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EDITORIAL

ACL AND ACL GRAFT FUNCTION *IN-VIVO*: GOING FROM SEMI-QUANTITATIVE TO QUANTITATIVE

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Of the thousands of papers published on anterior cruciate ligament (ACL) and ACL reconstruction in the last twenty years, a majority have been on new surgical techniques with a significant number of them reporting success rates of 90-95%. Meanwhile, there are also a large group of papers reporting complications that include significant osteoarthritis development in the long term (1-2). This dichotomy begs the question as to why should there be so many different ACL reconstruction techniques and a multitude of new devices even though the results are so good? Perhaps one of the answers lies in the need of more scientific and quantitative methods to objectively evaluate the ACL graft function, both short and long term after reconstruction.

To date, there are new technological advancements made available to accurately measure the *in-situ* forces in the ACL and ACL grafts as well as the *in-vivo* motion of the knee in 3-dimensional (3D) space. Thus, it is desirable to combine them for measuring the *in-vivo* ACL graft function throughout its healing and remodeling. A road map that involved a combined experimental and computational approach to address this issue objectively was proposed as early as 1999 (Fig. 1).

Within the last few years, novel biplanar fluoroscopy systems that are capable of capturing bone motions with high accuracy have been developed (3-4). Thus, it is possible to reconstruct 3D bone images to derive knee kinematics data during *in-vivo* activities within 0.2 mm and 0.3 degrees of accuracy during in-vivo activities such as dynamic jump landing and other tasks (4-5). The knee motion in 3D space can then be accurately reproduced on human cadaveric knees by means of a high payload robot while the robotic/UFS testing system determines the corresponding forces in the ACL and ACL grafts during those *in-vivo* activities (6-7).

Simultaneously, new and more sophisticated computational models of the knee have also become available. For example, a finite element model that incorporates the complex geometry of the ACL and ACL graft, including multiple bundles, variable cross-sectional area along the ligament, fiber twist and so on have been used successfully to calculate the forces as well as the stresses and strains in the ACL (8-9). Models that incorporate multiple muscles around the knee have also been used to predict the forces in the ACL (10). By using the same *in-vivo* kinematic data obtained from biplanar fluoroscopy as inputs for these models, the *in-vivo* forces in the ACL and ACL graft could be calculated.

The next step would be to validate these models by comparing the output data with those obtained experimentally by the robotic/UFS testing system with the knee subjected to identical 3D *in-vivo* kinematics. Once validated, the models can be used

Key words: in-vivo, 3-D joint kinematics, computer modeling, ACL and ACL graft function

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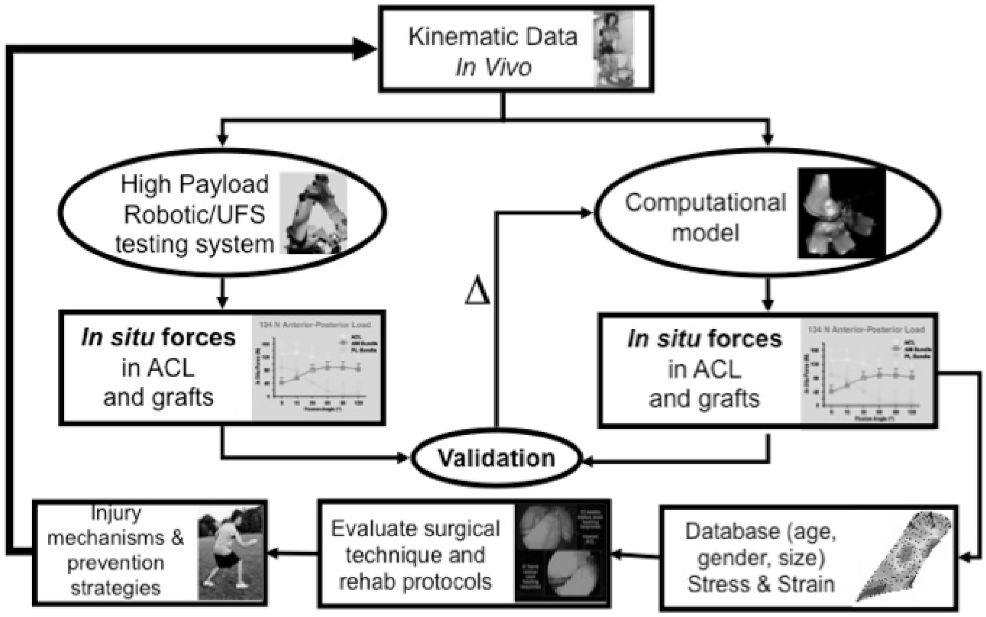

Fig. 1. *A roadmap illustrating a combined experimental and computational approach to objectively determine ACL and ACL graft function in-vivo.*

to predict the outcome of more complex external loading conditions, such as those during *in-vivo* activities including sports. In the end, this combined experimental and computational approach offers a new and exciting way to examine ACL graft function on a quantitative basis.

Further, it will be possible to use these validated knee models to develop large databases on the outcome of ACL reconstruction surgery with independent variables like gender, age, types of injury and so on. Such databases can serve as the baseline for scientifically evaluating successes and failures of new surgical procedures and postoperative rehabilitation protocols. Further, such an approach can be extended to examine the mechanisms of ACL injury as well as to develop appropriate injury prevention strategies.

