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Review Article / Derleme

Clinical tissue engineering approach and biotechnological advances to improve athlete healthcare

Sporcu sağlığını iyileştirmeye yönelik klinik doku mühendisliği yaklaşımı ve biyoteknolojik gelişmeler

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ABSTRACT

Sports activities have continued for centuries and have become essential to daily life. Professional athletes participating in various sports competitions have many advantages, such as a promising career and high income. On the other hand, being a professional athlete also has some disadvantages. The most dramatic one is the risk of injury. Even though injuries are a part of sports, they have become a significant problem today due to the long recovery period which in turn overshadows sports competitions. In addition, the performance loss is an extra handicap for the athletes compared to the pre-injury levels. In this case, biomedical and biotechnological sciences are a glimmer of hope for shortening the treatment process and minimizing performance loss in returning to professional sports life. Combinations of scaffolds, biological factors, and cells are utilized based on mentioned approaches to treat such injuries, which are frequently seen nowadays and have become the nightmare of professional athletes. This review discusses various regenerative medicine and biotechnology-based therapeutic methods used in the treatment of spinal cord, cartilage, tendon, and musculoskeletal injuries in athletes. Additionally, wearable technologies, which are used to evaluate physiological signals, monitor health, prevent possible injuries, and create personalized training programs are mentioned, as well.

Keywords: *Sports medicine, wearables, sports injuries, tissue engineering, biomedical engineering*

ÖZ

Yüzyıllardır devam eden spor geleneği, günlük yaşam aktivitelerinin vazgeçilmez bir parçası haline gelmiştir. Çeşitli spor müsabakalarına katılan profesyonel sporcular, iyi bir kariyer ve yüksek gelir gibi avantajlara sahiptir. Diğer yandan profesyonel sporcu olmanın bazı dezavantajları da bulunmaktadır. En çarpıcı dezavantajı ise yaralanma riski taşımalarıdır. Yaralanmalar sporun bir parçası olmasına karşın günümüzde spor karşılaşmalarını bile gölgede bırakabilmektedir. Uzamış tedavi süreleri gibi yaralanma öncesine göre performans kaybı önemli bir engel oluşturmaktadır. Bu durumda biyoteknolojik ve biyomedikal teknolojiler, yaralanma sonrası spora dönüşte tedavi sürecini kısaltmak ve performans kaybını en aza indirmek için bir umut ışığıdır. Günümüzde sıklıkla görülen ve profesyonel sporcuların korkulu rüyası haline gelen bu yaralanmaların tedavisinde yapı iskeleleri, biyolojik faktörler ve hücre kombinasyonları kullanılmaktadır. Bu derlemede sporcularda omurilik, kıkırdak, tendon ve kas-iskelet sistemi yaralanmalarının tedavisinde kullanılan biyoteknoloji temelli tedavi yöntemleri özetlenmeye çalışılmıştır. Ayrıca son yıllarda fizyolojik sinyalleri değerlendirmek, sağlığı izlemek, olası yaralanmaları önlemek ve kişiye özel antrenman programları oluşturmak için kullanılan giyilebilir teknolojilere de yer verilmektedir.

Anahtar Sözcükler: *Spor hekimliği, giyilebilir cihazlar, spor yaralanmaları, doku mühendisliği, biyomedikal mühendisliği*

INTRODUCTION

A well-known instance of sports competitions dating from the 8th century BC to the present is the Olympic games held in ancient Greece. Besides, Homer's Iliad and Odessa epics are among the oldest texts discussing sports activities and injuries. Herodicus, the first historical figure to combine sports with medicine, laid the foundation of sports medicine (1). From these dusty pages of the past to the present, sports medicine, and athletes' health, which have shown their importance in every age, are evolving. Due to this change, the worldwide popularity of the sports industry, in addition to physical and mental health, is also at the forefront of its economic aspects (2). It is estimated that this industry reached approximately 490 bn US dollars in 2018 and exceeded 500 bn US dollars today. It has also shown the highest growth in the industry's history, with a rate of 4.3% since 2014. The first three sports with the largest market share in this sector are football (43%), American football (13%), and baseball (12%) (3). For seriously injured athletes, returning to sports is usually long and challenging. Back to professional sports life is very laboring because the athlete has to feel psychologically ready, possess specific medical qualifications, and perform special training that requires strength and conditioning (4).

