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Advancements in Regenerative Sports Medicine: Exploring the Frontiers of Tissue Engineering and Cellular Therapies in Athletic Injury Management

Riaz Ahmed

ABSTRACT

Regenerative sports medicine represents a transformative approach to managing athletic injuries, leveraging advances in tissue engineering and cellular therapies to accelerate healing and improve recovery outcomes. This review examines recent innovations, including stem cell applications, platelet-rich plasma therapy, and biomaterial scaffolds, highlighting their roles in repairing musculoskeletal injuries commonly encountered in athletes. Emphasis is placed on the biological mechanisms underpinning these treatments, clinical efficacy, and current limitations. The integration of regenerative techniques into sports medicine holds the potential to reduce rehabilitation times, restore function, and extend athletic careers. However, challenges remain in standardizing protocols, ensuring safety, and translating preclinical successes into consistent clinical outcomes. Future directions include personalized regenerative strategies and combining therapies with biomechanical support systems. This review underscores the need for multidisciplinary collaboration to fully realize the potential of regenerative medicine in athletic care.

Keywords: Regenerative sports medicine, Tissue engineering, Stem cell therapy, Platelet-rich plasma, Musculoskeletal injury management

Introduction

Overview of Tissue Damage in High-Performance Sports

Regenerative sports medicine, an evolving subfield of orthobiologics, focuses on harnessing the body's intrinsic healing capabilities to treat musculoskeletal injuries commonly sustained in high-performance sports. It is concerned with restoring damaged tissues such as tendons, ligaments, cartilage, and bones, especially when it comes to injuries such as meniscus and ligament damage in the knee, ruptures of the Achilles tendon, tears in the rotator cuff and cartilage next to the bone.¹ Figure 1 shows that “regenerative sports medicine deals with sports and aging-related conditions in different parts of the locomotor system, such as the menisci, ligaments, tendons, cartilages, and bones.” College-level sports in the U.S. typically cost around \$1.5 billion per year due to injuries, not including rehabilitation costs.² With more women joining contact sports and people over 50 starting to exercise again, sports-related injuries have become more common and varied.² New treatments, such as using platelet-rich plasma (PRP) and stem cells, are now being used to help tissues recover faster and reduce

recovery time. PRP therapy works by focusing growth factors from platelets onto the injury.³ However, some issues have been raised regarding PRP's general standardization and usefulness due to the varying methods and compositions used. These therapies can use stem cells extracted from adipose tissue, blood, or bone marrow to repair damaged muscles and bones.³ Clinicians can use biotechnological tools to monitor the body, apply specialized agents, and utilize technology-based devices to rehabilitate areas that require it.⁴ The approach is meant to minimize the possibility of permanent disability and allow alternatives to surgery. Although studies are progressing, researchers are still working to translate these findings into clinical practice.

Research Objectives

- To study current developments using regenerative medicine for the treatment of sports-related bone, muscle, and joint damage, mainly involving tissue engineering (TE) and cell therapy.
- To explore whether stem cells, PRP, EVs, and scaffolds are useful in fixing athlete injuries.
- To examine current clinical applications, regulatory challenges, and the barriers to widespread implementation of regenerative interventions in sports medicine.
- To identify knowledge gaps and propose future research directions for optimizing recovery and performance outcomes using regenerative therapies.

Scope of the Review

This review focuses on the emerging role of regenerative sports medicine in managing athletic injuries through TE and cellular therapies. The field examines the advances in stem cell therapy (SCT) and PRP and how they are used to treat the frequent damage that occurs in high-performance athletics. The review highlights the effectiveness of the strategy and the challenges associated with its implementation in medical settings.¹ There is a strong focus on using regenerative treatments to help patients recover faster and perform better, recognizing how this influences both sports science and healthcare systems in regard to costs and skills needed.² This review examines the growing applications of regenerative sports medicine, specifically SCT and PRP treatments, in enhancing recovery and performance following athletic injuries. It evaluates both the therapeutic potential and implementation challenges