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CLINICAL STUDY

APPLICATION OF LOCAL VIBRATIONS IN DELAYED AND NON-UNION FRACTURES: A CASE STUDY

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A case study was performed to assess the efficacy of local vibration treatments (LV) in delayed-union and non-union fractures through therapeutic exercise vibration (TEV) by analyzing the radiological trend. A male patient presenting a right tibial fracture was treated with TEV. A monthly program was scheduled in 5 weekly treatments consisting of 6 series of 5 repetitions each at 35Hz. Already after the first applications the patient experienced improvements in the paresthetic symptoms and a reduction of the perilesional edema. At the end of the TEV program, clinical results confirmed independent ambulation with disappearance of perimalleolar edema and decrease of algic symptomatology, while radiographic images revealed the presence of bone repair activity around the fracture line. Where specific and local treatments are required in order to focus the effects of vibrations and favor bone regeneration and muscle strengthening the best solution is gained applying LV. Analyzing the results, TEV appears to have a determinant role regarding the activation of bone growth and its acceleration that should be studied in detail. Case Report

In recent years, the therapeutic application of vibration energy in Physical and Rehabilitation Medicine (PRM) has been established for the treatment of specific bone pathologies. The results of a meta-analysis study of International Publications in PubMed, not only show an increasing number of publications on vibration energy but mostly of those regarding PRM.

Many scientific studies argue that vibrations induce together metabolic and mechanical adaptive responses of the human body (1-4). Indeed mechanical factors hold an important role in human adaptive response, as they improve muscular functions and increase bone regeneration process by stimulating the muscle and triggering osteoblasts (5-6). Therefore, vibration is shown to be a powerful activation stimulus for the whole neuromuscular and skeletal system (7). In view of the evidence on the effectiveness of vibration energy on tissues and systems, mostly on the hormonal, neuromuscular and muscular systems, on the bone tissue and on the peripheral blood circulation, a therapeutic treatment that uses as stimulus vibration energy has been implemented. The vibration energy begins to be considered either as a therapeutic exercise as well as a physical mean applied directly on the body surface (8). Mechanisms for implementing vibration hold a critical role in the adaptive response of the body. While in the case of treatments which require a systemic response, the most appropriate solution

Key words: vibration energy, physical therapy, non union fractures, delayed fractures

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appears to be whole body vibration (WBV), in specific and local applications, limited to a particular body segment, the optimum is achieved with local vibration (LV).

Inadequate response to fracture injury can occur resulting in delayed-union or non-union. Non-union by definition is present when cessation of all reparative processes of healing has occurred without bone union; while delayed-union is the prolongation of time to fracture union. Differentiation between delayed union and non union is based on radiographic criteria and time. The failure to show any progressive change in the radiographic appearance after the period of time during which normal fracture union would be thought to have occurred is evidence of non-union. The changes in radiographic appearance may be slight and therefore radiographs should be scrutinized monthly to see if changes have occurred.

In this study the attention was focused on the application of local vibrations (LV) in bone fractures, in order to incite bone regeneration and remineralisation activity (9-11). The Medical Engineering Department and the Department of Physical and Rehabilitation Medicine at the Tor Vergata University, is developing a device dedicated to LV application for bone regeneration and muscle strengthening.

The aim of the study was to assess the efficacy of local vibration treatment in delayed-union and non-union fractures, using a therapeutic exercise vibration (TEV), by analysing the radiological trend.

Case Report

In this article, we present the case of a 42-years-old man who had a multiple right tibia fracture following a car accident in July 2005. He underwent fracture reduction with osteosynthesis as rings and plates at 1/3 right tibia distal level. The patient during the three years following the accident underwent another two operations, the first one for the rupture of osteosynthesis and the second one to clean the fracture site due to a local infection. After each surgical procedure the patient carried out several cycles of physiotherapy, constituted of an exercise program to recover range of motion and proprioception and physical therapy using antalgic currents, electro stimulation and magnotherapy. Despite these treatments, the patient continued to feel pain and slowly started to decrease his normal daily activity. In July 2009 he came under our clinical observation showing an antalgic gait with a short stance phase on the right side, decreased ankle range of motion, painful fracture site, a paresthetic symptoms, a postural venous insufficiency revealed by a perilesional edema. He brought us a right leg CT scan performed a week before our clinical examination that revealed a non-union fracture. A diagnosis of pseudoarthrosis was made.

Based on the patient clinical history and clinical findings according to the literature findings, we decide to apply local vibration (LV). Local vibration device (Rieti, 2008) is composed by a command console, that controls the rotation of the mass, designed to allow the operator to regulate the specific

Table I. *Reduction in Circometer at admission and discharge*

Circometer AAII	Admission (cm)		Discharge (cm)	
	R leg	L leg	R leg	L leg
Peri-malleolar	29.5	27	28.5	27
5cm above medial malleolus	28.5	24	28	24
10cm above medial malleolus	29.5	25.5	28.5	25.5

Table II. *Scores at admission and discharge*

Scores	Admission	Discharge
LEFS	31/80	46/80
Barthel Index	98/100	100/100
McGill Pain Questionnaire	25/60	10/60

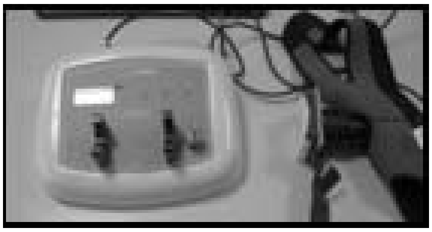

Fig. 1. *Device used for LV application.*

Fig. 2. *TEV application on heel.*

A B C

Fig. 3. *Radiographic images lateral view (**A**) at admission September 23, 2008; (**B**) at discharge October 30, 2008; (**C**) at follow up January 16, 2009.*

parameters for TEV, such as time and frequency (Fig. 1-2). The device delivers mechanical vibrations within a frequency range of 20-50Hz. Vibrations within this specific range induce positive effects,

A B C

Fig. 4. *Radiographic images anterior view (**A**) at admission September 23, 2008; (**B**) at discharge October 30, 2008; (**C**) at follow up January 16, 2009.*

causing a stimulation of bone regeneration and an increase in muscle distensibility and strength.

The TEV application was based on a four week training scheme with five weekly treatments organised as follow:

- daily treatments of 6 sets, 5 repetitions each;
- each repetition at 35 Hz for 30 seconds;
- 60 seconds pause between repetitions;
- 90 seconds pause between sets;
- application of sleeve to the heel.

