

International Olympic Committee Consensus Statement: Molecular Basis of Connective Tissue and Muscle Injuries in Sport

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More than 100 million musculoskeletal (tendon/muscle/bone) injuries occur annually worldwide. Of these, 30% to 50% are tendon and ligament injuries [1], which cause significant loss of performance in sport and decreased functional capacity in the workplace and negatively affect the

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ability of members of the general population to undertake exercise. A significant proportion of these injuries remain difficult to treat, and many individuals have long-term pain and discomfort [2].

The International Olympic Committee (IOC) assembled an expert group to discuss the nature of the problem, the current state of the art, and the need for further research. Recent advances in this field relate to (1) the discovery of novel genetic markers for risk of tendon injury; (2) improved understanding of structure and composition of tendon and its response to loading; (3) increasing clinical use of growth factors to treat a variety of tendon, bone and muscle injuries; and (4) research exploring the potential of applying stem cells to benefit patients who have musculoskeletal problems. This consensus statement addresses each of these advances in more detail.

GENETIC PREDISPOSITION TO MUSCULOSKELETAL INJURY

Musculoskeletal injuries have complex causes including both genetic and non-genetic factors [3]. The search for genes that may predispose athletes to these injuries is gaining momentum but remains in its infancy. For example, variants within two genes (which produce type V collagen and tenascin C, respectively) were discovered recently to be associated with Achilles tendon pain [4,5]. Large studies in various populations using high-throughput technologies such as genomics and proteomics [6–8] will be required to advance knowledge of genetic associations with musculoskeletal injuries. This approach will allow researchers to identify further genes that may be associated with these and other specific musculoskeletal injuries. The ability to identify people at risk for these injuries will extend to the general population; injury-prevention measures will ensure that people can exercise appropriately for their inherited genetic makeup.

STRUCTURE AND COMPOSITION OF TENDON AND ITS RESPONSE TO LOADING

When athletes experience tendon pain, structural abnormalities are already present [9,10]. At light microscopy, inflammatory cells generally are absent at the site of injury [11]. Hence, the term “tendinitis” (or “tendonitis”) has fallen out of favor [12]. Injured tendon has several characteristic features, such as increased or decreased cellularity and dramatic alteration in matrix structure and composition [13]. There are quantitative and qualitative changes in collagen, proteoglycan, and matrix-degrading enzymes and increased penetration of blood vessels and nerves [14,15]. A classical term to describe this overall appearance has been “tendinosis,” but these features are consistent with inadequate repair—a failed healing response [16].

Although load is important to maintain the normal tendon matrix, pathology in tendons often is linked to overuse. Exercise can increase the production of collagen and other proteins in tendons and thus can be used as part of the management of tendon injuries [17]. Tendon cells respond to load by increasing protein production [17,18], but it is presently unclear what stimulus is required

to restructure a damaged matrix. Chronic end-stage tendon disease may never fully recover the normal matrix structure and composition, although adequate pain-free function is still possible [9].

INCREASING CLINICAL USE OF GROWTH FACTORS

Growth factors include a number of proteins secreted by cells [19]. Numerous experimental studies have shown that growth factors are involved in bone and cartilage formation, fracture healing, tendon and ligament repair, and skeletal muscle regeneration [20–22]. Therefore their therapeutic use is of enormous interest in the field of sports medicine and in helping treat workplace-related injuries. Growth factors of current interest include growth hormone (GH), insulin-like growth factor-1 (IGF-1), mechano growth factor (MGF), basic fibroblast growth factor (B-FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), and bone morphogenic protein (BMP) (Table 1). Several of these growth factors are available commercially and are used in clinical settings [23].

BMPs enhance healing during different stages of fracture healing in various animal and human models. VEGF, PDGF, FGF, and TGF- β also have been shown to play an important role in ligament and tendon healing [24–37]. Although a body of research evidence exists in animal models [38], the results of late-stage, randomized, controlled clinical studies in humans are as yet unavailable (with the exception of BMPs), and the long-term local and systemic effects of these agents are unknown [39]. FGFs, TGF- β , and PDGF are important in the muscle regeneration process [22,40–47]. VEGF and PDGF increase blood flow to skeletal muscle [48–50]. The administration of B-FGF to improve blood perfusion has had limited success in other clinical studies, however [51–54]. A phase II trial of B-FGF revealed positive effects on peripheral blood flow [55].

