Future Treatments for Football Injuries

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Introduction

Football, or soccer as it is called in North America, is the most popular sport in the world, with about 200 million participants [1]. It is characterized by a complex collection of movements including running, short sprints, rapid deceleration, turning, kicking, and tackling. These characteristics predispose participants to the relatively high injury rate of 12–35 injuries per 1,000 player game hours in adult men's football [2]. The lower extremities are more often injured. Muscular strains are the most common traumatic injuries in football players, followed by contusions and ligamentous sprains [2–4]. All these injuries have an impact on the players' lives and hinder them from participating in training and matches. Furthermore, injuries can lead to a 22% re-injury rate [3]. Moreover, injuries such as anterior cruciate ligament (ACL) tears may force a player into retiring early. ACL tears can have a rate as high as 0.41 tears per 1,000 game hours at the male competitive level [5]. In addition to the injury and its consequences for the players, associated costs of treatment are also a relevant issue [2]. Therefore, it is important to know about preventive methods to avoid injuries, as well as future types of treatment using modern biological approaches.

Injury Prevention and Preventive Methods

In order to decrease the incidence of injuries in the near future, the International Football Federation (FIFA) Medical Assessment and Research Centre (F-MARC) has promoted injury prevention [1, 6]. Van Mechelen [7] recommended four steps to be followed for injury prevention in sports: (1) identify the frequency of common and serious injuries; (2) identify risk factors; (3) introduce preventive methods; and (4) monitor ongoing surveillance of preventive methods.

Improving the structure and content of the training by education and supervision of coaches and players has shown a 21% decrease in the number of injuries [6]. This preventive method is based on general interventions such as improvements in warm-ups, regular cool-downs, taping of unstable ankles, adequate rehabilitation, and promotion of fair play, as well as applying a specially designed set of 10 exercises (F-MARC Bricks) to improve stability of the ankle and knee joints; flexibility and strength of the trunk, hip, and leg muscles; and player coordination, reaction time, and endurance.

Prevention of muscle injuries has been described by using strengthening and stretching [8, 9]. The eccentric strengthening preventive method has been promoted to reduce hamstring strains rates (Fig. 1) [8]. The recurrence of ankle sprains can be minimized by using orthoses or by training proprioception on an ankle disk [10, 11] (Fig. 2); 54% of ankle sprains occur during tackles, and fair play education may decrease this rate [12]. Preventive treatments also decrease the incidence of ACL injury. Proprioceptive training with wobble boards, flexibility, plyometrics, and muscular strength training are described as effective methods to prevent ACL injury [13, 14].