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In this context, clinical tissue engineering and regenerative medicine approaches offer a faster and more effective treatment option instead of traditional treatment methods and promise to return sports in a shorter time. These novel treatments include a personalized medicine perspective applying the patient's cells, cellular materials, and so on (5). For instance, Kobe Bryant, who gained the Most Valuable Player Prize in 2008, was dramatically injured and returned to professional sports after receiving autologous conditioned serum treatment in 2011. This treatment that stimulates soft tissue and bone healing succeeded in Kobe Bryant and drew attention to the current potential of this approach (6). In addition, many different treatment approaches, such as bioscaffolds, stem/progenitor cells, spheroid/organoid cell cultures, and microfracture, continue to be developed for various tissue types (7) (Figure 1).

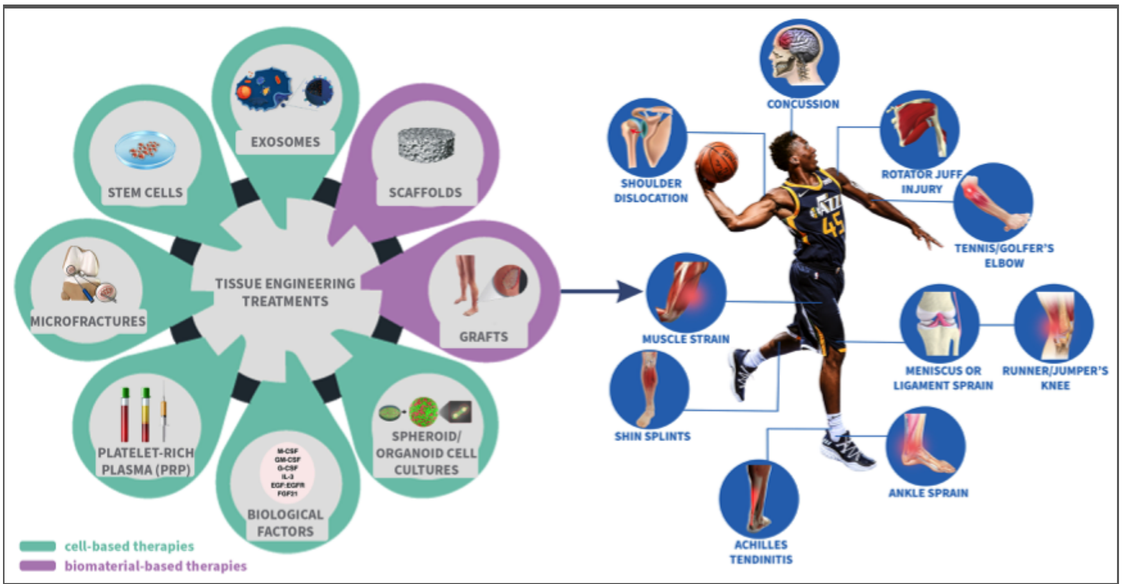

Figure 1. Common sports injuries and tissue engineering applications

Sports injuries generally occur in musculoskeletal, spinal cord, cartilage, and tendon tissues (8). This review discusses tissue engineering and biotechnological approaches to treat different types of tissue injuries that can occur in sports competitions and improve athletes' health quality.

