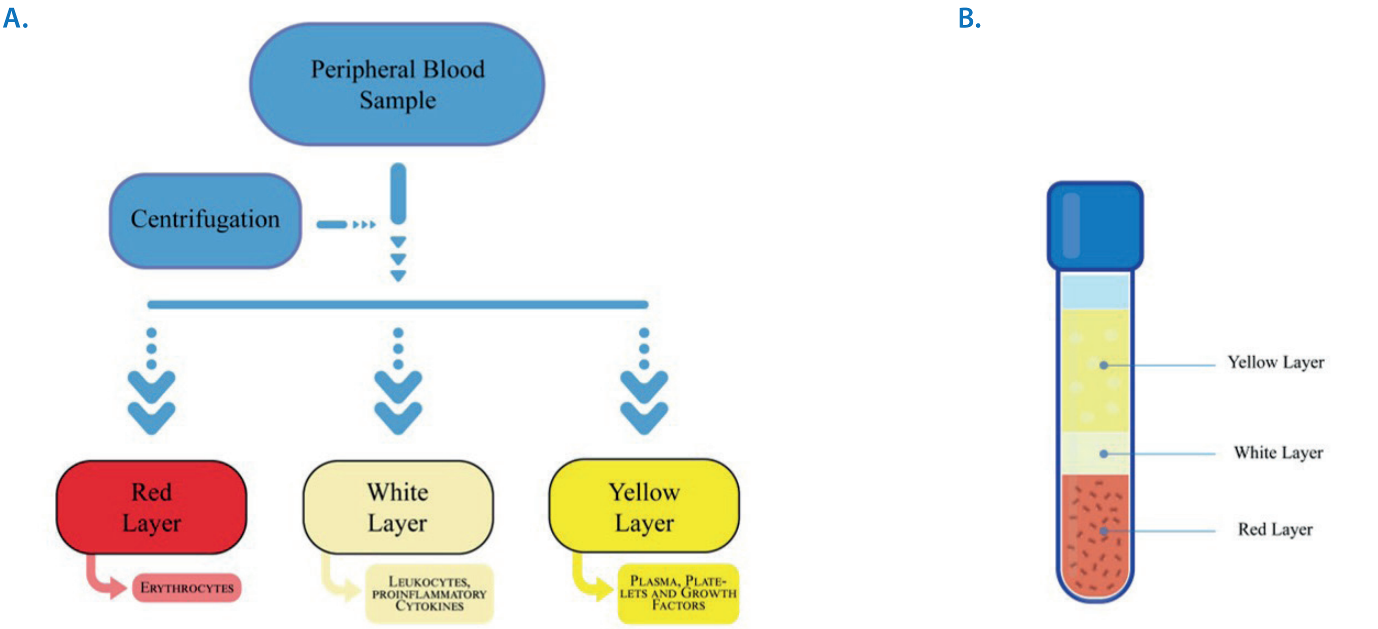

Figure 2. **A.** General process of PRP extraction, adapted from Lopez-Vidriero, 2010[12]; **B.** Final look of PRP gathering centrifugate.
About 10 mL of peripheral blood are collected and submitted to a centrifuge process. Stemming from this step are 3 layers visible to the naked eye and of these layers the red one and the white one are discarded. The yellow layer is the one located at the surface and will be injected at the point of interest.[7,14]
Different processes for the extraction of PRP vary according to velocity or number of spins (which leads to different concentrations of platelets), the usage (or not) of an anticoagulation agent in the collection tube, the presence of leucocytes in the preparation or the usage (or not) of activators (calcium chloride and/or thrombin).[11] Thrombin's use makes the platelet degranulation occur in about 1 hours; the use of calcium chloride extends this period to about 1 week.[15]

evaluated 12 athletes submitted to Achilles' tendon it was observed a faster recovery in the intervention group (7 weeks versus 11 weeks in the non-intervention group, p=0.025) and a faster return to physical activity (11 weeks versus 18 weeks, p=0.042) and training (14 weeks *vs*21 weeks, p=0.004). It was also observed a smaller growth of scar tissue in the intervention group at 18 months follow-up evaluation by echography (p=0.009).[11] Nevertheless, these are studies that generally present poor designs and a reduced number of subjects, which renders their validity as questionable.[11]

