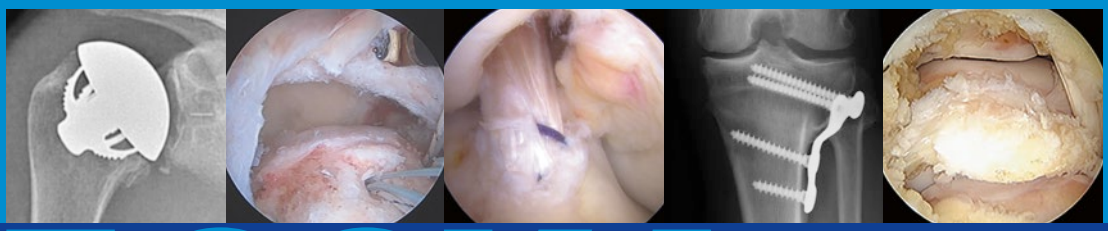
Michael Tobias Hirschmann
Elizaveta Kon
Kristian Samuelsson
Matteo Denti
David Dejour *Editors*



ESSKA Instructional Course Lecture Book

Milan 2021

ESSKA
MOREMEDIA
Springer

Tendinopathy: From Basic Science to Return to Play

34

F. Abat, U. G. Longo, B. Kocaoglu, F. G. Usuelli, L. Lempainen, A. Jiménez-García, G. Stelitano, G. Firatli, and R. D'Ambrosi

34.1 Basic Science and Diagnosis of Tendinopathy

Tendinopathy is a common clinical problem which affects a substantial portion of recreational and professional athletes and those in many occupations involving repetitive work [1].

Tendon injuries, which represent approximately 50% of all sports injuries, can occur in any tendon. It is often at the level of or near its insertion where there is the area of major mechanical stress concentration [2]. The most commonly involved tendons are the rotator cuff (particularly supraspinatus) tendons in the shoulder, the forearm extensor and flexor tendons in the forearm, the patella tendon in the knee, and the Achilles tendon in the ankle as they are more exposed to repeated loads, shear and compressive forces [3].

The term "*tendinopathy*" describes the clinical features in and around tendons which include activity-related pain, swelling, focal tendon tenderness, decreased strength and movement in the affected area associated with decreased exercise tolerance and function of the limb, up to total rupture [4].

The histologically descriptive terms "*tendinosis*" (a degenerative pathological condition with a lack of inflammatory change) and "*tendonitis*" or "*tendinitis*" (implying an inflammatory process associated to degenerative injury) should be used only after histopathological confirmation. The pathogenic mechanisms underlying the onset of tendinopathies are still unclear [5].

Historically, inflammation has been thought of as the central pathological process in tendon disorders, but histological studies of surgical

F. Abat (✉)
Department of Orthopaedic Sports Medicine, ReSport Clinic, Blanquerna Faculty of Health Science, Ramon Llull University, Barcelona, Spain
e-mail: abat@resportclinic.com

U. G. Longo · G. Stelitano
Department of Orthopaedic and Trauma Surgery, Campus Bio-Medico University, Rome, Italy

Centro Integrato di Ricerca (CIR), Campus Bio-Medico University, Rome, Italy

B. Kocaoglu
Department of Orthopedics and Traumatology, Faculty of Medicine, Acibadem University, Istanbul, Turkey

F. G. Usuelli
IRCCS Istituto Ortopedico Galeazzi, Milan, Italy

L. Lempainen
Sports Trauma Research Unit, Mehiläinen NEO Sports Hospital, Turku, Finland

A. Jiménez-García
Department of Strength and Conditioning, ReSport Clinic, Blanquerna Faculty of Health Science, Ramon Llull University, Barcelona, Spain

G. Firatli
Faculty of Medicine, Acibadem University, Istanbul, Turkey

R. D'Ambrosi
Humanitas San Pio X, Milan, Italy

M. T. Hirschmann et al. (eds.), *ESSKA Instructional Course Lecture Book*,
https://doi.org/10.1007/978-3-662-61264-4_34

specimens have consistently shown the presence of degenerative lesions, either absent of or with a minimal inflammatory component [6].

The most widely shared hypothesis sees inflammation's contribution only in the early phases of disease. Currently, mechanical overload and excessive mechanical stress on the muscle–tendon unit seem to play a key role in the onset and perpetuation of tendon degeneration even though a full understanding of the biomechanical basis for tendinopathy is still lacking and needs to evolve [3].

Histological changes in tendinopathies have been widely described [7]. Macroscopically normal tendon is white, brilliant and has a fibroelastic consistency. Affected tendons lose their normal sparkling white appearance and become gray or brown, amorphous, thinner and softer [8]. The typical thickening in the degenerated regions can be diffuse, fusiform, or nodular [9]. Microscopic histopathological changes include loss of the parallel orientation of collagen fibers along with a decrease in collagen fiber diameter and in the overall density collagen. There is also increased overall cellularity, increased deposition of mucoid ground substance and proteoglycans as well as the proliferation of new randomly oriented blood vessels. Moreover, an increase in type III (reparative) collagen fibers is usually described [10]. All these reflect a failure of the native tendon healing process.

Depending on the histopathological alterations, different theories on tendinopathy etiopathogenesis have been hypothesized.

The mechanical theory places overuse injury at the center of the pathologic process. The excessive load to which the tendon is exposed may cause repeated microinjuries that lead to biological alterations of ground substance and tenocytes with subsequent mechanical breakdown of the loaded tendon. The increase in E2 prostaglandin and B4 leukotriene production seems to be mainly responsible for degenerative process. The affected tendons lose their mechanical properties, resulting in a reduction of the tendon cross-sectional area over which muscular forces are transmitted thereby making them more susceptible to failure [11].

The vascular theory would explain the onset of tendinopathy as a consequence of an inadequate vascular supply during mechanical activities due to the presence of intratendinous avascular areas as occurs in the Achilles tendon or extensors tendon of the elbow [12]. In contrast to the vascular theory, a new pathogenic hypothesis is being put forth. It postulates that physical training could create a localized hyperthermia condition, causing a decrease in tenocyte survival [13].

The neuronal response to repetitive tendon microtrauma seems to be involved. In degenerated tendons, a high level of nervous mediators (such as glutamate, calcitonin, P-peptide) and small nerve ingrowth are widely noticed [14]. Finally, disuse has also been identified as tending to alter tendon properties. Denervation and immobilization have both been found to decrease tendon stiffness and reduce final tissue strength and, at the same time, inactivity and unloading could have an effect on tendon collagen homeostasis dysregulation [13–15].

Some individuals are more susceptible to developing tendinopathy than others who have similar levels of physical activity [16]. This predisposition derives from the interaction between several risk factors identified in two large categories, extrinsic and intrinsic factors. Among the intrinsic factors, individual's genetic characteristics must be considered. The ABO blood group and tendon molecular structure were suggested as possible predisposing factors. Gender is another genetic expression key. Women seem to have less tendinopathy than men, thanks to the protective role of estrogens. Estrogenic protection is supported by the evidence that tendon ruptures are almost exclusively described after the onset of menopause [16, 17]. Increased age is another important intrinsic risk factor and certainly the prevalence of tendinopathy seems to increase with age. Age-related intratendinous changes such as the reduction in proteoglycans and an increase in cross-links between collagen fibers make tendons stiffer and less capable of tolerating load [18]. Body composition has recently been linked to tendinopathy. A greater waist circumference and high levels of adipose

tissue suggest increased risk to the onset of tendinopathy. Ligamentous laxity, articular hypermobility, muscular stiffness or weakness, malalignment of the lower extremity, and limitation of joint mobility also has to be mentioned. Finally, the association between tendinopathy and several pathological conditions has been demonstrated [19]. Endocrine-metabolic diseases such as obesity, diabetes mellitus, hypertension, increased serum lipids, and hyperuricemia seem to have a positive association with the pathology [20]. Other diseases that have been found to be associated with tendinopathy include systemic diseases, neurological conditions, infectious diseases, chronic renal failure, psoriasis, systemic lupus erythematosus, hyperparathyroidism, and hyperthyroidism [21].

The main important extrinsic risks factors include mechanical overuse linked to sports activities like training errors (excessive distance, intensity, hill work, erroneous running technique, fatigue) and the use of several drugs (fluroquinolone antibiotics, statins, oral contraceptives, and locally injected corticosteroids) [22, 23]. Environmental conditions such as cold weather during outdoor training, faulty footwear and equipment, inadequate training surfaces or frequent changes in playing surface have been found to increase the prevalence of tendinopathy [19–23].

The clinical history and a physical examination are essential to making a diagnosis of tendinopathy. Clinically, tendinopathy is characterized by pain, swelling (diffuse or localized), and impaired physical performance. Pain is the cardinal symptom that usually occurs at the beginning of the training session or a short while afterwards. In advanced cases, it may interfere with the activities of daily living. Clinical examination is the best diagnostic tool and presupposes a careful valuation of the overall anatomical structures involved, and the use of specific tests to elicit pain and tenderness. Radiological imaging has a secondary role and it is used as diagnostic support. Ultrasound is considered the most appropriate and advantageous imaging modality for routine clinical evaluation despite it being operator dependent. MRI studies should be performed only if the ultrasound scan remains unclear.

34.1.1 Achilles Tendinopathy

Achilles tendinopathy is a clinical syndrome characterized by pain and swelling in and around the Achilles tendon associated with impaired physical performance [24]. The typical patient affected by Achilles tendinopathy is the so-called "*middle-age weekend warrior,*" a recreational athlete who practices sports, like running, with explosive accelerations and eccentric loads located on the lower limb [25]. The etiology of Achilles tendinopathy remains debatable and is likely caused by the interaction of intrinsic and extrinsic factors. In addition to the ones analyzed for tendinopathy etiopathogenesis in general, there are other specific factors responsible for the onset of the Achilles tendon disease. Intrinsic factors include an anatomical foot alteration like hypo-hyperpronation. It is often associated with ankle misalignment, varus or valgus hindfoot and forefoot, pes cavus or flat foot, tendon vascularity, weakness of as well as the lack of flexibility of the gastrocnemius–soleus complex and lateral ankle instability [26]. Excessive loading of the tendon is considered the major extrinsic causative factor for Achilles tendinopathy. Free radical damage occurring on reperfusion after ischemia, hypoxia, hyperthermia, and impaired tenocyte apoptosis has been linked to tendinopathy [27]. In a case-control study, subjects with painful Achilles tendinopathy had a lipid profile characteristic of dyslipidemia [28]. The use of local corticosteroid injections and of systemic antibiotics (in particular fluoroquinolones) has shown an increase in the development of the disease [29]. Achilles tendon pathology can be subdivided into acute and chronic tendinopathy, including the simple forms of tendinosis up to total rupture of the tendon.

Chronic tendinopathies are painful clinical conditions commonly found in athletes, often middle-aged male runners even though they can also affect sedentary subjects. They are typically associated with overuse damage and this would explain their greater incidence in athletes. However, 30% of patients with chronic tendinopathy do not participate in sports activities. Other pathogenetic mechanisms responsible of the

chronic damage have to be found. Metabolic and vascular imbalances seem to play a crucial role in the onset of the disease.

Chronic Achilles tendinopathy can be categorized as insertional or non-insertional. They are two distinct disorders with different underlying pathophysiologies and options.

Non-insertional tendinopathies (also known as "*tendinopathy of the main body of the Achilles tendon"* or *"midportion Achilles tendinopathy*") are caused by an inflammatory cellular response that occurs inside the tendon structure. They are associated with microcirculatory alterations and edema that can progress, in the chronic phase of the pathology, toward the formation of fibrosis and exudate [30].

Pain is the most common clinical symptom. In athletes, pain typically occurs at the beginning and end of a training session, with a period of diminished discomfort in between. As the condition progresses, pain may occur with even minor exertion, and may interfere with activities of daily living. Clinical examination is the best diagnostic tool. The patient is examined while standing and prone with both legs exposed from above the knees. The tendon appears diffusely swollen and edematous, and tenderness is usually greatest 2–6 cm proximal to the tendon insertion [31]. The most widely used diagnostic tests for non-insertional Achilles tendinopathies are the *Royal London Hospital Test* and the *Painful Arc test.* In the first one, once the tester has elicited local tenderness by palpating the tendon with the ankle in neutral position, the patient is asked to actively dorsiflex and plantarflex the ankle. With the ankle in maximum dorsiflexion and in maximum plantarflexion, the portion of the tendon originally found to be tender is palpated again. The Painful arc test, instead, helps the surgeon to distinguish between tendon and paratenon lesions. In paratendinopathy, the area of maximum thickening and tenderness remains fixed in relation to dorsi- to plantarflexion [32]. Again, the *Victorian Institute of Sports Assessment—Achilles* (VISA-A) questionnaire can be used to evaluate the severity of Achilles Tendinopathy. It covers the domains of pain, function, and activity and has a total score of 100. An asymptomatic patient would score 100 [33]. Ultrasonography (Fig. 34.1), though operator dependent, represents the primary imaging method to make the final diagnosis thanks to its interactive capability. Grey scale ultrasonography is associated with color or power Doppler to detect neovascularity [34].