For the evaluation of the treatment and assessment of the LV efficacy in non-union fractures, three radiographs were performed at different times: one at admission, one at discharge (at the end of treatment) and one at 60 days from the end of the treatment as a follow up. Clinical and radiological results were completed by the administration of scores for pain (Mc Gill Pain questionnaire) and functional evaluation (Barthel Index and LEFS - Lower Extremity Functional Scale).

Right from the first applications, the patient reported improvements in paresthetic symptoms and also presented a reduction in the perilesional edema (Table I). The results of the circometer show a difference of 1cm around the malleolus and at 10cm above the medial malleolus indicating a reduction of the perilesional edema. The LEFS Scale and the Barthel Index showed respectively an increase from 31/80 to 46/80 and from 98/100 to 100/100 before and after treatment. Furthermore, algic symptomatology, after a small increase in the early phase, clearly improved during the treatment period. Algic symptomatology decreased as shown by the McGill Pain Questionnaire: from 25/60 before treatment to 10/60 after treatment (Table II).

At the end of the TEV program, clinical results confirmed independent ambulation with disappearance of perimalleolar edema and antalgic gait.

The radiographic image performed at admission (September 23, 2009) showed some of the characteristic radiological features of non union fractures: presence of bone head remodeling, partial obliteration of the medullary canal and a typical hypertrophic appearance with external bone proliferation. The radiographic image taken at discharge (October 30, 2009) showed, especially in the lateral view, the presence of a scar-like formation at the fracture line is the expression of biological activity in progress.

Radiographic image at follow up, 60 days from the end of treatment (January 16, 2010), shows an increase of the scar-like formation already highlighted at discharge, reflecting persistence of biological activity, with the appearance of an osteo-reparative event along the fracture line (Fig. 3-4).

DISCUSSION

We could find no publications to compare with our case report. We applied LV in accordance with the literature findings about the metabolic and mechanical adaptive responses of the human body induced by vibration application. The obtained results confirmed an improvement in paresthetic and functional symptomatology and the resolution of perilesional edema. If in the case of perilesional edema the physiological reasons behind this improvement is quite clear given the known effects of vibration on blood circulation, in regards to the paresthetic and algic component we can hypothesize that the large number of forces and impacts induced by vibration produced local desensitization. In fact the pain, after an initial increase, rapidly disappeared, particularly in the final phase.

CONCLUSIONS

The positive results reported in the clinical study suggest that therapeutic exercise vibration could make a valid contribution to the treatment of pathological disorders of bone regeneration, by resolving delayed union consolidation or greatly reducing the time of recovery. A larger sample or a multi center trial is necessary to confirm our findings and to propose LV as a therapeutic standard for resolving bone healing problems

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CLINICAL STUDY

A COMPARISON BETWEEN PROXIMAL FEMORAL NAIL AND LOCKING COMPRESSION PLATE-DYNAMIC HIP SCREW DEVICES IN UNSTABLE INTERTROCHANTERIC FRACTURES -WHICH IS BETTER?

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The present study was undertaken to compare the functional outcome and complications associated with a proximal femoral nail (PFN) device with those of an extramedullary locking compression plate-dynamic hip screw (LCP-DHS). The study was undertaken in 80 patients with unstable trochanteric fractures. Of these, 50 patients were treated with the LCP-DHS and 30 were managed with the PFN. Perioperative information and complications were recorded, and assessments of functional outcome were made. The LCP-DHS group required a longer operative time and was associated with greater blood loss than the PFN group. The radiation exposure was more in the PFN group. There was no significant difference in the overall complication rate between the two groups. There were no significant differences in functional outcome between the PFN and the LCP-DHS groups. However, the best results with least perioperative and post operative complications were seen in the LCP-DHS group where percutaneous plating had been done, with least operating time, less blood loss and radiation exposure and early mobilization. Due to the overall improved results and least complications with percutaneous LCP-DHS fixation, we recommend this technique in unstable trochanteric fractures. Level of Evidence: III Case-Control Study

Intertrochanteric fractures of the femur are quite common in the geriatric population and often associated with moderate trauma as compared to the young adults who sustain this injury due to high velocity trauma. With increased age expectancy, the incidence of these fractures has also shown an upward trend. Surgery has become the nom de guerre to promote early mobilization and prevent life-threatening complications. Despite improvements in the operative management of such patients, the morbidity rate is still high (1). Several implant designs have been developed in an attempt to aid fracture fixation, facilitate early ambulation and reduce the risk of complications when treating trochanteric fractures (1–3). However, design or technical problems have been reported with all devices, especially in managing unstable, comminuted fractures. Implants can be divided into two groups –extramedullary and intramedullary devices. There is, however, a lack of clinical evidence on whether one type of device should be preferred over the other. Biomechanical studies have shown that intramedullary devices are more stable under loading; however, they have also been associated with a significant number of technical failures and complications (4–6). These potential complications may have limited their widespread acceptance. It seems that, compared with extramedullary fixation techniques, the price

Key words: trochanteric, fracture, proximal femoral nail, locking compression plate-dynamic hip screw, complications

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for the clear short-term advantages of intramedullary fixation, such as postoperative direct full weight-bearing potential, is a higher incidence of reoperation due to technical problems (7). Many intertrochanteric fractures are still treated with a long plate sliding hip screw or other extramedullary devices. In the light of these issues, implant modifications and improved operative techniques are being developed. In this study we have compared the functional outcome and complications of the PFN with the LCP-DHS in intertrochanteric fractures. To our knowledge this is the first study comparing the LCP-DHS with the PFN.

MATERIALS AND METHODS

In this study, 80 patients with intertrochanteric femoral fractures were operated with the LCP-DHS or the PFN device between January 2006 and December 2008. Plain radiographs were obtained on admission and all fractures were categorized according to AO/ASIF classification (8) (31-A1 stable intertrochanteric fracture or 31-A2/31-A3 unstable intertrochanteric fracture). All the cases included in our study group were fresh fractures and underwent surgery at the earliest possible in our set up. The delay was due to associated injuries and medical condition of the patient.