Due to PRP's autologous nature, safety issues are minimal.[11,14,17] Currently there are only records of pain at the injection site that can be attributed to the intense inflammatory response that is exacerbated.[11] Due to the lengthy experience in PRP's use in Maxillofacial Surgery, it is safe to assume that it is use is not dangerous.[14] On the other hand, although a recommendation for the use of these techniques is unavailable, they have been used off label without side effects being observed, either local or systemic, especially in patients with osteoarthritis.[14] No carcinogenesis, hyperplasia or tumoral growth cases were associated to the use PRP.[11,13,14,17] Counterindications associated with the use of these kinds of therapy include history of thrombocytopenia, use of anticoagulant agents, active infection, tumor, metastatic disease or pregnancy.[11,17]

Although general results are promising, several comparative studies have shown less auspicious results with outcomes similar to saline injections or even inferior when compared with corticoid short-term injections.[18] Nonetheless, especially when compared with corticoid, PRP's use seems to provide some advantages when results are evaluated at mid-long term (6-12 months).[18] A meta-analysis that included 16 studies has concluded that PRP was more effective than control therapies regarding pain reduction, with a moderate effect magnitude (0.47, 95%CI (0.22-0.72, p<0.001)).[18] These discrepancies in the results provided by studies conducted in humans so far can be attributed to the very small sample size that is not sufficient to draw conclusions about the magnitude of the effect.[18] Furthermore, procedures used in these studies are not yet standardized, providing an added difficulty in result comparison.[4,11,19-22] It is still necessary to investigate the ideal timing for this kind of treatments as well as the number of necessary interventions to obtain the best possible outcomes or the best rehabilitation program after injection.[11-13,21] Table 1 shows a summary of obtained results thus far with PRP application in several tissues.

Stem Cells

Stem cells are a target for research since the end of the 19th century, when its regenerative potential was discovered.[23] At the beginning of the 20th century, the first "real stem cell" was discovered with the first successful bone marrow transplant occurring six decades later.[23] From there, research relating to this kind of cellular type has grown exponentially. These cells

Table 1. Results of PRP application in several tissues.

Tissue	Pros	Cons
Muscle	- Useful in muscle strain injuries (animal studies).[9]	- The presence of TGFß-1 (profibrotic cytokine) can cause issues although the concomitant administration of PRP and losartan (TGFß-1 antagonist) minimizes thoroughly fibrosis in animal models.[6,9] - Lack of scientific basis, both in animal as well as human models.[16] - Lack of difference in effect between intervention and comparative groups as well as a lot of study design errors.[16] - Further human clinical trials are needed to better understand potential effect.[9]
Tendon	- Favorable results in several animal studies when comparing with corticoids and mid to long-term NSAIDs.[9,14,16] - Functional recovery period and patient's experienced degree of pain efficacy.[14] - Improvements in echotexture and a smaller number of calcifications in neovessels confirmed through echography.[9]	- Most published studies regarding human intervention are case-studies, mostly lacking methodological quality.[16] - Obtained results tend to vary according to the intervened tendon.[19] - Available scientific grounds thus far are not solid enough to allow for the recommendation of PRP use.[19]
Cartilage, ligaments and meniscus	- Regenerative properties in meniscus cells shown in vitro and animal models, both histologically as biomechanically.[9] - Favorable results in patients with osteoarthritis both in pain diminishing as well as functional improvement.[9,14,16]	- Further long-term studies are needed to support evidence.[9,14,16]

are especially appealing in Sports Traumatology due to their unique properties, namely their ability to remain in quiescence state; the ability to differentiate into several lineages; and their self-renewal abilities.[23,24] Their origin can be autologous or allogenic.[25] The main upside in using autologous cells relates to the elimination of potential unwanted immunological reactions.[23] However, one major setback is the morbidity caused by its harvesting and due to the fact that these cells lose part of their differentiation potential with ageing, which can result in older patient not possessing cells with the needed amount for an effective treatment.[23] On the other hand, allogenic cells have the advantage of being possible to produce them in large scales after harvesting and consequently being able for use almost immediately if necessary. However, when receiving cells from a donor, the receptor is in danger of contracting an infection or even receiving potentially pathological genetic material, besides the risk of immunological rejection.[23]

There are several types of stem cells, each with a different differentiation potential, as shown in Table 2.