Spinal cord injuries

The spinal cord is an essential organ for all vertebrates as it works the voluntary movements of the upper extremities and trunk and connects almost every body part to the brain (9). Sports accidents cause approximately 8% of spinal cord injuries (SCI), and they rank 4^{th} among the causes of SCI (10). Many famous athletes have suffered spinal cord injuries, including National Football League (NFL) quarterback Peyton Manning, golfer Tiger Woods, baseball player David Wright, and hockey player Mario Lemieux (11). During sports activities, more stress is placed on the spine than it can physiologically handle. This stress level can cause many spinal injuries, including a cervical dislocation, due to a slight sprain or stretching of the muscles around the spine (12). Common athlete injuries to the spine include muscle spasms, compression fractures, avulsion fractures and herniated discs. Higher SCI risks are present in wrestling, rugby, diving, skiing, ice hockey, and cheerleading (13).

One of the most critical problems in collision sports is concussion. In particular, detecting changes in the central nervous system due to the blows boxers receive on their heads is highly requested. Biomarkers that meet this demand have emerged to calculate the severity and the probability of injury, and also the rate of recovery in athletes. So, recent studies focus on detecting axonal damage with the use of biomarkers. These biomarkers are blood-based markers that use glial cell biomarker S-100 calcium-binding protein (S100B) and neuron-specific enolase (14).

In another treatment approach; stem cell transplantation, transplanted stem cells can reorganize the neuronal network in various conditions of SCI, reduce systemic and regional inflammation, promote axonal regeneration and neuroplasticity, and treat glial scars (15). Kim and his colleagues have used adipose-derived mesenchymal stem cells (MSCs) in acute spinal cord injury in dogs. As a result of the study, it was seen that adipose-derived MSCs strengthen anti-inflammatory and antioxidant mechanisms and further damage to the spinal cord was prevented (16). A clinical trial of stem cell transplantation was administered to former motocross champion Blake Colleton, who broke his back in an accident and was paralyzed from the chest down. Blake Colleton went to Panama for stem cell therapy where human umbilical cord tissue and mesenchymal stem cells originating from their bone marrow were used for the treatment. In an interview, the young athlete declared that he would like to participate in the Paralympic Games after his recovery (17).

Moreover, tennis player Rafael Nadal was treated for back ailments by injecting stem cells into a joint in his spine. Because it is a promising approach, the tendency of athletes to use stem cell therapy is increasing daily. Stem cell therapy is less invasive than surgical methods to provide neotissue formation (18). On the other hand, other methods have been developed for treating such injuries. These approaches aim to ensure axons' regrowth in spinal cord lesions via the coaxial cable feature of biomaterials. Biomaterials mimic the extracellular matrix structure and can serve as a scaffold and drug carrier (19). Biomaterials are often used with stem cells to increase the effectiveness of treatments and shorten the treatment process (20). Hydrogels combined with MSCs may be a good candidate to reduce the effects of SCI. The hydrogels can also be modified with adhesive molecules such as laminin and fibrinogen. In addition, scaffolds/hydrogels can also be supplemented with growth factors to enhance the therapeutic potential of MSCs (20). While new methods are being developed for the treatment of SCI, the importance of the 3D printing method is also emphasized. A 3D-printed spinal cord implant is usually made up of hydrogel. This implant can be fabricated individually and printed quickly in different shapes and sizes (21).

Cartilage injuries

Cartilage is a tissue with essential functions, such as keeping the synovial fluid in interosseous joints. The other functions can be listed as ensuring the bending of the joints and preventing abrasion and damage in the areas where the bones are affiliated (22). Cartilage injuries, if left untreated, prevent participation in sports in the long term and can cause significant tissue losses (23). The total prevalence of knee cartilage injuries in professional athletes was estimated at 36%, and after treatment, 45% to 78% of athletes returned to sports at the pre-injury level between 7-25 months (19). Cartilage repair in professional athletes requires cartilage surface restoration that can withstand significant mechanical joint stresses (23). Regenerative medicine and tissue engineering treatments promise potential to provide cartilage restoration with higher healing proportions. Nowadays, extensively used treatment modalities in the clinic consist of microfracture, PRP, osteochondral graft transplantation, autologous chondrocyte, and scaffold-supported chondrocyte transplantation. In addition to clinical applications, exosome, and 3D artificial cartilage topics, among ongoing research also promise in creating more advanced treatment options (24) (Table 1). There are limiting factors in the treatment of articular cartilage defects such as lesion size and location, patient age, and rehabilitation protocol (25).