Only if ultrasonography remains unclear, should magnetic resonance imaging (MRI) be performed. MRI gives more detailed information about the internal morphology of the tendon, surrounding bone, and soft tissues. Because of its high sensitivity in detecting incomplete tendon ruptures, the MRI data should be interpreted with caution and correlated to the patient symptoms before starting any treatments. However, both US and MRI show damaged tissue as focal or diffuse thickening of the Achilles tendon with focal hypoechoic areas.

34.1.2 Patellar Tendinopathy

Patellar tendinopathy is a painful condition of the knee caused by small tears on the patellar tendon, usually localized in its proximal region.

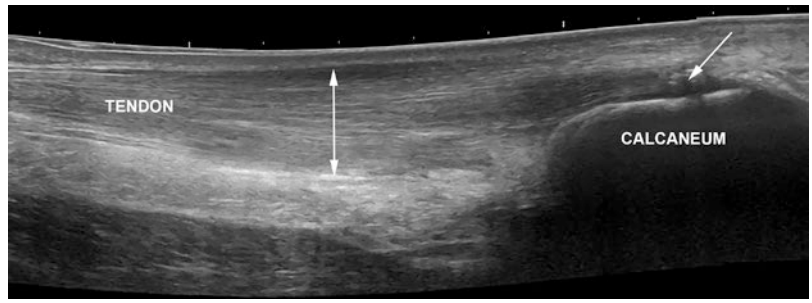


Fig. 34.1 Ultrasound image of the Achilles tendon in longitudinal view. Note the hypoechogenic area of the tendon (black zone inside the tendon), calcification (arrow) as well as a thickened tendon (double arrow)

It mainly occurs in sports which require strenuous jumping such as volleyball, track (long and high jump), and basketball. For this reason, patellar tendinopathy is also known as "*Jumper's knee*." This condition is a knee extensor mechanism overuse injury caused by repetitive mechanical stress to which the tendon is primarily exposed during knee extension [35]. The inferior pole of the patella, in correspondence of patellar tendon insertion, is the component of the knee extensor mechanism mostly involved. Less frequently, the injury is localized at the level of the quadriceps tendon insertion to the superior pole of patella and where the patellar tendon inserts into the tibial tuberosity. However, considering that most cases of Jumper's knee are due to problems on the patellar tendon insertion in the inferior pole of patella, the term patellar tendinopathy is used interchangeably. Patellar tendinopathy has a male predominance and usually affects adolescent athletes to those in their third decade and up [35]. The pathogenic mechanism underlying the disease includes the coexistence of several extrinsic and intrinsic factors. Overload on the knee extensor is the most important extrinsic factor which predisposes to the onset of patellar tendinopathy. Repetitive activities such as jumping, landing, acceleration, deceleration, and cutting cause microscopic changes within the tendon at high loads that causes progressive weakness and eventually leads to failure. Other extrinsic factors are the excessive frequency of training, the hardness of the ground on which sport is practiced, and the athletes' level of performance. On the other hand, intrinsic factors include joint misalignment, ligamentous laxity, abnormal patella height, quadriceps muscle weakness, and extreme hamstring muscles stiffness [36].

The diagnosis of patellar tendinopathy is mainly made through a patient's clinical history and physical examination. Anterior knee pain is the main symptom. Patients usually refer to well-localized pain on the inferior pole of the patella that is exacerbated by prolonged sitting, squatting, and stair climbing. Sudden tendon pain occurs with loading and usually stops almost immediately when the load is removed. Sometimes, patients even feel pain at rest. Physical examination presupposes a thorough evaluation of the entire lower extremity in order to identify the relevant abnormalities in the hip, knee, and ankle/foot region. Atrophy or reduced strength in antigravity muscles, including the gluteus maximus, quadriceps, and calf is often observed. Pain is elicited through palpation of the proximal portion of the tendon or by the complete extension of the leg. A positive *decline squat test* allows the surgeon to make a diagnosis of patellar tendinopathy. To do one, the patient performs a squat with a single leg, flexing the knee up to 30° and keeping the contralateral leg extended. In this way, the mechanical load is primarily exerted on the patellar tendon exacerbating the onset of symptoms [37].

The Victorian Institute of Sports Assessment—Patella (VISA-P) *questionnaire* specifically measures the severity of patellar tendinopathy. It covers the domains of pain, function, and activity. Scores are summed to give a total out of 100. An asymptomatic person would score 100. VISA-P can be used to assess the severity of symptoms as well as to monitor outcomes [38].

Currently, patellar tendinopathy is classified into five different stages according to the onset of pain in relation to physical activity: Stage 0: absence of painful symptoms; stage I: rare pain without performance limitation; stage II: moderate pain during sport without performance limitation (normal performance); stage III: pain with initial qualitative or quantitative limitation of performance (reduced training intensity); stage IV: pain with significant changes in sports performance; stage V: pain in everyday life with the impossibility of practicing sport. Ultrasound (Fig. 34.2) and magnetic resonance imaging (MRI) are widely accepted as first choice diagnostic techniques. Both can be used to detect abnormalities in the patellar tendon itself. Ultrasound is noninvasive, repeatable, accurate, and provides a dynamic image of the knee structure. Ultrasound images show the loss of tendon normal echogenicity, tendon thickening and irregularity, intratendinous calcifications and erosions localized primarily in the inferior pole of the patella. The use of the color Doppler makes

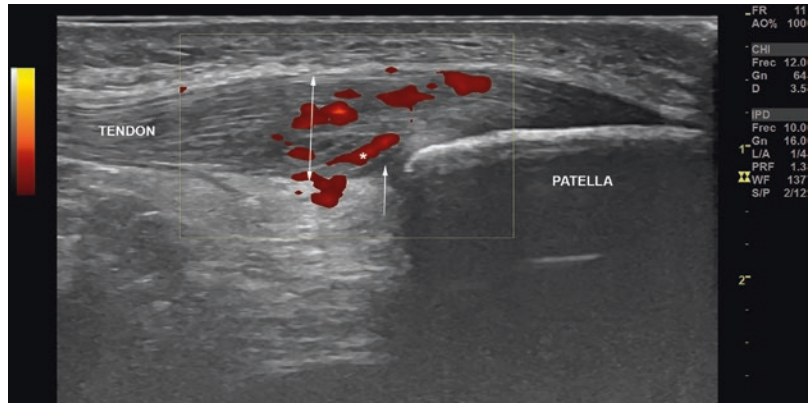


Fig. 34.2 High definition ultrasound image of the patellar tendon in longitudinal view. Observe the hypoechogenic area of the tendon (arrow) with hypervascular ingrowth (∗) as well as a thickened tendon (double arrow) and with involvement of the Hoffa fad pad

for visualization of the vascular neoformations in proximity to *Hoffa's* fat pad (also called the infrapatellar adipose *body*) [39]. Tardive changes such as elongation of the involved pole of the patella, calcification and increased density within the patellar tendon matrix are usually viewable after 6 months of symptoms.

The MRI shows, preferentially in sagittal sections, thickening of the patellar tendon along with foci of increased signal intensity in the affected region. A CT and bone scan may also be used in the initial stages of the disease even though they are not usually indicated. It is important to highlight that the radiological assessment must be considered only as a diagnostic support since the diagnosis of patellar tendinopathy cannot ignore the patient's clinical history and physical examination.

34.2 Traditional Conservative Treatment for Achilles and Patellar Tendinopathy

34.2.1 Achilles Tendinopathy

34.2.1.1 Noninvasive Methods

Noninvasive methods such as relative rest or a modification of activity, orthotics, heel lifts, massage, hot and cold compresses, strengthening exercises, ultrasound, and nonsteroidal anti-inflammatory drugs (NSAID) or oral corticosteroids can be applied as a first line treatment. The use of NSAIDs has been questioned as to their effectiveness because of the prostaglandin inflammatory mediator absence in Achilles tendinopathy (AT) [40].

34.2.1.2 Corticosteroid Injections

Corticosteroids are a group of medications that contain cortisone. They relieve pain by reducing the inflammation that occurs in a diseased tendon. There is controversy around the use of these injections in Achilles tendinosis since there is no inflammatory process. In some studies, cortisone injections bring about short-term pain relief. However, there is no pain relief after the injection according to some studies.

34.2.1.3 Eccentric Training

The eccentric training program designed by Alfredson et al. [41] improves tendon healing by enhancing the tendon's volume and the signal intensity that is thought to be a response to trauma. But after a 12-week program, the size and appearance of the tendon returns to normal in ultrasound and magnetic resonance imaging (MRI). With an extended eccentric loading program of the Achilles tendon, muscle–tendon unit length will be increased and the resistance of tendon to load will be increased overtime. Repetitive eccentric exercise could be the mechanism to eliminate pain in the tendon due to abnormal blood vessels and the nerves with the 12-week program as concluded by Alfredson et al. [42]. It has produced 90% good results with the midportion and 30% good results in insertional Achilles tendinosis.

34.2.1.4 Extracorporeal Shock Wave Therapy

Extracorporeal shock wave therapy (ESWT) is another treatment option for Achilles tendinosis (Fig. 34.3). There are two treatment strategies. The first one is the low-energy treatment strategy. It consists of three weekly sessions without local anesthesia or intravenous anesthesia. The second one is the high-energy treatment of one session but with local or intravenous anesthesia. Repeated shock waves to the affected area cause microtrauma that is then followed by neovascularization. Emerging blood flow stimulates tissue healing that results in relief of pain. It can also block afferent pain receptor functioning and increase nitric oxide synthase. This treatment strategy seems to be beneficial and may have a place in the treatment of Achilles tendinosis [43].

34.2.1.5 Low-Level Laser Therapy

Low-level laser therapy produces effects in a diseased tendon-like enhanced adenosine triphosphate production, enhanced cell function, and increased protein synthesis. It also reduces inflammation, increases collagen synthesis, and promotes angiogenesis. In a study by Stergioulas et al. [44], it was established that Achilles tendinosis patients who underwent eccentric exercises together with low-level laser therapy demonstrated decreased pain intensity, morning stiffness, tenderness to palpation, active dorsiflexion, and crepitus with no side effects in comparison to the patients who took up eccentric exercises exclusively. However, the data to confirm the efficacy of low-level laser therapy is still inadequate for the treatment of Achilles tendinosis.

Fig. 34.3 Extracorporeal shock wave therapy (ESWT) for Achilles tendinosis

34.2.1.6 Other Additional Methods

There are other methods that increase blood circulation. One of them is the Graston method. It is carried out with a metal rod (Fig. 34.4). It is mostly useful for tendon and soft tissue mobilization. The Tecar therapy is another method. It is endogenous thermotherapy based on the principle of capacitive and resistive energy transfer having an effect within the tendon, activating the body's natural repair and anti-inflammatory processes (Fig. 34.5). During those therapies, athletes should work at maintaining their cardiovascular form. In this situation, the antigravity treadmill helps patients with that maintenance.

34.2.1.7 Rehabilitation

Rehabilitation for an Achilles tendon rupture aids in regaining strength and flexibility in the tendon and leg. It can be done at home or in a gym.

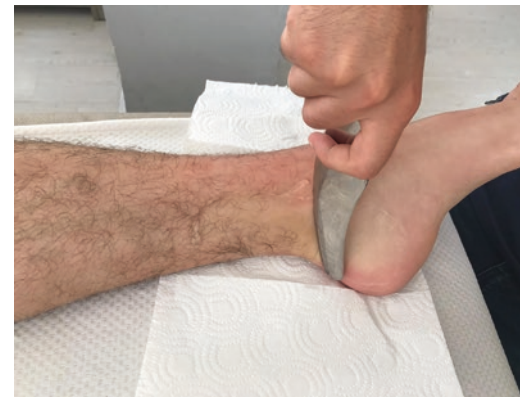


Fig. 34.4 Graston method in Achilles tendinopathy

Fig. 34.5 Application of Tecar therapy in Achilles tendon

The rehabilitation program may include:

- Stretching and flexibility exercises
- Strengthening exercises
- Endurance activities, such as riding a stationary bicycle
- Coordination and/or agility training

Recovery varies among people. It depends on how severe the tendon injury is and whether they complete your program. Giving time and energy to a rehab program will speed recovery and help prevent future injury.