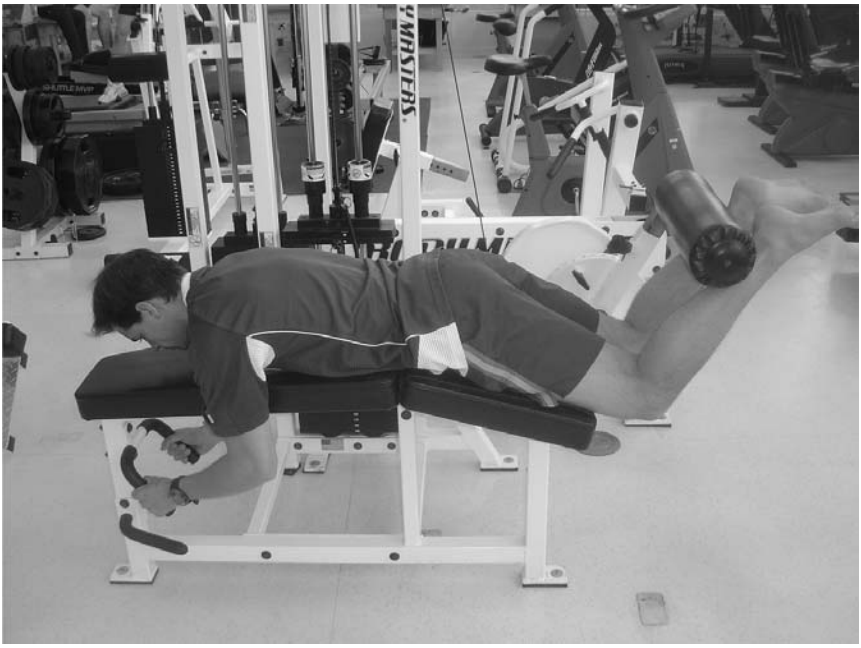

Fig. 1. The athlete exerts strength against the weight while extending the knee, performing the eccentric strengthening of the hamstrings

Fig. 2. Athlete performing the proprioceptive balance-board training. This training is used as prevention for sprains in the lower extremities

Biological Approaches

For injuries that could not be avoided by prevention, biological approaches may be an important tool for future treatments. Biological approaches have been used to avoid fibrosis formation in muscle, as well as to better heal tendon, ligaments, cartilage, and menisci. These approaches are based on the application of growth factors or cytokines. Growth factors are capable of stimulating cell proliferation, migration, and differentiation, as well as matrix synthesis and providing better tissue healing [15]. Direct application of growth factors is realized with very high dosages and repeated injections of these proteins because of their relatively short biological half-lives. In addition, growth factor effects are hindered by the difficulty of delivering to only the specific injured site. Different methods have been developed for administration and delivery of growth factors. Gene therapy techniques have shown the most promise. Using viral or non-viral delivery vehicles (vectors), the genetic information, usually a complementary deoxyribonucleic acid (cDNA), encoding the protein of interest is inserted into a living cell. The genetically modified cell has the potential to express the protein in a sus-

tained manner, making the long-term delivery of a protein or growth factor possible [16]. Tissue engineering is a technology based on the development of biological substitutes used for tissue repair using biomaterials capable of integrating molecules (e.g. growth factors). The biomaterial can also be used with stem cells from different sources (bone marrow, muscle, fat, etc.) [15]. Stem cells differentiate in specific cells according to the tissue environment and produce growth factors and proteins to heal the tissue. Tissue engineering and gene therapy are not yet a realistic therapeutic technique for the treatment of orthopaedic diseases. However, we believe that it has great potential for clinical applications in the near future and might help football players mainly for injuries in tissues with low capacity of healing, such as ligaments, menisci, and articular cartilage.

Muscle

Muscle strain is the most common injury in football [2–4]. The muscle healing process after an injury consists of three distinct phases. The first phase, of degeneration and inflammation, occurs in the first few days post-injury and is characterized by necrosis mediated by intrinsic proteases, local swelling, haematoma formation, and degeneration. Subsequently, the necrosis area is invaded by inflammatory cells. The lymphocytes secrete several cytokines and growth factors. Cytokines, such as interleukins and tumour necrosis factor-α (TNF-α), play a wide range of functions in the inflammatory process. At the injured site, growth factors, such as insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), transforming growth factor (TGF-β and TGF-α), and platelet-derived growth factors (PDGF-AA and PDGF-BB) regulate myoblast proliferation and differentiation to promote the second phase of muscle healing, the phase of regeneration and repair. In this phase, not only do the growth factors have an important role but also the satellite cells located between basal lamina and plasma membrane. These cells are responsible for the formation of new myofibres and muscle regeneration. This phase occurs 7–10 days after injury and peaks around 2 weeks and then decreases at 3–4 weeks post-injury. The TGF-β1 from the regeneration phase also triggers the formation of fibrosis, the third phase of muscle healing. The fibrosis-forming phase begins between the second and third weeks post-injury [17]. Despite the many treatments available, the formation of scar tissue seems to be the end product of muscle repair [17–20]. Therefore, complete regeneration of muscle tissue cannot occur. Based on the biological aspects of muscle healing, research has been conducted to better heal the muscle by enhancing muscle regeneration and by preventing muscle fibrosis [19, 20].