Table 1. Recovery time, the rate of return to sports, return to sports at preinjury level according to type treatments following cartilage injuries.

Treatment Approaches	Average Time to Return to Sports	Ratio of return to sport	Ratio of return to prior performance	References
Microfracture	8.7 months	75-77.4 %	62.3-69 %	(31,76)
Osteochondral Allograft Transplantation (OCA)	9.4 months	77.1-88 %	59.5-79 %	(31,76,77)
Osteochondral Autograft Transplantation (OAT)	4.9-7 months	88.2-89 %	70-79.3 %	(31,76)
Autologous chondrocyte transplantation (ACT)	11.6-18 months	79.7-84 %	57.3-76 %	(76,78)
Matrix-induced autologous chondrocyte transplantation (MACT)	12.4 months	84-86 %	74.3-80.6 %	(76,77)
PRP	3 months	76.6-83 %	48.9-100 %	(79,80)

Microfracture surgery, a current clinical treatment modality for cartilage injuries, is a standard surgical method used to treat patients with full-thickness damage extending to the bone. Harris et al. reported that 59% of patients returned to sports at pre-injury level after microfracture surgery (26). PRP-like treatment; Orthokine®, which uses a cell-free serum containing high concentrations of signaling proteins in patients to benefit from effects such as IL-1, bonding to specific cytokine receptors and stimulates inflammation (27). Former NBA player Kobe Bryant who had been administered this treatment following left knee injury was able to return to basketball (6). Osteochondral graft transplantation also emerges as an efficient option for recovering neuromuscular function and treating spacious cartilage defects in the knee (28). By using small-sized multiple grafts instead of a single large block graft in the transplantation, the integrity of the donor area is preserved and more tissue transplantation is enabled (29).

Focal chondral defects of the knee can lead to discomfort, impaired function, and in many instances, degeneration of the joint, ultimately resulting in osteoarthritis. In addition to cartilage restoration surgery, ortho-biologics can treat focused chondral defects in the clinical setting. Among the orthobiologics used to treat cartilage defects are bone marrow aspirate concentrates, mesenchymal stem cells derived from adipose tissue, platelet-rich plasma, and micronized allogeneic cartilage (30). Return to sports rate has been reported as 75-82% in 8-12 months following osteochondral allograft transplantation (28). Another study reported the rate of returning to sports increases to 88% at the end of 4.9-7 months following osteochondral autograft transplantation (31). Autologous chondrocyte transplantation (ACT) and matrix-assisted autologous chondrocyte transplantation (MACT) are the other well-known treatment modalities for repairing chondral defects and regenerating hyaline cartilage in athletes. The ACT technique involves the injection of chondrocyte suspension to the defective area, which is obtained by collecting cartilage cells from the patient and multiplying them in the laboratory (32). In the MACT technique, the patient's augmented chondrocytes are seeded on a bilayer membrane composed of collagen type I and III. Subsequently, the membrane is shaped according to the defect in the patient and it is fixed using fibrin glue. This surgical process causes less trauma to the tissue (33). Biopsies taken at the end of the first year after surgery revealed that hyaline-like cartilage or fibrocartilage hyaline-like cartilage formed in 43.9% of ACT and 36.4% of MACT. While 42.7% of the patients returned to sports at the pre-injury level after ACT, this rate was reported as 69.3% in MACT (34).