34.2.2 Patellar Tendinopathy

34.2.2.1 Correction of Intrinsic and Extrinsic Risk Factors

Training Errors

Training conditions like ground selection, intensity, style, and frequency are extremely important and well-studied in the literature.

Flexibility

Mobility limitations are one of the most important reasons behind tendinopathies, and the flexibility of the muscles is very important for the mobility of a joint. Witvrouw et al. [45] found that the lack of flexibility of the quadriceps and hamstring muscles may be the reason for this injury. Therefore, the correction for the limited flexibility of the responsible muscles with corrective exercises is a very logical option.

Biomechanical Abnormality

It has been hypothesized that intrinsic risk factors like foot hyperpronation, pes planus or cavus, forefoot varus or valgus, hindfoot varus or valgus, tibia vara, genu valgum or varum, patellofemoral malalignment, femoral neck anteversion, and leg length discrepancies play a role in biomechanical derangement in patellar tendinopathy. Unfortunately, there is no evidence in the literature which proves this theory. But of course, if an apparent biomechanical abnormality exists in a patient with patellar tendinopathy, correction of this could be logical.

34.2.2.2 Symptomatic Approach

Relative Rest

Tendinopathy results from mechanical overload. Therefore, decreasing the overload relieve the pain. That does not mean complete immobilization. Moreover, complete immobilization causes thinner and disoriented collagen fibers, and decreased blood volume that result in tendon atrophy.

Nonsteroidal Anti-inflammatory Drugs (NSAID)

The administration of anti-inflammatory medication for a degenerative injury (noninflammatory causes) should be questioned. There is no evidence on the supportive effect of NSAIDs in chronic tendinopathy. There is an isolated study on acute tendon pain. Currently, the histopathology of acute tendon pain remains unclear. NSAIDs can also have additional effects other than simply anti-inflammatory or analgesic effects [46]. Some studies have proven the potential favorable effects of NSAIDs in tendon healing while others have reported on deleterious

mechanisms of NSAIDs in tendons. Still, in the clinical management of chronic tendinopathy, the use of an NSAID can hide symptoms due to its analgesic effect and consequently prevent optimum therapeutic management. Therefore, until further evidence of exact effects of NSAIDs in tendinopathy is revealed, their use in patellar tendinopathy is not evidence based.

Corticosteroids

Corticosteroid use in tendinopathy treatment is a topical issue [47]. There are a lot of studies of this topic. Some of them say that they provide short-term pain relief, but others say there is no positive effect. The increased risk of tendon rupture is a fact to be considered. Nevertheless, due to patellar tendinopathy being a noninflammatory condition and as corticosteroids can impair collagen synthesis and tendon strength, the use of corticosteroids needs to be rethought.

Ice Application

Cryotherapy causes vasoconstriction and neovascularization within the tendinosis. Consequently, it decreases blood and protein leakage. Still, there is no precise protocol that includes parameters like duration, frequency, and repetition. Due to the masking of the pain effect caused by icing, avoiding using it before sport participation would be logical.

34.2.2.3 Local Physiotherapeutic Modalities

There are many studies on the beneficial effects of the different physical therapy strategies for the treatment of patellar tendinopathy. They include fine needling, electrotherapy, electromagnetic fields, ultrasound, and laser therapy. An increase in collagen synthesis and the tensile strength of the tendon has been described in some studies. As such, the local application of physical modalities is still debatable.

Ultrasound-Guided Galvanic Electrolysis Technique (USGET)

In recent years, the ultrasound-guided galvanic electrolysis technique (USGET) has been described in the scientific literature as giving the good results as seen yielded in the treatment of refractory tendon injuries in comparison to other previous conservative treatments (Fig. 34.6) [48].

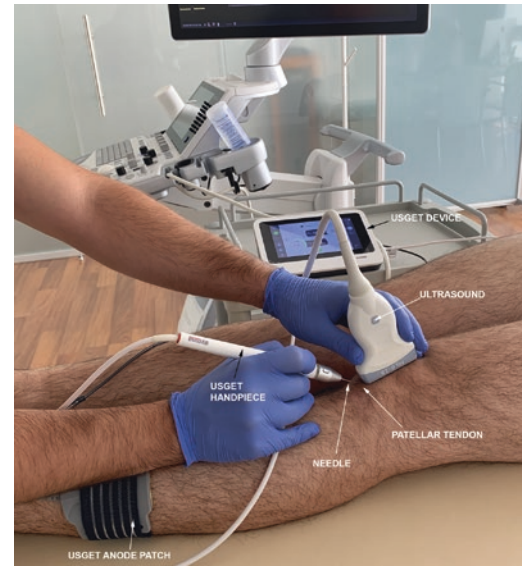


Fig. 34.6 Ultrasound-guided galvanic electrolysis technique (USGET) on patellar tendon. Use of ultrasound is mandatory to ensure the correct application

USGET is a nonthermal electrochemical ablation with a cathodic flow to the clinical focus of tendon degeneration. This treatment produces a dissociation of water, salts, and amino acids in the extracellular matrix that creates new molecules through ionic instability. The organic reaction, which occurs in the tissue around the cathodic needle causes a localized inflammation in the region dealt with. It produces an immediate activation of an inflammatory response and overexpression of the activated gamma receptor for peroxisome proliferation (PPAR-gamma). Furthermore, it acts to inhibit the action of IL-1, TNF, and COX-2, mechanisms of tendon degeneration through the direct inhibitory action of factor NFKB that facilitates phagocytosis and tendon regeneration [49].

Extracorporeal Shock Wave Therapy

An ESWT session consists of the application of shock waves, which are sonic pulses generating high stress forces in tissue. This modality is better known as a successful treatment method for urolithiasis. The analgesic process, the dissolution of calcific deposits and the stimulation of a

tissue regeneration process are the known mechanisms of action of this therapy and positive results with its use in patellar tendinopathy is supported by some studies [50]. The efficacy of ESWT was recently demonstrated in a randomized, double-blind, placebo-controlled trial of the short-term management of chronic patellar tendinopathy [50]. Further studies seem justified to clarify the contradictory results in other insertional tendinopathies and evaluate the long-term effects and the relative effectiveness of ESWT for patellar tendinopathy compared with other therapeutic approaches.

Rehabilitation

Due to heterogeneity in every single step of the diagnosis, therapy, patient selection, program design, and the results relative to the success rate are varied [51]. There is no strong evidence that one precise physical therapy program is superior to others. Still, it is true that rehabilitation of the afflicted muscle tendon is the cornerstone of tendinopathy management. Mostly strength training, especially eccentric exercise training, is becoming the key element in the treatment of chronic tendinopathy. Unfortunately, most of the studies are of Achilles tendinopathy.

The mechanisms through which eccentric exercise can alter pain in chronic tendinopathy remain still unclear. There are some in vivo studies that show increased metabolic activity and the increased formation of collagen type I in response to acute exercise of peritendinous tissue [52]. Therefore, it is scientifically impossible to say that one exercise program is superior to another in the treatment of patellar tendinopathy.

34.3 Orthobiologics in Management of Achilles and Patellar Tendinopathy

34.3.1 Achilles Tendinopathy

34.3.1.1 Growth Factors

Growth factors like the transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF-I) are signal molecules involved in the process of proliferation, differentiation, cell chemotaxis, and synthesis of the extracellular matrix. These factors are produced by tenocytes and white blood cells and are released by platelets during the process of degranulation. In the case of a tendon injury, numerous growth factors are involved in the activation and regulation of the cellular responses [53].

34.3.1.2 Transforming Growth Factor–β

TGF-β1 regulates cellular migration and proliferation and can increase the synthesis of collagen type I and III in tendon-derived cells. Moreover, TGF-β1 is overexpressed in tendon in the early postinjury period. Promising results have been obtained using TGF- β1 complementary DNA-transduced BMSCs grafts, injections of TGF-β, and delivery of TGF-β by adenovirus-modified muscle grafts in rat Achilles tendon models [54, 55].

Maeda et al. in 2011 [56] showed that the interruption of tendon continuity in an acute injury can cause a loss of tensile loading, resulting in the destabilization of the extracellular matrix and releasing excessively high levels of active TGF-β that lead to tenocyte death. Jorgenses and Katzel demonstrated, in an Achilles tendon model, that mannose-6-phosphate can reduce latent TGF-β activation, which results in an increase in elastin production and increased strain and peak stress failure [57, 58]. Recently, Potter et al. evaluated the role of TGF-β1 in regulating tendon extracellular matrix after acute exercise in rats. That work showed that TGF-β1 signaling is necessary for the regulation of tendon cross-link formation as well as collagen and lysyl oxidase gene transcription in an exercise-dependent manner. Target therapy with TGF-β can increase the mechanical strength of the healing Achilles tendon through the regulation of collagen synthesis, upregulation of cross-link formation, and enhanced matrix remodeling [59].

34.3.1.3 Vascular Endothelial Growth Factor

VEGF-mRNA plays a key role in neovascularization around the repair site. In fact, in vitro studies showed an increased peak at days 7–10 but

returned to baseline by day 14 [59]. In an Achilles tendon model, VEGF gene therapy increased TGF-β gene expression, and exogenous VEGF appears to increase tensile strength [60].

Recently, Tempfer et al. stopped VEGF-A signaling using a local injection of Bevacizumab in a rat model with a complete Achilles tendon rupture. After the treatment, angiogenesis was found to be significantly reduced in the Bevacizumab-treated repair tissue. It was accompanied by significantly a reduced cross-sectional area, improved matrix organization, increased stiffness and in Young's modulus, and maximum load and stress [61, 62].

34.3.1.4 Platelet-Derived Growth Factor

PDGF is a basic protein composed of two subunits, an A and a B chain, that exist in three different isoforms (PDGF-AA, PDGF-BB, and PDGF-AB). Each isoform acts as a chemotactic agent during inflammation and helps to increase type I collagen synthesis and induce TGF-β1 expression and IGF-I [63]. An in vitro study demonstrated that the addition of exogenous PDGF increases the expression of type I collagen of the tenocytes.

Thomopoulos showed, in vivo, that a sustained delivery of PDGF-BB via a fibrin matrix led to an increase in cell density, cell proliferation, and type I collagen mRNA expression. Additionally, a fibrin/heparin delivery system demonstrated that PDGF-BB improved tendon function but not tendon structure [64, 65].

34.3.1.5 Insulin-Like Growth Factor

IGF-I is one of the three single-chain polypeptides belonging to the IGF family (IGF-I, IGF-II, and insulin). The expression of this molecule increases during wound healing, and its absence is thought to impair dermal repair [66]. Kurtz reported promising results using IGF-I to increase the rate of healing in the transected rat Achilles tendon [67]. Following transection, each tendon was treated with 25 mg of a recombinant variant form of IGF-I. It showed a positive effect on healing within 24 h after the transection and addition of IGF-I. This effect continued up until the tenth and last measurement on day 15.

34.3.1.6 Platelet-Rich Plasma

Platelet-rich plasma (PRP) is the plasma fraction of blood containing concentrated platelets and white blood cells. Due to its autologous nature, PRP is inherent, safe, and provides a natural conductive scaffold containing several growth factors [53].

A new classification regarding the contents and the role of different PRP was published in 2009 [68]. The classification separates the products in accordance with the cell's content (mostly leukocytes) and the fibrin architecture.

PRP was divided into four main families:

- Pure platelet-rich plasma, or leukocyte-poor platelet-rich plasma, is a preparation without leukocytes and with a low-density fibrin network after activation. It can be used as a liquid solution or in an activated gel form. The gel form is often used during surgery and can be injected. Many methods of preparation exist, particularly using cell separators (continuous flow plasmapheresis) even though this method is too involved to be used easily in daily practice.
- Leukocyte and platelet-rich plasma is a preparation with leukocytes and with a low-density fibrin network after activation. It can be used as a liquid solution or in an activated gel form. Most commercial systems belong to this family, and several protocols have been developed in the last few years. It requires the use of specific kits that allow for minimum handling of the blood samples and maximum standardization of the preparations.
- Pure platelet-rich fibrin, or leukocyte-poor platelet-rich fibrin, is a preparation without leukocytes and with a high-density fibrin network. This product only exists in a strongly activated gel form and cannot be injected or used like traditional fibrin glues. However, it can be handled like a real solid material for other applications because of its strong fibrin matrix. Its main inconvenience remains its cost and relative complexity in comparison to the other forms of platelet-rich fibrin.
- Leukocyte and platelet-rich fibrin products are preparations with leukocytes and with a high-density fibrin network. These products only

exist in a strongly activated gel form and cannot be injected or used like traditional fibrin glues. However, because of their strong fibrin matrix, they can be handled like a real solid material for other applications.