Surgical procedures

Surgery was performed with the patient in the supine position on a fracture table, with the injured extremity slightly adducted to facilitate insertion of the implant. Fracture fixation with the PFN was performed according to the surgical technique described by Simmermacher et al. (9) and fracture fixation with the LCP-DHS was performed according to the surgical technique described for the standard DHS by Hoffman and Haas (10). We did percutaneous fixation in 33 out of the 50 DHS cases. The choice of the implant was was done by the surgeon according to his preference. No bone grafting was done in any case. After surgery, the patients were mobilized and given standard rehabilitation instructions. Partial weight-bearing (20–30 kg) was allowed as soon as the patient tolerated it, and full weight bearing was normally allowed 8–12 weeks after surgery based on the radiological situation.

Patient assessment and follow up

Patient information, including age and sex, and perioperative information, including operative time, blood loss, fluoroscopy time and length of hospital stay, were recorded for each patient. Follow-up evaluations consisting of clinical examination, assessment of functional outcome and radiographs, were performed at 6 weeks, 3, 6 and 9 months, and then annually. Patients were followed up for a minimum of 1 year. Functional outcomes for pain, walking, motion and muscle power, and function were assessed using the Salvati and Wilson scoring system (11). Patient outcome scores were categorized as excellent (≥ 32), good (24 – 31), fair (16 – 23) or poor (≤ 15). At each follow up, radiographs were evaluated for reduction status, displacement, screw position and successful fracture union. Radiographic fracture healing was defined as the presence of bridging callus and resolution of the fracture line on anteroposterior and lateral radiographs.

RESULTS

In our study 80 patients with intertrochanteric femoral fractures were operated with the LCP-DHS or the PFN device between January 2006 and December 2008. We managed 50 cases with the LCP_DHS and 30 cases with the PFN. The mean age of cases in the former group was 65 years (range 60-81), with 32 males and 18 females while in the latter, the mean age was 45 years (range 29-72) with 20 males and 10 females. In the LCP-DHS group, most of the cases (64%) were in the AO subtypes of 31-A2.1 or 2.2 (Table I) whereas in the PFN group, the majority of the cases (61%) were of the 31-A3.1 and 3.2 categories (Table II). An analysis of osteoporosis as per the Singh's index showed nearly 54% of cases

Table I. *Distribution of patients in A.O types. (LCP-DHS group)*

A.O Type	A 1.1	A 1.2	A 1.3	A 2.1	A 2.2	A 2.3	A3.1	A3.2	A3.3
No. of patients	18	2	7	14	7	0	2	0	0
Percentage	36	4	14	28	14	0	4	0	0

Table II. *Distribution of patients in A.O types. (PFN group)*

A.O Type	A 1.1	A 1.2	A 1.3	A 2.1	A 2.2	A 2.3	A3.1	A3.2	A3.3
No. of patients	0	0	0	7	1	1	8	10	3
Percentage	0	0	0	23	3	3	27	34	10

Fig. 1. *Unstable trochanteric fracture after LCP-DHS fixation.*

in the LCP-DHS group to be in the osteoporosis index of II or III whereas in the PFN group, most cases (57%) fell in the IV index group. The most common mode of injury in the former group was simple fall to the ground (54%) while in the latter, road traffic accidents (57%) predominated. Some associated injuries included distal radial and Galeazzi fractures, olecranon and humeral neck fractures.

We considered various intra operative parameters like radiographic exposures, duration of surgery and amount of blood loss. The average duration of surgery was 69 min for the PFN group and in the LCP-DHS group, closed or percutaneous plating took an average of 59 min and open plating required an average of 77 min. Radiographic exposure was more for PFN (average exposure of 1.80 min per case) where closed reduction was done and for comminuted fractures with difficult reduction as compared to the LCP-DHS group with an average exposure of 1.1 min. Blood loss was measured by mop count and collection in suction. Blood was more for DHS compared to PFN with only 5 patients of the PFN group (of whom 4 needed open reduction) requiring intraoperative transfusion while in the LCP-DHS group, 4 patients out of 33 who underwent percutaneous plating and 16 of the 17 who underwent open plating needed intra operative transfusion. The average hospital stay in both groups was 13 days (range 10-18 days). Full weight bearing was started at an average of 12.2 weeks with PFN and 12.4 weeks with LCP-DHS. Radiological union was apparent at an average of 12.41 weeks with the LCP-DHS (Fig. 1) and 12.28 weeks with PFN.

There were comparatively fewer intraoperative complications encountered during the LCP-DHS fixation as compared to PFN. Reduction was comparatively easier with the former, more so with open plating. In the latter, open reduction was performed in four cases (Fig. 2). One case in the PFN group had a fracture of the greater trochanter. The antirotation screw could not be placed in two cases as it could not be accommodated in the neck after putting neck screw due to a mismatch between the actual neck size (narrower) and the spacing of the holes in the PFN (wider) which is made according to the size of the Caucasian race and not the Asian who usually have smaller sized bones (Fig. 3). In the immediate post operative period, two patients in the LCP-DHS group had superficial infection while in the PFN group, one patient had localized infection, one had DVT and two had hematoma formation which needed evacuation. In late complications,

Fig. 2. *Comminuted unstable trochanteric fracture after open reduction with PFN.*

Fig 3. *PFN without the derotation screw.*

Fig 4. *Coxa vara after LCP-DHS fixation.*

Fig 5. *Superior migration of the derotation screw in PFN.*

the former group had one patient with cut out of the Richards screw and two patients had mild coxa vara (110^0 - Fig. 4) while in the latter, there was back out of the lag screw in one, superior migration of the antirotation screw in one (Fig. 5) and secondary varus in one case. In the LCP-DHS group, 5 patients had mild hip stiffness (flexion <100^0, abduction

$<35^0$) and 6 had restricted knee flexion ($<110^0$). In the PFN group, 2 patients had hip stiffness (flexion $<90^0$, abduction $<25^0$) and 2 had restricted knee flexion ($<100^0$).

