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EDITORIAL

WHY THE MULTIDISCIPLINARY RESEARCH IS ESSENTIAL IN ORTHOPEDICS?

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The creation of multidisciplinary teams is essential to modern-day orthopedic research for the advancement of scientific innovations as well as the translation of those novelties into useful clinical practice. The broad expertise of many disciplines is often required to solve complex research or clinical questions. To improve clinical outcomes, the research flow must integrate basic science and clinical science with two translation phases called bench-to-beside and bedside-to-practice translating from basic science to clinical science to clinical outcomes (Fig. 1). To be successful in multidisciplinary research, it is necessary to truly combine knowledge of engineering, physical science with life science expertise (1). This means the researchers from various fields must share the same research objectives and reciprocally influence their conceptual approaches to create personalized medicine at the bedside. This is called "convergence" (1).

Currently clinical orthopaedic research requires researchers to have extensive knowledge of a wide range of disciplines from molecular and cellular biology, tissue engineering to clinical biomechanics to develop new surgical approaches to repair or reconstruct damaged tissues for better functional outcomes of the patient. Young active adults are more prone to tendons and ligaments injuries whereas older adults are more affected by musculoskeletal degenerative diseases such as osteoarthritis and osteoporosis. In those cases, when treatment is necessary, the choice of interventions has immensely advanced over the past few decades. Molecular and cellular biologist brings the knowledge on the regeneration process by establishing the functions of molecules and growth factors (1). Tissue engineer brings new strategies to repair human tissues (e.g. bone, tendon or ligament) by seeding cells in or onto scaffolds to stimulate the rearrangement of the cells

Fig. 1. *Model of the Clinical Research Flow adapted from Sung et al. (2003) (2)*

Key words: orthopedic research, multidisciplinary research, translational research

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to a functional tissue (3). Biomaterial engineer has become increasingly important, as the potentials of new biocompatible materials have increased to treat patients with foreign material as optimized osteosynthesis after trauma and as arthroplasties for joint diseases. Clinical biomechanics brings the biomechanical outcome of treatments during the performance of daily activities of living such as muscle activity and functions, joint loads, torques and kinetics, motion and kinematics, as well as proprioception and kinaesthesia (4). Scientists of all disciplines have begun to break the traditional barriers in an effort to gain multidisciplinary interactions. Such collaboration of clinical and biomedical investigations would produce knowledge and data of unprecedented scope and clarity to resolve complex clinical issues such as the improvement of bony and ligamentous proliferation at the entheses. Once the advancement of the reengineered ACL entheses is successful. The clinical trial in human can begin and then biomechanical assessment can be performed to measure the function of the reengineered ACL.

The combined effort of the life, medical, engineering and physical sciences ensures a better knowledge and understanding of the complex clinical challenges of today. To answer the convoluted clinical challenges, the multidisciplinary researcher team must communicate with a common language meaning that researcher of a discipline is familiar with the scientific concepts and tools of other disciplines. From that point, the multidisciplinary team establishes common goals and approaches requiring a full investment and commitment of all members of the team. To reach the common goals (ie: improve the clinical practice), the multidisciplinary team are responsible to disseminate the research findings from basic science to clinical sciences (bench to bedside) and then from clinical science to clinical practice (bedside to practice). The success for the clinical research continuum depends of several factors such as critical mass of qualified researchers, infrastructure, funding, and common databases. Several multidisciplinary clinical research teams exist in the world but the one develops at Let People Move Research Institute in Arezzo, Italy can be used as an excellent model for the development of a multidisciplinary clinical research team.

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BASIC SCIENCE

ELECTROMECHANICAL DELAY OF THE KNEE FLEXORS MUSCLES AFTERANTERIOR CRUCIATE LIGAMENTS RECONSTRUCTION USING SEMITENDINOSUS TENDON. PRELIMINARY STUDY.

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Increasing in electromechanical delay has been found in patients after ACL reconstruction using both semitendinosus and gracilis tendons. Using only one tendon may improve electromechanical delay results in patients after ACL reconstruction surgery. The purpose of the study is to evaluate electromechanical delay in ACL reconstruction patients after one tendon surgery technique. In particular, in this study, patients undergone the reconstruction surgery using the semitendinosus tendon will be evaluated. An isokinetic dynamometer will be used for the test. After warming up, patients will be ask to perform a maximally explosive isometric. Torques will be measured by the dynamometer while the electrical activity of the semitendinosus and gracilis muscles will be detected using surface EMG. Results of the study will evaluate if one tendons technique may increase electromechanical outcomes for ACL reconstruction patients.

Basic Science Study

One of the greater issue for the anterior cruciate ligament (ACL) reconstruction is the selection of the graft type to be used (1-2). Several research used electromyographic (EMG) data to evaluate how muscular function is altered after this kind of surgery (3). Mechanical response of a muscle data can be combined with muscular activation to evaluate delay between contraction and development of the force/torque of a joint, showing how muscle can provide mechanical response and protection during everyday activities. This delay time is known as electromechanical delay (EMD) (4-6).

Different studies showed that the EMD time is related to mechanical properties of the muscle, shape, size and fiber type and presence of fatigue (7-9). These studies suggested that alteration in EMD should be expected after substantial changes in the muscle structure. In particular after an ACL reconstruction surgery, muscle tendons are harvested and a scar tissue is developed (10). There are contrasting results about different tendons: reconstruction performed with the medial third of the patellar tendon did not alter EMD of the extensors muscles (11), while EMD for the flexor muscles was found altered when semitendinosus (ST) and gracilis tendons were used as graft (12).

In this study EMD for flexor muscles is being investigated after ACL reconstruction surgery using one tendon surgery technique (semitendinosus tendon). The muscle investigates are the superficial

Key words: ACL reconstruction, Electromechanical delay, Semitendinosus tendon.

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muscles of the hamstring group, ST and biceps femoris (BF). Even if BF was not involved in the surgery, it was included in the study because previous research (12) demonstrated that surgery on the other hamstring muscles affected also the BF. It is hypothesized that one tendon technique may improve EMD outcome in patients after ACL reconstruction.

MATERIALS AND METHODS

Participants: 2 male patients with ACL reconstructed using only semitendinosus tendon (mean age, 30±1.5 years; mean body mass 73±9; mean height 1.75±0.07 m) ; 2 healthy males (mean age, 32±1.5 years; mean body mass 75±8; mean height 1.74±0.06 m) with no history of ACL surgery and pain, matching for age, weight, height and level of physical activity. Exclusion criteria for all participants: neurological disorders, symptomatic knee pain, history of knee flexor muscles injuries. KT-1000 arthrometer test for anterior knee instability was performed and participants with a side-to-side differences > 3 mm at the manual maximum test were excluded.

Other patients' requirements were same surgery technique (harvesting only one ST tendon), same surgeon (G.C.).

Experimental protocol

A isokinetic dynamometer was used for the test. All participants sat on the testing chair of the dynamometer and secured with body straps. Knee was flexed at 30° and hip joint at 30° (Fig. 1). After warming up, The dynamometer generated a specific sound that was used as a start and then participants performed a maximally explosive isometric contraction and maintained the contraction for at least 3 seconds. The participants was asked to repeat the maximal contraction 4 times. Participants were asked to relax completely before each contraction.

EMD measurement

Torques was measured and recorded by the dynamometer. Electrical activity of the muscles were detected using wireless surface EMG (BTS freeemg 300) and acquired with a sampling rate of 1000 Hz. A dedicated software was used for data collection and visualization. EMG probes were placed bilaterally on the BF and ST muscles. Electrodes were placed parallel to the muscle fibers and over the dorsomedial muscle bulge at two thirds of the proximodistal thigh length for the ST, and at the dorsolateral side of the thigh at one half of the proximodistal thigh length for the BF (12). A "zero offset" function was performed to establish a zero baseline for all muscles.

The raw EMG signals were firstly band-pass filtered (20-500 Hz) with a Butterworth filter to remove movement artifacts and high frequency noises, full-wave rectified, band and smoothed with a 100-millisecond RMS algorithm.

According with Ristanins et al.(12) EMD was calculated as the time differences between onset of muscular contraction and onset of torque development. The threshold was defined as 3.6 Nm above the baseline level for torque development and 15 μV deviations from baseline level for EMG signal (Fig. 2)

Paired t-test was used to compare left and right side in healthy subjects and not significant differences were found so, as consequence, right side was chosen as representative for control group. Paired t-test between was used to compared reconstructed leg with intact leg within ACL reconstructed group and to compare control group with reconstructed group.

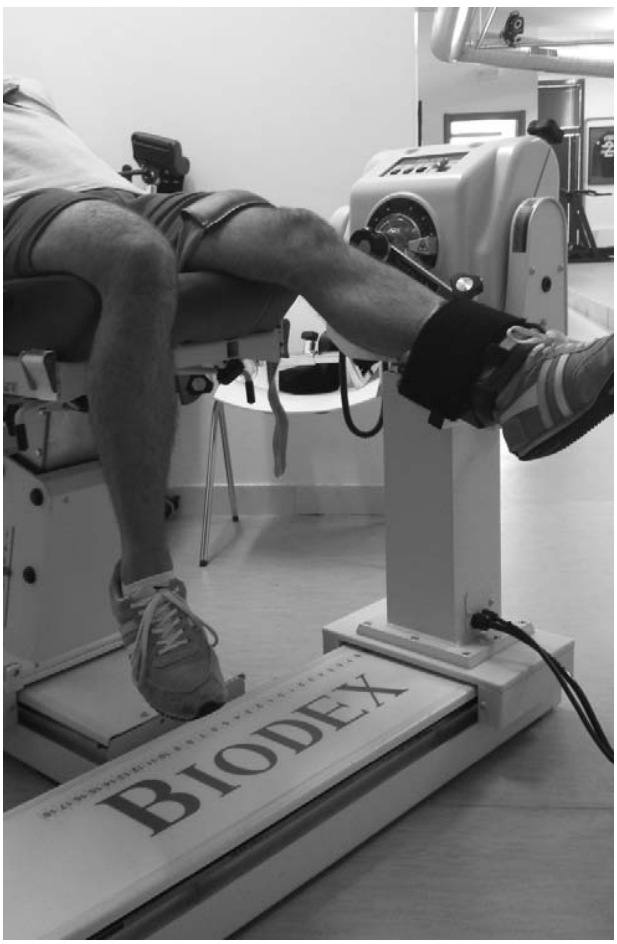

Fig. 1. *Participant on the isokinetic dynamometer.*

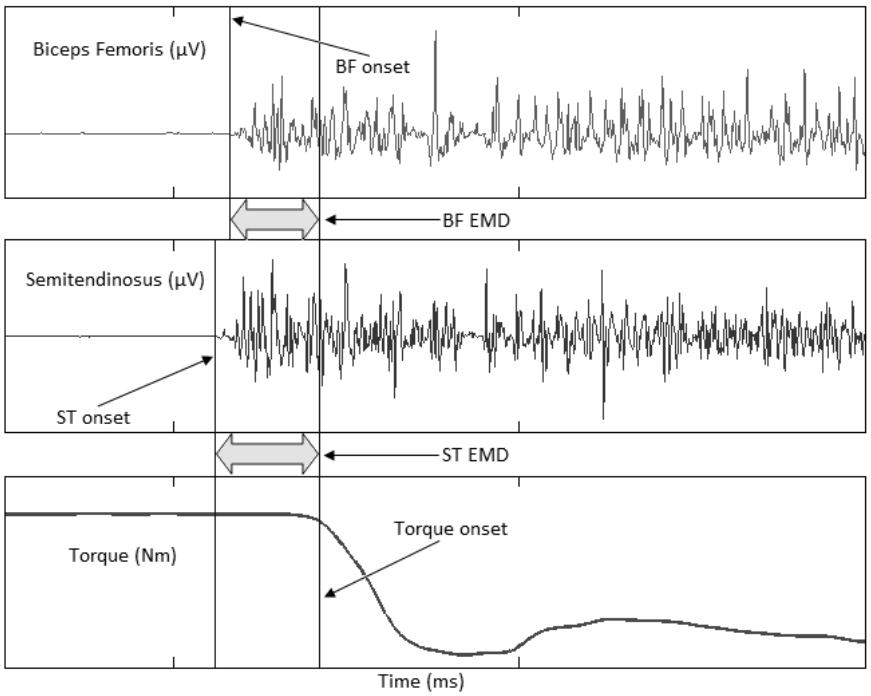

Fig. 2. *Plot of a single trial. EMG of both ST and BF muscles are presented together with the torque generated. Torque and muscles onset are shown.*

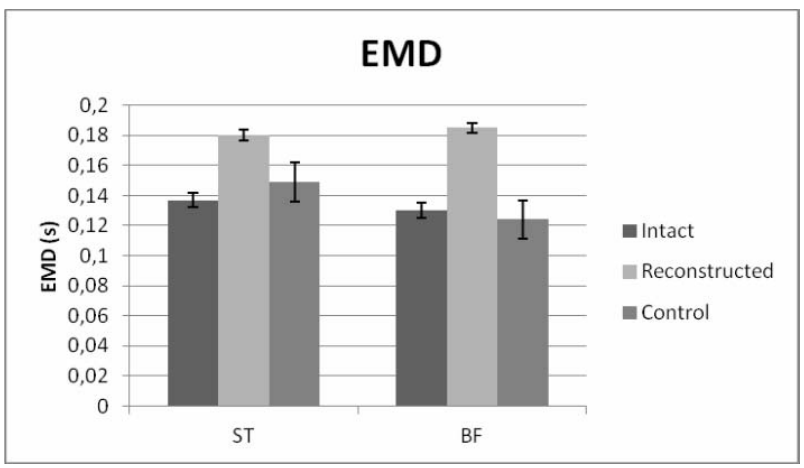

Fig. 3. *Groups mean and standard deviation for the EMD. Differences are significant between intact and reconstructed group and between control and reconstructed group for both muscles.*

RESULTS

Preliminary results of a total of 4 participants are shown in Fig. 3. Significant increasing in EMD ($p.< 0.05$) was found for both ST and BF when comparing the intact leg with the reconstructed leg in the patients group. Similar results were found when reconstructed leg was compared with control group. No significant differences were for both muscles were found when intact leg of the reconstructed group was compared with control group. All results are summarised in Fig. 3.

DISCUSSION

The results of the study seemed to be in contrast with our hypothesis, in particular the EMD seems to be affected by the reconstruction surgery even

if only ST tendons is used. Harvesting only one tendon don't seem to improve outcome for ACL reconstruction patients. Possible explanation for the ST muscle results is that the development of the scar tissue changed the material properties of the harvested muscle resulting in EMD alterations. The alteration in the EMD of the BF may be explained as a sort neuromuscular adaptation: in normal condition ST and BF work synergistically during knee flexion, the delay in the BF muscles may be seen as a strategy to maintain this condition (12).

It is needed to be highlighted that this article reports only preliminary results with 4 participants and the statistical relevance of the study is questionable. There are other limitations of the study as the absence of a specific method for EMD calculation. However results EMD values of this study seems to be similar to values of similar studies present in the literature (6,12).

CONCLUSION

One tendon technique, using only ST tendon, don't seem to improve EMD outcome for ST and BF muscles in patient after ACL reconstruction. However, further participants are needed to give a statistical relevance to the results.

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BASIC SCIENCE

ALTERNATIVE CELL SOURCES FOR TENDON/LIGAMENT ENGINEERING

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Tendons are connective tissues with low healing potential. In order to find new solutions for tendon regeneration, several models have been developed by combining different biomaterials with different cell populations. The choice of an opportune cell population is a fundamental step for engineering a tissue, since the cell source has to be competent for a specific phenotype and it has to be characterized by a minimally invasive approach on the patient for its isolation. According to these characteristics, different cell populations have been investigated for their tenogenic potential, in particular tenocytes, dermal fibroblast and mesenchymal stem cells from adipose tissue (ASCs). In the present study, these populations have been directly compared for their synthetic profile, both in monolayer culture and in combination to a collagen sponge, in order to evaluate if dermal fibroblasts and ASCs can be considered suitable alternative cell sources to native tenocytes for engineering tendons. The obtained data showed that these populations share the same synthetic profile of tenocytes, characterized by the expression of both collagen 1 and collagen 3; moreover, as well as the tenocytes, these cell populations were able to colonize and survive into a collagen sponge that is filled over time by the new matrix produced. In conclusion, dermal fibroblasts and ASCs can be considered suitable cell populations for tendon tissue engineering.

Basic Science

Tendon regeneration is one of the many clinical issues addressed by the field of tissue engineering. This connective tissue is, in fact, characterized by a slow natural healing process (1) that leads to a tissue with inferior structural and functional properties (2). Several studies have been developed by combining different biomaterials with different cell populations (3) in order to generate tissues with tendon-like properties. Among the different natural polymers that have been investigated, collagen derivatives and some polysaccharides have been proposed for the engineering of tendon, since they are among the major components of the tendon extracellular matrix (ECM); in particular, collagen derivatives are hydrophilic polymers that can support cell adhesion and proliferation (4). The optimal cell population to be combined with these biomaterials is represented by tenocytes, the native tendon cells that are directly involved in tendon matrix renewal and organization (5); in particular, tendon-derived stem cells (TDSCs) have been identified as a stem population that is able to differentiate into tenocytes and other different cell

Key words: tendon, stem cells, collagen, regeneration

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types (6-7). However, in a clinical setting, the use of autologous tenocytes or TDSCs would require an invasive approach, leading to a damage to another tendon area; for this reason, different cell populations have been investigated for their ability to assume a tenogenic phenotype or to produce a matrix that is close to that of tendons. Among these alternative populations, mesenchymal stem cells (MSCs) have been suggested as an appropriate cell source since it is represented by cells that are able to differentiate into tenocytes upon stimulation by the in vitro or in vivo environment (8-11). These cells can be isolated from different tissues (12), in particular from the adipose tissue (13-14) without requiring a widely invasive and demolishing approach on the patient (15). These cells (ASCs) resulted to be able to acquire a tenogenic synthetic profile both in vitro and in vivo conditions (16-19), suggesting a new and interesting solution for tendon engineering. Another alternative cell population is represented by dermal fibroblasts: these cells are derived from mesoderm, as well as tenocytes, and have similar cell morphology and extracellular matrix components with respect to native tendon cells (20). According to these characteristics, their potential for tendon engineering have been investigated, demonstrating that they are able to produce a tendon-like matrix (21-22).

According to these findings, this study focused on a direct comparison between these three cell populations (tenocytes, dermal fibroblasts and ACSs), both on a monolayer and 3D culture system represented by a collagen sponge. In particular, this work focused on their synthetic profile in terms of collagen 1 and 3 production, in order to evaluate if dermal fibroblasts and ACSs can be considered suitable cell populations to be combined with a collagenic scaffold for tendon tissue engineering.

MATERIALS AND METHODS

Study design

Tendons, dermis and adipose tissue were harvested from adult pigs and processed for cell isolation. The different cell populations were expanded in vitro and analyzed for actin, collagen 1 and 3 expression by immunofluorescent staining. Cells were also expanded in vitro for several passages and then seeded onto collagen sponges; the cell-seeded scaffolds were then cultured in vitro for 7 and 14 days in order to allow them to mature into tissues with tendon-like properties. Histological and immunofluorescent analyses were performed in order to evaluate the contribute of the different cell populations in terms of tissue morphology and matrix deposition.

Cell culture

Dermal fibroblasts and tenocytes were isolated respectively from swine dermis and Achilles tendons. Briefly, dermis and tendons were aseptically harvested from infant (10kg) hybrid (Landrace x Large White) pigs and washed in sterile PBS (Phosphate Buffered Saline) (Celbio, Italy), supplemented with 50 μg/ml of gentamicin (Lonza, Italy), 0.5 μg/ml of amphotericin B (Lonza, Italy), 100 U/ml of Penicillin/ Streptomycin solution (Lonza, Italy); after three washes, samples were finely minced and digested in DMEM High Glucose medium (Celbio, Italy) containing 0.1% collagenase Type I (DBA-Italia Srl, Italy), 10% fetal bovine serum (Celbio, Italy), 2mM ultra-glutamine, 100 U/ml of Penicillin/Streptomycin solution, 50 μg/ml of gentamicin and 0.5 μg/ml of amphotericin B. The specimens were incubated overnight in an oscillating water bath at 37˚ Celsius. Undigested tissue and debris were removed by filtering the cell suspension using a 100 micron sterile strainer (BD Falcon, USA). The cell suspension obtained was centrifuged at 1400 rpm for 10 minutes. The cell pellet was resuspended in DMEM High Glucose.