The clinical use of PRP in Achilles tendinopathies is still debated and the current literature is conflicting. A review published in 2018 by Lin et al. compared the effectiveness of autologous blood-derived product (ABP) injection with that of a placebo (sham injection or no injection or physiotherapy alone) in patients with Achilles tendinopathy [69]. A total of seven articles were included. The ABP injection and placebo revealed equal effectiveness in the Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A) improvement score at 4–6, 12, 24, and 48 weeks. In a meta-regression, there was no association between the change in the VISA-A score and duration of symptoms at 4–6 weeks (short term), 12 weeks (medium term), and 24 weeks (long term). The authors concluded that ABP injection was not more effective than a placebo in Achilles tendinopathy and that no association was found between the therapeutic effects and duration of symptoms [69].

Filardo et al. [70] analyzed four papers dealing with the use of PRP for Achilles tendon ruptures that highlighted that no beneficial effects of PRP administration during and/or immediately after tendon suturing were reported. It is worth noting that Schepull [71] hypothesized that PRP addition could even be detrimental in tissue healing because no biomechanical advantages and lower performance were reported in PRP patients with respect to the "suture-alone" group.

34.3.1.7 Adipose-Derived Stem Cells

In recent years, adipose-derived stem cells (ADSCs) have been the focus of several clinical and preclinical studies on tendon regeneration. The growing interest in them is mainly due to their high numbers in the human body (ADSCs are 5% of the nucleated cells in adipose tissue), the simplicity of harvesting and their rapid expansion and high proliferative potential [72, 73]. These cells can differentiate into different lines, such as adipocytes, chondrocytes, osteoblasts, hepatocytes, pancreatic cells, muscle cells, and neuron-like cells both in vitro and in vivo [72].

In tendon tissue, ADSCs can enhance the gene expression profile of the cartilage oligomeric matrix protein (COMP), an extracellular matrix protein. It is present primarily in cartilage. COMP is crucial to the binding and organization of collagen fibrils [72]. The use of ADSCs for the treatment of pathologic tendon conditions has been widely investigated in experimental animal models. The results have been encouraging. ADSCs can induce tenocyte differentiation, overexpressing the bone morphogenetic protein 12 gene [73].

Usuelli et al. first described the use of ADSCs to treat human non-insertional Achilles tendinopathy in comparison to PRP injections (28 patients in ADSCs group and 28 in PRP group). At final follow-up, there were no clinical (Visual Analog Scale pain, the VISA-A, the American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Score, and the Short Form-36 [SF-36]) or imaging (MRI and ultrasonography -US) differences between the two groups. Neither were any serious side effects nor adverse events observed during the follow-up period. Both treatments were effective, but patients treated with ADSCs obtained faster results and they should be taken into consideration for patients who require an earlier return to daily activities [74].

Moreover, a significant increase in tendon thickness, measured using magnetic resonance ($P = 0.013$) and ultrasound ($P = 0.012$) and a power Doppler signal ($P = 0.027$), was seen. There was no significant difference between the pre- and posttreatment cross-sectional area, signal intensity, and echotexture ($P > 0.217$). None of the pretreatment parameters was a predictor of treatment outcome ($P > 0.104$). There was excellent agreement for tendon thickness measurements between magnetic resonance and ultrasound (intraclass correlation coefficient = 0.986) [75].

34.3.1.8 Peripheral Blood Mononuclear Cells

Recently, several studies highlighted peripheral blood mononuclear cells (PBMNCs) (mono-

cytes/macrophages and lymphocytes) as a new generation of regenerative autologous cell concentrates as monocytes and macrophages promote tissue repair and regeneration [76].

In fact, monocytes and macrophages have a degree of plasticity comparable to that of marrow stem cells. They also have multiple action mechanisms [28], an angiogenic action thanks to the release of VEGF [77], a regenerative action through the release of growth factors, cytokines, and messenger molecules [78]. Furthermore, a recent study affirmed that osteo-inductive action is characteristic of monocyte populations rather than stem cells populations. They can activate resident MSCs through a paracrine effect and the release of exosomes [79]. They also have an anti-inflammatory and immune-modulatory action through the polarization of macrophages M1 in M2 [32] in injured tissues with a healing delay. Most of the macrophages are activated in the M1 state (degenerative inflammatory), whereas polarization in M2 (macrophages activated in anti-inflammatory regenerative state) allows for the regeneration of the injured or inflamed tissues.

Sugg et al. [80] performed a tenotomy and repair of the Achilles tendons of adult rats and evaluated changes in the macrophage phenotype (M1/M2) and related genes of both the extracellular matrix and the epithelial-mesenchymal transition pathways for a period of 4 weeks. The results suggest that changes in the phenotype of macrophages and the activation of epithelial-mesenchymal transition-related programs probably contribute first to the degradation of the injured tissue and then to the subsequent repair of the tendon tissue. The results also confirmed that the sequential transition between the M1 and M2 phenotypes supports the dual function of macrophages in the degradation and repair of damaged tendon tissue.

To date, no clinical studies have been reported in the literature. However, autologous cell therapy with injection monocytes could represent new perspectives. Moreover, it is not very invasive and has a solid scientific rationale in the treatment of tendinopathy. Moreover, the use of PBMNCs could be used as a complement during surgical procedures as biological augmentation to enhance the healing process, improve surgical outcomes, and reduce complication rates.

34.3.1.9 Bone Marrow Aspirate Concentrate

BMAC is the result of different density gradient centrifugations of bone marrow aspirated from the iliac crest [81]. This aspirate has a concentration of nucleated cells of less than 0.01%, and its role is to deliver MSCs to the injured tendon [82]. This procedure concentrates the mononucleated cells, hematopoietic stem cells, and platelets in one layer and the red blood cells in another. The efficacy of cells contained in BMAC is to modulate the healing response of the pathologic tendon by controlling inflammation, reducing fibrosis, and recruiting other cells, including tenocytes and MSCs [83].

Broese demonstrated, in vitro, an increase in cell proliferation in Achilles tendon scaffolds seeded with bone marrow aspirate [84]. Stein first reported outcomes in patients with sport-related Achilles tendon ruptures treated via open repair augmented with BMAC injection. A total of 27 patients treated with open repair and BMAC injection were reevaluated at a mean follow-up of 29.7 months and no re-ruptures were noted. Of those patients, 92% returned to their sport at 5.9 months. No soft tissue masses, bone formation, or tumors were observed in the operated extremity [85].

34.3.1.10 Scaffolds

Several natural and synthetic materials have recently been analyzed with the aim to promote cellular growth and provide mechanical support for tendon repair. The ideal scaffold for the Achilles tendon should allow a natural and fast bridging of tendinous defects as well as organized collagen-rich tissue with complete incorporation of the material within 8 weeks, returning functionality to the same. Moreover, the scaffold should release chemotactic factors to promote the recruitment of progenitor cells [53, 86].

Polyhydroxyalkanoates is a material that possesses several of the above qualities. It is part of

the family of biopolymers consisting of polyesters produced in nature by microorganisms to store energy and carbon. These materials, poly-3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHHx) in particular, are compatible with many mesenchyme-derived cell types and have adaptable mechanical properties along with delayed biodegradability [87]. A study by Webb and colleagues reported how tendon repair using a PHBHHx scaffold was mechanically and histologically superior in comparison to controls [87].

Another type of scaffold involves the use of decellularized tendon tissue, which maintains the native characteristics and preserves more than 90% of the proteoglycans and growth factors. In vitro, the decellularized tendon slices were able to facilitate repopulation and the attachment of fibroblasts. Farnebo et al. [88], analyzing the use of decellularized grafts in rats, demonstrated an enhancement of the mechanical properties and a reduced immune response.

Decellularized porcine tendon can also be recellularized with human tenocytes [89]. An acellular human dermal allograft (GraftJacket; Wright Medical Technology, Inc., Arlington, TN, USA) reported significant improvement in mechanical strength and stiffness in biomechanical tests. In in vivo studies, patients treated with GraftJacket showed a desirable return-to-activity time without complications [90]. Recently, interest has also increased around xenografts. They seem to improve tendon strength if compared with isolated repair. The most used tissue is porcine small intestinal submucosa (SIS) [91]. Preclinical studies reported on the ability of SIS to remodel the tendon. SIS retains several growth factors, including VEGF, TGF- β, and fibroblast growth factors. They likely contribute to the behavior and migration of cells into the scaffold [48, 49]. Moreover, SIS is subject to a rapid degradation, with 60% of the mass lost after 30 days and complete degradation within 90 days. After complete degradation, the extracellular matrix looks very similar to native tissue in terms of vascularity and organization. A strength of SIS is its ability to recruit marrow-derived cells involved in the remodeling and repair process [92].

34.3.1.11 FARG (Foot and Ankle Reconstruction Group) Algorithm for Use of Biologics for Achilles Tendinopathy

We created an algorithm for the use of biologics for Achilles tendinopathy based on our clinical experience. In developing the FARG (foot and ankle reconstruction group) algorithm for Achilles tendinopathy [53], we were inspired by the MRI-based classification of tendinopathy described by Oloff et al. [93], and we categorized symptomatic patients according to their level of sporting activity:

- sport-active patients (sports activity at least 2 times a week)
- nonathletic patients (sports activity <2 times a week)

The treatment scheme is shown in Table 34.1. It is noteworthy that the major differences concern grades 1 and 2 tendinopathy in which,

Table 34.1 Treatement options in achilles tendinopathy

Achilles tendinopathy grade	Sport-active patients	Nonathletic patients
Grade 0: Hypertrophy, with homogeneous signal	Conservative treatment	Conservative treatment
Grade 1: Hypertrophy, with isolated signal changes in <25% of tendon	Biologic treatment[b]	Conservative treatment
Grade 2: Hypertrophy, with signal changes in >1 area, or diffuse changes in >25% of tendon	Stripping[a] + biologic treatment[b]	Biologic treatment
Grade 3: Severe hypertrophy, <50% tendon signal changes, with interstitial tear	Stripping[a] + biologic treatment[b]	Stripping + biologic treatment
Grade 4: Severe thickening, >50% of tendon with abnormal signal, partial tendon tear	FHL transfer ± biologic treatment[b]	FHL transfer ± biologic treatment

[a]Stripping technique as described by Maffulli and colleagues [94]
[b]Authors' preferred biologic treatments are ADSCs and PBMNCs injections

considering the lower functional request, the nonathletic patient can probably benefit more from less-invasive treatments.

To get satisfactory results in the treatment of Achilles tendinopathy with biological treatments, three goals need to be achieved [53]:

1. Identify the most appropriate biological tools
2. Achieve a strong level of evidence
3. Create evidence-based and personalized treatment protocols

In fact, Achilles tendinopathies are a challenge for orthopedic surgeons, particularly so considering the scarce tendency to healing and that patients are often young with a high-functional demand. In recent years, several studies have focused on biologics for the treatment of Achilles tendinopathy with preliminary good to excellent results [53]. Despite the encouraging results, there is still a huge variability in biological treatments and a wide spectrum of techniques and technologies available with no standardized protocols. Combining imaging with clinical features might be the key to arriving at a protocol for the use of biologics for the treatment of Achilles tendinopathy. Considering this, we have described our recently published protocol [53].

34.3.2 Patellar Tendinopathy

34.3.2.1 Platelet-Rich Plasma

The use of PRP for patellar tendinopathy has been reported in 19 papers as reported in the review published by Filardo et al. [70]. All but two PRP were used as a conservative injective treatment for the management of tendinopathy not responsive to other previous therapeutic attempts. All papers performing a surgical procedure were randomized controlled trials (RCTs), whereas only 4 out of 17 papers dealing with conservative management were RCTs.