DISCUSSION

Trochanteric fractures occur mostly in elderly patients, and the outcome may be extremely poor if there is prolonged bed rest. Stable fixation that allows early mobilization is the treatment of choice. Opinions vary as to the best treatment for trochanteric fracture. Extramedullary devices such the DHS are widely used locally although intramedullary nails are being increasingly utilized for unstable trochanteric and reverse oblique hip fractures due to their biomechanical advantages. The successful treatment of trochanteric fractures depends on many factors, including the age of the patient, their general health, time from fracture to treatment, adequacy of treatment, concurrent medical treatment and the stability of fixation (7). Arguments about the ideal implant for the treatment of trochanteric fractures continues, mainly due to the fact that there is insufficient knowledge on the biological and biomechanical factors that lead to the uneventful healing of this type of fracture in patients, most of whom are elderly. Currently available devices all have their own specific problems. The DHS remains the implant of choice for the treatment of trochanteric fractures because of its favorable outcomes. By allowing controlled compression at the fracture site, the DHS has achieved a low rate of non-union and fixation failure (12). DHS placement requires a relatively large exposure, significant soft tissue stripping and anatomical reduction. Additionally, the screws and side plate create stress risers in the bone that can increase the risk of fracture distal to the implant (13-14). To overcome these deficiencies, the AO-ASIF in 1996 developed the Proximal Femoral Nail (PFN) with an antirotation hip pin together with a smaller distal shaft diameter which reduces stress concentration to avoid failures. From mechanical point of view an intramedullary device inserted by means of minimally invasive procedure seems to be a better option. Closed reduction preserves the fracture hematoma, an essential element in consolidation process. Intramedullary fixation allows the surgeon to minimize soft tissue dissection, thereby reducing surgical trauma, blood loss, infection and wound complications. However, significant complications have also been reported with such intramedullary devices including cutout, infection, fracture distal to the tip, fracture collapse, and hardware failure (15-16). Also, a higher revision surgery rate for intertrochanteric femur fractures stabilized with an intramedullary nail as compared with a dynamic hip screw have been reported (17). LCP-DHS is supposed to combine the advantages of a sliding hip screw with that of a locking plate. Locking plates theoretically do not compress the bone or periosteum and the risk of peri-implant fracture is also reduced. It has been suggested that by reducing avascularity within the bone the risk of infection may be reduced (18). Further, shorter locking plates could be used providing equivalent strength and requiring less dissection (19). The stability allows for immediate weight bearing in the case of a stable fracture with early consolidation.

Between the two groups, the mean anesthetic and operative times were shorter in the LCP-DHS group than in the PFN group. There was more blood loss within the LCP-DHS group especially in the open plated patients (34%). The mean time to mobilization was lesser with PFN. More patients needed a blood transfusion in the LCP-DHS group and the mean radiation time was shorter in this group. The Richards screw of the LCP-DHS cut out in one patient. All fractures in both groups were united when followed up after one year. Excellent results were seen in 64% and 70%, good in 24% and 20% and fair in 12 % and 10% cases of LCP-DHS and PFN respectively. There were no poor outcomes in either series. Similar findings have been reported previously (20-21). The Cochrane review in 2010 concluded that given the lower complication rate of the DHS in comparison with intramedullary nails, DHS appears superior for trochanteric fractures.; further studies are required to determine if different types of intramedullary nail produce similar results, or if intramedullary nails have advantages for selected fracture types (22). However, there are some confounding factors. The average age of patients in the LCP-DHS group was 65 years and the Singh's index in over half of these cases was II or III while the average age in the PFN group was 45 and the Singh's index was IV or V. The cases of LCP-

DHS were more than those of PFN since the former was commonly done at our institution and most surgeons were more familiar and comfortable with this procedure, which was also economically more viable for the patients. Overall, considering operative and fluoroscopy times, the difficulty of the operation, intraoperative complications, and blood loss; fracture healing and failure of fixation; pain, social functioning and mobility, the best results with least perioperative and post operative complications were seen in the LCP-DHS group where percutaneous plating had been done, with least operating time, less blood loss and radiation exposure and early mobilization. This option was also economically more viable in our setup as the cost of PFN was much higher than that of the LCP-DHS.

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CLINICAL STUDY

THE TREATMENT OF RADIAL HEAD DISPLACED FRACTURES (MASON III AND IV): EXCISION OR ENDOPROSTHESIS

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Radial head fractures account for about 30% of all elbow injuries in adults; treatment may be non-operative or operative. The aim of this study was to compare the results obtained with endoprosthesis versus those obtained with excision of the radial head. Forty-seven patients diagnosed with radial head fracture were treated in our Department between January 2009 and December 2009. Twenty-two were treated surgically, 17 had Type III fracture according to Mason's classification and 5 had Type IV. The data collected in the post-operative period using the SECEC Elbow Score were on an average good: 3 cases were excellent (score >95), 11 good (score 80-94), 3 moderate (score 69-79) and 1 poor (score <59). The results were correlated to the type of fracture (worse in Mason Type IV). Level of Evidence: III - Case-Control Study

The various surgical methods correspond to the different types of fractures and they all have the same aim: the anatomic reconstruction of the articular surface and the suture of capsular-ligamentous structures, which allow full functional rehabilitation of the limb and early elbow mobilization. In case of complex and plurifragmental fractures, surgical excision of the radial head may be indicated (1).

Furthermore, in the last few years several methods of fracture fixation have been developed, meaning that now excision is only carried out in those cases that cannot be treated by open reduction and internal fixation. To date, the increased safety of the materials used, as well as the development of modern prosthetic design, have led to a new therapeutic dimension, the results of which are still partial but encouraging: endoprosthesis (2).