Mesenchymal stem cells were isolated from swine adipose tissue as previously described (23). Briefly, adipose tissue was minced and digested in DMEM High Glucose medium containing 0.1% collagenase Type I for 1 hour at 37°C. The obtained cellular suspension was centrifuged at 3200 rpm for 10 minutes in order to discharge the adipose fraction; the cell pellet was resuspended in DMEM High Glucose and filtered with a 100 micron sterile strainer (BD Falcon, USA). The cell pellet was resuspended again in DMEM High Glucose. All cell populations were seeded on Petri culture dishes and cultured in DMEM High Glucose medium containing 20% fetal bovine serum, 2mM ultra-glutamine, 100 U/ml of Penicillin/Streptomycin solution, 50 μg/ml of gentamicin, 0.5 μg/ml of amphotericin B, 1mM sodium pyruvate (GIBCO, Italy) and 10mM HEPES (GIBCO, Italy).

Scaffold synthesis

Collagen sponges were fabricated at the Department of Innovation Engineering, University of Salento. A freeze-drying technique was used (24). Briefly, collagen flakes were obtained by pulverizing freeze-dried membranes of type I equine collagen (Antema®, kindly provided by Opocrin S.p.A, Italy) in a refrigerate mill. A 2%wt collagen slurry was poured into cylindrical moulds

(diameter=8 mm) and then the frozen samples were lyophilized. Finally, the sponges were thermally cross-linked (dehydrothermal treatment).

Scaffold seeding and culture

After the in vitro expansion (4 passages), cells were collected and resuspended in a solution containing bovine fibrinogen (110 mg/ml) (Fluka Chemic GmbH, Buchs, SG, Switzerland), aprotinin (0.2 mg/ml) (Sigma), tranexamic acid (1.5 mg/ml) (Sigma) and adjusted to a concentration of $80x10^6$ cells/ml. Then, 100 µl of the fibrinogen-cell suspension was seeded onto the collagen sponges (8×10^6 cells/ scaffold) and after the complete absorption of the cell solution, 100 µl of thrombin (1.37 mg/ml, Chemicon International Inc., Temecula, CA, USA) was added in order to form fibrin glue. After 30 minutes, complete polymerization was reached and the seeded scaffolds were placed in culture flasks for the in vitro culture. The seeded scaffolds were cultured in vitro for 7 and 14 days in basic culture medium containing DMEM High Glucose, 20% fetal bovine serum, 2mM ultra-glutamine, 100 U/ml of Penicillin/Streptomycin solution, 50 µg/ml of gentamicin, 0.5 µg/ml of amphotericin B, 1mM sodium pyruvate, 10mM HEPES and 50 µg/ml ascorbic acid (Sigma, Italy).

Immunofluorescent analysis

Cells were expanded for two passages and then seeded on matrigel (BD, Italy) coated cover-glasses at a density of 30000 cells/cm^2. After 24 hours, cells were washed three times with PBS and fixed with pre-cooled methanol for 10 minutes at -20°C. After three washes in PBS, samples were incubated for 30 minutes with the blocking solution, containing 10% goat serum (Vector Laboratories Inc., USA) and 0,1% triton (Sigma, Italy) in PBS. Then, samples were incubated for 2 hours with the primary antibodies: anti-actin (Sigma, Italy), anti collagen 1 (Novus Biologicals, USA) and anti-collagen 3 (Tebu-bio, Italy). Then, samples were washed 3 times with PBS and finally incubated for 1 hour with an anti-rabbit antibody conjugated to fluorescein (Life Technologies, Italy). Finally, nuclei were counterstained with 10 g/mL of Hoechst bisbenzimide (Sigma, Italy). The immunofluorescent stainings were observed using an Olympus BX51 light microscope equipped with an AFTER (Amplified Fluorescence by Transmitted Excitation of Radiation) Light Emitting Diodes (LED) Fluorescence Microscope kit (Lab Vision), thus providing an easy adaptation of a light microscope to a fluorescence one as described by Deponti et al (25).

In order to perform the immunofluorescent staining on the seeded scaffolds, they were fixed in 10% (v/v) phosphate-buffered formaldehyde, dehydrated in a graded 50% (v/v), 70% (v/v), 95% (v/v) and 100% (v/v) ethanol series, embedded in paraffin and cut into 4 µm-thick sections. After rehydration, heat-induced antigen retrieval was performed as previously described (25). Sections were washed 3 times in PBS (pH 7.4) and subsequently incubated with the primary antibodies, anti- collagen 1 (Chondrex Inc.,USA) and anti- collagen 3 (Tebu-bio, Italy) for 24 h at 18–20°C, then washed in PBS and subsequently treated with the Avidin-Biotin blocking kit solution (Vector Laboratories Inc., USA). The sections were then washed in PBS for 10 minutes and incubated with a solution of goat biotinylated anti-mouse IgG (Vector Laboratories Inc.) in Tris-buffered saline (TBS) for 1 h at 18–20°C, then washed in PBS and incubated with anti-rabbit IgG (Vector Laboratories Inc.) in Tris-buffered saline (TBS) for 1 h at 18–20°C. After rinsing twice in PBS, the sections were treated with Fluorescein-avidin D (Vector Laboratories Inc.) for 1 h at 18–20°C and then with Rhodamine-Avidin D (Vector Laboratories Inc.) for a further hour. Finally, slides with tissue sections were embedded in Vectashield Mounting Medium (Vector Laboratories Inc.) and observed using a Confocal Laser Scanning Microscope (FluoView FV300, Olympus, Italy).

Histological analysis

The seeded scaffolds were fixed in 10% (v/v) phosphate-buffered formaldehyde. The samples were then dehydrated in a graded 50% (v/v), 70% (v/v), 95% (v/v) and 100% (v/v) ethanol series, embedded in paraffin and cut into 4 µm-thick sections. After rehydration, sections were stained with Hematoxilyn/Eosin.

RESULTS

Cell morphology and synthetic activity

In order to compare dermal fibroblasts and ASCs to tenocytes, different immunofluorescent stainings were performed, in particular for actin, for the evaluation of cell morphology, and for collagen 1 and 3 in order to evaluate the cell synthetic profile. As depicted in Fig. 1, ASCs were characterized by a well-structured actin network (Fig. 1G) that was distributed throughout the whole cytoplasmic compartment. Also dermal fibroblasts (Fig. 1D) and tenocytes (Fig. 1A) were characterized by a similar actin network, showing a smaller cell size, that is particularly evident in tenocytes (Fig. 1A). Despite the differences in cell morphology, dermal fibroblasts and ASCs showed similar synthetic activity with respect to tenocytes, as demonstrated by the positive staining for collagen 1 (Fig. 1B, E and H) and collagen 3 (Fig. 1C, F and I) that are the main component of tendon matrix.

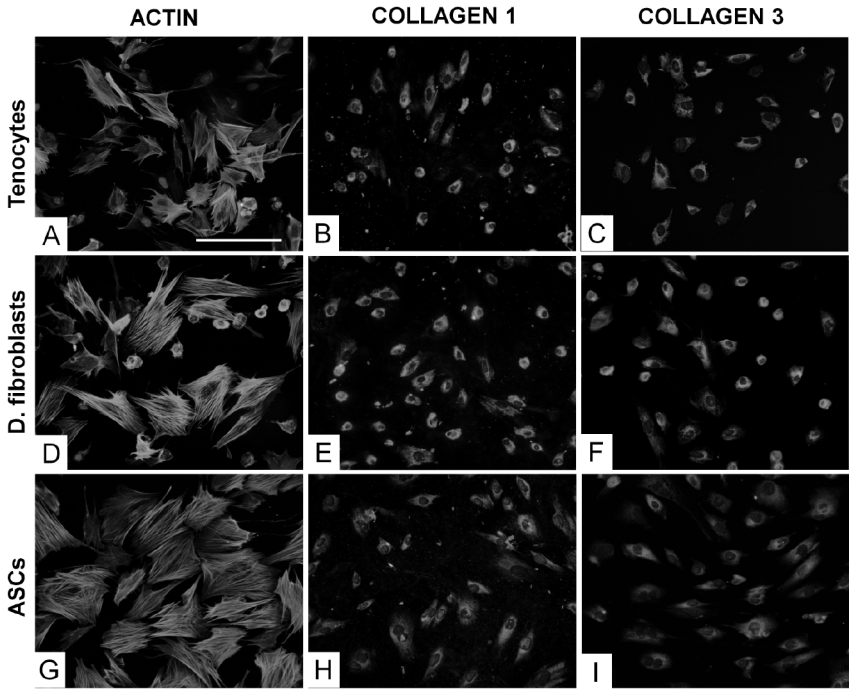

Fig.1. *Immunofluorescent staining for tenocytes (A-C), dermal fibroblasts (D-F) and mesenchymal stem cells from adipose tissue (ASCs) (G-I). Cell nuclei are visible in dark at the center of the cells, while tendon proteins are brighter, in particular: A, D, G: actin; B, E, H: collagen 1; C, F, I: collagen 3. Scale bar: 50 µm. (Color figures are available free on-line at http://www.jorthopedics.com/).*

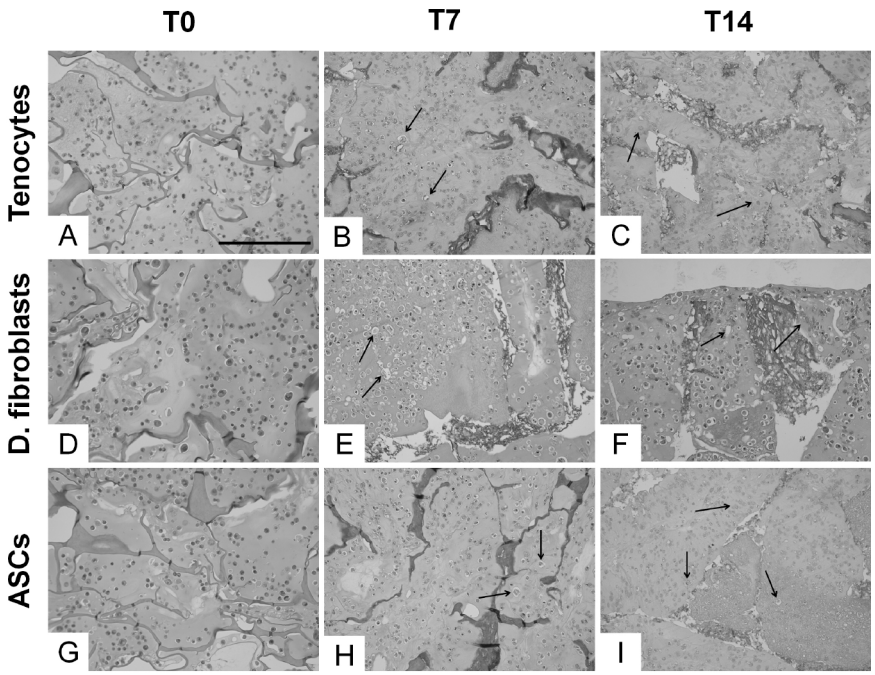

Fig.2. *Histological analysis of the collagen sponges seeded with tenocytes (A-C), dermal fibroblasts (D-F) and ASCs (G-I). Samples at time zero (A, D, G) and cultured in vitro for 7 days (B, E. H) and 14 days (C, F. I). Scale bar: 200 µm. (Color figures are available free on-line at http://www.jorthopedics.com/).*

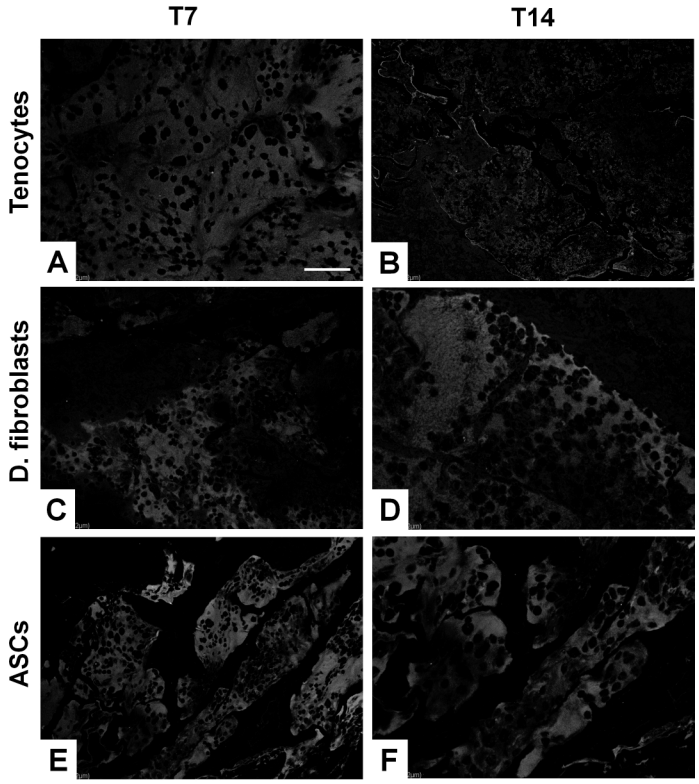

Fig.3. *Immunofluorescent staining for tenocytes (A, B), dermal fibroblasts (C, D) and ASCs (E, F). Samples were cultured in vitro for 7 days (A, C, E) and 14 days (B, D, F).Collagen 1 is visible as brighter, while collagen 3 appears darker. Scale bar: 50 μm. (Color figures are available free on-line at http://www.jorthopedics.com/).*

Histological analysis of cell-seeded collagen sponges

Collagen sponges were seeded with tenocytes, dermal fibroblasts and ASCs in order to evaluate cell distribution and survival within the scaffold and to make a comparison between the different cell populations. At time zero (Fig.2A, D and G), cell were homogeneously distributed within the scaffold in all samples. At 7 days of culture, the samples seeded with tenocytes (Fig.2B) showed a constant maintenance of cellularity, with few cells showing degeneration or apoptosis (Fig.2B: arrows); while, a higher presence of degenerating or apoptotic cells was observed in the scaffolds seeded with dermal fibroblasts and ASCs (Fig.2E, H: arrows). At 14 days of culture, degeneration or apoptosis occurred in most of the cells seeded into the scaffolds (Fig.2C, F and I: arrows), with particular evidence in the samples seeded with tenocytes and ASCs.

Immunofluorescent analysis for matrix deposition in cell-seeded collagen sponges

An immunofluorescent staining for collagen 1 and 3 was performed in order to evaluate the synthetic profile of tenocytes, dermal fibroblasts and ASC within the collagen scaffold, as a proof of the possibility to use alternative cell populations for the engineering of tendons. As depicted in figure 3, at 7 days of culture, all cell populations were able to produce a matrix that was positive for collagen 1 and 3 (Fig.3A, C and E); however, at 14 days, a degeneration of the matrix occurred in all samples, as demonstrated by a lower deposition of the two collagen isoforms, with particular evidence in the samples seeded with tenocytes and dermal fibroblasts (Fig.3B, D).

DISCUSSION

Tendons are connective tissue characterized by the presence of a typical fibroblast population that is able to produce collagen 1 and 3 fibers and to contribute to their spatial organization in response to mechanical stimuli (5): this specific composition is fundamental for the tissue functions. Engineering a tendon means building up a tissue with similar composition and organization to those of native tissue: for this reason, the choice of the cell source has to be very accurate and it has to focus on populations that share the synthetic profile of tenocytes or are able to assume it in response to proper stimuli.

The present study focused on a comparison between tenocytes and two putative cell populations for tendon engineering: dermal fibroblasts and ACSs. Their synthetic profile was assessed both in monolayer culture and in association to a collagen sponge in order to evaluate the potential of these cells for engineering a tendon. These cells showed a similar shape, characterized by a well-structured actin network that is typical of fibroblast populations (26); their size appeared to be different, in particular for tenocytes who resulted smaller with respect to dermal fibroblasts and ASCs. Although this physical difference, all the cell populations shared the same synthetic profile, characterized by the presence of both collagen 1 and 3, suggesting a potential role of these cells for the engineering of tendons. These cells were also combined to a collagen sponge as a model for tendon engineering: as demonstrated by the histological analysis, all populations were uniformly distributed within the collagen sponge and they survived for the first week of culture, with no evident distinction between the three cell populations; however, at 14 days of culture, degeneration occurred in all the seeded samples, as a consequence of the static culture, suggesting the need to sustain cell survival with specific growth factors and/or mechanical stimuli. An interesting observation is that all cell populations were able to produce collagen 1 and 3 within the scaffold during the first week of culture, as shown by the immunofluorescent staining for these collagen isoforms (fig.3), suggesting a tenogenic potential also for dermal fibroblasts and ASCs. As a consequence of the cell degeneration occurring in between 7 and 14 days of culture, also collagen deposition resulted to be lower at 14 days in all cell populations, suggesting again the need to improve the survival stimuli of the in vitro culture.

This study demonstrates that dermal fibroblasts and ASCs are able to colonize a collagen sponge and produce a tendon-like matrix: this evidence suggests a possible clinical application of these cell populations, combined to the collagen scaffold, for the regeneration of tendons, leading to the development of a less invasive solution for tendon rupture or degeneration. Further studies are needed in order to improve the prolonged in vitro culture of these cell populations on the scaffold, in particular by sustaining cell survival with growth factors and/or by stimulating matrix organization with a specific mechanical stimulation.

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BASIC SCIENCE

QUANTITATIVE BIOMECHANICAL MEASURES TO EVALUATE FUNCTION AND STRENGTH AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION IN DIFFERENT REHABILITATION STAGES.

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Anterior cruciate ligament (ACL) injury is common in knee joint accounting for 40% of sports injury. Returning to normal or high level athletic activity are the target of patients after reconstruction surgery. However, there are few standardized and objective protocols to evaluate patient's condition and safe return-to-activity after surgery. The purpose of this study is to present an assessment protocol in different rehabilitation stages after ACL reconstruction that includes neuromuscular control, strength, power, and functional symmetry evaluations. The proposed assessment methodology is based on quantitative measurement tools that provide the patient with objective feedback and targeted goal setting. KT-1000, stabilometry, gait analysis and isokinetic test were used in this assessment protocol to evaluate patient condition. These parameters may rationalize the work of clinician to provide the specific rehabilitation program based on the abilities of the specific patient. The proposed protocol may increase the outcome of the patient after rehabilitation and minimize injury risk.

Basic Science Study

Injuries occurred during sport activities are very common (21% in terms of cause of injury), and they often lead to long-term consequence (1), in particular when the knee is involved (2). Anterior cruciate ligament (ACL) injuries is one of the most common sport-relate knee injuries; it has been estimated that 20% of the knee injuries involves the ACL (1-3). ACL injury causes Knee instability and it can results in reducing or stopping of the sport activity (4).

Treatments available for this kind of injury can be divided into conservative and surgical (4). Conservative treatment can help patients with everyday life activities but it has been demonstrated that knee stability can not be restored and therefore return to sports rate is nearly zero (5). Operative treatment seems to be the only option for athletes that aim to return to their activities (6). After the surgery, the aim of the patients is to return to level athletic activity that they have before the injury as fast as possible, but there are not standardised and protocols to evaluate the rehabilitation programs and the patient's condition for a safe an return to activity. One of the most important factors used to evaluate safe return to sport is the functional knee stability (7). Moreover knee flexors and extensors strength evaluation give important information to assess the patient condition before return to normal activity level (8).

In this paper a methodology is proposed to evaluate patients condition after ACL reconstruction

Key words: ACL reconstruction, Rehabilitation, Biomechanical functional evaluation

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surgery. Various aspects are taken into account, in particular ACL laxity in the sagittal plane, knee flexors and extensor strength discrepancy between involved side and controlateral side, stabilometry and gait asymmetry. The aim of the study was to provide information about different biomechanical aspects of the knee that can help clinicians during rehabilitation program.

MATERIALS AND METHODS

Participants

12 male patients with diagnosed ACL injury after clinical evaluation were recruited (mean age 31.2±12.5 years; mean body mass 78.5±10.0; mean height 1.79±0.08 m); participants with other knee injuries (e.g. damage of meniscus) or relapse ACL injury were excluded.

Posterior-anterior knee laxity evaluation

The device used for this test is the KT -1000 arthrometer. The patient lies in a supine position and the knee flexed about 20°, a support is placed below the knee proximal to the popliteal space. The patient is told to relax in this position. The arthrometer is then placed above the tibia and attached firmly by two bands. After adjusting the zero, the tibia will be pulled anteriorly using the handle on the arthrometer . An audible indication will be noticed at 15, 20 and 30 pounds of force. Moreover a manual maximum measure is performed pulling the tibia with an hand on the back of the shank, until the foot is raised. Displacement is measured in millimeters and compared with not involved side.

Knee flexors-extensors strength

Isokinetic machine (BIODEX 4 PRO, city, USA) is used for this assessment. The patient performs a isokinetic concentric evaluation with a fixed velocity of 90°/s with a range of motion of 0-90° of knee flexion.

After warming-up, patient is asked to sit on the resting chair of the dynamometer and then the patient is secured with body straps. The starting position is 90° flexion for the knee and 90° for the hip joint. The patient is instructed to extend the knee till 0° flexion and then to flex the knee back at 90° with maximum exertion. The test is performed firstly on the uninvolved side and then on the involved side. Peak forces are compared between the sides.