The studies describing the intraoperative PRP application were authored by De Almeida et al. [95] and Seijas et al. [96], who injected PRP in the patellar tendon gap site after ACL reconstruction. In both trials, the results were in favor of the PRP group. Better pain control was documented in the initial post-op phases [95, 96] and, at the 6-month follow-up. The MRI evaluation also showed better tissue healing at the harvest site after PRP administration [95]. Looking at conservative treatment, the literature showed overall good results, but the heterogeneous therapeutic protocols differ in terms of number of injections performed and time interval between administrations. Some authors performed a single injection. It was followed by a second one in some cases only when a poor clinical outcome was reported, whereas other authors opted for a multiple injection regimen (2 or even 3 injections) ab initio. In most of the published studies, the injection treatment was followed by a rehabilitation program. Two RCTs [95, 96] investigated the correlation between clinical results and the number of PRP administrations, with controversial conclusions. In both studies, 40 patients were included and randomized to receive one or two PRP injection at two-week intervals. Kaux et al. [97] failed to show any significant beneficial effect related to the 2-injection protocol, whereas Zayni et al. [98] documented superior clinical outcome in patients treated with multiple PRP injections. Up to now, the low number of patients evaluated in these trials does not allow for drawing any reliable conclusions on the usefulness of multiple- vs. single-injection protocols. The other published RCTs compared PRP injections versus external shock wave therapy (ESWT) [99] and dry needling [100]. In the study authored by Vetrano et al. [99], 46 patients were randomized to receive either two PRP injections (at 2-week interval) or three weekly sessions of ESWT. The overall results were positive, but the best outcome was obtained in the PRP group. Those in the PRP group experienced more significant pain reduction and greater functional recovery at 6 and 12 months after treatment. In the trial by Dragoo et al. [100], 23 patients were included and randomized to receive a single PRP injection or dry needling alone. The authors documented that, at 12 weeks of follow-up, only the PRP group presented with a statistically significant improvement in pain and functional scores. These differences were not maintained at the final 26-week evaluation when the clinical outcomes

were comparable between groups. However, it was significantly better in both cases than at the basal evaluation. The positive results described in said RCTs were confirmed by lower-quality studies. They reported encouraging results for PRP therapy in all cases.

34.3.2.2 Bone Marrow Aspirate Concentrate

Pascual-Garrido et al. [101] reported on the clinical results of a case series of ultrasound-guided BMAC injection for refractory patella tendinitis unresponsive to nonoperative treatment. Their report included eight patients (four males and four females) aged between 14 and 35 years. The study reported a significant improvement in pain, daily living activity scores, knee-related quality of life, and functional knee scores (International Knee Documentation Committee (IKDC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS)) in seven out of eight patients treated with ultrasound-guided BMAC injection. Seven out of eight patients stated they would have the procedure again and categorized the outcome of their treatment as excellent. In this study, the number of nucleated cells in the BMA was 37×10^3 and it reached to 45×10^3 after concentration.

34.3.2.3 Hyaluronic Acid

High molecular weight hyaluronic acid has been reported to have an anti-inflammatory effect in addition to promoting tendon healing at the bone–tendon interface as well as tissue regeneration [102]. The current literature reports only a level IV study of 50 patients with patellar tendinopathy with no improvement after a minimum 2-month course of nonsurgical treatment. Patients were treated with a mean of two injections of hyaluronic acid and reported positive effects on recovery. High-quality evidence regarding this treatment is still lacking. More studies are needed to determine the efficacy of this treatment option, which remains at an investigational stage.

34.3.2.4 Sclerosing Agents

Neovascularization is a phenomenon that plays a key role in the pathophysiology of patellar tendinopathy. It is present in 60–80% of patients with pain [36]. The aim of sclerosing agents is to inhibit vessel formation and vessel collapse that have already formed and destroy the accompanying vasa nervorum, which has a denervating effect.

Alfredson [103] reported a considerable reduction in pain during activity following an ultrasound-guided injection of a sclerosing agent (5 mg/mL polidocanol) to the paratenon in his study. It indicates that sclerosing agents can reduce pain.

Additionally, Hoksrud et al. [104] administered an ultrasound-guided injection of polidocanol (10 mg/mL) into the paratenon in patients with painful chronic patellar tendinopathy and found a substantial difference in the Victorian Institute of Sport Assessment-P score in the group treated with a sclerosing agent versus a placebo. However, more than one-third of the group treated with sclerosing agents underwent surgery for pain in a subsequent study of the same group with a longer follow-up (44 months) [105]. Therefore, the usefulness of sclerosing agents remains unclear, and the agents still are at an experimental stage.

34.3.2.5 Additional Treatments

Various other treatments have been examined in level I studies. Glyceryl trinitrate delivers nitric oxide, which has exhibited a role in fibroblast proliferation, collagen synthesis, and the contraction of collagen lattices. Macrophage angiogenic activity, which is important for wound healing also depends on nitric oxide synthase, and nitric oxide synthase activity is upregulated in tendinopathy [36].

Steunebrink in 2013 [105] assessed whether continuous topical glyceryl trinitrate treatment (GTN) improved outcomes in patients with chronic patellar tendinopathy when compared to eccentric training alone. Randomized double-blind, placebo-controlled clinical trial comparing a 12-week program of using a GTN or placebo patch in combination with eccentric squats on a decline board. Measurements were performed at baseline, 6, 12, and 24 weeks. The primary outcome measure was the Victorian Institute of Sports

Assessment-Patella (VISA-P) questionnaire. VISA-P scores for both groups improved over the study period to 75.0 ± 16.2 and 80.7 ± 22.1 at 24 weeks. The results showed a significant effect for time ($p < 0.01$) but no effect for treatment × time ($p = 0.80$). The mean visual analogue scores for pain during sports for both groups increased over the study period to 6.6 ± 3 and 7.8 ± 3.1. Those results showed a significant effect for time ($p < 0.01$) but no effect for treatment × time ($p = 0.38$). Patient satisfaction showed no difference between the GTN and placebo groups ($p = 0.25$) after 24 weeks but did show a significant difference over time ($p = 0.01$). Three patients in the GTN group reported some rash.

Stasinopoulos and Warden [106, 107] each conducted a randomized study on the effectiveness of low-intensity pulsed ultrasonography and found that this modality provided no benefit compared with eccentric exercises for the management of patellar tendinopathy. These findings are supported by an earlier study by Giombini et al. [108] that showed that hyperthermia was more effective than low-intensity pulsed ultrasonography for the treatment of patellar tendinopathy. All these modalities remain at an investigational stage and are not recommended for patellar tendinopathy management.

34.4 Surgical Treatments of Achilles and Patellar Tendinopathy

34.4.1 Achilles Tendinopathy

34.4.1.1 Indications for Surgery

There are no absolute indications for surgical treatment in Achilles tendinopathy. Often the pain comes gradually and is first tolerated pretty well. If Achilles tendinopathy makes training impossible or symptoms reoccur after rest, proper conservative treatment surgery can be the last treatment option [109]. If surgery is considered, the decision to operate must be done individually and the operation scheduled for when best suited for the athlete. Often enough, the symptoms have lasted more than 6 months before the operation is performed. It is important to know that conservative management is unsuccessful even in 24–45.5% of patients with Achilles tendinopathy [110, 111].

34.4.1.2 Non-insertional Achilles Tendinopathy

In Achilles tendinopathy, the aim of the surgery is to relieve the pain and stimulate tendon healing. The pain in non-insertional Achilles tendinopathy can have several reasons. For example, peritendinous edema, thickened crural fascia, adhesions, tendinosis, partial tearing, and adherent plantaris tendon can be the reason for non-insertional Achilles tendinopathy. Sometimes there is only one reason for chronic pain and sometimes the pain is developed because of a combination of these factors.

All these reasons may be an indication for operation. Using an open surgical technique, the crural fascia covering the Achilles tendon is opened longitudinally. Kager's triangle is freed on both sides and fibrotic adhesions are removed. A fascial incision is continued proximally. Good hemostasis is very important. Excessive pathological blood neovessels locating ventrally to the Achilles tendon can be cut and cauterized. In tendinosis, longitudinal tenotomies may be needed to remove soft degenerative nodules. Sometimes in tendinosis, the so-called microtenotomy technique with Topaz radiofrequency may be needed as well. In partial Achilles tears, suturing or fascia augmentation may be used to repair the ruptured and scarred area. Pain because of an adherent plantaris tendon is often resolved by doing liberation and a simple resection of part of the plantaris tendon.

34.4.1.3 Insertional Achilles Tendinopathy

Insertional Achilles tendinopathy is a frequent cause of chronic heel pain in athletes [112]. Chronic and disabling symptoms can be a result of the prominence of the posterosuperior corner of the calcaneus and an irritated retrocalcaneal bursa [113]. Sometimes, intratendinous calcifications and a partial insertional tear can also aggravate symptoms [114].

In the operation, the posterosuperior corner of the calcaneus is resected as well as the inflamed retrocalcaneal bursa. Intratendious calcifications are removed. If the insertional tear is large, the tendon may also need suture anchor fixation or even graft reinforcement. The endoscopic technique is increasingly used nowadays for the excision of a prominent calcaneus corner [115].

Postoperative rehabilitation after common Achilles tendinopathy operations

Sutures 10–12 days
First 1–2 weeks limited weightbearing, crutches, elastic bandage allowing light ankle movements
Then gradually increasing weight with help of crutches, important to increase stress for the Achilles tendon and calcaneus using a step-by-step rehabilitation protocol
Aqua training after 3 weeks
Stationary cycling, spinning, and cross trainer after 4–6 weeks
After pain-free cycling, proceed to Alter-G treadmill running and walking
Progressive return to sports-specific exercise without pain, usually 3–6 months

The patients are often encouraged to weight-bear soon after surgery. If there is a big partial tear or augmentation and suturing or suture anchor fixation is needed, then early protection with a cast or orthoses is often required. Then, more careful postoperative rehabilitation is followed.

34.4.1.4 Results of Surgery

The end results following Achilles tendinopathy operations are usually good in general. According to Khan et al. and Traina et al., the overall success rates after surgery were 83.5% in non-insertional tendinopathy and 89.6% in insertional tendinopathy [116, 117]. It is important to note that careful patient selection is an essential factor relating to good surgical results. Moreover, the experience of orthopedic surgeons has its own effect on the result. One needs to see and examine many athletes and tendon problems to be able to determine which disorders require surgery and which ones heal with conservative means.

34.4.1.5 Complications

Using proper surgical techniques and taking potential risk factors (good planning, patient selection, tissue handling, postoperative wound control) into consideration, the number of operative-related complications (infection, hematoma) can be reduced [118]. However, severe complications may also occur like skin necrosis. They call for significant plastic surgery repair to cover skin defects using vascularized graft.

34.4.2 Patellar Tendinopathy

34.4.2.1 Indications for Surgery

Like in Achilles tendinopathy, there are no absolute indications for surgery in patellar tendinopathy. If high-quality conservative treatment has failed and MRI or ultrasound reveals a partial patellar tendon rupture/large tendinosis area (tendinotic nodule) and scar, surgery can be considered.

34.4.2.2 Surgical Technique

There is no consensus as to the optimal surgical technique to use. Surgery can be done using an open procedure via vertical or horizontal incision or by using the arthroscopic technique.

In open surgery, the paratenon is excised and the tendon structure is opened longitudinally so that the tendinotic area can be removed from the posterior side of the proximal patellar tendon. The lower edge of the bony patella is also removed and then flattened [119]. The arthroscopic procedure is also possible in this Jumper's knee operation [119, 120]. Debridement and excision of the pathological tissue is done by shaving and vaporization. The microtenotomy technique with Topaz radiofrequency can also be used.

Sometimes the tendinotic area is more distally located [121]. Intratendinous calcifications can be a reason for the patellar tendinopathy, too.

34.4.2.3 Postoperative Rehabilitation

Very similar postoperative guidelines can be used after patellar tendinopathy surgery like in the Achilles surgery. The patient is encouraged to do light early mobilizations and practice full range-of-motion. It is very important is to achieve vastus medialis activation during early rehabilitation.

34.4.2.4 Results of Surgery

Surgery is not a "quick fix" for patellar tendinopathy. If after failed conservative treatment and the decision to operate has been taken, the surgeon must advise the patient about the possibly long rehabilitation process and told not to be too optimistic about the result [122–124]. Even though the symptomatic benefit is very likely to occur after surgery, the return to sport cannot always be guaranteed. If the previous sport level is achieved, it can take several months and even 1 year in some cases.

34.5 Return to Play After Achilles and Patellar Tendon Injury

In the process of tendon lesion treatment, the diagnostic phase [51] is as important as the therapeutic phase [48]. Of course, making for optimum Return to Play [125] and the subsequent Return to Performance are equally critical.