The radial head is fractured in about 30% of elbow trauma and the working age (30-60 years) is the worst hit by this injury; which is frequently associated with ligamentous and articular capsule lesions and loss of osseous substance.

Radial head fractures occur between 1.7% and 3.4%; they also occur in about 30% of adult elbow injuries and in 5-10% of children's injuries, with an incidence rate of 2.5 per 10,000 persons/year. They are more frequent in women than in men (3:2) and in the 20-60 yrs age range, i.e. in the so-called working age (an average of 45.9 years) (3).

Approximately 30-50% of radial head fractures involve more severe injuries, such as elbow dislocation, olecranon fractures, fractures of the coronoid process of the ulna and capsular-ligamentous injuries. To classify the patients we use the commonest Mason-Johnston classification of radial head fractures which includes four main types of lesion (4).

The treatment for radial head fractures can be

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conservative or surgical (screws, splints, Kirschner wire, temporary external fixator, resection, and endoprosthesis).

Conservative treatment is recommended for Mason fracture type I, and for type II, when these fractures are slightly displaced and when they are not associated with other injuries.

Surgical treatment aims to keep the articular function of rotation, allowing early mobilization of the elbow and avoiding articular rigidity. Surgery is limited to the cases of: comminuted fractures; dissection associated with dislocation of fragments; complex fractures or fractures associated with injuries and when quick and early mobilization is necessary. Surgery is therefore recommended for every radial head fracture of Mason type III and type IV (5-8) Fig 1-2.

MATERIALS AND METHODS

From January to December 2009, 47 patients suffering from a radial head fracture were treated at our Department. The patients who were treated surgically were 22 (12 by resection and 10 by Bipolar Endoprosthesis); among them, 17 had Mason fracture type III and 5 type IV. The other patients were treated conservatively or by open reduction and internal fixation Fig 3-4.

Their average age was 44.1 years (min 27 yrs, max. 72 yrs); in spite of traditional casuistic, 59.1% were female patients (13 patients), while men were 40.9% (9 patients). Fifty-five percent (12 patients) showed a fracture on the left side, whereas 17.3% (3 patients) had a fracture associated with elbow dislocation. One patient also showed a fracture of the distal third of ulna, which was surgically reduced and synthesized with a plate. All patients underwent a clinical and radiological follow-up. An arthrogoniometer which can take measurements of 360°±1, was used to measure R.O.M.. Moreover, elbow function was evaluated by administering a questionnaire to the patients for the SECEC Elbow Score. The case study included 18 patients: 8 operations of radial head endoprosthesis and 10 excisions Fig 5.

RESULTS

The data collected in the postoperative period were positive but not statistically significant: 3 excellent cases (score >95 points), 11 good (score 80-94 points), 3 fair (score 69-79 points) and 1 poor (score <59 points) (Table I). 4 Cases were lost at

Table II. *Average of Secec Elbow Score*

SECEC ELBOW SCORE		
	MEN	WOMEN
SCORE	94	89
	99	86
	92	89
	90	78
	92	97
	87	78
	83	79
	87	98
		90
AVERAGE	90.5	87.1

Table I. *Pie chart of postoperative data.*

Table III-IV: *Outcome scores of the Resection and Endoprosthesis groups*

Parameters	***RESECTION***									***AVERAGE***
Pain	12	10	11	13	13	11	11	11	13	12
Sleep	2	2	2	2	2	2	2	2	2	2
Work	3	3	3	4	3	3	3	3	4	3.3
Spare time	4	3	4	4	3	3	4	3	3	3.5
Movement	10	10	10	10	10	10	10	10	10	10
Flexion	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	Average= 0°
Extension	10 (8°)	5 (12°)	10 (7°)	10 (8°)	10 (7°)	10 (7°)	5 (15°)	10 (8°)	10 (8°)	Average = 7.8°
Supination	5 (85°)	5 (83°)	2 (48°)	5 (79°)	5 (86°)	5 (80°)	5 (78°)	5 (80°)	5 (85°)	Average = 79.4
Pronation	10 (80°)	5 (58°)	5 (54°)	10 (78°)	10 (82°)	10 (72°)	10 (75°)	10 (78°)	5 (58°)	Average = 72.3
Force	8+11	7+12	7+10	7+10	9+12	8+11	8+12	7+11	8+12	Average= 7.9 + 11.4
Valgism	8°	14°	12°	8°	7°	9°	8°	9°	8°	Average = 8.6
Confidence in the use	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO
TOT	90	78	79	90	92	87	83	89	87	Average = 87.3
Parameters	***ENDOPROSTHESIS***									***AVERAGE***
Pain	15	12	12	15	10	13	15			13.1
Sleep	2	2	2	2	2	2	2			2
Work	4	4	3	4	3	3	4			3.6
Spare time	4	4	3	4	3	4	4			3.7
Movement	10	10	10	10	10	10	10			10
Flexion	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)	15 (0°)			Average =0
Extension	10 (-2)	10 (4°)	10 (5°)	10 (0°)	5 (12°)	10 (2°)	10 (3°)			Average =3.7°
Supination	5 (84°)	5 (82°)	5 (80°)	5 (90°)	5 (78°)	5 (86°)	5 (90°)			Average = 84.2°
Pronation	10 (78°)	10 (75°)	10 (72°)	10 (90°)	10 (68°)	10 (80°)	10 (86°)			Average = 78.4°
Force	7+12	6+11	7+9	9+15	6+9	8+12	9+13			Average = 7.4 + 11.6
Valgism	NO	NO	NO	NO	NO	NO	NO			NO
Confidence in use	YES	YES	YES	YES	NO	YES	YES			YES
TOT	93	89	86	99	78	92	97			Average = 90.714

follow-up.