Table 2. Cellular types and main characteristics.

Cell Types	Main Features
Totipotent	The potential to differentiate into any kind of cell type that comprises an organism having the ability to fully "produce" it. This cell type model are embryonic cells.[28]
Pluripotent	They possess the ability to differentiate into anyone of the main germ layers (endoderm, ectoderm and mesoderm) but they don't possess the ability to differentiate into trophoblastic cells.[26]
Multipotent	They are able to differentiate into only one germ layer.[26]
Unipotent	They only possess the ability to differentiate into one cell type. For that reason they are called "precursor cells"[26]

Cells that have the ability to differentiate into multiple cell types will follow the differentiation pathway that is determined by the environment in which they are introduced.[25] One of the main concerns with the use of these cells is related to the absence of full knowledge of the differentiation processes as well as the potential ways to modulated said differentiation.[26]

Stem cells' sources are diverse in nature, both pre and postnatal. Regarding embryonic cells, they can be obtained in 3 different ways: directly from a human embryo; from clone of embryos; or through adult cells reprogrammed to return to their pluripotency state (induced pluripotent stem cells – IPSC).[26] The use of these cell types rises some ethical issues that motivate a great array of stances from different countries, some allowing from the harvest of these cells from discarded embryos or *in vitro* fertilization, a small number allows the creation of new stem cells only for research purposes and others that ban every type of pluripotent cell use.[26] One way that has been studied by the scientific community to solve the ethical issues that underlie the harvest of these cell types relates to the use of cells obtained from placental tissue.[26] Several anatomical parts that constitute the placenta have been researched due to their regenerative potential, as well as the amniotic membrane and the umbilical cord. Products derived from the amniotic membrane have been used in fields such as ophthalmology, for treatment of cornea lesions, and treatment of ulcers in the context of diabetic foot.[27] These cells seem to have important effects, from their immunomodulating and anti-inflammatory role to their well-documented antimicrobial effect against gram-positive coccus, including *Streptococci* and *Staphylococcus aureus*, and gram-negative bacilli, including *Escherichia coli* and *Pseudomonas aeruginosa*.[16,27] However, the use of these cells in the specific context of Sports Traumatology is much less studied although they are identified as potentially useful to restoring cartilage, tendons and ligaments as well as for the non-invasive treatment of osteoarthritis and plantar fasciitis.[27] The strategy for the use of this cell type has been studied in 3 branches: the use of amniotic membrane as matrix for the application of bone marrow derived stem cells; use of amniotic membrane as matrix for the application of chondrocytes; induction of amniotic membrane stem cells differentiation to a chondrogenic phenotype.[27] Nonetheless, there are not studies with enough solidity to immediately advance to the application of said strategies in human clinical trials.[27]

Stem cells can also be grouped according to their differentiation potential. For instance, hematopoietic stem cells are progenitors for endothelial and peripheral blood cells, and mesenchymal stem cells (MSC) are progenitors to chondrocytes, myocytes, adipocytes and osteoblasts.[24] As for stem cells derived from muscle tissue, these possess a great advantage that favors their potential use: a huge availability since muscle tissue represents the largest body proportion and can be obtained through minimally invasive procedures.[24] Moreover, they possess the ability to differentiate into endodermic, ectodermic or mesodermal cell types.[24] Stem cells from adipose tissue are also attractive since they are very easy to obtain and abundant in fat tissue.[24] Their use in Sports Traumatology is still largely unexplored with a greater research in Plastic Surgery.[24] Stem cells from bone morrow are the most abundant and studied in scientific literature.[24] Their harvest calls for more invasive procedures however they can also be considered relatively accessible cells. They possess the ability to differentiate into several cell types that compose conjunctive tissue, namely cartilage, bone, tendon, ligament and muscle constituents.[26] Stem cells from synovial tissue have also been studied due to their chondrogenic differentiation and expansion potential.[24]