With the establishment of the Ardent et al. in Return to Play consensus as of 2016 [125], different levels are stratified according to the individual objective of each person in terms of rehabilitation. The goal is common regardless of whether we are talking about a professional athlete, an amateur athlete or just an active person. The aim is to return to the initial levels prior to the injury [126].

At the end of the last century, Alfredson et al. [41] had already proposed a rehabilitation program based on high-load eccentric exercise. In an antithesis to this proposal, heavy-slow resistance training (HSRT) arose [127] and was subsequently advocated for in a relatively review [128]. With a combination of different exercises with eccentric and concentric components along with a progression proposal, the last program proposed by Silbernagel & Crossley was defined [129].

As a result of these programs, a multitude of studies arose that attempted to validate the most appropriate program for a correct rehabilitation. Thus, we find those that compare the Alfredson Program vs the Silberganel Protocol, from which no definitive data was obtained [130]. On the other hand, there are studies in which the Alfredson Program vs HSRT were compared and no conclusive data was obtained from either [131]. Some studies have also been conducted to analyze the differences between concentric and eccentric exercises in the rehabilitation process, but no global consensus was arrived at in it either [132].

Finally, the main idea is defined by the impossibility of determining a unique and effective program. Therefore, the design of a program based on the individual characteristics of each individual (injury, progression, treatment, functional requirements, and expectations) must take precedence.

There is no doubt that eccentric work is not for everyone [133] even though it has been shown to be beneficial in many cases [134]. Similarly, it is worth noting the known beneficial effect of isometric work in the management of pain caused by the injury [135]. Therefore, opting for one or another method would lead to eliminating the possibility, right from the start, of using countless different stimuli in pursuit of a correct recovery. This is even more so the case when we are talking about a process that lasts no less than 12 weeks, thus demonstrating the need to provide constant stimuli.

The readjustment process must have an adequate progression in which the tendon assimilates the different loads gradually. The patient needs demanding situations in which the tendon needs to perform actions similar to the activity to be readapted to in a final phase of the process [136]. In this way, very high force peaks have been seen in actions such as the jump that are also generated in a very short time. Thus, in the final stages, the objective in patellar or Achilles tendinopathies should be to look for actions such as those described.

In addition to the stretching-shortening and velocity cycle, one of the elements that causes the tendon the most stress is the work with eccentric overload. Since its implementation in a NASA program [137], the use of flywheels and conical pulleys has moved to the training field. Although not without reluctance, given the difficulty of its use both from the execution technique and from

Fig. 34.7 Patient during eccentric exercises session. Note the use of isoinertial device. Execution technique and load management controlled by our strength and conditioning coach

the load management, this factor can be easily solved with qualified personnel (Fig. 34.7). The benefits of eccentric work have been demonstrated relative to the improvement in strength and hypertrophy [51, 138]. These two are necessary in tendinopathies when muscular atrophy is a factor [136]. There have been improvements in the implications that it may have on actions in team sports [139] as well as in direction changes [140]. This type of exercise has also proven beneficial for older people, in achieving an improvement in balance and mobility [141], more specifically, in patellar tendinopathies [142] and in terms of injury reduction [143].

All this will not come to fruition without proper planning of the process. For this, it is vital that the tendon regeneration processes as well as the individual characteristics of the case be taken into account. For this, the recording methods of both load management and the rating of perceived exertion (RPE) [144] should be used. In addition, it is fundamental to implement constant pain monitoring.

In conclusion, the importance of designing a program adapted to the individual characteristics of each case is stressed. This will not be possible without a coordinated work team and different competencies in medicine, physiotherapy, psychology, nutrition, and sports sciences.

References

1. Rees JD, Maffulli N, Cook J. Management of tendinopathy. Am J Sports Med. 2009;37(9):1855–67. https://doi.org/10.1177/0363546508324283.
2. Herring SA, Nilson KL. Introduction to overuse injuries. Clin Sports Med. 1987;6(2):225–39.
3. Del Buono A, Battery L, Denaro V, Maccauro G, Maffulli N. Tendinopathy and inflammation: some truths. Int J Immunopathol Pharmacol. 2011;24(1 Suppl 2):45–50.
4. Riley G. Tendinopathy—from basic science to treatment. Nat Clin Pract Rheumatol. 2008;4(2):82–9. https://doi.org/10.1038/ncprheum0700.
5. Dean BJF, Dakin SG, Millar NL, Carr AJ. Review: emerging concepts in the pathogenesis of tendinopathy. Surgeon. 2017;15(6):349–54. https://doi.org/10.1016/j.surge.2017.05.005.
6. Almekinders LC, Temple JD. Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. Med Sci Sports Exerc. 1998;30(8):1183–90.
7. Ruzzini L, Longo UG, Campi S, Maffulli N, Onetti Muda A, Denaro V. Adhesion and collagen production of human tenocytes seeded on degradable poly(urethane urea). Knee Surg Sports Traumatol Arthrosc. 2013;21(8):1834–40. https://doi.org/10.1007/s00167-012-2249-2.
8. Longo UG, Franceschi F, Ruzzini L, Rabitti C, Morini S, Maffulli N, Forriol F, Denaro V. Light microscopic histology of supraspinatus tendon ruptures. Knee Surg Sports Traumatol Arthrosc. 2007;15(11):1390–4.
9. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med. 1999;27(6):393–408.
10. Maffulli N, Longo UG, Maffulli GD, Rabitti C, Khanna A, Denaro V. Marked pathological changes proximal and distal to the site of rupture in acute Achilles tendon ruptures. Knee Surg Sports Traumatol Arthrosc. 2011;19(4):680–7. https://doi.org/10.1007/s00167-010-1193-2.
11. Magnusson SP, Hansen P, Aagaard P, Brønd J, Dyhre-Poulsen P, Bojsen-Moller J, Kjaer M. Differential strain patterns of the human gastrocnemius aponeurosis and free tendon, in vivo. Acta Physiol Scand. 2003;177(2):185–95.
12. Ahmed IM, Lagopoulos M, McConnell P, Soames RW, Sefton GK. Blood supply of the Achilles tendon. J Orthop Res. 1998;16(5):591–6.
13. Wilson AM, Goodship AE. Exercise-induced hyperthermia as a possible mechanism for tendon degeneration. J Biomech. 1994;27(7):899–905.
14. Gibson W, Arendt-Nielsen L, Sessle BJ, Graven-Nielsen T. Glutamate and capsaicin-induced pain, hyperalgesia and modulatory interactions in human tendon tissue. Exp Brain Res. 2009;194(2):173–82. https://doi.org/10.1007/s00221-008-1683-3.

15. Maganaris CN, Narici MV, Almekinders LC, Maffulli N. Biomechanics and pathophysiology of overuse tendon injuries: ideas on insertional tendinopathy. Sports Med. 2004;34(14):1005–17.
16. Magra M, Maffulli N. Genetic aspects of tendinopathy. J Sci Med Sport. 2008;11(3):243–7.
17. Maffulli N, Waterston SW, Squair J, Reaper J, Douglas AS. Changing incidence of Achilles tendon rupture in Scotland: a 15-year study. Clin J Sport Med. 1999;9(3):157–60.
18. Maffulli N, Ewen SW, Waterston SW, Reaper J, Barrass V. Tenocytes from ruptured and tendinopathic Achilles tendons produce greater quantities of type III collagen than tenocytes from normal Achilles tendons. An in vitro model of human tendon healing. Am J Sports Med. 2000;28(4):499–505.
19. Cook JL, Kiss ZS, Khan KM, Purdam CR, Webster KE. Anthropometry, physical performance, and ultrasound patellar tendon abnormality in elite junior basketball players: a cross-sectional study. Br J Sports Med. 2004;38(2):206–9.
20. Longo UG, Petrillo S, Berton A, Spiezia F, Loppini M, Maffulli N, Denaro V. Role of serum fibrinogen levels in patients with rotator cuff tears. Int J Endocrinol. 2014;2014:685820. https://doi.org/10.1155/2014/685820.
21. Ames PR, Longo UG, Denaro V, Maffulli N. Achilles tendon problems: not just an orthopaedic issue. Disabil Rehabil. 2008;30(20–22):1646–50. https://doi.org/10.1080/09638280701785882.
22. Casparian JM, Luchi M, Moffat RE, Hinthorn D. Quinolones and tendon ruptures. South Med J. 2000;93(5):488–91.
23. Ferry ST, Dahners LE, Afshari HM, Weinhold PS. The effects of common anti-inflammatory drugs on the healing rat patellar tendon. Am J Sports Med. 2007;35(8):1326–33.
24. Longo UG, Ronga M, Maffulli N. Achilles tendinopathy. Sports Med Arthrosc Rev. 2018;26(1):16–30. https://doi.org/10.1097/JSA.0000000000000185.
25. Egger AC, Berkowitz MJ. Achilles tendon injuries. Curr Rev Musculoskelet Med. 2017;10(1):72–80. https://doi.org/10.1007/s12178-017-9386-7.
26. Kaufman KR, Brodine SK, Shaffer RA, Johnson CW, Cullison TR. The effect of foot structure and range of motion on musculoskeletal overuse injuries. Am J Sports Med. 1999;27(5):585–93.
27. Leadbetter WB. Cell-matrix response in tendon injury. Clin Sports Med. 1992;11(3):533–78.
28. Gaida JE, Alfredson L, Kiss ZS, Wilson AM, Alfredson H, Cook JL. Dyslipidemia in Achilles tendinopathy is characteristic of insulin resistance. Med Sci Sports Exerc. 2009;41(6):1194–7.
29. Järvinen TA, Kannus P, Paavola M, Järvinen TL, Józsa L, Järvinen M. Achilles tendon injuries. Curr Opin Rheumatol. 2001;13(2):150–5.
30. Chimenti RL, Cychosz CC, Hall MM, Phisitkul P. Current concepts review update: insertional Achilles tendinopathy. Foot Ankle Int. 2017;38(10):1160–9.
31. Hutchison AM, Evans R, Bodger O, Pallister I, Topliss C, Williams P, Vannet N, Morris V, Beard D. What is the best clinical test for Achilles tendinopathy? Foot Ankle Surg. 2013;19(2):112–7.
32. Longo UG, Berton A, Stelitano G, Madaudo C, Perna M, Ciuffreda M, Guarnieri A, Papalia R, Maffulli N, Denaro V. 2017 Marathon of Rome: anthropometry and sport profile in 350 runners and association with Achilles and patellar tendinopathy. Clin J Sport Med. 2018. https://doi.org/10.1097/JSM.0000000000000695.
33. Robinson JM, Cook JL, Purdam C, Visentini PJ, Ross J, Maffulli N, Taunton JE, Khan KM, Victorian Institute Of Sport Tendon Study Group. The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy. Br J Sports Med. 2001;35(5):335–41.
34. van Schie HT, de Vos RJ, de Jonge S, Bakker EM, Heijboer MP, Verhaar JA, Tol JL, Weinans H. Ultrasonographic tissue characterisation of human Achilles tendons: quantification of tendon structure through a novel non-invasive approach. Br J Sports Med. 2010;44(16):1153–9.
35. Hägglund M, Zwerver J, Ekstrand J. Epidemiology of patellar tendinopathy in elite male soccer players. Am J Sports Med. 2011;39(9):1906–11.
36. Figueroa D, Figueroa F, Calvo R. Patellar tendinopathy: diagnosis and treatment. J Am Acad Orthop Surg. 2016;24(12):e184–92.
37. Malliaras P, Cook J, Purdam C, Rio E. Patellar tendinopathy: clinical diagnosis, load management, and advice for challenging case presentations. J Orthop Sports Phys Ther. 2015;45(11):887–98.
38. Maffulli N, Longo UG, Testa V, Oliva F, Capasso G, Denaro V. VISA-P score for patellar tendinopathy in males: adaptation to Italian. Disabil Rehabil. 2008;30(20–22):1621–4.
39. Hoksrud A, Ohberg L, Alfredson H, Bahr R. Color Doppler ultrasound findings in patellar tendinopathy (jumper's knee). Am J Sports Med. 2008;36(9):1813–20.
40. Aström M, Westlin N. No effect of piroxicam on Achilles tendinopathy. A randomized study of 70 patients. Acta Orthop Scand. 1992;63(6):631–4.
41. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. Am J Sports Med. 1998;26(3):360–6.
42. Alfredson H, Ohberg L, Forsgren S. Is vasculoneural ingrowth the cause of pain in chronic Achilles tendinosis? An investigation using ultrasonography and colour Doppler, immunohistochemistry, and diagnostic injections. Knee Surg Sports Traumatol Arthrosc. 2003;11(5):334–8.
43. Lake JE, Ishikawa SN. Conservative treatment of Achilles tendinopathy: emerging techniques. Foot Ankle Clin. 2009;14(4):663–74. https://doi.org/10.1016/j.fcl.2009.07.003.
44. Stergioulas A, Stergioula M, Aarskog R, Lopes-Martins RA, Bjordal JM. Effects of low-level laser