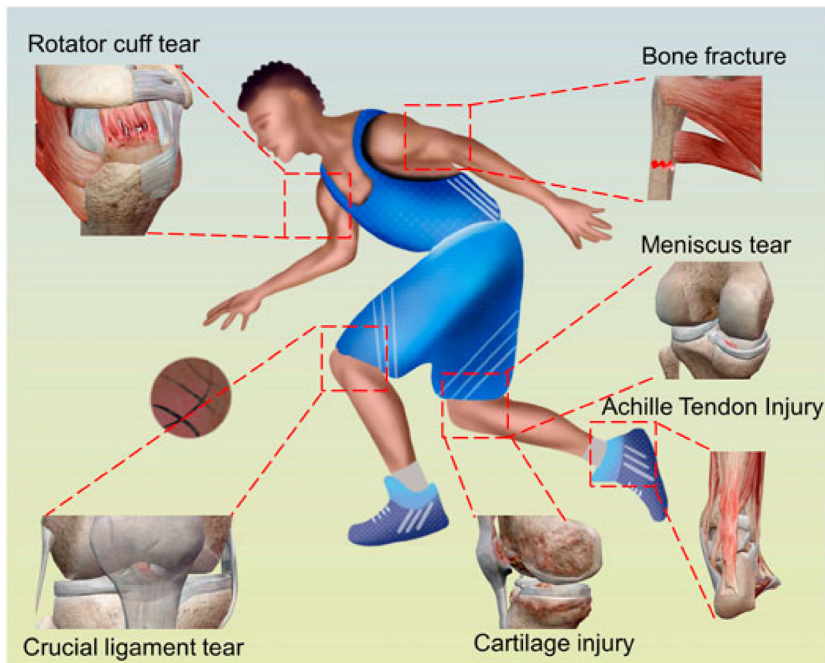


Fig 1 | Sports-related injuries¹

of these advanced biologics in clinical sports medicine practice. The analysis considers their impact on rehabilitation timelines, athletic performance outcomes, and healthcare system requirements.

Biological Basis of Regenerative Healing in Sports

Skeletal muscle, a major component of the human body, possesses a unique innate capacity for regeneration following injury. Even so, aging processes such as sarcopenia and fibrosis delay regeneration because they prevent the proper repair of the body.⁵ While research has studied both cell and biological therapies using factors from the blood, such as PRP and PPP, existing opinions on their effectiveness remain divided.⁵ It is also clear that senescent cells weaken the healing process, and although ways to remove them are being researched, no effective treatments are currently available.⁵ The use of bone marrow, subcutaneous fat, PRP, and conditioned media has gained attention in recent research in the field of regenerative sports medicine. Although biologics interact within the blood, tissue, and repair cells, it is challenging to compare their outcomes due to the wide spectrum of these treatments.⁶ Although data on their long-term safety is limited, studies show that mesenchymal stem cell (MSC) products are safe in the short and medium term and could be used to treat certain diseases.⁶ Figure 2 represents that “mechanical signals from exercise are transduced into biochemical responses through Piezo1-mediated Ca^{2+} signaling, integrin-FAK activation of YAP/TAZ via Hippo pathway inhibition, and FAK-driven HDAC5 nuclear translocation that suppresses SOST expression.”⁷

It has become clear that physical exercise plays a crucial role in promoting regeneration, particularly in the context of limited regeneration in adult tissues.

Regeneration that occurs through exercising helps various systems, such as the musculoskeletal, cardiovascular, and nervous systems, and drugs have been developed to replicate this effect in those who do not exercise.⁷ Experts believe that the build-up of injury over many years, caused by heavy training, is the main reason for ACL injuries in young athletes.⁸ Modern regenerative therapies focus on “recovery science,” which means using research-based fitness, nutrition plans, rest, and specialized medicines to encourage recovery and injury prevention.⁸ In addition, Mayo Clinic scientists are interested in using stem cells, PRP, and amniotic products for regenerative purposes through surgery. They have helped ease pain and increase functioning in conditions such as femoral head osteonecrosis.⁹

TE in Sports Injury Management

TE has emerged as a promising multidisciplinary approach in orthopedic sports medicine, offering innovative therapeutic possibilities for treating musculoskeletal injuries. TE uses the benefits of scaffolds, cells, and various biological compounds to create functioning tissues and to overcome the barriers of other treatments.¹⁰ By using these strategies, doctors can now help with defects that were thought to be untreatable and also speed up healing. While there is a lot of promise in growth factors, scaffolds, and stem cells in research and clinical trials, TE-based approaches are still not seen as the standard treatment approach in medicine.¹⁰ The same idea is presented by Abdolmaleki et al.,¹¹ who summarize the difficulties in clinically managing sports injuries and the potential of TE to improve tissue healing. Some important ways to treat these injuries involve microfracture, mechanical stimuli, PRP therapy, and MSC therapy (see Figure 3).¹¹ PRP aids wound healing by adding growth factors and MSCs, as it is autologous and has the ability to differentiate into various cell types, making it a valuable tool in regenerative medicine.