In the specific context of Sports Traumatology, the most relevant cell types are the ones derived from (MSC), namely fibroblasts, adipocytes, bone, cartilage and muscle tissue, all part of the mesoderm.[24] These cells have the ability to segregate growth factors and cytokines with chemiotactic and immunosuppressor properties.[23,25] According to the environment in which they are introduced, these cells have a remarkable ability to adapt their response, from anti-inflammatory to proinflammatory.[4] These cells possess the best known potential to date for tissue regeneration since they have demonstrated a great ability to regenerate tissue through direct replacement of damaged cells as well as through their anti-inflammatory effect, through paracrine signalization and angiogenesis promotion.[28] Furthermore, they appear to have a special ability to escape the immune system, since they express a low amount of class 1 HLA surface markers, a great upside from their allogenic use.[28,29] They also possess anti-apoptotic and proliferative abilities, reason why they have, besides repairing tissues, the ability to limit their destruction. For this reason, Arnold Caplan, which named mesenchymal stem cells (MSC) in 1991, now considers the abbreviation MSC as being the most adequate to refer to these cells as medicinal signaling cells.[28]

Stem cells can be obtained from fat tissue, peripheral blood, periosteum, bone marrow, skeletal muscle, umbilical cord, placenta, dentary pulp, skin, tendon, synovial tissue or fluid, epithelial tissue or even menstrual blood.[23-25,27] It is important to mention that the origin of the cells can influence their quality, namely their potential to fight inflammation. For instance, cells collected from the placenta or the umbilical cord can be grown longer, multiply more and have a better anti-inflammatory response when compared with bone marrow or fat tissue cells.[23,30] As mentioned before, it is thought that these differences have to do with cell age since younger cells possess a more intact DNA. Thus, the age of the donor will affect the response potential for stem cells, although it seems that potential changes are not significant when patients with an age of 50 are compared with 80-year-old patients.[16,23] Notwithstanding, it is believed that bone marrow cells will be more affected by age than by those of fat tissue.[16] Additionally, it is assumed that the donor's body mass index (BMI) also affects the potential of collected stem cells, namely in patients with a BMI bigger than 30 kg/m^2. A diminishing in the proliferation rate, an increase in senescence, increase in stress related gene expression as well as a diminish in osteogenic capacity.[23]

To isolate human MSC there are criteria based on their properties, defined by the International Society for Cell Therapy, namely: adherence to plastic in standard culture conditions; surface molecule expression; the ability to differentiate into osteoblasts adipocytes and chondroblasts *in vivo*.[23,24] The process of obtaining these cells has some fundamental initial steps, such as harvest, isolation and cellular expansion.[23] However, there isn't a properly standardized protocol which raises several problems for the use of these products for medical ends.[25] Besides, these differences make comparison attempts between studies conducted in this area more difficult.[25]

To use stem cells efficiently, several interlinked criteria must be fulfilled, as shown in Fig. 3.

The above figure intends to show two successive but totally dependent phases, essential for the adequate conduction of the process. Peripherally a priori characteristics can be found; centrally are located the necessary characteristics after cell implantation.