therapy and eccentric exercises in the treatment of recreational athletes with chronic Achilles tendinopathy. Am J Sports Med. 2008;36(5):881–7. https://doi.org/10.1177/0363546507312165.
45. Witvrouw E, Danneels L, Asselman P, D'Have T, Cambier D. Muscle flexibility as a risk factor for developing muscle injuries in male professional soccer players. A prospective study. Am J Sports Med. 2003;31(1):41–6.
46. Schwartz A, Watson JN, Hutchinson MR. Patellar tendinopathy. Sports Health. 2015;7(5):415–20. https://doi.org/10.1177/1941738114568775.
47. Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res. 2008;466(7):1539–54. https://doi.org/10.1007/s11999-008-0260-1.
48. Abat F, Alfredson H, Cucchiarini M, Madry H, Marmotti A, Mouton C, Oliveira JM, Pereira H, Peretti GM, Spang C, Stephen J, van Bergen CJA, de Girolamo L. Current trends in tendinopathy: consensus of the ESSKA basic science committee. Part II: treatment options. J Exp Orthop. 2018;5(1):38. https://doi.org/10.1186/s40634-018-0145-5.
49. Abat F, Valles SL, Gelber PE, Polidori F, Stitik TP, García-Herreros S, Monllau JC, Sanchez-Ibánez JM. Molecular repair mechanisms using the intratissue percutaneous electrolysis technique in patellar tendonitis. Rev Esp Cir Ortop Traumatol. 2014;58(4):201–5. https://doi.org/10.1016/j.recot.2014.01.002.
50. Liao CD, Xie GM, Tsauo JY, Chen HC, Liou TH. Efficacy of extracorporeal shock wave therapy for knee tendinopathies and other soft tissue disorders: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord. 2018;19(1):278. https://doi.org/10.1186/s12891-018-2204-6.
51. Abat F, Alfredson H, Cucchiarini M, Madry H, Marmotti A, Mouton C, Oliveira JM, Pereira H, Peretti GM, Romero-Rodriguez D, Spang C, Stephen J, van Bergen CJA, de Girolamo L. Current trends in tendinopathy: consensus of the ESSKA basic science committee. Part I: biology, biomechanics, anatomy and an exercise-based approach. J Exp Orthop. 2017;4(1):18. https://doi.org/10.1186/s40634-017-0092-6.
52. Kjaer M, Langberg H, Skovgaard D, Olesen J, Bülow J, Krogsgaard M, Boushel R. In vivo studies of peritendinous tissue in exercise. Scand J Med Sci Sports. 2000;10(6):326–31.
53. Indino C, D'Ambrosi R, Usuelli FG. Biologics in the treatment of Achilles tendon pathologies. Foot Ankle Clin. 2019;24(3):471–93.
54. Hou Y, Mao Z, Wei X, et al. Effects of transforming growth factor-beta1 and vascular endothelial growth factor 165 gene transfer on Achilles tendon healing. Matrix Biol. 2009;28:324–35.
55. Kashiwagi K, Mochizuki Y, Yasunaga Y, et al. Effects of transforming growth factor-beta 1 on the early stages of healing of the Achilles tendon in a rat model. Scand J Plast Reconstr Surg Hand Surg. 2004;38:193–7.
56. Maeda T, Sakabe T, Sunaga A, et al. Conversion of mechanical force into TGFbeta- mediated biochemical signals. Curr Biol. 2011;21:933–41.
57. Jorgensen HG, McLellan SD, Crossan JF, et al. Neutralisation of TGF beta or binding of VLA-4 to fibronectin prevents rat tendon adhesion following transection. Cytokine. 2005;30:195–202.
58. Katzel EB, Wolenski M, Loiselle AE, et al. Impact of Smad3 loss of function on scarring and adhesion formation during tendon healing. J Orthop Res. 2011;29:684–93.
59. Potter RM, Huynh RT, Volper BD, et al. Impact of TGF-b inhibition during acute exercise on Achilles tendon extracellular matrix. Am J Physiol Regul Integr Comp Physiol. 2017;312:R157–64.
60. Boyer MI, Watson JT, Lou J, et al. Quantitative variation in vascular endothelial growth factor mRNA expression during early flexor tendon healing: an investigation in a canine model. J Orthop Res. 2001;19:869–72.
61. Zhang F, Liu H, Stile F, et al. Effect of vascular endothelial growth factor on rat Achilles tendon healing. Plast Reconstr Surg. 2003;112:1613–9.
62. Tempfer H, Kaser-Eichberger A, Lehner C, et al. Bevacizumab improves Achilles tendon repair in a rat model. Cell Physiol Biochem. 2018;46:1148–58.
63. Wurgler-Hauri CC, Dourte LM, Baradet TC, et al. Temporal expression of 8 growth factors in tendon-to-bone healing in a rat supraspinatus model. J Shoulder Elbow Surg. 2007;16:S198–203.
64. Thomopoulos S, Zaegel M, Das R, et al. PDGF-BB released in tendon repair using a novel delivery system promotes cell proliferation and collagen remodeling. J Orthop Res. 2007;25:1358–68.
65. Thomopoulos S, Das R, Silva MJ, et al. Enhanced flexor tendon healing through controlled delivery of PDGF-BB. J Orthop Res. 2009;27:1209–15.
66. Chetty A, Cao GJ, Nielsen HC. Insulin-like growth factor-I signaling mechanisms, type I collagen and alpha smooth muscle actin in human fetal lung fibroblasts. Pediatr Res. 2006;60:389–94.
67. Kurtz CA, Loebig TG, Anderson DD, et al. Insulin-like growth factor I accelerate functional recovery from Achilles tendon injury in a rat model. Am J Sports Med. 1999;27:363–9.
68. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27:158–67.
69. Lin MT, Chiang CF, Wu CH, et al. Meta-analysis comparing autologous blood derived products (including platelet-rich plasma) injection versus placebo in patients with Achilles tendinopathy. Arthroscopy. 2018;34:1966–75.
70. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: results and indications. Knee Surg Sports Traumatol Arthrosc. 2018;26(7):1984–99.
71. Schepull T, Kvist J, Norrman H, et al. Autologous platelets have no effect on the healing of human

Achilles tendon ruptures: a randomized single-blind study. Am J Sports Med. 2011;39:38–47.
72. Longo UG, Lamberti A, Petrillo S, et al. Scaffolds in tendon tissue engineering. Stem Cells Int. 2012;2012:517165.
73. Usuelli FG, D'Ambrosi R, Maccario C, et al. Adipose-derived stem cells in orthopaedic pathologies. Br Med Bull. 2017;124:31–54.
74. Usuelli FG, Grassi M, Maccario C, Vigano' M, Lanfranchi L, Alfieri Montrasio U, de Girolamo L. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up. Knee Surg Sports Traumatol Arthrosc. 2018;26(7):2000–10.
75. Albano D, Messina C, Usuelli FG, De Girolamo L, Grassi M, Maccario C, Bignotti B, Tagliafico A, Sconfienza LM. Magnetic resonance and ultrasound in Achilles tendinopathy: predictive role and response assessment to platelet-rich plasma and adipose-derived stromal vascular fraction injection. Eur J Radiol. 2017;95:130–5.
76. Ogle ME, Segar CE, Sridhar S, et al. Monocytes and macrophages in tissue repair: implications for immunoregenerative biomaterial design. Exp Biol Med (Maywood). 2016;241:1084–97.
77. Barbeck M, Unger RE, Booms P, et al. Monocyte preseeding leads to an increased implant bed vascularization of biphasic calcium phosphate bone substitutes via vessel maturation. J Biomed Mater Res A. 2016;104:2928–35.
78. Caplan AI. New era of cell-based orthopedic therapies. Tissue Eng Part B Rev. 2009;15:195–200.
79. Henrich D, Seebach C, Verboket R, et al. The osteoinductive activity of bone-marrow-derived mononuclear cells resides within the CD141 population and is independent of the CD341 population. Eur Cell Mater. 2018;35:165–77.
80. Sugg KB, Lubardic J, Gumucio JP, et al. Changes in macrophage phenotype and induction of epithelial-to-mesenchymal transition genes following acute Achilles tenotomy and repair. J Orthop Res. 2014;32:944–51.
81. Salamanna F, Contartese D, Nicoli Aldini N, et al. Bone marrow aspirate clot: a technical complication or a smart approach for musculoskeletal tissue regeneration? J Cell Physiol. 2018;233:2723–32.
82. Hegde V, Shonuga O, Ellis S, et al. A prospective comparison of 3 approved systems for autologous bone marrow concentration demonstrated nonequivalency in progenitor cell number and concentration. J Orthop Trauma. 2014;28:591–8.
83. Imam MA, Holton J, Horriat S, et al. A systematic review of the concept and clinical applications of bone marrow aspirate concentrate in tendon pathology. SICOT J. 2017;3:58.
84. Broese M, Toma I, Haasper C, et al. Seeding a human tendon matrix with bone marrow aspirates compared to previously isolated hBMSCs—an in vitro study. Technol Health Care. 2011;19:469–79.
85. Stein BE, Stroh DA, Schon LC. Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation. Int Orthop. 2015;39:901–5.
86. D'Ambrosi R, Ragone V, Comaschi G, Usuelli FG, Ursino N. Retears and complication rates after arthroscopic rotator cuff repair with scaffolds: a systematic review. Cell Tissue Bank. 2019;20(1):1–10.
87. Webb WR, Dale TP, Lomas AJ, et al. The application of poly (3-hydroxybutyrateco- 3-hydroxyhexanoate) scaffolds for tendon repair in the rat model. Biomaterials. 2013;34:6683–94.
88. Farnebo S, Woon CY, Bronstein JA, et al. Decellularized tendon-bone composite grafts for extremity reconstruction: an experimental study. Plast Reconstr Surg. 2014;133:79–89.
89. Lohan A, Stoll C, Albrecht M, et al. Human hamstring tenocytes survive when seeded into a decellularized porcine Achilles tendon extracellular matrix. Connect Tissue Res. 2013;54:305–12.
90. Lee DK. A preliminary study on the effects of acellular tissue graft augmentation in acute Achilles tendon ruptures. J Foot Ankle Surg. 2008;47:8–12.
91. Wisbeck JM, Parks BG, Schon LC. Xenograft scaffold full-wrap reinforcement of Krackow Achilles tendon repair. Orthopedics. 2012;35:e331–4.
92. Zantop T, Gilbert TW, Yoder MC, et al. Extracellular matrix scaffolds are repopulated by bone marrow-derived cells in a mouse model of Achilles tendon reconstruction. J Orthop Res. 2006;24:1299–309.
93. Oloff L, Elmi E, Nelson J, et al. Retrospective analysis of the effectiveness of platelet-rich plasma in the treatment of Achilles tendinopathy: pretreatment and posttreatment correlation of magnetic resonance imaging and clinical assessment. Foot Ankle Spec. 2015;8:490–7.
94. Longo UG, Ramamurthy C, Denaro V, et al. Minimally invasive stripping for chronic Achilles tendinopathy. Disabil Rehabil. 2008;30:1709–13.
95. de Almeida AM, Demange MK, Sobrado MF, Rodrigues MB, Pedrinelli A, Hernandez AJ. Patellar tendon healing with platelet-rich plasma: a prospective randomized controlled trial. Am J Sports Med. 2012;40(6):1282–8. https://doi.org/10.1177/0363546512441344.
96. Seijas R, Cuscó X, Sallent A, Serra I, Ares O, Cugat R. Pain in donor site after BTB-ACL reconstruction with PRGF: a randomized trial. Arch Orthop Trauma Surg. 2016;136(6):829–35. https://doi.org/10.1007/s00402-016-2458-0.
97. Kaux JF, Croisier JL, Forthomme B, Le Goff C, Buhler F, Savanier B, Delcour S, Gothot A, Crielaard JM. Using platelet-rich plasma to treat jumper's knees: exploring the effect of a second closely-timed infiltration. J Sci Med Sport. 2016;19(3):200–4. https://doi.org/10.1016/j.jsams.2015.03.006.
98. Zayni R, Thaunat M, Fayard JM, Hager JP, Carrillon Y, Clechet J, Gadea F, Archbold P, Sonnery Cottet B. Platelet-rich plasma as a treatment for chronic patellar tendinopathy: comparison of a single versus