The group, led by González-Quevedo, searched an extensive list of 388 references and reviewed 35 animal model experiments examining TE strategies used to treat tendon damage.¹² Though methods varied and materials were different, improvements in biomechanical markers, including maximum load, maximum stress, and Young's modulus, were observed in groups that used engineered biomaterials, proving their usefulness for tendon healing.¹² Likewise, Xing¹³ looked into the effects of scaffolds on cartilage repair by using a composite porous scaffold made from PLGA/NHA and PLGA, both filled with mesenchymal rat bone marrow stem cells. Results indicated that 0.5% PLGA-MSCs reached a tensile force of 1.1 MPa and contained high cell density in the experiment on rats, resulting in strong improvements to cartilage.¹³ Han¹⁴ further studied how tissue-engineered nanomaterials can be applied to repair injuries of the meniscus. By using molecular biology, the study found that meniscus injuries among those older than 40 years rose from 57% in 2013 to 66% in 2020, pointing to the higher

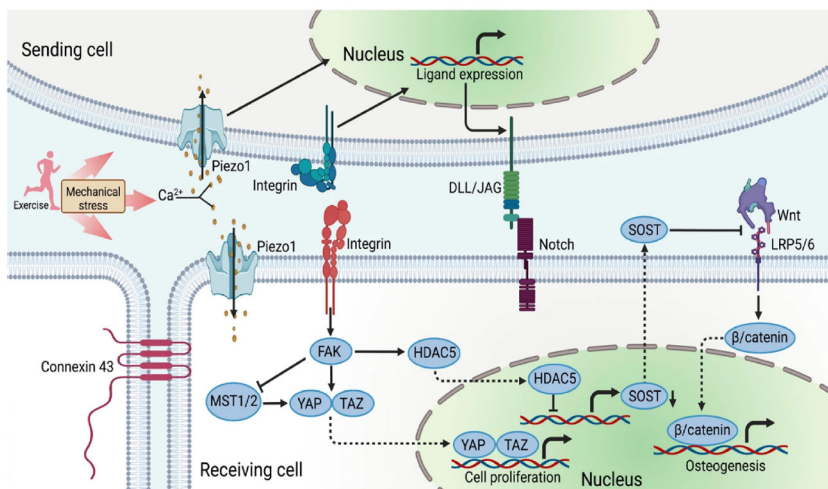


Fig 2 | Mechanotransduction-regulating regenerative responses⁷

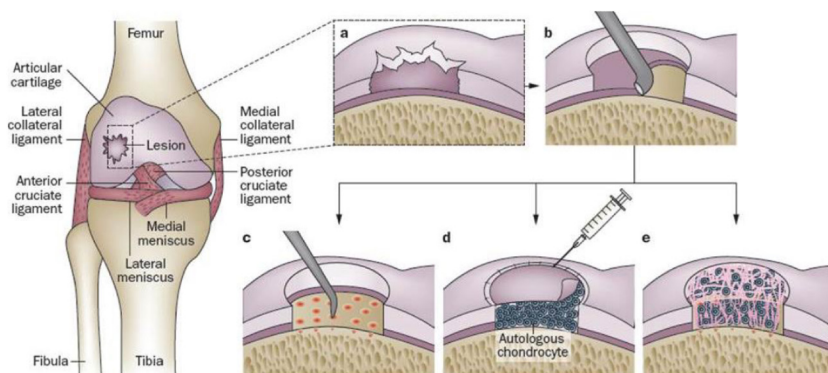


Fig 3 | Microfracture techniques for regeneration of cartilage¹¹ (a) Shows the full-thickness focal chondral lesion. (b) The lesion is debrided to ensure healthy, stable margins for integration of the host tissue with the neotissue. (c) Microfracture channels are created using a 45° awl. The channel allows MSC to migrate from the marrow to the cartilage defect. (d) ACI. The debrided lesion is filled with 12–48 million autologous chondrocytes and covered with a periosteal flap or mixed collagen type I and III membrane. (e) MACI. The autologous chondrocyte population is expanded *in vitro* and then seeded for 3 days onto an absorbable 3D (collagen type I and III membrane or hyaluronic acid) matrix prior to implantation. The cell-seeded scaffold is then secured into the lesion with fibrin glue. Abbreviations: ACI, autologous chondrocyte implantation; MACI, matrix-assisted autologous chondrocyte implantation; MSC, mesenchymal stem cell.²³

occurrence of such injuries with age. It was found that a KOA exercise therapy adapted from the Kalman filter theory might help improve bone rehabilitation.¹⁴