Relevant studies are increasing each day to develop more functional tissue-engineered products that support cell migration and proliferation using scaffolds, cells, and secretions in a more advanced way, such as Computer Aid Designs and 3D bioprinting. For instance, a study published in 2021 used a 3D bioprinting method to repair significant chondral defects. For this purpose, human-induced pluripotent stem cells (hiPSCs) were differentiated into chondrocytes, and functional cartilage structure was assembled using Kenzan needle array technology. It has been shown and reported that structures suitable for cartilage anatomy are produced with 3D bioprinting (35). Furthermore, artificial (synthetic) cartilage designed as a solid elastomeric layer or a biocompatible hydrogel has been developed by the cartilage tissue engineering which is expected to replace knee prostheses and joint replacement surgeries (36).

Tendon injuries

Tendons are fibrous connective tissues that connect muscles to bone and enable the body to move. Tendons can be injured and lead to severe loss of mobility for a prolonged time (37). Tendon injuries carry significant morbidity in ordinary people and athletes. It accounts for approximately 30-50% of musculoskeletal injuries affecting 100 million people worldwide (38). The most sports-related one is the Achilles tendon injury. These injuries are common in athletes playing football, basketball, track and field, and tennis (39). The overstretch on the Achilles tendon from daily activities or sudden movements can cause it to rupture. Famous basketball player Kobe Bryant, former tennis champion Boris Becker and famous American football player Vinny Testaverde are among the athletes who experienced Achilles tendon rupture (40). Between 70% and 90% of athletes with Achilles tendon rupture successfully recover after surgery, while 20% of the injured athletes require re-operation and 3 to 5% of athletes could not return to sports (41). Former baseball player Mark Mulder, basketball players Jay Williams and Danny Manning, and tennis player Maureen Connolly are famous athletes who ended their careers due to tendon injuries (42). One of the most dramatic examples of this injury in Türkiye was Rıdvan Dilmen's, who was the captain of Fenerbahçe FC for many years who had to end his career at the pinnacle of his career between 1991-1994 (43).

Soft tissue injuries, including tendon and muscle tissue injuries in athletes cause time loss and high-cost for athletes and teams. In 2002, the money spent on treating these injuries reached 15.8 billion dollars (44). The difficulty of clinical management of sports injuries necessitates new treatment methods combined with tissue engineering approaches in sports medicine (5). Cell-based and other biological therapies for sports injuries are of great interest to high-profile athletes today, as well as for clinical research and basic science (45). Due to the low self-healing potential of the tendon and the inadequacy of clinically applied physical therapy methods, the search for new treatment methods and the use of stem cells to support tendon regeneration seem exciting for sports medicine and orthopedic surgery. Stem cells have the potential to differentiate into tenocytes, the main cellular component of tendons (46). Using MSCs that have frequently encountered in tissue engineering and regenerative medicine in the last 10 years, is an alternative treatment method for athletes. Published and ongoing clinical studies support the healing effect of stem cells on damaged tissues and their positive effects on tissue regeneration (47). In addition, although the treatment modalities like shock wave therapy, injection of autologous blood products, oral or parenteral NSAIDs, steroids are frequently used in tendon injuries, studies on new methods with better and precise results are continuing (48).

Muscle and bone injuries

The human body contains a large amount of muscle tissue, which helps with movement, posture, and support. The most common injuries to this high-volume tissue are muscle strains, which can cause bruising and tears. Muscle injuries prevent athletes from participating in training and can cause pain and functional disorders (49). In addition, muscle injuries can lead to fibrotic tissue formation and permanent damage if not treated properly. Various biomedical and tissue engineering approaches are available to treat serious muscle injuries. These include injection of growth factors, transplantation of muscle stem cells with or without biological scaffold support, anti-fibrotic therapies, mechanical stimulation, and PRP (50).