two consecutive injections. Muscles Ligaments Tendons J. 2015;5(2):92–8.
99. Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. Am J Sports Med. 2013;41(4):795–803. https://doi.org/10.1177/0363546513475345.
100. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. Am J Sports Med. 2014;42(3):610–8. https://doi.org/10.1177/0363546513518416.
101. Pascual-Garrido C, Rolón A, Makino A. Treatment of chronic patellar tendinopathy with autologous bone marrow stem cells: a 5-year-followup. Stem Cells Int. 2012;2012:953510. https://doi.org/10.1155/2012/953510.
102. Muneta T, Koga H, Ju YJ, Mochizuki T, Sekiya I. Hyaluronan injection therapy for athletic patients with patellar tendinopathy. J Orthop Sci. 2012;17(4):425–31.
103. Hoksrud A, Ohberg L, Alfredson H, Bahr R. Ultrasound-guided sclerosis of neovessels in painful chronic patellar tendinopathy: a randomized controlled trial. Am J Sports Med. 2006;34(11):1738–46.
104. Hoksrud A, Bahr R. Ultrasound-guided sclerosing treatment in patients with patellar tendinopathy (jumper's knee): 44-month follow-up. Am J Sports Med. 2011;39(11):2377–80.
105. Steunebrink M, Zwerver J, Brandsema R, Groenenboom P, van den Akker-Scheek I, Weir A. Topical glyceryl trinitrate treatment of chronic patellar tendinopathy: a randomised, double-blind, placebo controlled clinical trial. Br J Sports Med. 2013;47(1):34–9.
106. Stasinopoulos D, Stasinopoulos I. Comparison of effects of exercise programme, pulsed ultrasound and transverse friction in the treatment of chronic patellar tendinopathy. Clin Rehabil. 2004;18(4):347–52.
107. Warden SJ, Metcalf BR, Kiss ZS, et al. Low intensity pulsed ultrasound for chronic patellar tendinopathy: a randomized, double blind, placebo-controlled trial. Rheumatology (Oxford). 2008;47(4):467–71.
108. Giombini A, Di Cesare A, Casciello G, Sorrenti D, Dragoni S, Gabriele P. Hyperthermia at 434 MHz in the treatment of overuse sport tendinopathies: a randomised controlled clinical trial. Int J Sports Med. 2002;23(3):207–11.
109. Kvist M. Achilles tendon injuries in athletes. Sports Med. 1994;18(3):173–201.
110. Paavola M, Kannus P, Paakkala T, Pasanen M, Järvinen M. Long-term prognosis of patients with Achilles tendinopathy. An observational 8-year follow-up study. Am J Sports Med. 2000;28(5):634–42.
111. Kvist H, Kvist M. The operative treatment of chronic calcaneal paratenonitis. J Bone Joint Surg Br. 1980;62(3):353–7.
112. van Dijk CN, van Sterkenburg MN, Wiegerinck JI, Karlsson J, Maffulli N. Terminology for Achilles tendon related disorders. Knee Surg Sports Traumatol Arthrosc. 2011;19(5):835–41.
113. Maffulli N, Saxena A, Wagner E, Torre G. Achilles insertional tendinopathy: state of the art. J ISAKOS. 2019;4:48–57.
114. Johansson KJ, Sarimo JJ, Lempainen LL, Laitala-Leinonen T, Orava SY. Calcific spurs at the insertion of the Achilles tendon: a clinical and histological study. Muscles Ligaments Tendons J. 2013;2(4):273–7.
115. Jerosch J, Schunck J, Sokkar SH. Endoscopic calcaneoplasty (ECP) as a surgical treatment of Haglund's syndrome. Knee Surg Sports Traumatol Arthrosc. 2007;15(7):927–34.
116. Khan WS, Malvankar S, Bhamra JS, Pengas I. Analysing the outcome of surgery for chronic Achilles tendinopathy over the last 50 years. World J Orthop. 2015;6(6):491–7. https://doi.org/10.5312/wjo.v6.i6.491.
117. Traina F, Perna F, Ruffilli A, Mazzotti A, Meliconi R, Berti L, Faldini C. Surgical treatment of insertional Achilles tendinopathy: a systematic review. J Biol Regul Homeost Agents. 2016;30(4 Suppl 1):131–8.
118. Paavola M, Orava S, Leppilahti J, Kannus P, Järvinen M. Chronic Achilles tendon overuse injury: complications after surgical treatment. An analysis of 432 consecutive patients. Am J Sports Med. 2000;28(1):77–82.
119. Lorbach O, Diamantopoulos A, Paessler HH. Arthroscopic resection of the lower patellar pole in patients with chronic patellar tendinosis. Arthroscopy. 2008;24(2):167–73. https://doi.org/10.1016/j.arthro.2007.08.021.
120. Coleman BD, Khan KM, Kiss ZS, Bartlett J, Young DA, Wark JD. Open and arthroscopic patellar tenotomy for chronic patellar tendinopathy. A retrospective outcome study. Victorian Institute of Sport Tendon Study Group. Am J Sports Med. 2000;28(2):183–90.
121. Sarimo J, Sarin J, Orava S, Heikkilä J, Rantanen J, Paavola M, Raatikainen T. Distal patellar tendinosis: an unusual form of jumper's knee. Knee Surg Sports Traumatol Arthrosc. 2007;15(1):54–7.
122. Khan WS, Smart A. Outcome of surgery for chronic patellar tendinopathy: a systematic review. Acta Orthop Belg. 2016;82(3):610–326.
123. Panni AS, Tartarone M, Maffulli N. Patellar tendinopathy in athletes. Outcome of nonoperative and operative management. Am J Sports Med. 2000;28(3):392–7.
124. Testa V, Capasso G, Maffulli N, Bifulco G. Ultrasound-guided percutaneous longitudinal tenotomy for the management of patellar tendinopathy. Med Sci Sports Exerc. 1999;31(11):1509–15.
125. Ardern CL, Glasgow P, Schneiders A, Witvrouw E, Clarsen B, Cools A, Gojanovic B, Griffin S, Khan KM, Moksnes H, Mutch SA, Phillips N, Reurink G, Sadler R, Silbernagel KG, Thorborg K, Wangensteen A, Wilk KE, Bizzini M. 2016 consensus statement on return to sport from the first world congress in sports physical therapy, Bern. Br J Sports Med. 2016;50(14):853–64. https://doi.org/10.1136/bjsports-2016-096278.

126. Habets B, van den Broek AG, Huisstede BMA, Backx FJG, van Cingel REH. Return to sport in athletes with midportion Achilles tendinopathy: a qualitative systematic review regarding definitions and criteria. Sports Med. 2018;48(3):705–23. https://doi.org/10.1007/s40279-017-0833-9.
127. Kongsgaard M, Reitelseder S, Pedersen TG, Holm L, Aagaard P, Kjaer M, Magnusson SP. Region specific patellar tendon hypertrophy in humans following resistance training. Acta Physiol (Oxf). 2007;191(2):111–21.
128. Malliaras P, Barton CJ, Reeves ND, Langberg H. Achilles and patellar tendinopathy loading programmes : a systematic review comparing clinical outcomes and identifying potential mechanisms for effectiveness. Sports Med. 2013;43(4):267–86. https://doi.org/10.1007/s40279-013-0019-z.
129. Silbernagel KG, Crossley KM. A proposed return-to-sport program for patients with midportion Achilles tendinopathy: rationale and implementation. J Orthop Sports Phys Ther. 2015;45(11):876–86. https://doi.org/10.2519/jospt.2015.5885.
130. Habets B, van Cingel REH, Backx FJG, Huisstede BMA. Alfredson versus Silbernagel exercise therapy in chronic midportion Achilles tendinopathy: study protocol for a randomized controlled trial. BMC Musculoskelet Disord. 2017;18(1):296. https://doi.org/10.1186/s12891-017-1656-4.
131. Beyer R, Kongsgaard M, Hougs Kjær B, Øhlenschlæger T, Kjær M, Magnusson SP. Heavy slow resistance versus eccentric training as treatment for Achilles tendinopathy: a randomized controlled trial. Am J Sports Med. 2015;43(7):1704–11. https://doi.org/10.1177/0363546515584760.
132. Couppé C, Svensson RB, Silbernagel KG, Langberg H, Magnusson SP. Eccentric or concentric exercises for the treatment of tendinopathies? J Orthop Sports Phys Ther. 2015;45(11):853–63. https://doi.org/10.2519/jospt.2015.5910.
133. Cook JL, Stasinopoulos D, Brismée JM. Insertional and mid-substance Achilles tendinopathies: eccentric training is not for everyone—updated evidence of non-surgical management. J Man Manip Ther. 2018;26(3):119–22. https://doi.org/10.1080/10669817.2018.1470302.
134. O'Neill S, Watson PJ, Barry S. Why are eccentric exercises effective for Achilles tendinopathy? Int J Sports Phys Ther. 2015;10(4):552–62.
135. Rio E, van Ark M, Docking S, Moseley GL, Kidgell D, Gaida JE, van den Akker-Scheek I, Zwerver J, Cook J. Isometric contractions are more analgesic than isotonic contractions for patellar tendon pain: an in-season randomized clinical trial. Clin J Sport Med. 2017;27(3):253–9. https://doi.org/10.1097/JSM.0000000000000364.
136. Scott A, Docking S, Vicenzino B, Alfredson H, Murphy RJ, Carr AJ, Zwerver J, Lundgreen K, Finlay O, Pollock N, Cook JL, Fearon A, Purdam CR, Hoens A, Rees JD, Goetz TJ, Danielson P. Sports and exercise-related tendinopathies: a review of selected topical issues by participants of the second international scientific tendinopathy symposium (ISTS) Vancouver 2012. Br J Sports Med. 2013;47(9):536–44. https://doi.org/10.1136/bjsports-2013-092329.
137. Berg HE, Tesch PA. Force and power characteristics of a resistive exercise device for use in space. Acta Astronaut. 1998;42(1–8):219–30.
138. Tesch PA, Fernandez-Gonzalo R, Lundberg TR. Clinical applications of iso-inertial, eccentric-overload (YoYo™) resistance exercise. Front Physiol. 2017;8:241. https://doi.org/10.3389/fphys.2017.00241.
139. Gonzalo-Skok O, Tous-Fajardo J, Valero-Campo C, Berzosa C, Bataller AV, Arjol-Serrano JL, Moras G, Mendez-Villanueva A. Eccentric-overload training in team-sport functional performance: constant bilateral vertical versus variable unilateral multidirectional movements. Int J Sports Physiol Perform. 2017;12(7):951–8. https://doi.org/10.1123/ijspp.2016-0251.
140. Núñez FJ, Santalla A, Carrasquila I, Asian JA, Reina JI, Suarez-Arrones LJ. The effects of unilateral and bilateral eccentric overload training on hypertrophy, muscle power and COD performance, and its determinants, in team sport players. PLoS One. 2018;13(3):e0193841. https://doi.org/10.1371/journal.pone.0193841.
141. Sañudo B, González-Navarrete Á, Álvarez-Barbosa F, de Hoyo M, Del Pozo J, Rogers ME. Effect of flywheel resistance training on balance performance in older adults. A randomized controlled trial. J Sports Sci Med. 2019;18(2):344–50.
142. Abat F, Gelber PE, Polidori F, Monllau JC, Sanchez-Ibañez JM. Clinical results after ultrasound-guided intratissue percutaneous electrolysis and eccentric exercise in the treatment of patellar tendinopathy. Knee Surg Sports Traumatol Arthrosc. 2015;23(4):1046–52. https://doi.org/10.1007/s00167-014-2855-2.
143. Gual G, Fort-Vanmeerhaeghe A, Romero-Rodríguez D, Tesch PA. Effects of in-season inertial resistance training with eccentric overload in a sports population at risk for patellar tendinopathy. J Strength Cond Res. 2016;30(7):1834–42. https://doi.org/10.1519/JSC.0000000000001286.
144. Foster C, Florhaug JA, Franklin J, Gottschall L, Hrovatin LA, Parker S, Doleshal P, Dodge C. A new approach to monitoring exercise training. J Strength Cond Res. 2001;15(1):109–15.