The literature has shown that either high-dosage serial injections of

growth factors, such as IGF-1 and basic fibroblast growth factor (b-FGF), applied directly at the injured site, or IGF-1 secretion mediated by gene therapy improve muscle healing [17–20]. However, neither can prevent fibrosis formation. This necessitates the use of anti-fibrotic agents in order to block scar tissue formation. Because of the critical role of TGF-β1 in the development of fibrosis formation, it is essential to create approaches to antagonize this molecule. Decorin, gamma-interferon, and suramin have been described as promissory agents to avoid fibrosis formation in lacerated muscle by blocking TGF-β1 [15, 17–20]. Suramin promotes significantly less fibrous scar formation in muscle strain and provides better strength recovery [19]. It is also important to note that treatment with IGF-1 and decorin is not better than treatment with decorin alone in terms of reducing fibrosis [20]. This fact suggests that the blocking of fibrous scar tissue is the key for complete muscle healing (Fig. 3).

All the experiments performed in animal models encourage the clinical trial of anti-fibrotic agents. Moreover, some of these agents are approved by the Food and Drug Administration (FDA) and have already been used in humans for different pathologies [17]. Further research is needed before beginning to use growth factors and/or anti-fibrotic agents in athletes. However, we believe that these biological approaches are the future for muscle strain in football players.

Ligaments

The ACL tear is a major lesion that hinders play in athletes for approximately 6 months. Only 60% of professional players affected return at the same level

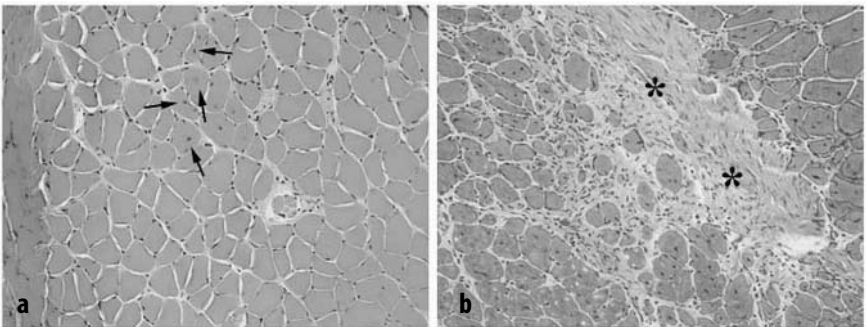

Fig. 3. Histologic evaluation (hematoxylin and eosin stained: x200) of injured skeletal muscle. Injured muscle treated with suramin showing fewer fibrotic areas (**a**) than untreated control sample (**b**). *Arrows* indicate regenerated myofibres in each sample. *Asteriks* show fibrotic area (Courtesy: Dr. Johny Huard and Dr. Jong Li)

as before the injury [5]. We believe that this reduced level of skill may be associated to the lack of rotation stability after ACL reconstruction [21]. Turning, a factor of rotational stability, is essential for football practice and associated movements. The ACL consists of two distinct bundles: the anteromedial and the posterolateral. In order to increase rotational stability and improve outcomes of ACL reconstruction, anatomic ACL double-bundle reconstructions have been performed on patients [22] (Fig. 4). Biomechanical study of anatomic ACL double-bundle reconstruction has been shown to be a superior technique when compared with single-bundle reconstruction by better restoring the rotation of the knee joint [23]. Further clinical comparative long-term studies are needed to definitively demonstrate that anatomic double-bundle ACL reconstruction is the best option for ACL tear treatment. However, based on the anatomy, biomechanics, and *in vivo* kinematics, we believe that this double-bundle concept may improve the quality of ACL reconstruction in athletes and provide a better recovery to the pre-injury level of skillfulness.