Bone is a dynamic tissue that can respond to mechanical effects over time. Although bones are the most durable structure in the body, they can be fractured in athletes due to repetitive stress, acute sports-related traumas, and nonsport traumas (51). These fractures are mostly observed in the lower extremities in athletes (52). Malunion or nonunion are main complications seen after fractures. Ranaletta et al. reported that 15% of 52 patients with clavicular fractures had nonunion and 31% had malunion following nonsurgical intervention, whereas 94% of 54 patients who were undergone open reduction and internal fixation returned to sport (53).

One of the hot topics in regenerative medicine is exosomes (i.e., extracellular vesicles) which are cellular secretomes and serve as the regulatory agents of molecular mechanisms. They have been also reported to be critical in repairing skeletal muscle and bone damage, maintaining homeostasis, and tissue regeneration. Research has shown that when extracellular vesicles placed on scaffolds to treat bone injuries, bone volume, and mineral density increased (54). In addition, the implementation of extracellular vesicles to repair skeletal muscle injuries has been specified to increase the expression of muscle-specific transcription factors and fiber cross-sectional areas and reduce scarring (55).

Autologous bone grafts are considered to be the gold standard with their osteoinductive, osteoconductive and osteogenic properties. Bone autograft has been shown to be effective in case of nonunion following mid-shaft clavicle fractures (56). Composite grafts containing a combination of osteogenic cells, osteoinductive growth factors, and a synthetic osteoconductive matrix are considered as one of the most promising strategies for treating bone defects. Various metallic implants in the form of plates and screw systems are used for bone defects to increase the stress resistance of the bone and achieve internal fixation (57). For instance, F1 pilot Fernando Alonso suffered an upper jaw bone fracture in an accident during cycling training in 2021, and treated with two titanium plates and he got ready to return to racing in just a few weeks (58). Furthermore, it has been reported that two athletes, a basketball player (23-years-old) and an amateur football player (30-years-old), returned to sports only four weeks after being treated with the percutaneous hole screw system and the percutaneous mini screw system (59).

A recent approach in treating musculoskeletal injuries is transplanting stem cells to the damaged area via biocompatible scaffolds. Mercacci et al. reported that bone fusion was complete in 5 to 7 months following transplantation of bone marrow mesenchymal stem cells (BMMSCs) seeded with hydroxyapatite scaffolds for treatment of critical-sized bone defects (60). In a recent study, BMMSCs with calcium phosphate bioceramic granules were used to treat femur, tibia and humerus fractures with significant improvement in 26 of 28 patients (61).

The concept of prolotherapy is one of the practical treatment approaches introduced in the mid-1950s as a treatment method that strengthened the damaged tendons and ligaments (62). Application of 12.5% dextrose and 0.5% lidocaine injections to 22 rugby and 2 football players with chronic inguinal pain resulted with pain cessation in 20 athletes and return to sports in 22 athletes (63).

Along with these treatments, courtesy of today's developing computer-aided design and production technologies, personalized implants and grafts are produced from biomimetic calcium phosphates, which mimic the composition and structure of bone minerals (64). Organoid technology is another promising approach. The extensive proliferation and multiple differentiation potential of induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs) lead to their implementation in musculoskeletal injuries (65).

Wearable technologies

Recently, wearable technologies have been used to evaluate physiological signals in areas such as competitive sports or individual studies. Wearable technologies help to create personalized training programs to fulfill demands such as follow-up of well-being (66). The system detects sudden changes in the athlete's body and is based on wireless transfer of data to a smart device. Hip and knee joint motions are calculated using an algorithm to make the necessary analysis with these sensors attached to the athletes' bodies. Biomechanical analyses via this technology may provide relevant information for optimal movements to be able to prevent sports injuries, as well. (67). By utilizing bi–

ocompatible materials, wearable technologies can also be directly embroidered into the skin (Figure 2). Furthermore, systems with smart screens can be attached to human body or implanted directly into the tissue (68). For instance, intelligent shoes are produced using sensors that detect ground reaction forces that aim to reduce the incidence injuries. Load and pressure on the tibial bone may be determined by this technology (69). Compression forces may increase several times and can cause damage to the joints, primarily the knees. Knee implants have been used for years to alleviate the symptoms and restore functions (70). A new technology developed by Zimmer Biomet called "Smart Knee" can be implanted in the patient's knees to transmit motion data via sensors to the patient's device. It was stated that the recovery rate could be easily observed by comparing the pre- and post-operative periods (71).