A greater loss of mobility was observed in one patient: approximately 40° in flexion-extension and 60° in pronation-supination. It was necessary to remove one patient's prosthesis due to neuro-apraxia of the ulnar nerve and a self-reported intolerance to the prosthetic material, which, however, was never confirmed by the blood and allergy laboratory tests we perfomed. The same patient also showed paresthesia of the 4th and 5th finger, associated with constant painful symptomatology and rigidity when flexing her elbow at 70°. After removing the prosthesis, her

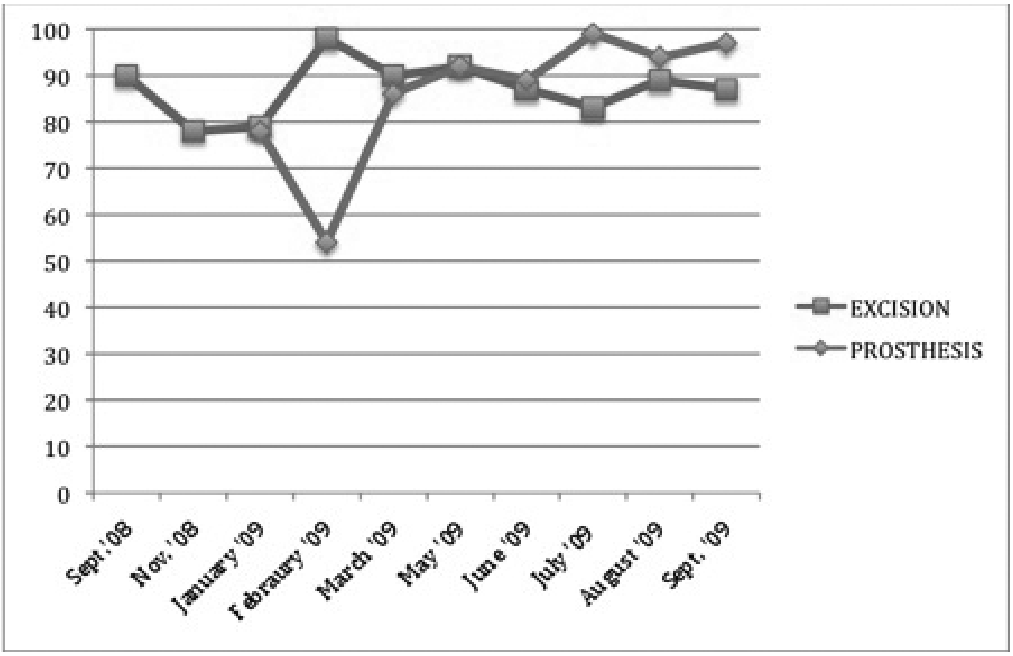

Table V. *Recurrences in the course of time*

functional recovery was good, with a score of 89 points in the SECEC Elbow Score (Table II).

The patient who had had the prosthesis removed and had scored 54 points, was not put in the table. The summary of complete casuistic and corresponding outcome results are reported in Tables III-IV.

Nevertheless, the graph highlights that the results following removal have a stable curve progress, i.e. they do not show particular differences in the outcome scores, recorded at the beginning and at the end of the follow-up period; on the contrary, in patients who received a radial head replacement, a significant improvement is evident 5-6 months after surgery (Table V) (Fig. 6).

DISCUSSION

The radial head plays a secondary mechanic role in elbow joint: 65% of the force in elbow extension transmitted from wrist to humerus is exerted by the capitulum humeri, while only 15% is exerted by the radial head; on the front surface of the elbow, the primary stabilizer is the medial collateral ligament (9).

Radial head prosthesis is therefore advisable only in the case of trauma associated with severe injuries (10-11). In Europe the use of radial head prostheses spread from the end of the eighties, achieving varied and contradictory results.

At the beginning, prostheses were almost disastrous and their main use was for cases of failed ostheosynthesis or excision, where the patient's functional outcome had got worse (12).

The difficulty in applying the surgical method was associated with the use of inappropriate materials that often caused rejection crises, and imperfect designs that were unable to re-establish the articular morphology and function (13).

Since then, things have dramatically changed: now the state of art requires treatment of synthesis for most radial head fractures, confining removal and substitution with prosthesis to a limited, selected number of cases. Metal prostheses were created to improve both clinical and radiological results. The first article that described the use of these models was published by Knight et al. in 1993 (14); these authors achieved better results than Swanson's prostheses (15).

In 1994 Judet et al. described their 7-year-experience of treatment of radial head fractures in

Fig. 1. *Dislocation with associated radial head fracture in a 32 year-old patient after sports injuries.*

Fig. 2. *Rx of the elbow in plaster in Figure 1 after treatment of radial head excision.*

12 patients with a minimal follow-up of 53.3 months (minimum 24 months); 5 of them were treated by means of bipolar prostheses, introducing thus the use of these new prostheses, which would then be broadly used with excellent clinical and radiological results (16).

In 2000 Smets et al. conducted a study on 15 patients with an average follow-up of 25.2 months

Fig.3. *X-ray of patient with olecranon fracture associated with radial head injury.*

and Judet prostheses; they reported 7 excellent results, 3 good, 1 fair and 2 poor results. Only one prosthesis was removed after 8 months because of impaired elbow function (17).

The use of metal prostheses was then supported by Holmenschlager et al.'s study on 15 patients in 2002 According to the Morrey scale, the results were good in 11 cases and excellent in 2 (18).

In 2005, Bain et al. implanted titanium prostheses in 16 patients, who presented Mason fracture type II. They got excellent-good results after an average follow-up of 2.8 years. The three bad results depended on those patients who underwent surgery after months. Bain and his colleagues remarked that an effective recovery of function needed early elbow mobilization (19).