Stabilometry

The patients is asked to stay still on a force platform for 10 seconds, firstly standing only on the right leg with the arms folded across the chest. The test was repeated on the left leg. Motion of the centre of pressure was used to quantify ellipse area to measure stability (9).

Gait analysis

Gait analysis can be performed before and after ACL reconstruction. This test is conducted in a gait laboratory equiped with a 3 dimensional (3D) motion capture system. This system used 12 infrared cameras to reconstruct the motion of the lower limbs of the patients capturing the 3D trajectory of reflective markers positioned on the patients following the Helen-Hays markerset. The motion capture is synchronized with two force platforms that detect ground reaction forces. Kinematics and kinetics of the ankle, knee and hip joints was computed during gait to detect abnormalities or asymmetry. In this study weight acceptance (WA) and push off (PO) peak parameters from the vertical component of the ground reaction forces (GRF) were used and compared between involved and healthy side.

Student t-test were used to compare results from kt-1000, gait analysis and stabilometry test between healthy and involved side.

RESULTS

Manual maximum test with the arthrometer (Fig. 1), ellipse area from stabilometry test (Fig. 2), WA and PO gait analysis parameters (Fig. 3) showed to be significant different ($p. < 0.05$) when comparing results between involved and healthy sides. Isokinetic test showed that extensors muscles force of the involved sides was reduced of 26.6% (SD=10.2) when compared with extensors muscles force of the healthy side.

DISCUSSION

The article proposed different biomechanical test in order to assess patient's condition after ACL reconstruction. The tests proposed give important quantitative information about function of the involved side. KT-1000 test evaluates the laxity of the ACL comparing with the controlateral side, it can be performed before and after the reconstruction to evaluate surgery outcome and it has been validated by the scientific community (10). As reported in this study, manual maximum parameter of the arthrometer test showed to be significant different between healthy and involved side in ACL patients.

Isokinetic test gives information about the strength of the knee flexors and extensors muscles,

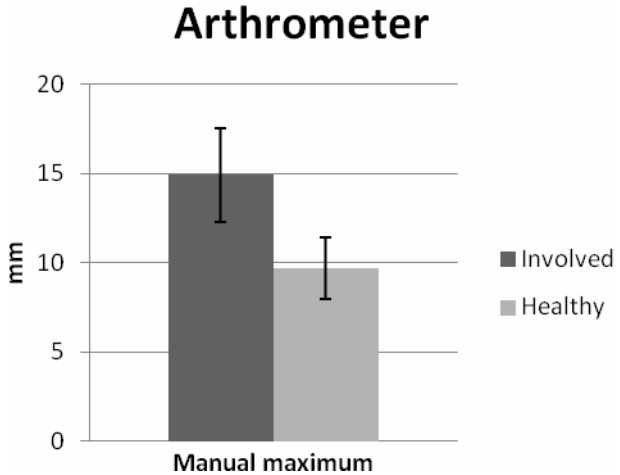

Fig. 1. *Manual maximum results for the KT-1000 test showing significant differences (p.< 0.05) between healthy and involved side.*

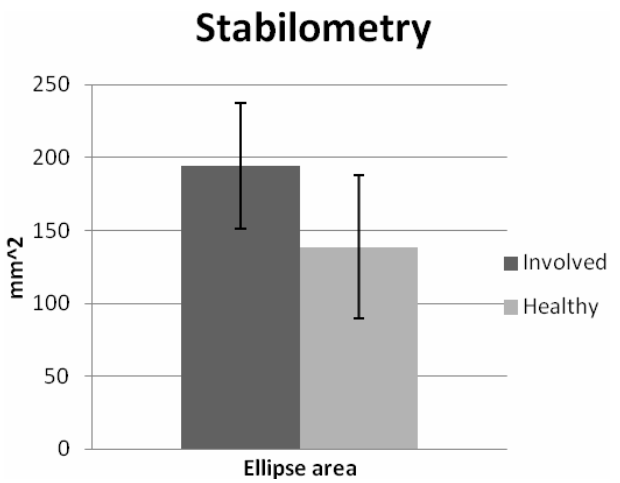

Fig. 2. *Ellipse area results for stabilometry test showing significant differences (p.< 0.05) between healthy and involved side.*

showing muscular condition during rehabilitation program and it has been proposed to evaluate muscular strength of athletes (8). Muscular strength differences between healthy and involved side can be compared and progression of the rehabilitation monitored. This can give quantitative and objective information about muscular condition and it can be used to prevent further injuries and to evaluate rehabilitation steps.

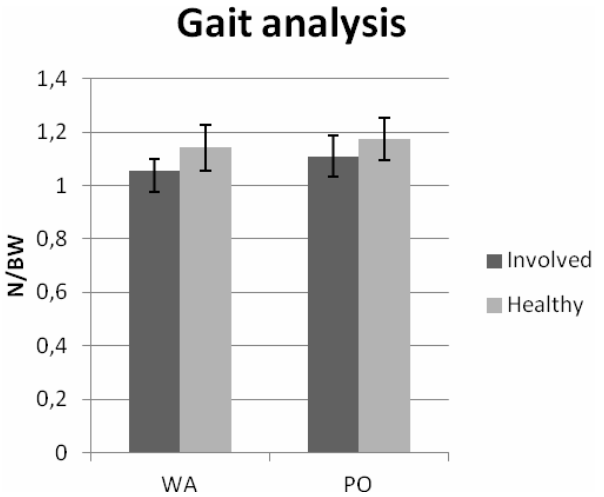

Fig. 3. *WA and PO results for gait test showing significant differences (p.<0.05) between healthy and involved side.*

Stabilometry test is an objective method to quantify postural equilibrium. In this test the stability is evaluated in single limb stance. The motion of the centre of pressure is collected giving a quantitative measure of the stability of each limb (9). In the study the involved side showed to be significantly instable compared with the healthy side before the reconstruction surgery as the ellipse area was increased in affected limb. The test can be repeated after a proprioceptive training to evaluate improvement in limb stability.

Gait analysis is a detailed test of the walking and several information can be extrapolated from it. Firstly, the analysis of the GRF can show how the load is distributed in the two limbs during walking, and asymmetry between the two sides can be detected. In particular in our study we demonstrated that two parameters of the vertical components of the GRF, WA and PO, were significantly different in the involved side when compared with healthy side before the reconstruction surgery. More complete information can be taken from kinematic and kinetic analysis where 3-D motion of the knee, ankle and hip joints together with dynamic joint loading profile can be obtained and analyzed. As for the other tests, gait analysis can be performed before and after the surgery and in different rehabilitation stages to evaluate, for example, if adaptation in gait as results of the injury (11-12) or, in particular, differences in

WA and PO parameters that we found in our study before the surgery, are restored after a rehabilitation program.

In this paper data from patients with ACL injury were shown. Results showed significant differences in biomechanical measures between involved and healthy side (Fig. 1,2 and 3) before the reconstruction surgery. The same evaluation protocol can be performed 3 and 6 months after the surgery and it can help clinician to evaluate patients progression and to adapt rehabilitation programs to specific needs of the patients. Further studies can be performed to evaluate rehabilitation program effectiveness using the proposed protocol.

CONCLUSION

It is important to assess the condition of a patient before and after ACL reconstruction surgery, in particular there is a need of standardized and objective protocols to evaluate patient's condition for a safe return-to-activity.

In the present article a protocol, including ACL laxity quantification, knee flexors and extensor strength discrepancy between involved side and controlateral side measure, stabilometry and gait asymmetry, has been presented. The proposed protocol will give information about patient's condition before the surgery and it can be used at different rehabilitation stages that can help clinicians to control rehabilitation progressions for a safe return to activity.

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BASIC SCIENCE

DOES MEDIAL PATELLO-FEMORAL LIGAMENT RECONSTRUCTION ALTER PATELLO-FEMORAL MECHANICS? A PILOT STUDY.

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Medial patello-femoral ligament (MPFL) reconstruction is the recommended treatment for recurrent lateral patellar dislocation. However, long term follow-ups following MPFL reconstruction are not available in literature and the patello-femoral mechanics is not well known in terms of contact forces, contact area and contact pressure. Few studies have shown the biomechanical consequences of the MPFL reconstruction. We believe that the knowledge of the patello-femoral mechanics after this surgical procedure is fundamental to prove its efficacy and eventually to improve the reconstruction technique. The purpose of this study is to compare the patello-femoral contact force, contact area, and contact pressure and patellar translation after MPFL reconstruction in comparison with native knee joint.

Basic Science

Patello-femoral instability is challenging for orthopedic surgeons and rehabilitators due to its multifactorial etiology. The etiologies that predispose patients to lateral patellar dislocation are believed to be genu valgum, patella alta, ligament laxity, contracture of the lateral patellar soft tissues, hypoplasia of the lateral femoral condyle, a laterally located tibial tubercle, vastus medialis insufficiency, and abnormal attachment of the iliotibial tract (1). Medial patello-femoral ligament (MPFL) is the primary passive restraint against lateral translation of the patella (2-6). The MPFL extends from the superior two-thirds of the medial patellar margin to just distal of the adductor tubercle, with superficial fibers extending to the posterior capsule (7). Previous studies have demonstrated that this structure is always injured after lateral patellar dislocation (8-9) thus MPFL reconstruction is commonly performed to restore the patello-femoral stability. However many technical errors during MPFL reconstruction could overload and alter the patello-femoral joint. MPFL reconstruction reproduces a postero-medial force that increases contact pressure on the medial patellar facet. For these reason understanding the correct biomechanics of the patello-femoral joint following MPFL reconstruction is the primary goal to restore the anatomy and the function of the patient which is affected by patello-femoral instability.

The purpose of this study is to assess the biomechanical behavior of the patello-femoral joint after MPFL reconstruction using the semitendinosus autograft in anatomic double bundle technique with

Key words: knee, MPFL reconstruction, patello-femoral joint, contact force, contact area

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converging fashion. Also, an investigation on the differences in contact kinetics and kinematics between the native knee and after MPFL reconstruction has been performed.

MATERIAL AND METHODS

Preparation of the specimen

One fresh frozen human cadaveric knee was used for this study. Prior to testing the specimen was thawed for 24 hours at room temperature. During preparation and mechanical testing the leg was kept moist using saline solution.

In preparation for testing, the femur and the tibia were cut approximately 20 cm from the joint line and all soft tissue was removed 10 cm away from the joint line on both the femur and the tibia, leaving the quadriceps muscle. Then the femur and the tibia were potted using cement and fixed to the tensile machine by custom-made clamps (Fig. 1).

The knee was placed on a table to allow the fixation of an articulated frame by mean three metal rods at the femoral and tibial shaft (Fig. 2). The frame and its fixation allowed to keep the correct joint alignment and to change the flexion angle during the mechanical testing. The quadriceps muscle was wrapped around a metal rod to apply a constant force during testing (Fig. 1B).

After the fixation of the frame, a the pressure sensor (TekScan Inc., South Boston, MA, USA) was placed between the patella and the femoral groove by mean a modified-Insall medial arthrotomy and by a 1 cm incision at the supero-lateral aspect of the patella.

The sensor was correctly positioned to cover the femoral groove then it was sutured to the skin (Fig. 3). Three markers were used to analyze the kinematics of the patella during the testing protocol. One marker was placed on the tip of a pin fixed at the centre of the patella itself. Other markers were fixed to the medial and lateral side of the articulated frame along to the intercondylar axis of the knee.

A bi-dimensional analysis was performed to record the translation of the patella in medio-lateral direction during loading and unloading configuration. Static pictures have been taken and marker position have been recorded in pixel and consecutively converted in mm.

Mechanical test

The specimen was positioned on a tensile machine (Instron Inc., Norwood, MA, USA) using custom-made clamps. The testing protocol included several flexion angles. In particular, the knee was tested at 0°, 30°, 60° and 90° (Fig. 4).

Once the specimen was fixed to the tensile machine, a static test was performed to analyze the patello-femoral contact forces, the contact area and the contact pressure for all the flexion angles applying 200 N in proximal-distal direction through the quadriceps muscle wrapped

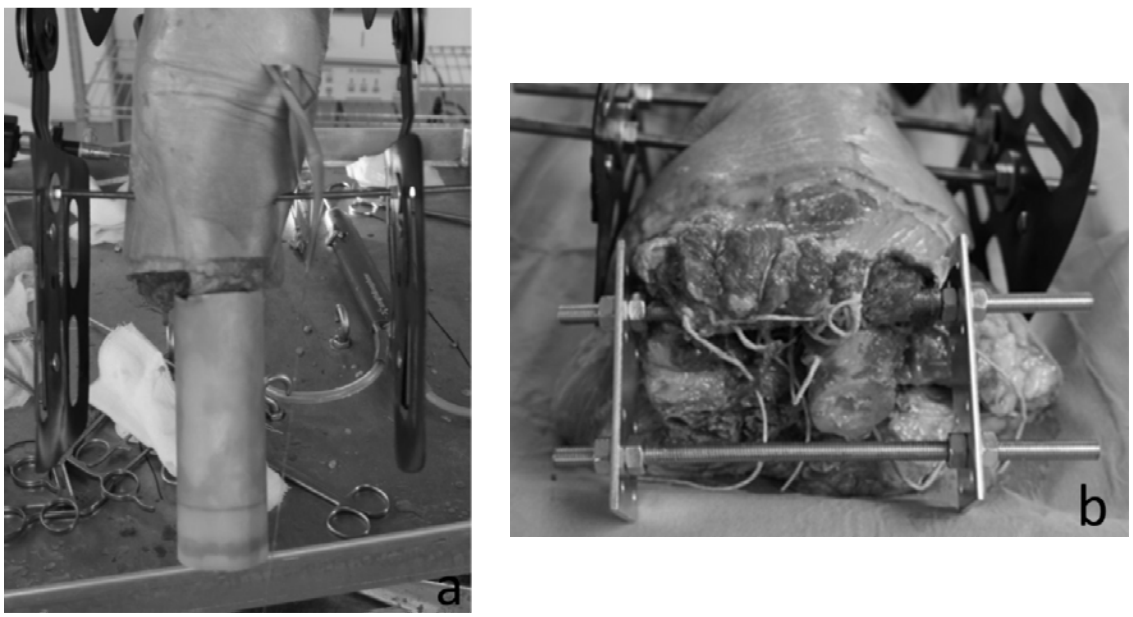

Fig.1. *Preparation of the specimen: a) the cemented pot on the tibia and the b) quadriceps muscle wrapped on a metal rod for applying axial load.*

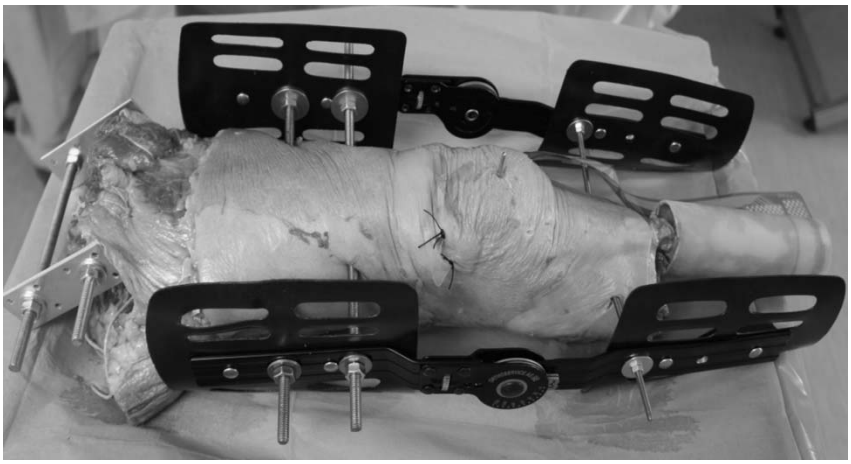

Fig. 2. *The articulated frame fixed to the specimen. Metal rods are perpendicular to the mechanical axes, approximately 10 cm away by the joint line*

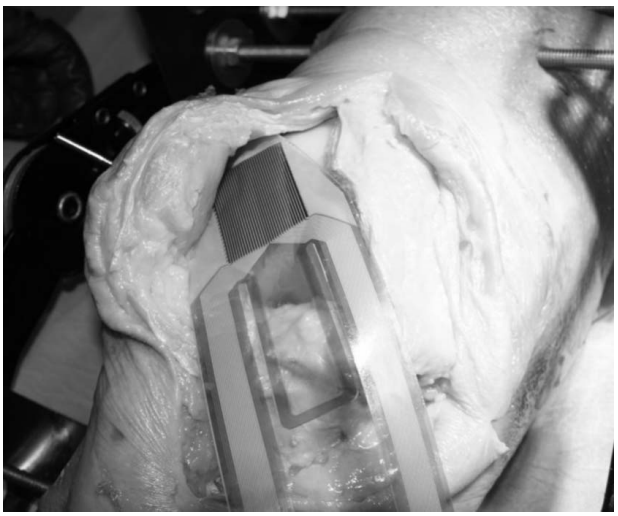

Fig. 3. *Positioning of the pressure sensor in the patello-femoral joint during arthrotomy.*

around a metal rod.

The load was applied after a pre-test performed for stretching the muscle fibers of the quadriceps.

Following a linear curve, the maximum load was applied on the quadriceps muscle and was kept constant for 10 seconds to simulate an isokinetic motion.

While the constant load was applied, the patello-femoral contact force and contact area was recorded each 0.25 s using IScan (Tekscan Inc., South Boston, MA, USA). Every test was performed for three times for each configuration to provide better repeatability of the procedure. The same testing protocol was performed after the MPFL reconstruction and final outputs were analyzed

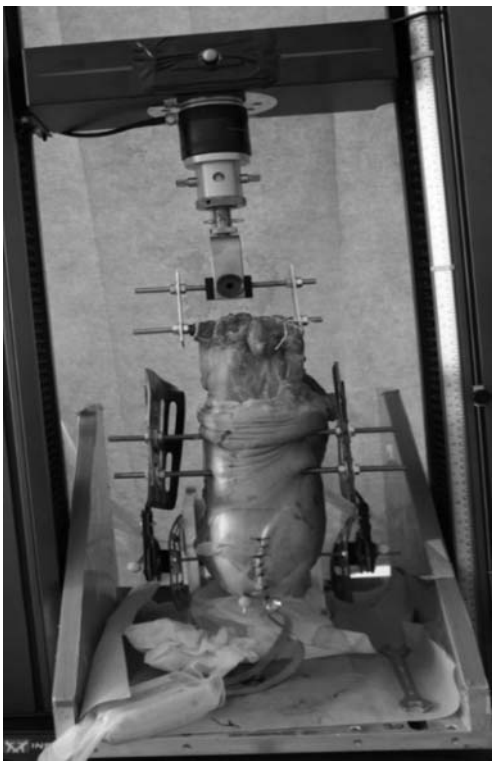

Fig. 4. *Machine boundary conditions with the knee at 90° of flexion.*

and compared with the previous test.

Double Bundle MPFL reconstruction with a modified-Ochi technique

By mean 2 cm incision at the pes anserinus the semitendinosus was freed by the muscle and harvested with a tendon stripper. Using a work station the free ends

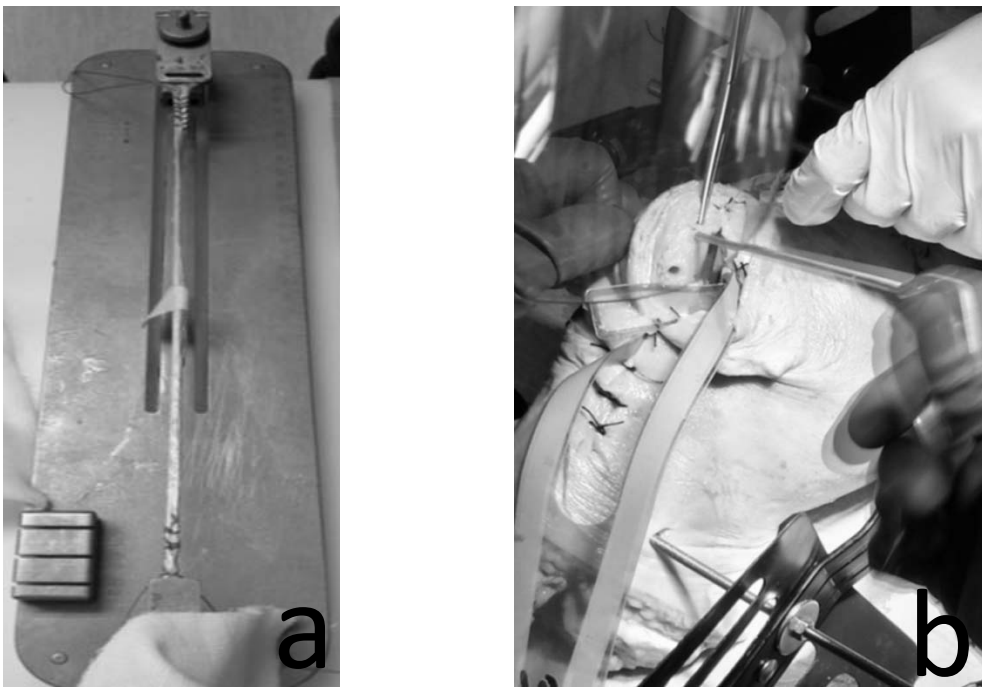

Fig. 5. *MPFL reconstruction:* **A)** *Semitendinus autograft is prepared and pretensioned.* **B)** *Double bundle technique with converging fashion of the patellar tunnels; the sensor is kept at the same position of previous test.*

of the tendon were sutured with no.2 Ethicon sutures by Krackow suture and pretensioned for 10 minutes with 40 N to avoid tendon creep (Figure 5a). Through a 3 cm incision, the medial boder of the patella was exposed and two Kirshner wires were drilled in a converging fashion at the proximal one third and at the center of the medial edge trying to reproduce an angle of 90° (1,10). Patellar guide wires were overdrilled using a 4.5 mm cannulated reamer until the sockets were in communication. The femoral tunnel was anatomically placed at the insertion of the native ligament, between the adductor tubercle and medial epicondyle. The graft was passed through the patellar converging tunnels and then the free ends were pulled through the femoral tunnel. The graft tensioning was performed manually pulling the suture on the lateral aspect of the femur and the fixation was achieved by a 8 x20 mm bioreasorbable interference screw at the medial side, at 60° of flexion angle. During the MPFL reconstruction, the sensor was kept at the same position of previous test (Fig. 5b).