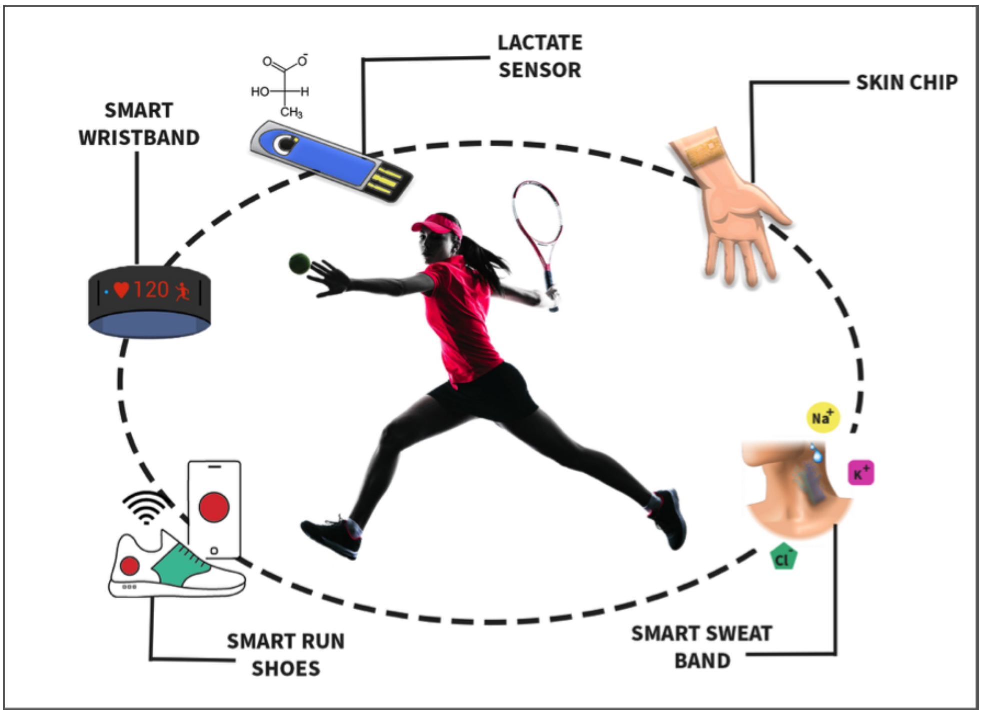

Figure 2. Devices used in wearable technology

Blood lactate measurements are used to adjust individual training loads (72). Piezoelectric biosensors that facilitate lactic acid measurement are also adapted to wearable technology. These biosensors make it easier to prepare a personalized program suitable for training and competition requirements (73). Wearables combined with non-invasive biomarkers increase the efficiency of the technology (74). It is thought that significant progress will be achieved by improving the energy efficiency and reducing the size of the devices. Furthermore, with improved individualization and safe data sharing, utilization of wearable devices is expected to be common in all over the world (75).

CONCLUSION

This review aims to review new approaches in treatment of sports injuries and improve sports performance. Regenerative medicine, tissue engineering and biotechnology aim to restore function by benefiting from the interactions of cells, biomaterials, and bioactive molecules. However, the high cost of these personalized treatments is a significant disadvantage that reduces the accessibility. We believe that tissue engineering-based therapy may rapidly improve by means of funds and investments supported by the sports industry.

Extensive studies on the accessibility and applicability of treatments are necessary to improve athlete healthcare.

Conflict of Interest / Çıkar Çatışması

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