Biological approaches have been tested to improve the healing of the tendon graft in the bone tunnel in animal models [24]. Semi-tendinosus tendon

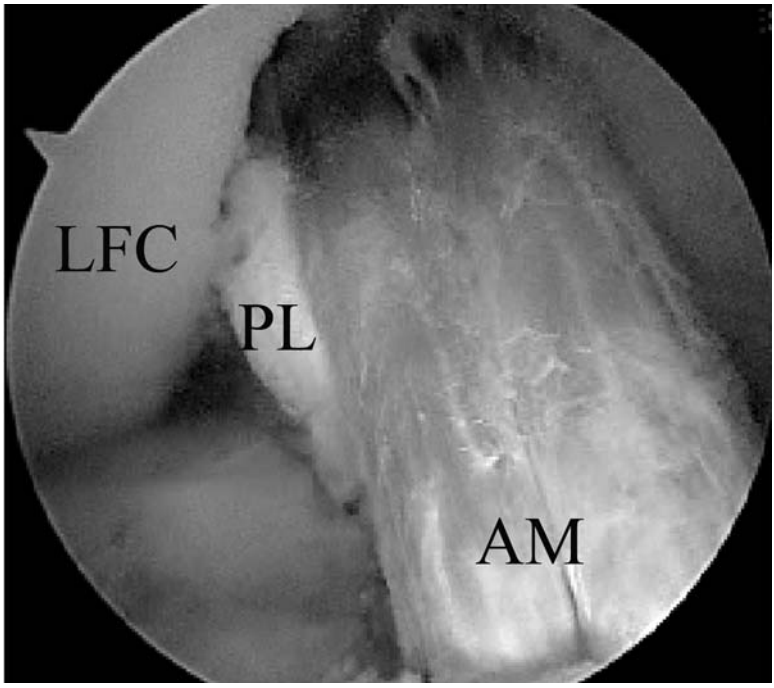

Fig. 4. Arthroscopic view of an anatomic anterior cruciate ligament (ACL) double-bundle reconstruction. *AM*, anteromedial bundle; *PL*, posterolateral bundle; *LFC*, lateral femoral condyle

grafts were transduced in vitro with adenovirus BMP-2 and implanted as ACL grafts in rabbits. This experiment showed a tendon-bone interface histology close to a normal ACL, and the stiffness and ultimate load at failure were significantly enhanced when compared with the control group (without AdBMP-2) [24]. This study suggests that gene therapy can improve the integration of soft tissue graft into bone and may be an important tool in the treatment of ACL tear, as well as in different ligaments such as in the ankle.

The direct administration of PDGF and IGF to injured ligaments and tendons has been shown to promote healing of ligaments and tendons [15]. Therefore, the possibility of using gene therapy to enhance ligament and tendon healing is a treatment to be used in the near future.

Cartilage and Meniscus

The treatment of chondral lesions is a challenge for physicians, with several techniques described. However, none of the techniques used for treatment is recognized as being outstanding. Cartilage has a poor regenerative capacity, with lack of stem-cell availability, poor vascularization, and low cellular turnover [15]. Tissue engineering and gene therapy have been used in animal models to deliver growth factors and proteins and better heal the cartilage injury and degeneration [15, 16]. The use of BMP-2, BMP-7, epidermal growth factor (EGF), IGF-1, and TGF-β1 has been shown to positively affect cartilage healing [15]. This is a potential research field to be explored for clinical applications. The same principle of gene therapy is also applied to the meniscus. Potential growth factors are bFGF, PDGF AB, TGF-α and β, BMP-2, and EGF [15].

Bone

Fractures are less common in football players-around 3% [3]. However, a fracture can lead to a long term without playing. The concept of tissue engineering and gene therapy is also functional to the bone. The BMPs (BMP-2, 4, 7) are already described as good proteins for bone healing and can improve and accelerate the bone-healing process [15, 16]. We believe that players experiencing fracture treatment will benefit from these therapies and may heal faster and better.

Overview

The use of preventive programs to avoid injuries, better surgical technique and rehabilitation, and biological approaches with high technology to better heal tissue will become the treatment of injuries for football players in the

near future. These treatments aim to restore histology, anatomy, and mechanical properties of tissue, providing athletes with optimal performance.

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