RESULTS

Contact force

The mean value and the standard deviation for all the configurations has been calculated.

Figure 6 shows patello-femoral contact forces at 0°, 30°, 60° and 90° of flexion angle for the intact knee and after MPFL reconstruction.

MPFL reconstruction increased the contact forces between 0° to 30° with respect to the native knee, while at higher flexion angles the force decreased up to 50% than for intact joint.

Contact Area

MPFL reconstruction increased the contact area at 0° and 30° of flexion whereas it decreased at higher flexion angles in comparison with the intact knee (Fig. 7).

Mean Pressure

After MPFL reconstruction, the mean pressure was higher in the first 30° of flexion and lower at 60° and 90° than the native joint (Fig. 8).

For all the outputs (Fig. 6-8) the value of the standard deviation showed suitable repeatability of the tests.

Patellar translation

Patellar translation was modified by MPFL

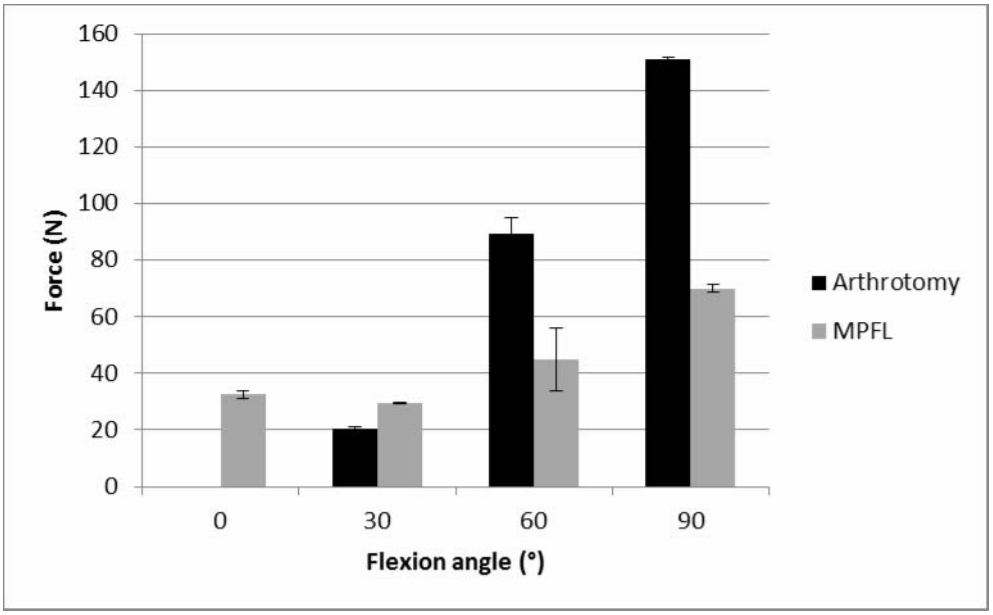

Fig. 6. *Maximum patello-femoral contact force, and the relative standard deviation, for the native knee (black) and after MPFL reconstruction (grey).*

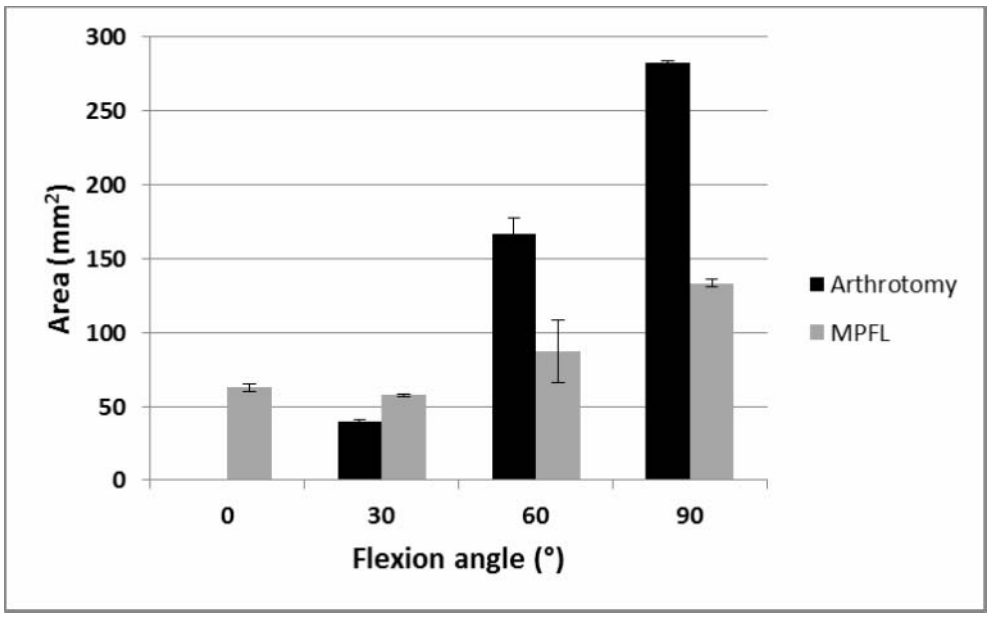

Fig. 7. *Patello-femoral contact area, and the relative standard deviation, for the native knee (black) and after MPFL reconstruction (grey)*

reconstruction. Lateral translation was restricted after MPFL reconstruction in comparison with the intact condition (Fig. 9).

DISCUSSION

Treatment of patello-femoral instability is challenging for orthopedic surgeons due to its multifactorial etiology and the disability that affect the patients. Several techniques to restore the patellar track have been reported in the last decades. Recently MPFL reconstruction using hamstring reported good clinical and functional results. Our results, according to previous studies, confirm that

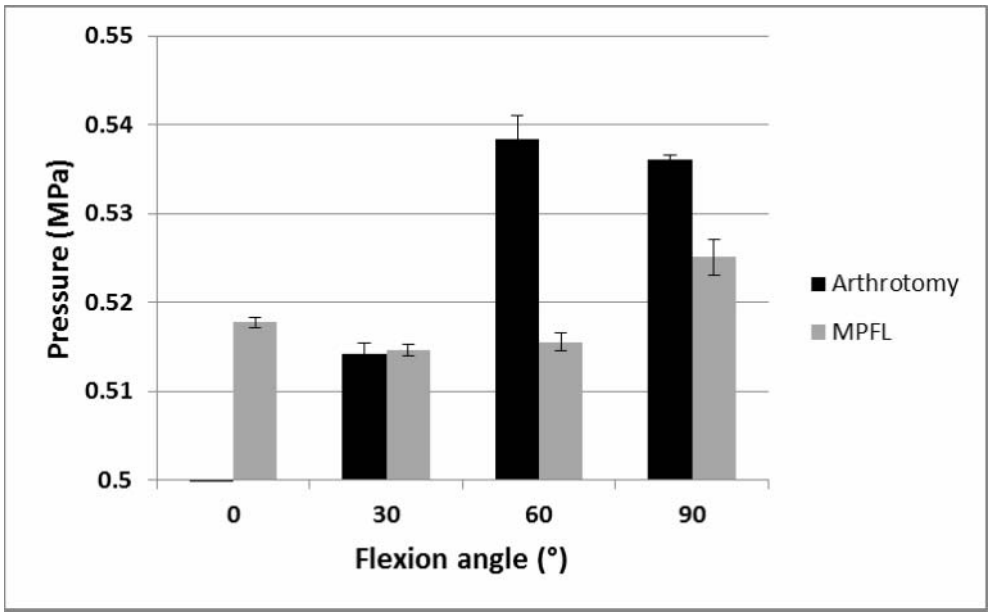

Fig. 8. *Patello-femoral contact pressure, and the relative standard deviation, for the native knee (black) and after MPFL reconstruction (grey).*

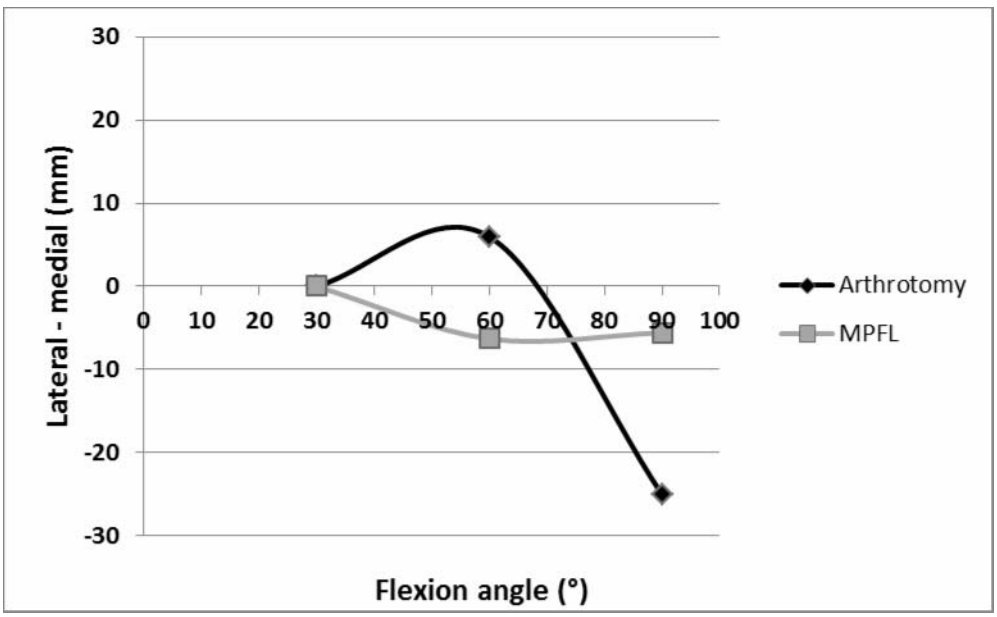

Fig. 9. *Medio-lateral movement of the patella for the native knee (black) and after the MPFL reconstruction (grey).*

MPFL reconstruction can reduce the patellar lateral tilt and modify the patellar track. In particular, the use of semitendinosus tendon can reduce the patellar lateral dislocation and modify the contact pressure and area, with different behavior between 0°-30° and between 60°-90°.

The aim of the MPFL reconstruction is to restore the contact pressure of the patello-femoral joint and to provide a passive restraint to lateral patellar translation. We have demonstrated that MPFL reconstruction restore the contact area and the contact pressure at 30° of flexion in comparison

with the intact joint. In addition, the lateral patellar translation was restricted after MPFL reconstruction. However, at low flexion angles between 0°-30° the contact force, the contact area and lastly the contact pressure were higher than native knee.

In a cadaveric study, Beck et al. (11) found out that high loads (from 10 N to 40 N) applied to the graft during the MPFL reconstruction increased significantly the contact force and the contact pressure of the patello-femoral joint in comparison with the native joint.

Our results are in agreement with Beck et al. (11) thus between 0° to 30° of flexion the patello-femoral joint can be overloaded as showed by our data.

Excessive contact pressure at the patello-femoral joint can lead to cartilage degeneration at the medial patello-femoral facet as reported by Kita et al. (129 after MPFL reconstruction at 6 to 26 months follow-up study.

Our study has several limitations. First, we used only one specimen to perform this preliminary study. We are planning to improve our data set enlarging the specimens in use. The patello-femoral joint was loaded only by quadriceps muscle; we didn't use any other force to simulate a patellar maltracking.

Other technical errors during MPFL reconstruction could overload medial patello-femoral cartilage. Elias and Cosgarea (13) found out that small errors in femoral graft placement and graft length can dramatically increase the force and the pressure applied to patello-femoral cartilage. In a biomechanical study (13) they found that 5 mm proximal malpositioning of the femoral attachment and a short graft increased the peak medial pressure by more 50% at low flexion angle.

In contrast, Melegari et al. (14) found that femoral placement of the graft did not alter contact pressure after MPFL reconstruction using a quadriceps tendon distally inserted to the inferior pole of the patella.

Our technique includes an anatomical placement of the femoral tunnel between the adductor tubercle and the medial epicondyle according the native anatomy of the ligament (14). At the patellar attachment our double bundle technique with converging tunnels restores the insertional area and the sail shape of the native ligament.

The MPFL reconstruction using our anatomical double bundle reconstruction provides a passive restraint against lateral patellar translation and restores the contact force, the contact area and the contact pressure of the patello-femoral joint in comparison with the native knee between 0° to 30° of flexion. A larger study with a bigger sample will be performed to convalidate this preliminary study.

AKNOWLEDGEMENTS

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REVIEW ARTICLE

TENDON LESIONS AROUND THE ANKLE

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Ankle tendons' injuries are very frequent diseases in athletic population, also due to the raise in number of people practicing sports activities at recreational or professional level. Some author suggests that, among lower limb soft tissue injuries, tendinous lesions represent the 24% for Achilles tendon, 7% for tibialis anterior, 2% for tibialis posterior, and 1% for peroneal tendons. Each tendon can be affected by different conditions, like peritendinitis, tendinitis, tendinosis, insertional tendinosis, rupture or luxation. The most frequently affected tendons are represented by Achilles tendon, tibialis posterior tendon and peroneal tendons. The treatment of these conditions can be conservative or surgical, depending on several factors like age, athletic level, funtional requests, functional residual abilities, anotomopathological findings and duration of symptoms. Both in case of surgical or conservative treatment, it is mandatory to find and correct the intrinsic and estrinsic predisposing factors, in order to avoid the recurrence of the disease. Aim of this contribution is to describe the most common tendon lesions interesting Achilles, tibialis posterior and peroneal tendons and to analyze the most effective conservative and surgical treatments intended to relieve pain and to improve the functional outcome.

Narrative Review: V Level of Evidence

Ankle tendons' injuries present ah high incidence in athletic population, also due to the raise in number of people practicing sport activities at professional or recreational level. These lesions account for the 17% of all tendons lesions in elite athletes. In recreational athletes this percentage is even higher reaching the 24 % of all the tendons lesions (1).

The most frequently affected tendons are represented by Achilles tendon, tibialis posterior tendon and peroneal tendons (2).

Multiple diseases can affect ankle tendons in the main portion or at the insertional area, derived from acute events or chronic mechanical overload. The etiology recognizes intrinsic factors like age, systemic diseases, structural deformities of the foot or sovrasegmental ones or extrinsic factors, like excess of intensity or duration of the physical exercise, non adequate rehabilitation protocol, errors of coordination or training, inappropriate shoes or ground alterations (2-4).

A wide pattern of tendon lesions can be observed in the clinical practice and a correct diagnostic process is necessary to guide the orthopaedic surgeon to the best treatment. Based on an anotomopathological classification the most common lesions are represented by peritendinitis, peritendinitis with tendinosis, tendinosis, insertional tendinosis, rupture, subluxations and dislocations (3).

Another useful classification is based on the duration of the clinical symptoms. According to this classification acute lesions present a symptoms duration within 14 days, subacute lesions between 2

Key words: Tendon lesion, Achilles tendon, Peroneal tendons, Tibialis posterior, tendinosis.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

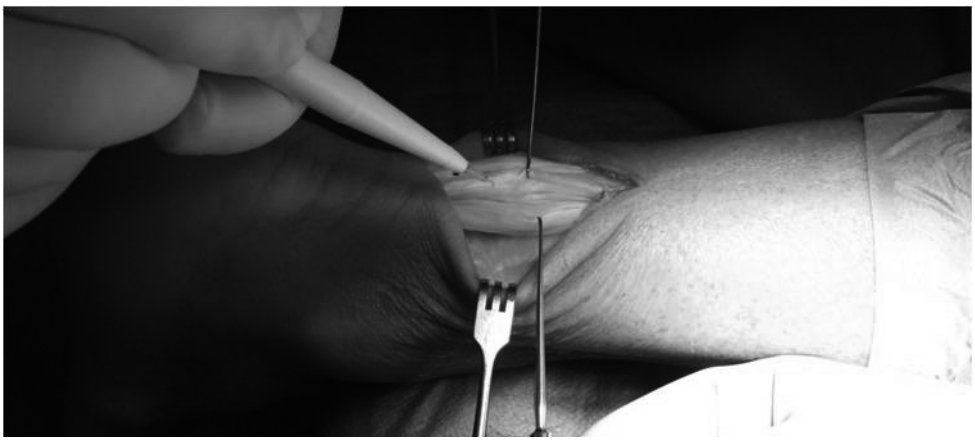

Fig. 1. *Surgical field showing a peritendinitis associated to tendinosis of the Achilles tendon treated by scarifications and PRF injection.*

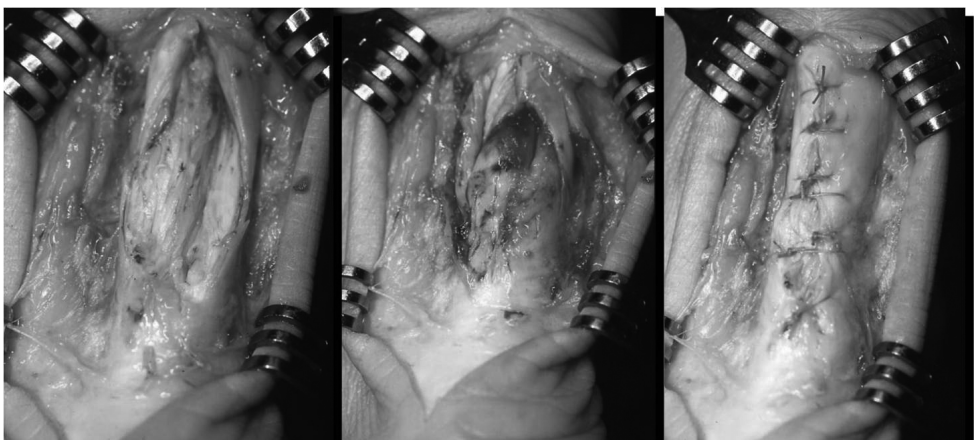

Fig. 2. *Surgical field showing Achilles tendinosis with excision of the degenerated tissue and repair.*

and 6 weeks and chronic lesions over 6 weeks.

The treatment of these conditions can be conservative or surgical, depending on several factors like age, athletic level, funtional requests, functional residual abilities, anotomopathological findings and duration of symptoms (5).

Both in case of surgical or conservative treatment, it is mandatory to find and correct the intrinsic and estrinsic predisposing factors, in order to avoid the recurrence of the disease.

Aim of this contribution is to describe the most common tendon lesions interesting Achilles, tibialis posterior and peroneal tendons and to analyze the most effective conservative and surgical treatments intended to relieve pain and to improve the functional outcome.

ACHILLES TENDON

The Achilles tendon is the strongest and largest tendon in the human body, and is also the most commonly ruptured. The Achilles tendon is surrounded by the paratenon, which is thinner than the synovial sheathes surrounding other tendons (6). The lesions interesting this tendon are represented by peritendinitis and tendinosis and by subcutaneous ruptures.

Peritendinitis and tendinosis are the results of repetitive impact loading and microtrauma (7).