There seems to be a role in using PRP and LED lights (*light-emitting diode*) for the adequate activation of stem cells.[24] Applying this kind of light into fat tissue derived stem cells in adequate culture mediums increases their viability and proliferation.[24] PRP plays a role in cell proliferation and differentiation in the chondrogenic pathway, besides the important role of platelets not only because they possess relevant growth factors but also because they are one of the first responders to arrive at the tissue lesion's site.[23,29] Alternatively, there is a great potential for

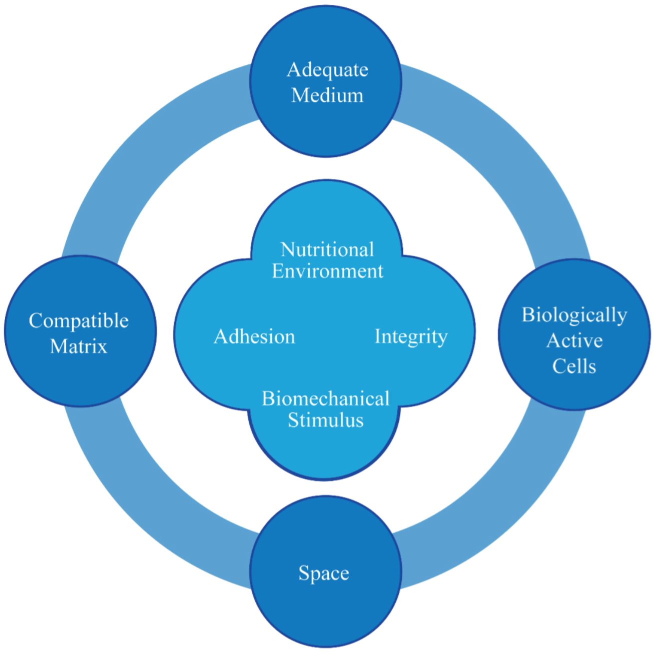

Figure 3. Key steps for the success of stem cell-based intervention.

For this process to happen in the optimal way, four components are needed, namely: biological viable cells; a bioactive medium, with adequate growth factors; a compatible matrix able to promote cell growth; enough room in implantation site[8,24] Matrixes can be synthetic or natural, since synthetical are made of polymers and naturals made of collagen, hyaluronic acid, chitosan and alginate.[24] These three components are responsible for determining cell behavior. Biochemical and biomechanical necessary stimuli must be adequately studied in order to permit cell proliferation and differentiation in the intended pathway.[8]

After cellular implantation, in order for it to be successful it is necessary that the following phenomena occur: conservation of obtained cells' integrity; proper cellular adhesion to the intended lesion; adequate biomechanical stimulus for tissue remodeling; maintenance of an appropriate nutritional environment for adequate cell growth and differentiation.[23] Cellular adhesion occurs in the first 3 hours after cell injection and if these steps have not occurred until 8 hours post-injection fibroblastic differentiation will occur.[23]

the use of hyaluronic acid along with stem cells, increasing growth kinetics, adhesion and the secretion of important regeneration trophic factors.[23] Table 3 shows a summary of different results obtained so far with stem cells application in several tissues.

Conclusion

A great portion of observed lesions in sports activities involve tissues that have a limited regeneration potential and to which the currently available therapeutic techniques do not offer the best results. Although some viable options already exist, with a special emphasis on platelet-rich plasma (PRP) and stem cells, it is imperative to cement knowledge in this area, so it is possible to move safely towards the application of these techniques in humans in a widespread manner. Focus should be put on the understanding of the biochemical and biomechanical environment that should be created considering the intended goal. It is also paramount to establish ethical guidelines that allow the research in this field to flourish.

PRP seems to represent a quite viable option for tissue treatment and regeneration in the context of sports' lesions since it stimulates these natural processes. It is a promising therapy with a low potential for side effects. However, further studies are necessary to support its efficacy in specific context of sports' lesions since procedures used in several studies thus far are not standardized, making it challenging to compare them. It is also necessary to study the best timing to perform these kind of treatments as well as the number of needed interventions to obtain the best possible outcomes and the effect of the use (or not) of echography to guide the injection.

Stem cells will play an unquestionable role in the future of sports' lesions treatment. It is acknowledged that there have been promising effects proven by laboratory research and even through the progression of said research onto animal models. Thus far, available data allows us to assume that the use of mesenchymal stem cells (MSC) will be safe on short-term. However, evidence is still scarce and clinical trials are needed to support the use of these cells as a true therapeutic option.