Many fractures do not heal properly, and the bone-healing process therefore needs to be augmented. Recombinant human bone morphogenic protein

Table 1
Growth factor expression in musculoskeletal tissues

Factor	Muscle	Cartilage	Tendon/ligament	Bone
GH	+	+	+	+
IGF-1	++	+	+	+
MGF	+++	?	+	?
B-FGF	+	+	\pm	+
PDGF	–	–	\pm	\pm
VEGF	+	–	\pm	–
TGF- β	\pm	+	\pm	+
BMP	+	+	–	–

Abbreviations: B-FGF, basic fibroblast growth factor; BMP, bone morphogenic protein; GH, growth hormone; IGF-1, insulin-like growth factor-1; MGF, mechano growth factor; PDGF, platelet-derived growth factor; TGF- β , transforming growth factor- β ; VEGF, vascular endothelial growth factor.

2 and recombinant human bone morphogenetic protein 7 or osteogenic protein 1 have been used clinically. At present, there are several published clinical studies on the effects of BMPs in bone healing or in delayed unions/non-unions, and several studies have reported the effects in fusion of the lumbar spine. This use of BMPs now constitutes a well-established practice in orthopaedic surgery.

GH, produced by the pituitary, induces the liver to produce systemic IGF-1, which forms a tripartite binding complex with IGF binding protein 3 and the acid labile subunit, to stabilize IGF-1 in the serum [56]. The levels of GH and IGF-1 reach their peak during adolescence [57]. With increasing age, however, there is a marked decline in the circulating levels of GH and a somewhat smaller decline in circulating IGF-1. Treatment of GH-deficient adults for an extended period of time results in increased muscle strength and decreased body fat [58]. These findings have encouraged the illicit use of GH and GH-like substances among athletes, even those competing at the secondary school level, in an attempt to enhance performance, an ongoing problem for anti-doping agencies. At present, there are methods for detecting GH and its isoforms, but none have been validated for IGF-1 yet. The matter is complicated by the fact that local forms of IGF-1, such as MGF, are produced after exercise by the splicing of the IGF-1 gene; its sequence differs from the regular endogenous type of IGF-1 released by the liver but also is not detectable by current anti-doping methods [59–64]. MGF is very potent for increasing muscle mass and strength [65–67]. MGF apparently acts as a separate growth factor that is involved in activating satellite cell proliferation and replenishing the pool of these muscle stem cells [68,69]. In summary, studies in animal models have highlighted some interesting candidates that await evaluation in human clinical trials.

RESEARCH EXPLORING THE POTENTIAL OF APPLYING STEM CELLS

Mesenchymal stem cells are adult tissue-producing cells that have been isolated from various parts of the body, including cartilage, bone marrow, synovium, adipose tissue, articular cartilage, muscle, and tendons [70–72]. Potentially, mesenchymal stem cells can be used for tissue-engineering strategies through implantation of scaffolds and gels, for gene delivery, and for production of growth factor to stimulate tissue repair or inhibit tissue degradation [73–75]. Most studies have been conducted in animal models. Some studies of human bone, cartilage, and tendons have produced positive results [76–78]. Further controlled clinical trials in musculoskeletal injuries in humans are warranted, however. Reasons for the lack of progress in this field include the need to find the optimal sources of and methods for the differentiation of cells and for the development of optimal surgical delivery materials and methods [79,80]. Although some studies have shown negative effects, including ectopic calcification and connective tissue overgrowth [78], further clinical trials should be undertaken to determine whether long-term complications exist.

POSSIBLE FUTURE RESEARCH DIRECTIONS IN GROWTH FACTOR THERAPY

The implementation of new biologic therapies based on the administration of growth factors and the manipulation of adult stem cells will require an improved understanding of the genetic regulatory networks affected by these agents. This understanding will be necessary for two reasons: to ensure that these therapies are optimized and to ensure the safety of patients and athletes. Knowledge of the genomic and proteomic impacts of growth factor-based therapies on the target cells and of the biomarkers reflecting stem cell differentiation status will underpin the development of tests capable of monitoring therapeutic efficacy and minimizing adverse events.

POTENTIAL FOR MISUSE OF GROWTH FACTORS AND CELL-BASED THERAPIES

The ability to manipulate existing muscle cells and muscle stem cells has the potential for use in the context of illegal performance enhancement. Knowledge of the underlying genetic and cellular events affected by growth factor administration can be used to develop tests capable of detecting the illegal use of such technologies for performance enhancement. The IOC will monitor developments in this field to ensure that such practices are discouraged, and detected if used, by working with the anti-doping agencies.

SCIENTIFIC ADVISORS

The IOC now has high-level scientific advisors who are capable of monitoring new developments in the field of growth factor- and cell-based therapies and of advising the IOC as to the use and abuse of these technologies. These advisors will help ensure that athletes and coaches receive the benefits of these developments in improving their ability to prevent injury and to enhance therapy if injured. In addition, the illegal use of these technologies for performance enhancement will be increasingly difficult as methods of detecting such use become available.

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