Numerous factors usually cooperate in the onset of Achilles tendon lesions, such as foot morphology, gastrocnemius-soleus dysfunction, age, gender, poor tendon vascolarity and degeneration, involvement

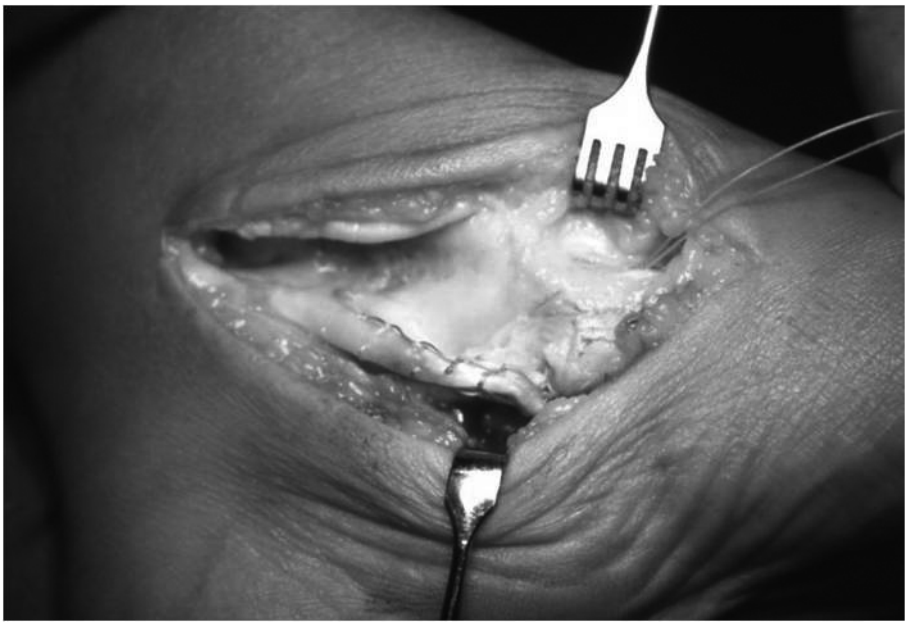

Fig. 3. *Surgical field showing grade III tibialis posterior lesion treated by transposition of the flexor digitorum longus.*

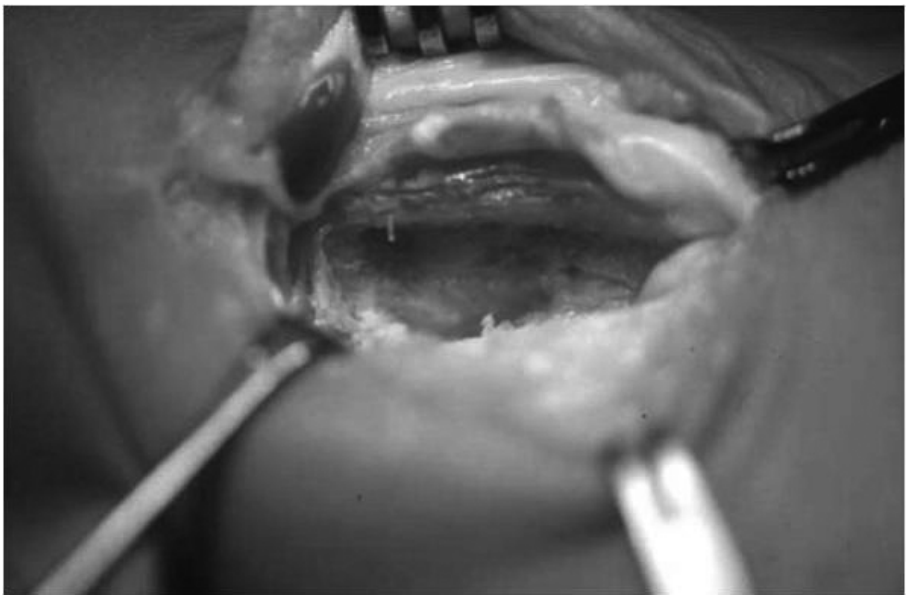

Fig. 4. *Surgical field showing the groove deepening procedure aimed to correct recurrent peroneal tendons dislocation.*

in sport activities, changes in training pattern, inadequate technical equipment employed during sport activity (e.g. footwear). With the increase of the age, degeneration of tendons occurs as a result of changes in the molecular properties of collagen, primarily caused by a low rate of regeneration and replacement. In addition aging causes a reduction in the water content and a reduction in blood supply. The degeneration encompasses a weakening and stiffening of the tendon's cellular structure, predisposing the tendon to lesions during stress loads. Although pathological processes affecting the

tendon can strike every kind of patients, even non-sportive, there is an increasing scientific evidence that sports activities lead to a higher frequency of injuries to achilles tendon (8, 10-11).

Puddu (9) classifies Achilles tendon lesions in three stages:

1. Peritendonitis with inflammation of the sheath
2. Peritendonitis with tendinosis and possible partial lacerations, calcifications
3. Pure tendinosis degeneration with poor or no sheath inflammation and with possible partial tear.

The first step for treatment is represented by conservative treatment with rest, fans, and phisical therapy. In case of persistence of pain over 6 months the surgical treatment is required. In case of peritendinitis the choice is oriented toward tenolysis. In case of concomitant tendinosis the tenolysis is not sufficient. In this case it's necessary to associate tendon scarifications. It is possible to add PRF to enhance the repair process of the degenerated tendon. In clearly degenerative forms it's indicated the excision of nodules and calcifications and the tendon thickening with eventual repair of lacerations. If the residual tissue is less than 50% of the thickness of the normal tendon it is mandatory to augment the Achilles using a tilted band of the gastrocnemius, the peroneus brevis tendon or the flexor hallucis longus tendon. The surgical treatment of peri-tendinitis and tendinosis of the Achilles tendon must also contemplate the need to correct any defects of the foot that can cause recurrence such as over-pronation of the hindfoot or cavus foot deformity.

The subcutaneous ruptures of the Achilles tendon represent 35% of all tendon ruptures (12). Achilles tendon rupture is more common in men, with a male/female ratio ranging between 1.7:1 and 30:1 (10).

The pathogenesis has not yet been clarified with several scientific articles advancing many hypotheses. The two main theories that have been advanced are represented by the degenerative and the mechanical one. The degenerative theory states that the chronic degeneration of the tendon leads to rupture without application of excessive loads. Conversely the mechanical one investigate the different type of traumas occurring with the tendon in tension (17-19).

The classic tendon rupture is unilateral; bilateral rupture is often associated to systemic diseases. In 74% of the cases the rupture is localized between 2 and 6 cm from the calcaneal insertion (19).

The management of acute rupture of the Achilles tendon is up to now an hot topic. Mainly treatment options in case of Achilles rupture are represented by:

- Conservative treatment;
- Open surgical repair;
- Percutaneous surgical repair (with different accesses and different sutures);
- Mini-invasive surgical repair (with the use of specifically designed instrumentations);

A huge number of studies have been performed to determine the best treatment for these lesions (20). The Literature demonstrated that conservative treatment encompasses an high rate of recurrence of the lesions varying from 10% to 30% according to the different case series (21). Conversely the recurrence rate is lower after surgical repair of the torn tendon (5% according to the most important case series), but this procedure clearly contemplate an higher rate of complications such as dehiscence, infection, injury of the sural nerve or keloids formation (22).

Percutaneous or minimally invasive surgical techniques present lower complication rates with respect to open surgery but higher rates of recurrence of the lesions (up to 10% according to some case series). In addition these procedures expose to an higher risk of sural nerve entrapment and elongation of the repaired tendon that may result insufficient (23-24).

It is therefore clear that the correct treatment for Achilles tendon ruptures should be based both on the type of the lesion and both on the patient specific characteristics such as age, presence of predisposing factors, risk factors for the onset of complications, general conditions, functional capacity, sport activity involvement, type of sport practiced and interval between lesion and treatment (21, 25-27).

A therapeutic algorithm should be the following:

1. Nonoperative treatment should be reserved to elderly patients with low functional demands and concomitant debilitating systemic diseases;

2. The percutaneous or minimally invasive techniques should be used within 6 days after the trauma, in sedentary patients not involved in high impact sport activities or in patients with high risk to

develop post-operative complications;

3. Open surgery should be adopted in active patients involved in high impact sport activities to guarantee the best mechanical outcome and to permit a fast rehabilitation protcol aimed to achieve a rapid sport resumption (25-27).

In case of recurrence of the lesion or in presence of inveterate lesions (over 4 weeks), the surgical treatment should be more aggressive requiring in all cases an open procedure. (24) Typically the surgical procedure used are represented by:

- Termino-terminal suture;
- Plasty with autologous tissues (semitendinosus, gracilis, patellar tendon)
- Transposition of local tendons (Flexor hallucis longus, flexor digitorum longus, peroneal tendons)
- Tilted band of the gastrocnemius
- Augmentation with synthetic tissue
- Augmentation with allograft or xenograft.

TIBIALIS POSTERIOR

Tibialis posterior lesions are usually chronic and recognize a strong correlation with the adult acquired flat foot (28). In some cases the loss of function of the tibialis posterior tendon is the cause determining the onset of the adult acquired flat foot which represents a source of pain and functional impairment for the patient. In other cases the degeneration of the tibialis posterior tendon is a consequence of the flat foot itself being caused by the persistent pronation of the hind foot and by the mechanical overload on the medial compartment. A wide Literature recognize this strong correlation between lesions of the tibialis posterior tendon and adult flat foot (28-30).

Acute tibialis posterior rupture has been rarely described usually in association to high energy traumas and ankle fractures. In these cases it is mandatory to fix the tendon rupture in the same surgical step of reduction and fixation of the fracture to avoid the onset of a chronic over-pronation of the foot in the post-operative period (30-31).

Conversely, in case of chronic tibialis posterior lesions, it is mandatory to recognize the presence of an associated flat foot and to correct it in order to avoid pathological stresses on the repaired tendon which may result in failures.

Chronic tibialis posterior lesions are usually classified accordingly to Rosemberg et al. (32) as follows:

- Type I lesions: Tendon hypertrophy with longitudinal fissuring;
- Type II lesions: Tendon elongation and partial lesions;
- Type III lesions: Complete tendon lesion

The conservative treatment relies on the use of drugs, laser therapy and orthotics. A correct orthotic should be made in a semi-rigid material and should envelop the hind foot avoiding the overpronation, substain medially the arch of the foot and should decrease the stresses on metatarsal heads.

The surgical treatment is based on the stage of tendon lesion.

In presence of a type I lesion the surgical treatment is represented by the tenolysis and repair of the degenerated tendon. Once the tendon sheat has been opened the tendon is manually tractioned to evaluate its range of motion. If the tendon slides more than 2 cm the deformity cannot be classified as grade I lesion thus requiring a more aggressive surgical treatment. The sinovitic tissue is recognizable as a brown, friable tissue which is removed. The tendon is carefully explored, longitudinal fissuring are recognized and the tendon is tubularized with absorbable sutures (32-33).

In presence of type II lesion the treatment is represented by excision and re-tensioning of the tendon. After opening of the sheat and sinovitic tissue asportation the degenerated portion of the tendon is excised and the tendon is sutured. (34) In case of more advanced tendon degeneration an augmentation using the flexor digitorum longus should be performed.

In presence of type III lesion the treatment is represented by transposition of the flexor digitorum longus. The tibialis posterior tendon is visualized and excised starting from the medial malleolus and leaving distally a tendon remnant of approximately 1 cm aimed to optimize the tenodesis. The flexor digitorum longus is isolated and detached distally and tacked. A tunnel is then drilled on the most medial portion of the navicular bone and the tacked flexor digitorum longus is then passed in the tunnel in caudal-cranial direction. With the midfoot in adduction and the hindfoot in inversion the tendon

is sutured on itself and on the tibiali posterior distal remnant (35).

As previously stated the repair of the tibialis posterior tendon must be accompanied by the correction of the concomitant flat foot. Pre-operatively the state of the mid-tarsal and sub-talar joint should be evaluated. In case of midtarsal or subtalar arthritis none of the previously described procedure on the tibialis posterior should be performed and the surgical treatment should rely on mid-tarsal and subtalar arthrodesis. In absence of mid-tarsal and sub-talar arthritis the correction of the flat foot should be achieved with calcaneal osteotomy, subtalar arthrorisis with bioadsorbable plug and Evans osteotomy in cases of severe midtarsal abduction. Once the realignment of the hind foot is achieved associated procedures should be performed such as Achille tendon lengthening and plantar-flexion osteotomy of the first ray (35-36).

The acute rupture of the tibialis posterior tendon is quite uncommon and it's usual presentation is in combination with an ankle fracture caused by a trauma with a pronation and external rotation of the foot which affect the medial compartment of the ankle. The surgical treatment consists in the open reduction and fixation of the malleolar fracture associated to a termino-terminal Bunnel suture of the two portions of the ruptured tendon (33-34).

PERONEAL TENDONS

Peroneal tendon lesions are quite common presenting the 4th incidence among all the tendon lesions in the foot and ankle. The pathogenesis of these lesions is often traumatic but usually it is related to a degenerative condition in which a low entity trauma can cause the onset of tendons alterations. Risk factors are represented by diabetes, neuropathy, dyslipidemia, hyperparathyroidism and hyperuricemia (37-40). Anatomical abnormalities may play an important role in the onset of these lesions, particularly a strong correlation between these lesions and cavus foot deformity has been reported in the Literature (42).

It is therefore mandatory to correct this deformity, when present, in combination to the peroneal tendons repair in order to achieve a satisfactory post-operative result. The procedures aimed to correct cavus foot deformity may affect the hind foot, such as valgus calcaneal osteotomy and Steindler's plantar fasciotomy, or the forefoot such as the dorsi-flexion osteotomy of the first ray.

The most frequent lesions of the peroneal tendons are represented by:

Tenosynovitis and tendinitis;

Longitudinal fissures and transverse ruptures;

Subluxations and dislocations.

Tenosynovitis and tendinitis are usually treated in a conservative fashion using rest, drugs, orthotics, laser therapy and anti-inflammatory injections in the tendon sheath. In case of failure of the conservative treatment the surgical treatment typically relies on tenosynoviectomy, tenolysis and tendon repair in the most advanced cases (43-44).

Longitudinal fissures are quite common interesting more frequently the peroneus brevis tendon with respect to the peroneus longus tendon. These fissures are usually located at the distal portion of the fibula. The most common causative agents are represented by friction and instability. The fissure is realized by the friction of the tendon against the sharp posterior margin of the fibula. The laxity of the superior peroneal retinaculum can cause a subluxation of the tendons which may result in an increased friction against the fibula causing the tendon lesion (45). Other causes of longitudinal fissures are represented by tenosynovitis of the peroneal tendons, hypertrophy of the peroneus longus tendon, an abnormal insertion of the peroneus brevis tendon or the presence of peroneus quartus tendon. Longitudinal fissures of the peroneal tendons has been divided in 4 stages according to the anatomo-pathological findings as follows (47):

- Grade I: Flattened tendon;
- Grade II: Partial thickness lesion under 1 cm in length;
- Grade III: Full thickness tear with length between 1 and 2 cm;
- Grade IV: Full thickness tear with length over 2 cm.

Conservative treatment present an high rate of failure, up to 83% of the cases according to the Literature (51). Surgical treatment is based upon the state of the tendon. When the fissure interests a small portion of the tendon it is usually sutured. In presence of more advanced disease, when the

fissure of the tendon is accompanied by a tendinosis, the degenerated tissue is removed and the tendon is tabularized (45-47).

The lesions of the peroneus longus tendon are less common with respect to peroneus brevis tendon, being described in the Literature only in case reports. These lesions are usually located more distally with respect to the lesions of the peroneus brevis. Many Authors reported that rheumatoid arthritis, psoriasis, presence of the os peroneum, diabetes, hyperparathyroidism and steroidal local injections may lead to the rupture of the peroneus longus tendon (51-52).

The main causative agent is again represented by an ankle sprain in inversion. The conservative treatment has an high rate of failure (80% according to some Authors), therefore the treatment is often surgical and it is represented by an excision of the os peroneum associated to the repair of the injured tendon or by a tenodesis of both the proximal and distal portions of the peroneus longus tendon with the peroneus brevis tendon.

Peroneal tendons sub-luxation and dislocations are quite common and they're usually caused by a sport injury which affect the superior peroneal retinaculum (38). The injury is usually represented by an ankle sprain in inversion and dorsi-flexion accompanied by a sudden contraction of the peroneal muscles aimed to stabilize the joint. Oden (48) proposed a classification in 4 stages for peroneal tendons dislocations:

- Grade I: The superior peroneal retinaculum and the periostium are relieved from the lateral malleolus and the tendons are migrated anteriorly;
- Grade II: The superior peroneal retinaculum is detached at the level of its anterior insertion;
- Grade III: The superior peroneal retinaculum is detached with a small bony fragment from the lateral malleolus;
- Grade IV: The superior peroneal retinaculum is detached at the level of its posterior insertion.

The treatment acute lesions is controversial with an high risk of failure of the conservative treatment (49). The treatment of chronic lesions typically relies on surgical procedure aimed to restore the retinaculum such as the retinaculum re-tensioning or the retinaculum plasty which may be associated to bony procedures like the deepening of the peroneal groove.

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REVIEW ARTICLE

BIOLOGICAL SCAFFOLDS FOR TENDON AND LIGAMENT REPAIR: NEW TREND

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Tendon is not able to heal itself: this raises the need of implantable devices, synthetic or biological, to use for augmentation or as substitutes. Pre-clinical studies on bio-scaffolds show very optimistic results however clinical studies reported high incidence of adverse events and implant failures. This gives remarks about manufacturing process must be ameliorated, searching a compromise between safety and mechanical resistance. Today, because of their mechanical weakness, scaffolds should be used only for augmentation and not as substitutes of tendons or ligaments. New trend will be the combination of synthetic and biological devices to take advantages from both.

Systematic Review: I Level of Evidence

Tendons are defined as connective tissues involved in movement (1). They are extremely specialized tissues, with poor vascularization and cellular population: that explains why after an injury they can very seldom heal showing the so-called *restitutio ad integrum*. After an injury, these connectives appear degenerated, atrophic or metaplasic, so that is impossible to function within a physiologic range of normality: the re-rupture risk is indeed very high (2). Given these conditions, and given the higher functional patients' demand nowadays, raised a need to give support to weak and damage tendons and ligaments, by a reconstruction or reinforcement with auto-, homo-, xeno-grafts or even synthetic ones. Autografts, which still remain the main option as tendon and ligament substitute for many, is maybe still the best option for tissue quality and the low rate of failure and vanishing phenomena; however, criticisms to autograft for the donor-site morbility have been raised. Allografts as well, are widely used in daily surgical practice, especially in revision procedures. They are as well show some limits, first of all the availability and the costs, then the higher failure risk as the potential risk to potentially induce diseases in host (3).

Several artificial materials have been used as graft in tendon and ligament surgery, at first in preclinical tests and then in surgical practice (4). In 1903 Lange first used silk threads to reinforce a lesioned semitendinosus, although unsuccessful (5). Corner performed an ACL reconstruction with a silver implant (6). From the '70-'80 synthetic fibers have been introduced with great enthusiasm in clinical practice. Carbon fibers based implants (7), then Gore-Tex(8), Leeds Kejo or LARS (9-10) ones became very popular and were used without very precise indications. However, after an optimistic beginning, lots of issues raised regarding the long term durability and resistance (11). As well, quite frequently inflammatory host reactions and necrosis phenomena have been reported in literature (12): these adverse events were the major cause of failure,

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so that surgeons and researchers thought was best to focus on a biological pathway, to substitute the torn tissue with a membrane able to provide a re-growth, a "regeneration" of tendon, showing the same histological and biomechanical features of the native tissue.

Since the early '90, first biomaterials for tissue engineering have been tested in vitro and in animal study. Artificial polymers, biodegradable films and multi-layer membrane of animal or human origin, born by the combination of engineering and biology has quickly become available on the market. Nowadays such products are named Extra Cellular Matrix (ECM) or Bio-scaffolds (13).

Bio-scaffolds are protein-based extracellular matrices that are usually derived from human or animal connective tissues. Thanks to the big advances in the manufacturing process, both biological and synthetic scaffolds, changed from simple "patch" to "biologically active" device, a neo-tendon. Their advantages are a well-defined three-dimensional surface microstructure (allowing host cell integration), porosity (providing adequate host cell migration, attachment, proliferation, favouring metabolites diffusion). These properties allow biological scaffolds to interact with host tissue and induce new tissue faster than synthetic devices. Limitations of biological scaffolds are low mechanical properties (often resulting in failure of surgery), non-specific induction ability, undefined degradation rate, variation in biocompatibility depending on the source of raw materials, which can cause inflammatory response and even implant rejection. On the other hand, synthetic scaffolds are manufactured from chemical compounds, which permit better control of the chemical and physical properties leading to stronger mechanical strength and consistency in quality. However, biocompatibility of synthetic scaffolds is very poor, as they can never be absorbed or integrated into host tissue. High incidences of postoperative infection and chronic immune response have been reported with the use of such materials.

One further aspect is regarding the use of proper terminology, when it's dealt with bio-scaffolds. For many years, with the first product derived from human dermis and bovine pericardium, bio-scaffolds has been considered suitable for tendon substitution, so that were popularized as tendon substitutes (14).

After the publications by Barber (15-17) and (18), bio-scaffold were well-defined "augmentation", standing for a biological device able to lead the host cells proliferation and potentially regeneration. In fact, thanks to these articles it has clearly demonstrated in animal models that it is not possible for the raw bio-scaffold to resists to mechanical loads like the ones normally applied to rotator cuff, Achilles tendon or patellar tendon.