Alas it is indisputable that PRP and stem cells will play an important role soon for the treatment and rehabilitation of sports' lesions, whether separately or, possibly, combined. It is important to state the essential role of an adequate rehabilitation for the success of every therapeutic approach to be applied in sports' lesions. Therefore, efforts should be guided to the development of a therapeutic approached adapted to each injury, that reflects the multidisciplinarity that they encompass and that it maintains current and relevant, evolving with scientific effort.

Considerations

Only one database was used for study research and selection so one cannot rule out the possibility of bias in this process and must consider it an important limitation to this article. Furthermore, the exclusion of articles written in languages other than English, Spanish or Portuguese may constitute another source of bias that needs to be noted.

This article's goal was not to provide an exhaustive review of all the regenerative therapies available in the context of treatment and rehabilitation of sports' lesions but to focus on the two interventions that are more developed and closer to being viable on short-term. Thenceforth, the authors focused on collecting the information regarding the state of the art which led to a tangential description of the techniques and serve as the foundations to proceed with more advanced studies.

Table 3. Results of applying Stem Cells in several tissues.

Tissue	Pros	Cons
Articular cartilage	- Improvement of several outcomes and of the cartilage's macroscopic structure (observed through arthroscopy). [10] - Improvement in articular function and architecture with especially promising results in older population. [10] - Results from rat studies that show autologous as well as allogenic potential. [25] - Combination of collagen gel or fibrin with used cells increases the cell adhesion potential to the native cartilage present at the edge of the injury. [25] - Recent studies in horses have shown that effect would be improved if cell implantation were performed through arthroscopic procedures in comparison with intra-joint injection. [6] - In 2016 the use of autologous chondrocytes harvested from a healthy cartilage area and grown in a porcine bioabsobable collagen matrix was approved by the FDA for injured joint surfaces implantation in adult patients' knees. [24]	- Studies performed mainly in older patients with osteoarthritis. More studies designed for a young population as well as other kinds of injuries are needed to better suit the context of Sports Medicine.
Ligaments	- MSC have shown promising results for anterior cruciate ligament repair in bunnies while using allogenic grafts from the Achilles tendon. [25]	- Fat tissue stem cells have not shown acceptable results. [25] - Further human studies are needed to investigate its regenerative potential.
Tendons	- Very promising short-term results (in the range of plus 200% tolerated force). [24] - Patients that have been submitted to treatments that involved the concomitant administration of PRP during anterior cruciate ligament reconstruction showed better results in the donor's tendon recovery (specifically, patellar tendon) observed through MRI 5 months after the intervention. [10]	- Results fade away after a couple of months, reaching a degree of tolerated strength up to a third of the observed in healthy tendons. [24] - No functional or patient's questionnaires differences were observed. [10] - Intervention strategies for this tissue must be perfected.
Meniscus	- In studies with pigs it was observed that meniscus regeneration is significantly better in patients injected with MSC when compared with control patients, both through MRI and histological evaluation. [10] - In humans it was noted that PRP previously exposed chondrocytes allows for an improved cellular adhesion. Better results were observed through histological and MIR observation but, more importantly, in reported pain by patients. The injections were well tolerated and did not cause any side effects that differ from the ones observed in other kinds of intra-articular injection. [10] - The use of stem cells to repair meniscal injuries has a potentially promising future, allowing for more conservative approaches.	- More research is required, especially more clinical trials that allow a more solid ground to support the investigation hypothesis. [10]
Muscle	———	- Muscle injuries present a poor prognosis due to the large formation of fibrous tissue that results in muscle contractions and chronic pain. [24] - Although the great potential of stem cells for intervention in these injuries, the transition from laboratory research to human intervention has been limited. [24]
Bone	- Studies conducted in animals have shown a recovery speed twice as big as the one found in the control group, treated with fibrine gel injections. [25]	- Human studies are still necessary to better understand the effect of this treatment but it shows potential. [25]

Responsabilidades Éticas

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