Cellular Therapies in Athletic Injuries

SCT has emerged as a pivotal innovation in sports medicine, offering regenerative possibilities for various sports-related injuries. Based on Rahim,¹⁵ stem cells are now being applied to manage injuries and problems involving tendons, ligaments, muscles, and cartilage. Treatment includes direct surgery, the use of sutures with stem cells, and injections, all supported by medical imaging for real-time assessment of the effects. Although SCT is hopeful, we still do not fully understand how it works in this case. Orozco and Soler mention¹⁶ that Spain's RD 477/2014 is aligned with EU regulations to label stem cell products as “advanced therapy medicinal products.” These items

need to be made following strict principles, and both preclinical and clinical testing must be done. However, the study highlights that people should expect only registered cell therapies and be skeptical of treatments with unverified cells. The authors in a recent study primarily addressed the use of SCT for neuronal injuries, focusing on SCI and injuries to the peripheral nervous system.¹⁷ The stem cells aid tissue regeneration by releasing neurotrophic factors, reducing inflammation, and facilitating the strengthening of axons and the growth of myelin. Issues such as selecting suitable stem cells and fostering a good environment for repair are difficult challenges. Moreover, SCT is being explored for its potential to repair and regenerate tissue in various sports injuries. Studies also address ethical considerations and potential directions in SCT.¹⁸ Additionally, Vaish and Vaishya discuss how stem cells can be applied to orthopedics and sports injuries, focusing on the most important aspects and potential future studies. The study highlights the lack of research in specific areas of musculoskeletal healing.¹⁹ “SCT shows potential for treating various orthopedic conditions, including osteoarthritis, avascular necrosis, bone defects, fracture non-unions, ligament/tendon injuries, and spinal fusion” (see Figure 4).¹⁹

Clinical Applications and Evidence for Sports Medicine

Recent developments in sports medicine have highlighted significant clinical and technological advancements, particularly in the diagnosis, treatment, and rehabilitation of musculoskeletal injuries. Sun and Chen²⁰ published an extensive review of recent innovations, mentioning surgical fixes, teamwork with various disciplines, and treatments such as biologically enhanced demineralized bone matrix for large rotator cuff tears and using the albumin-to-alkaline phosphatase ratio to predict outcomes in spinal fusion. Of the 20 patients treated for rotator cuff tears, 10 still experienced a retear, showing that the problem persisted. Trofa et al.²¹ noted that therapeutic techniques such as Kinesio taping, acupuncture, and sports massage therapy were gaining popularity. Even though these treatments are affordable and rarely have side effects, there is not enough evidence to prove that they are effective for treating acute shoulder symptoms or carpal tunnel syndrome.

In a study, McNamee et al.²² analyzed the issues related to the use of PRP therapy in the English Premier League. The analysis revealed that 38 interviews highlighted a struggle between basing decisions on clinical expertise and moving toward practices that rely on scientific evidence, as well as doubts about placebo-like methods and the issue of informing patients. Through research by Hayashi et al.,²³ it is understood that T2 mapping, diffusion tensor imaging, sodium imaging, and contrast-enhanced ultrasound have emerged in imaging diagnostics and greatly assist in understanding musculoskeletal disorders. For example, Figure 5 indicates that “advanced imaging techniques for musculoskeletal assessment such as (1) T2/T2* mapping quantifies tendon/ligament healing, (2) DTI analyzes

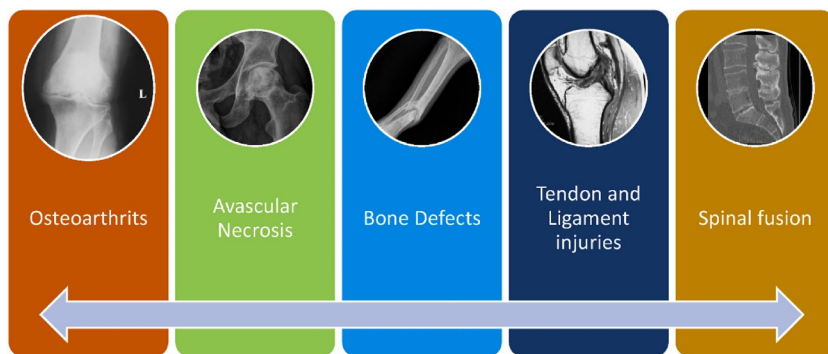
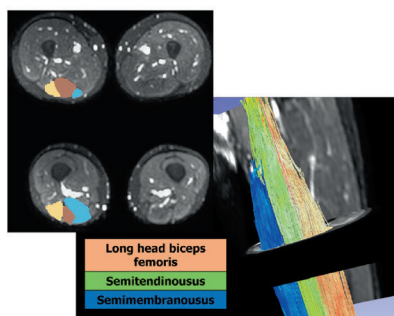