From the regulatory aspect, human tissue derived bio-scaffolds are considered as human tissue for allo-transplantation (Code of Federal Regulation, 21 CFR part. 1270) so that any FDA or other administration approval is strictly required. Animal-derived scaffolds are on the other hand, prior to commercial distribution need to obtain the FDA approval. Just because of these strict rules on scaffolds distribution, currently few of the large amounts of membranes tested in vitro or in animal models arrived to a commercialization phase.

Thus, aim of this paper is to report details about the commercially available bio-scaffolds of human and animal origin, clarifying their indication of use and summarizing the current literature.

MATERIALS AND METHODS.

We performed a comprehensive search of PubMed, Medline, Cochrane, and Embase databases using combinations of the commercial names of each scaffold and the keywords 'tendon', 'rotator cuff', 'Achilles tendon', 'scaffold', 'bio-scaffold' 'biomaterials', 'extracellular matrix', 'tendon substitute', and 'augmentation' over the years 1980–2013. All the relevant papers in English, French and Italian language were retrieved, and their bibliographies checked for further insights. Article reporting on scaffolds for ligament repair were also excluded from the study given the subject of the current article focuses on scaffolds for tendon augmentation. As well all the articles reporting results of synthetic scaffold were not considered suitable for our aims. In results section are briefly listed the commercially available products and data coming from studies preclinical and clinical studies.

RESULTS

Porcine Small Intestine Submucosa (SIS)

The milestone of bio-scaffolds is the one

produced from the porcine small intestinal submucosa (SIS) (19). A main feature of this scaffold is biodegradability, made easier because of the cross-links absence. In animal model, it has been shown to contribute significantly in improving mechanical resistance, as demostrated an increased peak at failure (20).

CuffPatch (Organogenesis, Canton, MA, licensed to Arthrotek)

It is one of the first commercial products obtained from porcine SIS. It is available for human purposes since 2002, so one of the first available. It is now suggested as suitable for rotator cuff augmentation. It is composed of 97% collagen and 2% elastin (21). It is manufactured as a multi-layer, it is acellular, and it is provided in a 6.5 x 9 cm sheet. To ensure proper collagen content maturity, SIS is harvested from pigs weighing more than 205 Kg. The raw material is mechanically processed through a series of customized rollers and the inner and outer mucosal and muscular layers are removed to determine a uniform base product. The tissue purified and acellularized is cut and processed with a series of chemical cleansing solutions. The chemical lavage destroys and washes away cells and debris from SIS, albeit controlling swelling of the collagen fibres preserves the tissue structure. The product is cross-linked with water-soluble carbodiimide, which is not cytotoxic reaching a final dehydrated thickness of 0.6 mm thick. Sterilization is performed recurring to a γ radiation of 25-kGy (22). When used, it has to be hydrated for about 5-10 before implantation.

Zimmer Collagen Repair Patch (Tissue Science Laboratories, Covington, Ga, USA, licensed to Zimmer)

This is a porcine dermis monolayer membrane of 1mm thickness, made of acellular collagen reinforced by crosslinks and elastin fibres. It is derived by dermis after a proper removal of hair and skin annexes. The use of dermic products to repair tendons is not new: already in the'70 Grewal and Mittal used skin graft to fill tendon defects, like in biceps, flexors or Achilles one (23).

TissueMend (Stryker, Mahwah, NJ) is a monolayer membrane. Several lavages remove cells in order to reduce any cell, debris and DNA residuals. It results in a 99% collagen membrane without crosslinks. TissueMend is sterilize in ethilen dioxide and packed in 5x6 cm for 1.2mm thickness.

GraftJacket Regenerative tissue Matrix™ (Wright Medical Technology, Arlington, TN) is at present the only product of human origin, officially approved for augmentation purposes, like in rotator cuff (24-25). Product preparation requires a complete separation of epidermidis and dermis, followed by a freeze-drying step to prevent ice crystal formation and preserve its integrity. It results an acellular matrix, composed of collagen I III, IV and VII, elastin, chondroitin-sulphate, proteoglycans and growth factors like b-FGF. Furthermore it shows a porosity and 3D structure that favours cells migration and adhesion. As other products, the membrane must be hydrated in saline solution 10-15 prior to implantation. In literature it has been reported by ex vivo study on animal model that cells proliferation on the scaffold starts at 14 days after the implantation, and apparently does not give any inflammatory response (26-27).

BioBlanket Surgical Mesh (Kensey Nash Corporation, Exton, PA) is a porous matrix made of different soluble collagens. This material is liofilize and then reconstituted to produce a native-like tissue. It received FDA approval as agumentation for cuff disorders (28).

OrthoADAPT (Pegasus Biologics, Irvine, CA) is made by equine pericardium. It is an acellular membrane with crosslinks and it is not irradiated to obtain sterilization. Its composition is 90% collagen I and 10% Collagen II.

DISCUSSION

Tissue engineering nowadays, as term historically introduced by Langer and Vacanti (29), is a branch of the biomedical sciences devoted to tissue repair through artificial polymers, or biomaterials derived from animals or human (15). In particular ECM also known as bio-scaffold, seem to be the most suitable product for soft tissue repair since they are resorbable and substituted by new autologous tissue. Furthermore it is demonstrated to accelerate the healing timing, by hosting cells into the treated area attempting to lead the reparative process and enhance the tissue maturation (30). Since the introduction of

ECMs scaffolds in surgical practice, advantages like the biomechanical reinforcement, the prevention of a gap formation between the repaired tendon edges and show again a "normally organized tissue" and not a chaotic scar. These last are unfortunately still supposition since there is not incontrovertible evidence about. The ideal scaffold muse favour the tissue ingrowth and tendon regeneration while it undergoes a process of degradation: the graft reabsorption is very different if considered the several commercially available scaffolds (21). The capability of host-tissue ingrowing appears superior in biological scaffolds compared to synthetic products, albeit it is not controlled and really tissue-specific (4). It has been pointed on the interaction between scaffold surface and host cells the key aspect of the use of scaffolds for tendon reconstruction. In the first phase of tissue repair using bio-scaffolds, from the borders through the contact surfaces, host cells migrate into the scaffold and start the synthesis of new collagen fibers and adhesions. The cell proliferation phase starts when the right relationships with the scaffold surface and intercellular connections are set up (31). Porosity (32), crosslinks (33) and scaffold structure (34) appear today perhaps the most crucial aspect to obtain the maximal host cells migration and proliferation. Several chemical cross-linking molecules like carbodiimide, glutaraldehyde, isocyanate and others have been employed to stabilize the structure of the scaffold, improving strength and the mechanical properties; however clinical studies have not confirmed the expected beneficial effect of chemical cross-linking scaffolds. On the other hand our in vitro experimental study clearly assessed how the parallel collagen I fibers were able to drive an higher number of cells into the scaffold and have consequently an higher proliferation. In fact to our observation, host cells "felt as favourite" the scaffold that repeated a physiologic tendon structure (with collagen I and II organized in parallel fascicles) instead of a disorganized ones. This aspect, which belongs basically to the manufacturing process, could be now obtained through the electrospinning process (35).

The surface of biological scaffolds composed of natural-derived type I collagen protein. On the other hand, the surfaces of synthetic scaffold are composed of macromolecules lacking a well-defined structure that allows host cell to produce stronger bindings.

Even though biological scaffolds are becoming more popular because they are someway the first step in orthopedic regenerative strategies, they are still missing clinical well-conducted human studies. Indeed, the majority of clinical trials reported mostly about failures, complications or adverse events associated with ECMs (36). Major concern about as biological as synthetic scaffolds is the biocompatibility and the inflammatory response associated with graft rejection. Part of this issue is solved recurring to an extensive purification of the raw materials used to produce scaffolds. Cells, DNA, proteins and lipids are physically removed by lavages, chemical and mechanical treatments (34). For long periods nevertheless, some proteins have been maintained in the scaffold structure, because considered to be important for biomechanical properties: this is, for example how it happens with elastin and other elastic proteins, which has been recently discovered to be cause of rejections through inflammatory response (37). Aseptic inflammatory reaction has been reported in patient in about 16–22% (38): histopathological samples allowed to identify granulation tissue, without a proper granuloma characterized with giant cells. The paper by Valentin (21) furthermore pointed out how the structure and a longer reabsorption timing were directly correlated with giant cells concentration within the specimen, development of chronic inflammation. Bio-scaffolds manufactured from human or animal tissue might carry a risk of unknown disease transmission, and albeit not reported to date, it is stil a potential issue. One of the advantages of these biomaterials is the potential role in delivering growth factors o cell pre-seeded on the surface. According to Chen (31), bio-scaffolds are still manufactured in a simple way, just to miming the tendon or ligament body structure, without consider the extremities like the osteo-tendineous junction and myotendineous junction. This aspect would be particularly important for large defects reconstructions, where the different parts of the tendon should be fixed by the scaffold.

In fact, since the different structure at the tendon borders is different, when scaffold are used it has been reported an easy failure of the procedure. Looking at this, further investigation still have to be performed. The prospective in bio-scaffold is to

reproduce as much as possible the different parts of tendon structural anatomy, improving the resistance to failure and the cells viability.

What might play a key role in future, opening perhaps a new bio-scaffold era is the interaction between synthetic and biological product. The idea of develop a product made of a superficial part of collagen, miming the native tissue and and inner body of synthetic fibres, which might provide an higher reliability, overcoming the limitations of the very first period when the biological implant is weaker due to a degradation and remodeling. It this view our group has recently started an experimental study, but no preliminary data are at moment available.

CONCLUSION

In conclusion, by the review of literature and our direct experience, we support the idea that these biomaterials can provide an aid to reconstruct tendon defects. There is a big field of application of such devices, but the few clinical data available report of postoperative complications encountered with their employment. Thus, in our opinion, we would suggest to go back to basic science and lab to improve the final products through a better manufacturing process, from the tissue harvesting, purification, deantigenation to the final sterilization. To date, any of these steps might leave impurities and antigens that cause reject of the implant. For the moment, we suggest to consider these membranes just as scaffolds for reinforcement, since they don't show the required structure and strength to completely substitute a native tendon.

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REVIEW ARTICLE

CHONDROGENETIC PROPERTIES OF THE SYNOVIAL TISSUE AND A REVIEW OF THE LITERATURE ON SYNOVIAL MESENCHYMAL STROMAL CELLS

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The cartilage pathologies have been frequently seen in clinics. If they are not treated properly, they may cause significant functional disabilities and may even finally progress to osteoarthritis of the affected joint. There are various methods, which have been described for their treatment. The use of mesenchymal stromal cells has been intensively studied for their differentiation to chondrocytes. There are also a variety of enhancing factor involved in this process. This study demonstrated that the synovial tissue is a highly suitable in-vivo culture for the growth of native articular cartilage tissue, especially involving subchondral bone -osteochondral tissues-. This intimate relationship between the synovial and hyaline cartilage tissues –which we prefer to call "biological tropism"- may open new frontiers on the treatment of cartilage lesions as an alternative "biological treatment". Human can produce his own hyaline cartilage via synovial command and induction!

Basic Science: Randomized Experimental Study

The biological healing of hyaline cartilage is one of the partially solved clinical problems in the human body. The researches on the biological treatment of cartilage lesions have been going on increasingly. The current and novel methods of treatment include: intraarticular (IA) hyaluronic acid (HA) injections, arthroscopic debridement, microfracture, osteochondral transplantation, chondrocyte transplantation, meniscal allografts, tissue engineering, and genetic strategies (1-10). Among these, the most frequently methods used in clinics include IA HA injections, arthroscopic debridement, microfracture, osteochondral transplantation and autogenous chondrocyte transplantation.

The mesenchymal stromal cells have been attractive cell sources for autogenous chondrocyte transplantation (11). Their chondrogenetic properties vary according to the different tissues where they are found such as: bone marrow, periosteum, tendon, skeletal muscle, adipose tissue, neural tissue, hepatic tissue and synovial tissue. Among these tissues, the synovial tissue has mesenchymal stromal cells that have the highest chondrogenetic potential (12). The chondrogenetic properties of the synovial tissue

Key words: synovial tissue, knee, chondrogenesis.

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have been investigated in current studies, which will probably lead to a probable promising alternative treatment method for chondral or osteochondral pathologies (12-17).

The two main aims of this manuscript are to demonstrate the in-vivo chondrogenetic properties the synovial tissue and to review the relevant current literature.

MATERIALS AND METHODS

In this experimental study, twenty-four knees of twelve New Zealand Rabbits were included. The study was started after getting official permission from the local ethical committee of Hacettepe University School of Medicine.

The surgeries were started after the induction of anesthesia with aseptic and sterile preparation of all knees of the animals. After mid-line incision and medial parapatellar arthrotomy, standardized chondral and osteochondral tissue samples were obtained from the non-weight bearing surfaces of lateral femoral condyles of the right and left knees, respectively. Their size were 4 mm and 6 mm in depth, respectively. One tissue sample per each knee was taken as control sample. The animals were divided into two equal groups: Group I and group II. In group I, chondral and osteochondral samples were sutured into the supracondylar synovial tissue. Whereas the samples were sutured posterior to the patellar tendon in the group II.

After a follow-up period of four months, the animals were operated with the same surgical technique described before. The samples, which were put into the synovial tissue and patellar tendon, were taken out for their microscopic and macroscopic analysis. Macroscopic

Table I. *Mean chondrocyte numbers +/- SD in all groups*

	Osteochondral samples	Chondral samples
Preoperative control group	15.5 +/- 1.9	19.7 +/- 2.0
Group I	20.2 +/- 0.5	18.1 +/- 1.4
Group II	18.7 +/- 1.1	15.6 +/- 1.4

Table II. *Mean volumes (mm^3) +/- SD in all groups*

		Volume (mm^3 +/- SD)
Preoperative control group	Osteochondral	96.0
	Chondral	64.0
Group I	Osteochondral	1124.8 +/- 633.5
	Chondral	232.8 +/- 68.2
Group II	Osteochondral	757.3 +/- 360.2
	Chondral	261.6 +/- 74.6

measurements of all samples were done with the same ruler by a single investigator. Microscopic analysis was evaluated by using a Nikon Optiphot light microscopy equipped with a "Camera Lucida" device by the same investigator. The number of chondrocytes was counted according to the camera lucida method in order to obtain more objective results (18).

The statistical analysis of the data was done using SPSS Base 16.0 software with Mann-Whitney U test and regression analysis, with a statistical significance of $p < 0.05$.

RESULTS

The results after four months of follow-up period were according to the five and six rabbits from group I and II, respectively. As the most important result of this study, the microscopic mean chondrocyte numbers are shown in Table I. Although the mean chondrocyte numbers of osteochondral samples were found to be lower in the preoperative control group, the mean chondrocyte numbers of osteochondral samples were found to be greater in group I and II after four months of follow-up period ($p<0.05$). Another result was the decrease of chondrocyte numbers in the group II with chondral samples compared with preoperative control samples, which was statistically insignificant (n.s.). These findings clearly demonstrated the in-vivo chondrogenetic potential of the synovium together with the increasingly recognized importance of subchondral bone.

Subsequently macroscopic measurements yielded volumetric increase of all samples in groups I and II, compared with preoperative control group, as shown in *Table 2*. This increase was more striking both in the group I and in osteochondral samples than in the group II and chondral samples, respectively ($p<0.05$). Both findings clearly demonstrated the importance of synovial tissue as a perfect in-vivo culture for chondrocytes and cartilage tissue and the critical role of subchondral bone in biological cartilage healing.

Table III. *Some important factors enhancing chondrogenetic differentitation of mesenchymal stromal cells*

Magnesium
Antioxidation of decellularized stem cell matrix
Synovial fluid and its osmolarity
Hyaluronic acid
Transforming growth factor - β (β1 and β3)
Bone morphogenic protein – 2, 4 and 7
Insulin-like growth factor – 1
Fibroblast growth factor - 2
Matrillins – 1 and 3
Continuous passive motion
Weight bearing

As the final results of this study, a logarithmic correlation was found between the mean chondrocyte numbers and mean volumes for all samples in all groups, with statistical significance ($p<0.05$).

DISCUSSION

This study clearly demonstrated the important role of synovial tissue and subchondral tissue in the in-vivo chondrogenesis. The studies on the close histoanatomic and cellular relationships between synovial tissue and cartilage tissue has been increasing over years, which we strongly believe that a novel concept of "biological tropism" will be possible to emerge to describe their intimate contiguity.

The treatment of hyaline cartilage injuries have always been a challenge due to several factors such as: avascularity, limited proliferative capacity, chondral senescence, chondrocyte immobility, difficulties in the formation and regeneration of original hyaline cartilage and problems in cartilage integration (19-20). Despite these difficulties, the efforts have increased on this hot topic. Especially the recent advances have focused on the chondrogenetic differentiation properties of mesenchymal stromal cells (11, 21-22). The subsequent studies focused mostly on their in-vitro chondrogenetic effects (23-25). Although the mesenchymal stromal cells are available in many tissues of human body, the synovial tissue was found to be the most chondrogenetic of all these (14, 26-28). The synovial tissue is highly proliferative. It is anatomically the nearest tissue to the joint hyaline cartilage. Moreover, it is available via arthroscopic excision.

In the literature, various factors were shown to enhance this intimate process of differentiation of synovial mesenchymal stromal cells to chondrocytes. Some of these factors were shown in Table III. (23-24, 29-38)

In conclusion, the intimate contiguity between the synovial tissue and cartilage tissue may be described as an example of "*biological tropism*", which would possibly lead to an alternative "in-vivo biological treatment" for articular cartilage lesions. Further multi-centric, high-quality randomized-controlled studies are necessary before making definitive conclusions.

As a future prospect, our next step i to investigate and to compare the influences of bone marrow, tendon, muscle, omentum and peritoneum on hyaline cartilage.

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SURGICAL TECHNIQUE

ANATOMIC ALL-INSIDE ACL RECONSTRUCTION: SURGICAL TECHNIQUE AND RESULTS

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The reconstruction of the anterior cruciate ligament (ACL) has become a common procedure permitting to restore the normal anterior stability of the knee and its correct kinematics with many techniques described in literature. Recently technical improvements led to the development of minimally invasive techniques capable to obtain an anatomical ACL reconstruction. The aim of this study is to report the clinical results obtained with an anatomic single bundle All-inside technique using a triplicated or quadruplicated autologous semitendinosus (ST) tendon fixed with a second-generation cortical suspensory fixation device.

Case series: IV Level of evidence

Recently the emphasis on ACL reconstruction has been focused on procedures that can ensure the least morbidity for the patient, a solid and reliable primary fixation and the best potential for biologization. The concept of a mini-invasive surgery in order to save bone and soft tissue associated with a faster rehabilitation and an early return to sport activities is becoming an issue of more and more interest. The All-Inside technique, first described by Cerulli, is one of the best techniques that respect these features (1-4). The technique encompassed the unconstrained creation of an half tunnel both on the tibial and on the femoral side using guide pins of 3.5 mm in diameter that became retrograde drills (Flipcutter, Arhtrex Ltd). The use of a socket instead of a complete tunnel results in a monocortical reaming with a better bone-graft contact that further enhances the ligamentization process (5-11). The choice of the graft and its fixation still remain cause of concern (12-16). The use of hamstrings have been widely reported for ACL reconstruction, but the residual deficit in knee flexion at extreme degrees and the lost of the protective role of hamstrings on the ACL are the major drawbacks (17). Hence the use of both the ST and gracilis (GR) tendons is not the ideal solution to preserve knee biomechanics. The All-Inside technique avoid this inconvenience using only the ST tendon triplicated or quadruplicated in order to obtain the optimal graft lenght (18). Femoral and tibial fixation was achieved with second-generation cortical suspensory fixation devices with adjustable graft loop length (ACL Tight rope RT, Arthrex Ltd).

The aim of this study is to report the clinical results obtained with an anatomic single bundle All-inside technique using a triplicated or quadruplicated autologous ST tendon fixed with a second-generation cortical suspensory fixation device (ACL Tight rope RT, Arthrex Ltd).

MATERIALS AND METHODS

Since October 2010, 32 males with a mean age of

Key words: ACL reconstruction, All-inside, retrograde-drill, ligamentization

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27 ± 8.7 years with unilateral ACL injury underwent reconstruction with the All-Inside technique. Exclusion criteria were the presence of lower limb misalignment greater than 5 degrees, multi-directional instability and revision surgery. Mean time elapsed from injury to surgery was 88.7 ± 32.5 days. In 28 patients the trauma occurred during sports activities while in 4 cases the trauma was caused by a car accident. 5 lesions of the medial meniscus, 2 lesions of the lateral meniscus, 8 lesions of both the medial and lateral meniscus, 1 grade IV osteochondral lesion of the medial femoral condyle (MFC) associated with a lesion of the lateral meniscus and 1 osteochondral lesion of the lateral femoral condyle (LFC) associated with a lesion of the medial meniscus were found as associated lesions. Patients were evaluated with clinical examination, KT-1000 Arthrometer and the International Knee Documentation Committee (IKDC) score pre-operatively and at a minimum follow-up of 12 months.

Surgical technique:

Surgery is performed under general or spinal anesthesia with the patient in a supine position on the operating table, with a C-shaped leg holder at the proximal thigh. A pneumatic tourniquet is positioned, and the leg is prepped. Anteromedial (AM) and Anterolateral (AL) portals are performed. After treatment of the meniscal tear and cartilagine injury, the ruptured ACL is identified and tested with a probe. The ACL tibial and femoral foot-print are carefully debrided.

Graft Harvesting

A vertical 3 cm skin incision is made approximately 2 cm medial to the apex of anterior tibial tuberosity. A fascial incision is made parallel of the pes tendon and the semitendinous tendon is bluntly freed from the surrounding fascial attachments. The tendon is collected using a blunt tendon stripper while the knee is in more than 90° of flexion and detached from its tibial insertion. Subsequently the tendon is sutured and loaded with 2 ACL femoral and tibial Tight Ropes RT according to the technique described by Lubowitz JH. et al (2). (Fig. 1)

Graft passage and fixation

Both the femoral and tibial half-tunnel are created using an otuside-in technique. For this purpose, a second-generation retrograde drill is used (Flipcutter, Arhtrex Ltd) according on the surgical technique described by Lubowitz JH et al (2). The graft is then positioned with the help of a messenger wire through both the femoral and tibial tunnels. Once the button of the ACL tight rope is flipped over the femoral and the tibial cortical the graft tensioning is performed by pulling the femoral and tibial pull sutures. 5 cycle of knee flexion-extension are performed and then the graft tension is checked again. (Fig. 2)

RESULTS

We experienced an intraoperative rupture of a retrograde drill and a traumatic failure (6 months after surgery) revised using the same sockets with an allograft. All the patients were evaluated at 3, 5, and at a minimum follow-up of 12 months. Clinical evaluation was performed by submitting the IKDC score and the stabilometric analysis was performed using the KT-1000 Arthrometer manual maximum

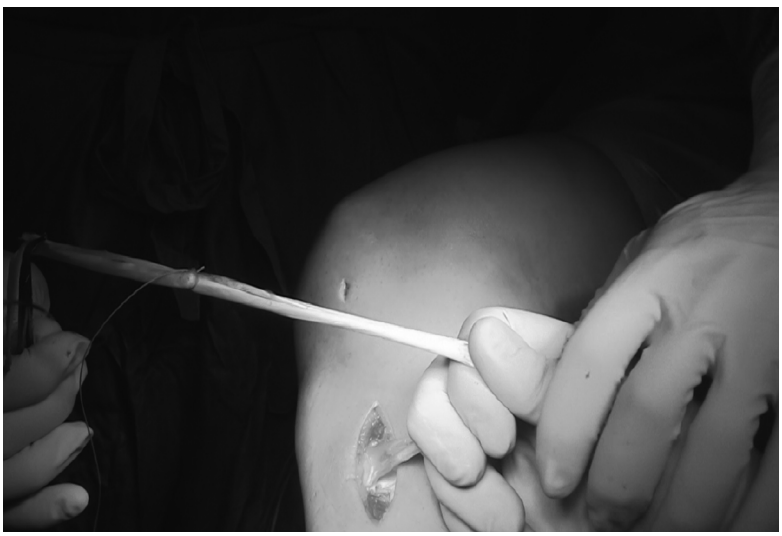

Fig. 1. *Surgical field showing the harvested tendons sutured together using 2 non-absorbable No. 2 stitches.*

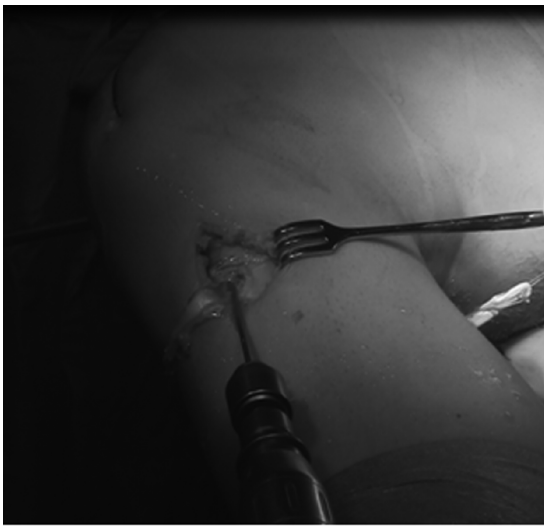

Fig.2. *Surgical field showing the drilling of the tibial tunnel preserving hamstrings insertion*.

displacement test and the passive displacement test. The subjective IKDC score improved from 59.3 ± 6.1 preoperatively to 95.7 ± 3.1 at final follow-up ($p < 0.005$); the objective IKDC score was normal in 24 cases (A) and nearly normal in 7 cases (B) at final follow-up. ROM was found normal in all the patients. Regarding knee stability assessed through the Lachman test performed at 25 ° of flexion, 30 patients had a normal knee, while only one patient had objective mild instability. Arthrometric analysis performed at final follow-up showed an average side to side difference of 0.7 ± 0.2 mm in the manual maximum displacement test and 0.9 ± 0.3 mm in the passive displacement test. The Pivot-shift was normal in 28 patients and nearly normal in the other 3.

All 31 patients resumed sport activity after an average of 130 days (range 120-190); 28 patients resumed the pre-injury sport activity level, while the other 3 patients resumed a lower sport activity level. The statistical evaluation showed no significant relationships between the outcome (subjective and objective) and age, sex, time elapsed from trauma to surgery, associated injuries and graft diameter.

DISCUSSION

Preliminary results showed that the All-Inside technique enables the surgeon to perform a mini-invasive procedure with a good biologic potential, helping the physiatrist in reaching the goal of a rapid return to sports activities. The technique achieved good subjective and objective clinical results and all patients were satisfied with the surgery. The ability to obtain an anatomic ligament reconstruction performing an unconstrained outside-in drilling of the femoral and tibial socket using a single bundle ST graft, the preservation of the integrity of the extensor mechanism through the use of hamstring tendon graft and the use of sockets instead of tunnels resulting in a monocortical reaming with a better bone-graft contact that further enhances the ligamentization process, are the main advantages of this technique. An improvement in the ligamentization process of the graft implanted is obtained with a manual drilling of the sockets, as previously stated by Cerulli et al (19). Disadvantages of this technique are the high costs of the instrumentations and fixation devices, the technically demanding technique and the necessity of a good cortical bone to ensure a solid primary fixation. In conclusion the described technique showed to be minimally invasive and effective in restoring knee stability, but the development of sophisticated instrumentations and tissue engineering should cooperate to reduce morbility and enhance the biologization process in order to achieve the fastest functional recovery for the patient.

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SURGICAL TECHNIQUE

ALLOGRAFT RECONSTRUCTION OF KNEE EXTENSOR MECHANISM

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The reconstruction of an interrupted extensor mechanism after excision of a bone or soft tissue tumor around the knee joint is a challenging procedure and few options are available to avoid knee arthrodesis. In the last 17 years, 50 patients underwent excision of a tumor around the knee joint and different types of reconstructive procedures employing an osteotendineous fresh frozen allograft. Group I included 26 patients who underwent intra-articular proximal tibia resection distal to patellar tendon attachment and reconstruction with an allograft-prosthesis composite implant with direct suture of the patient's patellar tendon to the allograft tendon stump. In group II 18 patients underwent extra-articular knee resection and reconstruction with an allograft-prosthesis composite implant with a direct tendon suture at the level of the quadriceps tendon. Group III included 6 patients who had an isolated graft of the extensor mechanism with bone to bone osteosynthesis at the tibial tuberosity and tendon to tendon suture at the quadriceps tendon. The minimum follow-up was 1 year (average, 7 years; range, 1–16 years). Six patients of the entire series died of disease and one in group one underwent amputation for osteosarcoma local recurrence. One deep infection was recorded in group I and two in group II. Moderate aseptic allograft resorption was recorded in one patient in group I and in group II. One failure of the tendinous portion of the allograft was observed in group I and 2 in group II and two of them were revised. Two prosthetic mechanical failure (femoral component breakage) was observed in group II. All patients were able to walk without aids and active extension was possible in all the patients with an extensor lag >10 degrees in 6 patients of the entire series. In conclusion an osteotendineous allograft is a valid and functional option to reconstruct knee extensor mechanism after its sacrifice for oncologic purposes with stable results over the years.

Retrospective Observational Study: III Level of Evidence

Knee extensor mechanism reconstruction in total knee revision surgery or for traumatic or oncologic reasons is a relatively unfrequent challenge for the orthopaedic surgeon who has to manage not only tendinous discontinuity but also a severe bone loss which is often present.

Few reconstructive options are available to avoid knee arthrodesis and include local grafts, synthetic materials and allograft tissues.

Tendinous reconstruction with autologous tissues locally harvested or rotated, including semitendinosus or gracilis tendons, quadriceps tendon turn-down or fascia lata, has been described in the past with variable and unpredictable results (1-2). Gastrocnemius rotational flaps have been reported to successfully restore extensor mechanism continuity and short-term function after major traumatic acute defects (3) or after oncologic excisions (4).

Key words: osteosarcoma, total knee revision, reconstructive surgery

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Synthetic augmentation with a Dacron graft has been first described in the 80's with encouraging preliminary results (5). Longer follow-up series with early synthetic grafts have never been published. However the unsuccessful long-term fate of first generation synthetic grafts has been reported in cruciate ligaments reconstruction series (6). New generation synthetic materials (polypropylene) have been later on introduced with promising mid-term results (7).

Allogenic tissues to reconstruct extensor mechanism defects have been used for at least 20 years (8) with alternating popularity due mainly to availability, government regulations and disease transmission concern. As to outcome, tendinous allografts have been demonstrated to successfully restore knee extension and function also long term follow-up (9-11) and are considered the gold standard to replace a deficient extensor apparatus. Furthermore, differently from the above described solutions, allografts have the unique property of restoring both tendinous and bone loss and then are particularly indicated in major revision and in oncologic surgery alone or in combination with a metal prosthesis (12).

The purpose of this paper is to retrospectively assess the outcome of osteotendineous knee allografts employed to reconstruct knee extensor mechanism, alone or in combination with a metal prosthesis, mainly in oncologic cases.

MATERIAL AND METHODS

From 1996 to 2012 at the Orthopedic Oncology and Reconstructive Surgery Unit of the Careggi University Hospital (Florence, Italy) fifty patients received fifty-two osteo-tendineous allograft procedures to reconstruct a major extensor mechanism defect. According to the type of surgery the patients were divided into three groups.

Group I included those patients (n. 26) who underwent a conventional intra-articular proximal tibia resection distal to patellar tendon attachment and reconstruction with an allograft-prosthesis composite implant with direct suture of the patient's patellar tendon to the allograft tendon stump (Fig. 1). Group II patients (n. 18) underwent extra-articular knee resection and reconstruction with an allograft-prosthesis composite implant with a direct tendon suture at the level of the quadriceps tendon (Fig. 2). Group III included 6 patients who received an isolated allograft of the extensor mechanism with bone to bone osteosynthesis at the tibial tuberosity and tendon to tendon suture at the quadriceps tendon (Fig. 3). Demographics and diagnoses of the three groups are summarized in Table I.

Preoperative chemotherapy was administered to 6 patients in Group I, 8 in Group II and one in Group III.

Surgery was performed under general anaesthesia and a tourniquet was inflated for the first 90 minutes of the operation. In Group I a lateral approach to the knee joint was performed, proximal tibio-fibular joint was disarticulated or resected and proximal tibia resected at mean length of 10.5 cm from tibial plateau. In one patient who was diagnosed a grade I chondrosarcoma, the entire tibia was resected. In these patients the excision was throughout the patellar tendon and reconstruction was then performed with a direct suture of the patient's patellar tendon over the allograft stump.

In Group II the knee joint was excised en bloc (Fig. 4). The distal femur osteotomy was performed above the suprapatellar pouch, the proximal tibia osteotomy was performed below the tibial tuberosity and popliteal muscle insertion and the knee joint removed en bloc including the full extensor apparatus (quadriceps tendon, patellar bone and the entire patellar tendon) and the entire joint capsule which was removed closed and intact with its gastrocnemius attachment.

In Group III only the extensor apparatus was sacrificed through its entire length and in 4 cases (66%) the skin was excised as well, thus requiring a rotational (2 cases) or free (2 cases) microsurgical flap.

Size-matched fresh-frozen non-irradiated allografts harvested from donors younger than 40 years, were provided by the local tissue bank. The allograft was thawed at room temperature and excessive soft tissues were removed from bone. On a back table graft size was adjusted to match the host bone defect. A modular revision megaprosthesis hinged implant (Waldemar-Link) was used in all the cases. The artificial joint consisted of a semiconstrained sferocentric type mechanism (endomodel) subsequently substituted in a semiconstrained hinged type mechanism (SL).

In group I and II the tibial component was cemented into the allograft with antibiotic loaded cement. Group I patients received a conventional total condylar Endo-model femoral component, while in Group II the distal aspect of the femur was replaced with a reconstructive modular prosthesis. After component fixation and knee reduction the allograft tendon was sutured in extension with non-absorbable sutures to the host one at the patellar tendon level in Group I and at the quadriceps tendon level in Group II. Primary skin closure was achieved in all the cases without the need of extra soft tissue procedures or local grafts in Group I. In group II four patients required a microsurgical rotational (2) or free (2) flap.

In Group III the extensor mechanism allograft tibial bone block was secured with screws at the host tibial tuberosity level in a size matched bone through and the quadriceps tendon sutured in extension to the host one, and to the edges of the vastus medialis and lateralis as well, with non-absorbable sutures.

Postoperatively, the knee was immobilised in a brace or cast for 6 weeks without weight-bearing. Isometric strengthening exercises were allowed.

Six patients received postoperative chemotherapy in Group I, six in Group II and three in Group III.

RESULTS

Early complications were recorded in Group I and II. One patient in Group I had developed a compartment syndrome with transient peroneal and tibial nerve palsy which healed spontaneously. One patient in Group I who had delayed wound healing underwent surgical debridement which lead to successful healing. Knee joint stiffness occurred in 2 patients in group I and in one in Group II; only one patient in group I needed an open release while the other two underwent a successful manipulation under anaesthesia.

Five patients in Group II and one in Group III patients died for disease. One patient in group I received thigh amputation for osteosarcoma local recurrence. Two patients in Group II and one in Group III underwent a local recurrence excision without revision of the implant. One patient in Group III underwent extra-articular knee excision for local recurrence and allograft-composite reconstruction thus entering Group II series.

Three infections were recorded in the entire series, one in group I and two in group II. They occurred within one year from index procedure and all were managed with implant and graft removal and two stage revision with knee arthrodesis.

Table I.

	Group I (#26)	Group II (#18)	Group III (#6)
Age			
Male : Female	13 : 13	10 : 8	2 : 4
Diagnosis:			
Osteosarcoma	7	5	
Chondrosarcoma	4		
Giant cell tumor	10	1	
Ewing Sarcoma		2	
High grade STS		9	5
Chondroblastoma		1	
Desmoid tumor	1		
Failed OA allograft	2		
Failed TKA	2		
Failed tendinous allograft			1

Table II.

	Group I (#26)	Group II (#18)	Group III (#6)
Died of disease	0	5	1
Infection	1	2	0
Amputation	1	0	0
Ext mech fail (reoperated)	1 (0)	3 (2)	0
Revision for mec reasons	0	2	0
Graft resorp (reoperated)	1 (0)	1 (1)	0
Ext deficit >10 deg	4	0	2
Ext lag >10 deg	3	5	1
Flexion <90 deg	6	1	1

a) b)

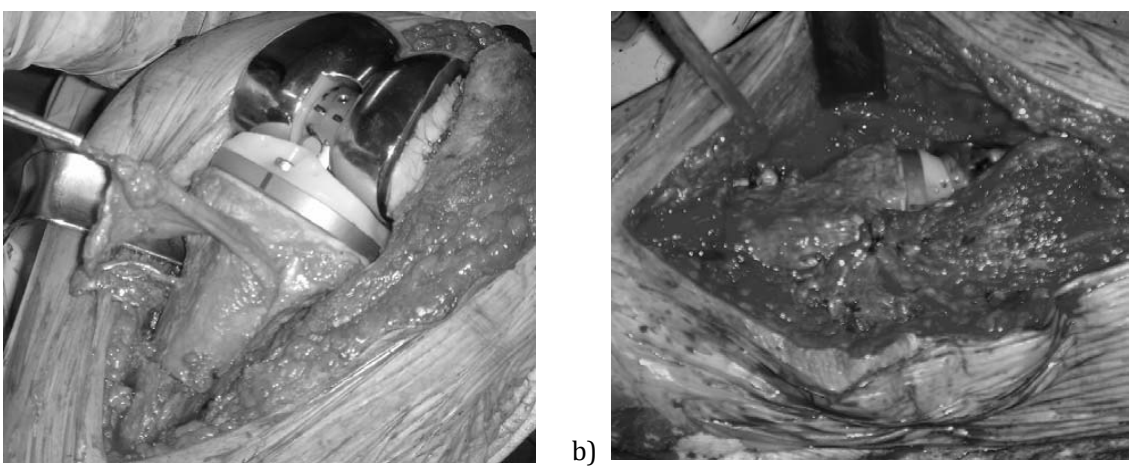
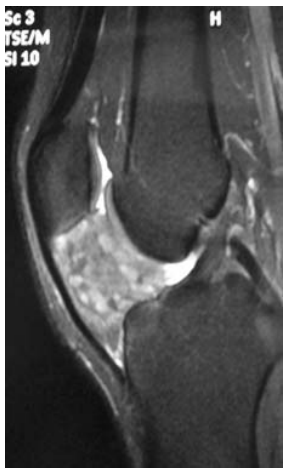


Fig. 1. ***a****) Knee reconstruction in Group I patients with an allograft-prosthesis composite implant and b) suture of the host patellar tendon to the allograft one.*

Two allografts were revised for graft failure in Group II: one quadriceps tendon failed during rehabilitation and underwent direct suture and augmentation with a synthetic graft (the same patient then developed knee infection and implant removal); one patellar tendon broke 9 years after index procedure and underwent isolated extensor mechanism allograft thus joining Group III patients.

Four years after index procedure one patient in group I and one in Group II had patellar and quadriceps tendon atraumatic failure, respectively, but did not undergo revision surgery because of minimal dysfunction: both of them can ambulate without aids and show a minor extensor lag (<20 degrees).