Fig 4 | Clinical applications of stem cells in orthopedics and sports injuries¹⁹

Emerging Quantitative Imaging Techniques in Sports Medicine



- Quantitative T2 mapping and UTE T2* mapping enable evaluation of tendon and ligament biochemical composition, potentially providing objective evidence of successful healing.
- Diffusion tensor imaging (DTI) measurements such as mean diffusivity and fractional anisotropy in acute muscle tears show changes related to recovery, but evidence is inconsistent on whether DTI can predict a return to play.

Fig 5 | Quantitative imaging techniques²³

muscle recovery but lacks consensus on return-to-play predictions, (3) shear-wave elastography screens shoulder capsule elasticity in throwers.”²³ New techniques, such as dual-energy CT and MR elastography, can now accurately measure the mechanical and elastic properties of tissue; however, their usefulness in clinical practice must still be confirmed through more extensive trials. Font²⁴ pointed out how nuclear medicine plays a role in diagnosing injuries in sports. Before anatomical changes occur, bone scintigraphy and hybrid imaging (SPECT/CT) can provide valuable information to assess and treat injuries quickly. They suggest a greater line of integration for imaging, ethics, and other fields in sports medicine.

Regulatory and Ethical Considerations for Sports Medicine

Healthcare professionals working in sports medicine often encounter a range of complex ethical challenges, balancing conflicting obligations between athletes and their teams. Prill et al.²⁵ explain that people working in team sports have to find a balance between supporting athletes and making decisions for clubs or sponsors. Ethics must be observed by these experts in everything they do, particularly when dealing with return-to-play and performance improvements. Building on this, Testoni and colleagues note that physicians must balance the needs of their athlete patients with those of the team. This challenge is compounded by financial awards and no evidence-based standards while playing

American football. Allen et al.²⁶ note that in the field of equine sports medicine, ethical points are brought up through five recurrent topics: multiple competing interests, the rules applied, proper care for horses, privacy, and the veterinarian’s license to practice. Most people mentioned that using drugs on performance horses was the main ethical problem. Physicians working in the lines of combat sports, as mentioned by Sethi, frequently deal with situations where medical decisions are unwelcome by the audience or are beyond their jurisdiction, endangering the fighters.²⁷ It is reported that about 20% of professional boxers develop chronic traumatic brain injury, and 15–40% go on to show symptoms after retirement, with subdural hematoma being the main cause of death. Vasilescu et al.²⁸ focus on doping in both able-bodied and Paralympic sports and describe it as “boosting.” Doping, they claim, erodes the most fundamental rules of sports, and they favor creating programs to educate athletes and preserve their health in the upcoming years.

Figure 6 illustrates the body’s response during autonomic dysreflexia, where a distended bladder serves as the afferent stimulus, triggering peripheral sympathetic activation that leads to vasoconstriction and subsequent hypertension.

Current Debates and Research Gaps in Sports Medicine

A significant challenge in sports medicine is the persistent gap between research findings and their practical application in clinical settings, particularly in elite sports environments. Despite the availability of evidence-based principles for injury prevention, coaches and clinicians continue to struggle with translating this knowledge into elite athlete training. Most of these reasons are caused by different factors, such as team’s dynamics, schedule, and the presence of many stakeholders involved in giving care. Results indicate that what works in studies may not be as effective for elite athletes as intended. To make the most of the research, the entire organization should cooperate, not only the athlete and the clinician.²⁹ Similarly, Sugimoto et al.³⁰ investigated the challenges and opportunities faced by members of the PRISM Society in terms of research involvement. A survey of 100 respondents (yielding a 35.7% response rate) revealed that the primary barrier was “lack of time” for both SM physicians and AH practitioners. However, the key factors for research facilitation differed between SM physicians, who noted the “presence of research support staff,” and AH practitioners, who underlined “access to research mentors.” While both groups were highly interested in research, AH physicians said they were less comfortable reading research articles than SM doctors ($p = 0.018$).³⁰ These studies make it clear that incorporating research into sports practice is challenging, especially due to time pressures, job titles, and limited access to resources.