One patient in Group II had severe tibial graft resorption which lead to component mobilization: the prosthesis was then revised leaving in place the residual graft and the extensor mechanism. One patient in Group I had minor graft resorption which



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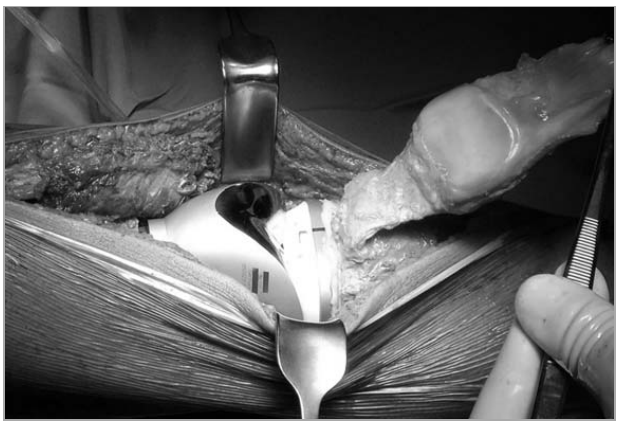

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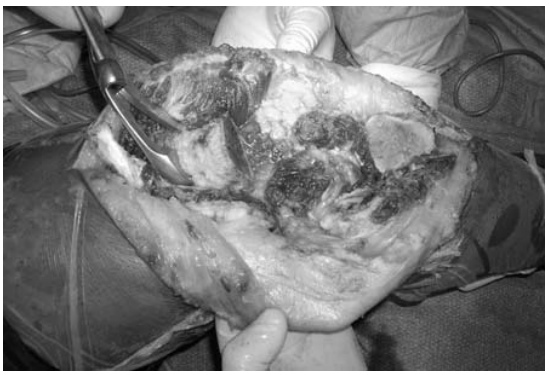

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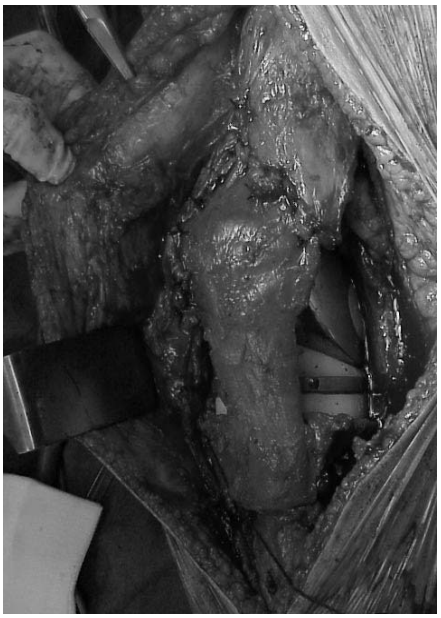
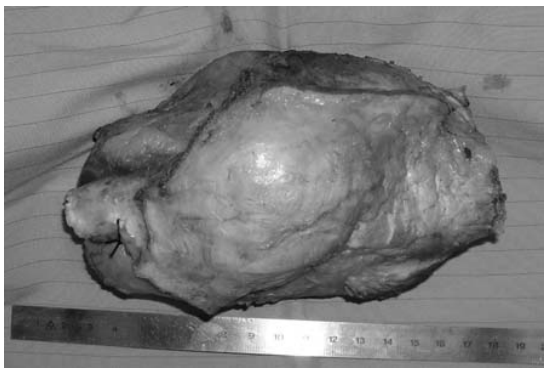


e)



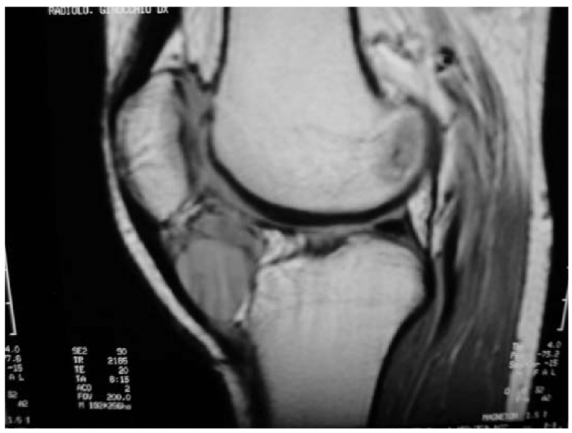
c)

Fig. 2. *Patient included in Group II affected by high grade soft tissue sarcoma at the level of the Hoffa fat pad a) who underwent en-bloc extra-articular knee excision b-c) and reconstruction with a allograft-prosthesis composite implant d) and direct suture of the patient's quadriceps tendon to the allograft one e).*

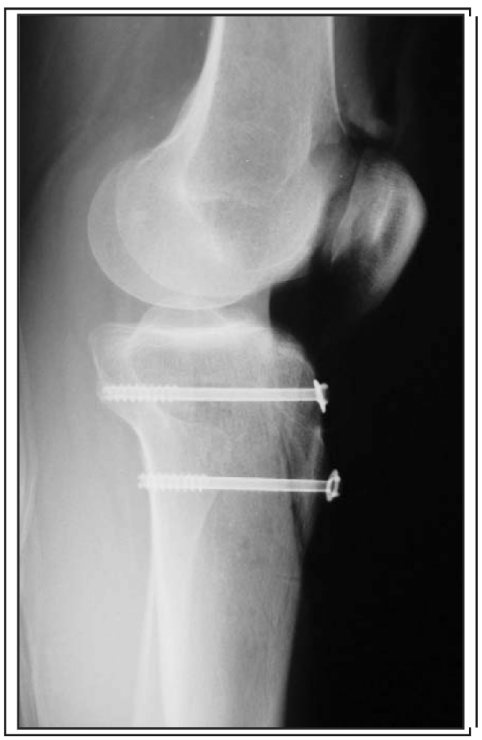
did not interfere with impant fixation.

In two patients in group II the femoral component broke and underwent component revision: in one of them during the second procedure the patella tendon allograft was damaged during exposure and replaced with an Achilles tendon allograft.

After an average follow-up of 7 years, 34 patients were still alive with the same index implant (24 in



a)



b)

Fig. 3. *Patient from Group III who suffered from high grade soft tissue sarcoma at the level of the Hoffa fat pad* ***a)*** *and underwent whole extensor mechanism excision and reconstruction with an extensor mechanism allograft* ***b)****.*

Group I, 6 in Group II and 2 in Group III). All of them are able to walk without aids and only a minority (6) are unable to reach full knee extension. 8 patients of the entire series show a moderate extensor lag (between 10 and 20 degrees) and only one patient had an extensor lag of 30 degrees.

Results from the three groups are summarised in Table II.

DISCUSSION

Knee extensor mechanism reconstruction is a challenging procedure particularly when the surgeon has to deal both with soft tissue (tendon) and bone loss as occurs after most intra- and extra-articular knee excision for oncologic purposes: in such a scenario limb savage surgery often recurs to knee arthrodesis and the only option. In our retrospective study we showed that an osteo-tendineous massive allograft, alone or in combination with a metal prosthesis, allows a long lasting functional outcome without interfering with the oncologic safety. In our series only 6 patients (12% of the entire series) had a re-operation related to the allograft and 84% of the alive patients still have the index implant after a mean follow-up of 7 years.

Allograft popularity and utilization in knee reconstructive surgery after bone tumor excision has had alternating popularity in the past decades not only for safety reasons and disease transmission concern but also for their unpredictable results. Biau et al (13) reported high incidence of allograft fracture (27%), resorption (23%) and extensor mechanism failure (23%) with proximal tibia allograft-prosthesis composite implants after intra-articular resection and a 33% 10 years implant survivorship and discouraged its employment. The inferior success rate of Biau's series can be explained with the utilization of irradiated allografts whose mechanical properties impairement has been reported (14).

In our series patients who received an intra-articular resection (Group I) had the best outcome with low complication incidence and long lasting results. Other investigators[15] failed to achieve satisfactory results with a similar surgical technique and employing fresh frozen non irradiated allografts, not different from those employed in the present study. They reported infection, extensor mechanism failure and graft non union in 24%, 14% and 13% of the patients respectively with a 10 years implant survivorship of 68%. The inferior results of this investigation can be ascribed to the patients population which suffered in 90% of the cases of

a malignant tumor and underwent postoperative chemotherapy in 77% of the cases. On the contrary in the present study 58% of the patients in Group I had a benign pathology and only 27% of the series received postoperative chemotherapy.

As to group I series and reconstructive technique we can conclude that when a fresh-frozen non-irradiate graft is employed in a selected cohort of patients durable results and low complications can be expected.

Group II patients in this study were affected by severe and extensive disease at the knee joint level which required an aggressive en-bloc knee resection as limb-salvage procedure and allograft-prosthesis composite implant was an alternative to arthrodesis. This ensured a safe tumor excision with wide margins and a functional implant in poor-prognosis patients.

Other techniques for reconstruction of the extensor mechanism after en bloc resection of the knee have been described. Anract et al. (16) and Kendall et al. (17) reported their experience with extraarticular resection and reconstruction of the extensor apparatus by a gastrocnemius rotational flap but despite the safe oncologic results, functional outcome was poor. Alternatively, other Authors (18) have proposed a resection that spares part of the extensor apparatus by splitting the patella on the frontal plane thus preserving the dorsal patellar aspect and the patellar and quadriceps tendons as well. Although good results are presented by the originators we are concerned about the oncologic margins with a not true extra-articular procedure with the true possibility to violate the knee joint and contaminate nearby tissues.

Isolated extensor mechanism grafting (Group III) in our hand was confirmed to be a valid strategy to reconstruct a more contained defect. Although few cases were included in our series isolated extensor mechanism reconstruction has ben demonstrated in the literature to be a safe and functional reconstructive technique (9-10).

In conclusion our study confirms the efficacy of osteotendineous extensor mechanism allograft, isolated or in combination with a metal prosthesis, to reconstruct contained or extensive defects. Proper allograft preservation without irradiation and adequate patient selection are keys to success for this technique.

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SURGICAL TECHNIQUE

ANATOMIC ACL RECONSTRUCTION USING DISTALLY INSERTED DOUBLED HAMSTRINGS TENDONS: SURGICAL TECHNIQUE AND RESULTS

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The anatomical anterior cruciate ligament (ACL) reconstruction using hamstring tendons is still a matter of debate in orthopedic surgery. Many techniques are currently available, but all of them require the detachment of the tibial insertion of the hamstrings, damaging the neurovascular supply of the tendons: it results in a lower residual proprioceptivity and worse ligamentization of the graft. To avoid these problems Marcacci described a non anatomical "over the top technique" able to spare the tibial insertion of the hamstring. The long term results presented by the Author are satisfactory. Recently we used a new surgical technique that allows to spare the tibial insertion of the hamstring and also allows anatomical recostruction. The femoral tunnel can be reamed using a antero-medial approach or an outside-in femoral drilling depending to the skill of the surgeon.

Case Series: IV Level of Evidence

Anterior cruciate ligament (ACL) reconstruction is a is a commonly performed orthopaedic procedure (3). Surgical techniques for anterior cruciate ligament injury have evolved considerably over the years, together with our understanding of the anatomy of the ACL . With this new knowledge, interest has increased in recreating an anatomical reconstruction to reduce the long-term incidence of osteoarthritis (4-6). The concept of anatomic or footprint ACL reconstruction reduced the applicability of transtibial drilling of the femoral tunnel because it failed to replicate the anatomical femoral footprint of the ACL (7-9). For these reasons, the anteromedial and outside-in techniques for femoral tunnel placement or socket reaming gained popularity (10).

Most of single or double-bundle anatomic reconstructions procedures using hamstrings tendons are described in literature but need the detachment of the tendons from their tibial insertion (11-12). It has been demonstrated that preservation of the hamstrings tendons insertion allows preservation of the neurovascular supply of the tendons, resulting in residual proprioceptivity and better ligamentization of the graft (13). According to the latest knowledge, the only technique that spare the hamstrings tibial insertion encompass a femoral over-the-top (OTT) passage. This technique is able to achieve good long-term results but does not respect an anatomical reconstruction (14-16). Aim of this study is to describe a new technique to preserve the hamstring tendon insertion of providing the respect of the anatomy using distally inserted doubled hamstrings tendons fixed at the femoral level with a second generation cortical suspensory device.

SURGICAL TECHNIQUE

Surgery is performed under general or spinal

Key words: Knee, ACL Reconstruction, Hamstring.

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anesthesia with the patient in a supine position on the operating table, with a C-shaped leg holder at the proximal thigh. A pneumatic tourniquet is positioned, and the leg is prepped. Anteromedial and anterolateral portals are performed. After treatment of eventual meniscal tear and cartilage injury, the ruptured ACL is identified and tested with a probe. The ACL tibial and femoral foot-print are carefully debrided

A vertical 3-cm skin incision is made approximately 2 cm medial to the apex of anterior tibial tuberosity. As an alternative, to avoid damaging of the infrapatellar branch of the saphenous nerve, the incision can be performed in the same direction as the hamstrings tendons. A fascial incision is made parallel to the orientation of the pes tendons, and the gracilis and semitendinosus tendons are bluntly freed from the surrounding fascial attachments. The tendons are collected using a blunt tendon stripper while the knee is in more than 90° of flexion. The tibial insertion of the tendons must not be disturbed to maintain their neurovascular supply.

The harvested tendons are then sutured together using 2 nonabsorbable No. 2 stitches (Fig.1). A guide pin is inserted from the anteromedial portion of the tibial metaphysis approximately 1 cm medial and 1 cm proximal with respect to the tibial insertion of the hamstrings tendons. The pin is advanced under arthroscopic visualization until it emerges at the level of the medial tibial spine .A reamer is inserted along the guide pin to create the tibial tunnel (Fig.2) . The diameter of the reamer depends on the ligament diameter. A messenger wire is inserted in the joint through the tibial tunnel and retrieved from the anteromedial portal.

The femoral half-tunnel can be created using either the anteromedial or outside-in technique. For the anteromedial technique, the transportal ACL femoral guide (TPG; Arthrex Ltd, Naples, Florida) is used. The guide is inserted through the anteromedial portal with the knee at 90° of flexion. The knee is then brought to 110° of hyperflexion. The tip of the guide is placed at the level of the posterior wall of the lateral femoral condyle and the guide is positioned at the level of the ACL femoral footprint. A millimetered guide wire is advanced in the aimer until it reaches the second cortical to evaluate the width of the lateral femoral condyle. A millimetered reamer is advanced over the guide wire according to the previous measurement to obtain at least a 25-mm socket with 7 mm of cortical bone bridge .Once the drilling of the socket has been completed, a messenger wire is inserted through the anteromedial portal and through the femoral socket.

For the outside-in technique, a second-generation retrograde drill is used (Flipcutter; Arthrex Ltd). With the arthroscope in the anteromedial portal, the ACL femoral marking hook is inserted through the anterolateral portal and placed at the level of the femoral ACL footprint. The Flipcutter guide pin sleeve is advanced to the skin level at a point approximately 1 cm anterior to the posterior border of the iliotibial tract and 1.5 cm proximal to the lateral femoral epicondyle. After measurement of the femoral intraosseous distance, the guide pin is advanced until its entrance in the joint. The guide pin end is flipped to create a retrograde drill, and a 25-mm retrosocket is produced. A messenger wire is advanced through the femoral socket and retrieved through the anteromedial portal

The femoral messenger wire is retrieved outside the tibial tunnel using the tibial messenger wire. A femoral ACL Tightrope (Arthrex Ltd) is placed over the graft. The messenger wire is then used to shuttle the femoral Tightrope suture through the tibial tunnel, the femoral socket, and outside the lateral femoral condyle. Once the button is flipped over, the cortical of the lateral femoral condyle the femoral pull suture is then retrieved outside the anteromedial portal and the free portion of the graft is pulled to tighten the inserted portion of the hamstrings tendons. With the knee at 90° of flexion, femoral fixation is achieved by pulling the femoral pull suture. With the knee at 30° of flexion, the graft remnant is then fixed with a titanium staple placed at the level of the tibial metaphyisis distally with respect to the hamstrings tendon insertion.

MATERIALS AND METHODS

57 patients (32 men - 25 women) affected by unilateral ACL injury were operated. The mean age of 23.3 years (range, 16–32 years). Mean time elapsed from injury to surgery was 2.9 months (range, 1–6 months). All patients were involved in sports at a recreational level. Patients evaluation was

carried out by IKDC score, Tegner activity scale and KT-1000 pre-op, at 3, 5 and 12 months up to the final follow-up of 22.0 ± 2.5 months.

RESULTS

We did not observe any intra-operatively and post-operatively complications . Normal R.O.M. was observed in all patients at follow-up. The mean IKDC subjective score at final follow-up was 97.1 ± 1.4. According to the IKDC objective score, at final follow-up, 50 patients were rated A and 7 patients were rated B. Among the patients rated B, 4 reported anterior knee pain related to a patellofemoral chondropathy despite an objective stable knee. The other 3 patients rated B had an objective mild instability; in 1 patient, both the Lachman and the Pivot-shift tests showed an objective mild instability, whereas only the Pivot-shift test was nearly normal for the other 2 patients.

Arthrometric analysis performed at final follow-up showed a side-to-side difference of 0.9 ± 0.2 and 0.7 ± 0.2 mm according to the manual maximum displacement test and to the passive displacement test, respectively. Return to sport was observed in all patients at a mean of 154.7 ± 15.2 days. Among the

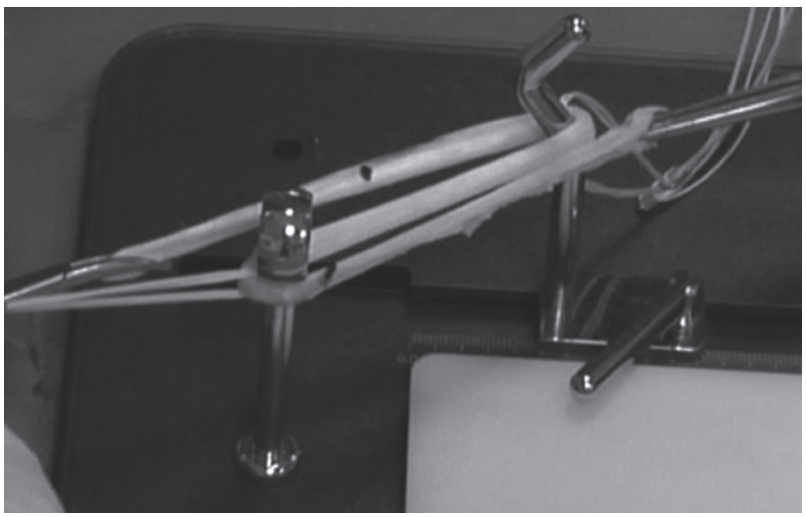

Fig. 1. *Surgical field showing the ST tendon loaded with 2 ACL femoral and tibial Tight Ropes RT.*

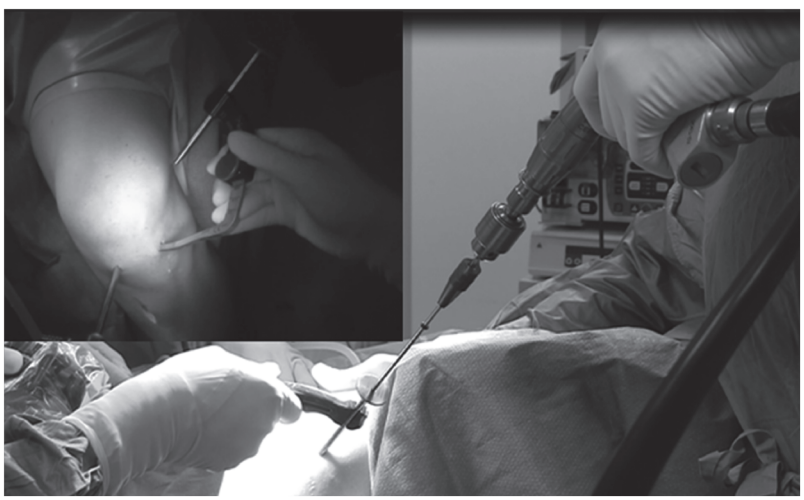

Fig. 2. *Surgical field showing the positioning of the femoral guide and the subsequent creation of the femoral socket using the femoral retrograde drill.*

patients who resumed sport activity, 5 changed type of sport practiced for fear of reinjury. According to the Tegner Activity scale, the mean prelesional level of activity was 7.0 and was 6.9 at final follow-up.

DISCUSSION

The debate that arises regarding the detachment of the hamstrings tibial insertion and the non-anatomical positioning of the graft is still compelling. The described technique permits an anatomical ACL reconstruction with the advantage of the preservation of hamstrings insertion and the creation of a femoral half-tunnel with an enhancement of the ligamentization process of the graft. The development of this technique has been possible due to the evolution of cortical suspensory fixation button devices that can be tightened after the button flips becoming fixed on the cortex. This permits the graft to slide over the loop to tense the inserted portion of the hamstrings tendons (16). Sparing the hamstrings tendon insertion avoids graft fixation on the tibial side, which is commonly achieved with a bioabsorbable interference screw and reduces the costs and complications related to this fixation method, such as postoperative stiffness, cyst and abscess formation, tunnel enlargement, screw breakage, and intra-articular migration(19).

On the femoral side, the technique requires the drilling of a femoral socket without a second incision, resulting in a better cosmesis for the patient. The use of a socket instead of a tunnel results in a monocortical reaming with a better bone-graft contact that further enhances the ligamentization process (20). The possibility to chose between antero-medial and outside-in femoral drilling make this technique suitable for all the surgeons depending on their preferences and background. The anteromedial technique is effective in reaching the femoral ACL footprint but is extremely technically demanding with a long and insidious learning curve (21). The outside-in technique seems to overcome the majority of the technical issues connected with the anteromedial technique (10,18,22), with the only drawback being higher costs.

The advantages of this technique are the ability to obtain an anatomic ligament reconstruction using an autologous graft; maintaining distal insertion of the tendons; precise adjustment of the tension of the graft due to a second-generation cortical suspensory device.

The disadvantages of the technique, particularly with respect to the all-inside technique (16), are: the joint cavity is not maintained isolated from the outside because it uses a full tibial tunnel; it always requires a tibial incision to pick the tendons and prepare the tibial tunnel; and it cannot be performed with an allograft.

Indications for this technique are comparable with those of the other anatomical techniques, particularly in young athletes who require a rapid recovery. However, it cannot be used in cases of reoperations, in cases of non-validity of the hamstrings tendons, and in the presence of bone changes (especially at the femoral level) that do not allow for the correct execution of the half-tunnel.

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Dall'**esperienza** e dalla **collaborazione**
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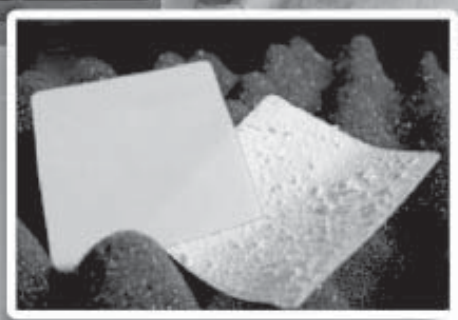

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