Future Directions for Sports Medicine

The evolution of sports medicine continues to be shaped by both national developments and advancements in specific clinical areas. Wang and Huang³¹

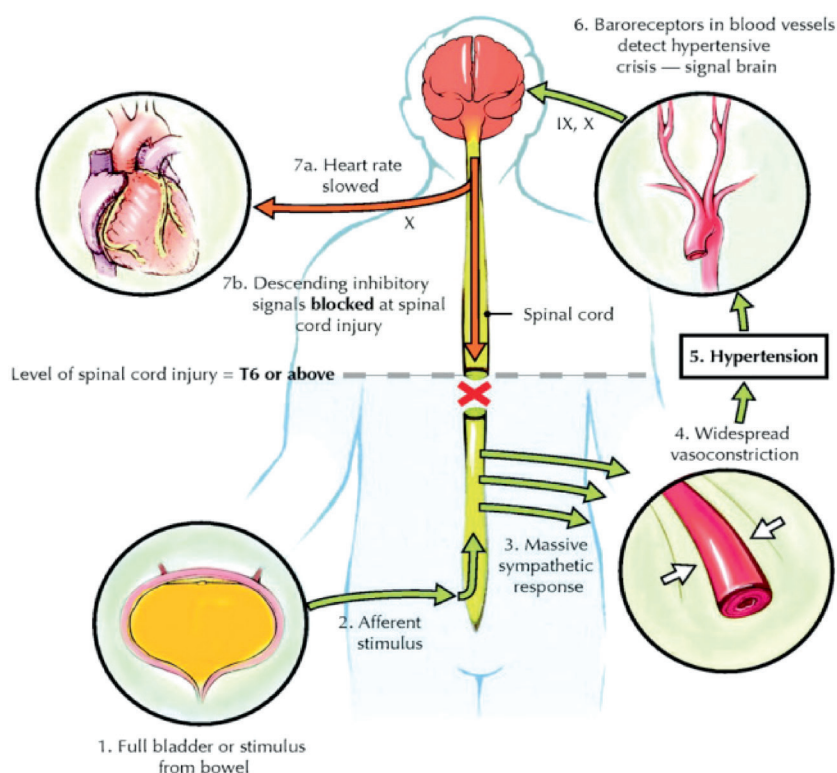


Fig 6 | Autonomic dysreflexia pathway showing bladder distension triggering sympathetic vasoconstriction and hypertension²⁸

provide a detailed summary of the progress and current state of sports medicine in China, offering suggestions on how to address existing issues. The five core areas that have been identified are the development and improvement of arthroscopy, support for athletes, sports rehabilitation, prescription and assessment of exercise, and professional training and education. Furthermore, scientists emphasize the importance of three key topics for future growth: engaging the public in science, preventing illness and ensuring safety in sports, and developing innovative scientific approaches to treatment and diagnosis.³¹ During the same period, Kerr et al.³² discussed future steps in managing concussions in sports, emphasizing the importance of finding a reliable diagnostic test. Experts believe that techniques such as functional MRI and diffusion tensor imaging can be effectively applied in medical scenarios. Additionally, the article highlights the study of biomarkers and genetic tests, as well as the use of accelerometers on the side of the head to measure the speed at which the brain moves. Allowing replacements during evaluation and including video review are among the suggested methods to enhance the detection of concussions.³² Future sports medicine should prioritize (1) public engagement in science, (2) advanced diagnostic tools like functional MRI for concussions, and (3) standardized protocols for injury prevention and rehabilitation.

Conclusion

The field of sports medicine is evolving rapidly, yet several challenges remain in translating research into

clinical practice. While evidence-based recommendations are clear, their implementation in elite sports can be challenging due to practical issues and the diverse needs of each athlete. While many practitioners are interested in research, a lack of resources and time makes it challenging for them to engage in it effectively. While most doctors utilize research support, allied health staff benefit from mentorship, suggesting that each job requires a tailored approach to involve personnel in research tasks. In locations such as China, efforts are underway to develop sports medicine through new minimally invasive techniques, comprehensive rehabilitation services, and proper training. Extractions are being performed to demonstrate to athletes the importance of caring for themselves and their health. Improvements in technology are helping to change sports medicine, especially when it comes to diagnosing concussions. Generally, it is becoming increasingly evident that working together, encouraging advancements, and training are important ways to move forward in sports medicine.

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