In 2008 Schofer's cohort study on 25 patients who received a Bipolar Endoprosthesis, divided by treatment period and fracture type, reported 8

Fig. 4. *X-ray of the patient in Fig. 3 after treatment with cerclage of the olecranon and radial head endoprosthesis.*

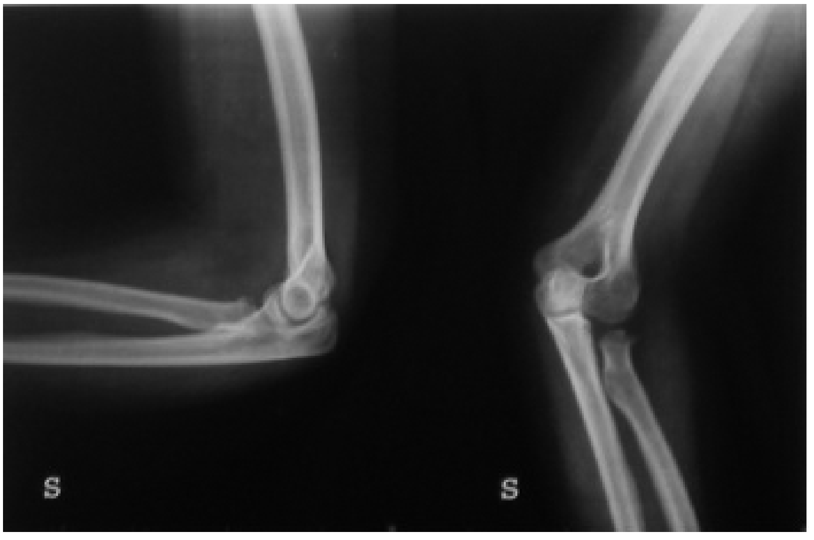

Fig. 5. *Effects of excision of the radial head in 28-year old female patient.*

excellent results, 13 good, 3 fair and 1 poor, according to the Mayo Score. The comparison with the control group did not highlight significant differences in quality of life (20).

In 2010 Celli et al. conducted a study with clinical functional and radiological outcome in 16 patients who had an average follow-up of 41.7 months and Judet metal prostheses. Their study obtained successful results: 87.5% of cases showed good elbow stability and an important increase in function compared to the original injury (21).

Val Riet et al. tried to discover the reasons for radial head prosthesis failure by performing a large study on 44 patients between 1998 and 2008. Prosthesis removal occurred on average after 32 months and the main predictive factor seemed to be the operation timing. They found more relevant complications if the prosthesis was implanted 6 months after the traumatic lesion. Bipolar prostheses did not show subluxation in any of the cases, while unipolar prostheses were heaped with a percentage of 15. Moreover, it did not seem that prosthesis instability depended on their design since bipolar and unipolar prostheses reported similar results (22).

Fig. 6. *Loss of prono-supination in a 72 years woman in left elbow after excision of the radial head.*

Nonetheless, in the last 6 years particular attention has been paid to this therapeutic method by several authors who have analyzed the use of prostheses instead of synthesis and resection. However, in these studies follow-up is short-term and the number of cases is extremely small. Therefore, the indication is limited for prostheses, in view of the small amount of literature available on the topic, and resection is still the commonest therapeutic choice.

Regarding international casuistics, in 1996 a retrospective analysis conducted by the French authors from "Hôpital de la Conception, Marseille", indicated that the results of resection and synthesis treatment for Mason fracture types III and IV were much less reassuring than those achieved with radial head endoprosthesis for the same kind of fractures (23).

The same results were obtained by Holmenschlager et al. with a study comparing different therapeutic methods, with a particular interest in endoprosthesis and resection, using unipolar and bipolar prostheses. After a 45-month-follow-up, this study concluded that it was more advantageous to use an endoprosthesis, especially bipolar prostheses, than perform resection (24).

In our study the scores were lower in women (87.1 points) than in men (90.5 points) because the female patients were considerably older than the male ones: on average women were 47.5 years old, while men were 39.6 years old. Therefore, age and the advanced menopausal state of some of the female patients inevitably affected their recovery of limb function (Table II).

The cases showed marked differences in results, mainly due to the patients' age; for people who were over 50 years old, the scores were all lower than 90, with an average of 84.4 points; only one prosthesis was implanted in an over 70-year-old patient. Older patients, having fewer functional needs than the younger ones, prematurely abandoned rehabilitation. Analyzing the results of each surgical method, at least two differences are evident. First of all, the cases of resection showed a definite likeness in results (an average score of 87.9 which is close to the extremes, 98 and 78).

Secondly, on the other hand, the cases of endoprosthesis achieved more heterogeneous results (an average score of 90.7, far from the extremes 99 and 86).

At present, prostheses are therefore considered the best solution in those cases that would otherwise end badly. Nevertheless, more experience is still necessary in terms of casuistic and follow-up duration. In addition, the results of endoprosthesis are considerably better than those achieved with removal, perhaps due to a refinement in the surgical learning curve of the implantation method.

CONCLUSIONS

Treatment for radial head fractures is continuously changing: what seemed a certainty in the past, is today just a memory, thanks to improved implants and emerging novel techniques.

In case of complex elbow instability, due to injuries of the Medial Collateral Ligament and the Interosseus Membrane (Essex-Lopresti), elbow dislocation, coronoid and/or olecranon fractures (Type III and Type IV), endoprosthesis is necessary because it assures the elbow and the forearm stability and it allows recovery of radio-humeral contact reducing significantly complications related to excision.

Our study was characterized by a short-term follow-up but it shows encouraging results: Endoprostheses, which is subject to a long learning curve, has had significantly better results than those obtained with excision. Although an enlargement of casuistic would be advisable in order to obtain a mid/long-term outcome.

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REVIEW ARTICLE

MECHANISMS OF ANTERIOR CRUCIATE LIGAMENT INJURIES IN FEMALE ATHLETES: A NARRATIVE REVIEW

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Epidemiological observations have shown female athletes to be more susceptible to Anterior Cruciate Ligament (ACL) injuries than males. The reasons for the sex difference have been incompletely clarified. Anatomic factors (increased depth of femoral condyles, and narrower femoral notch width in females) and deficits of the neuromuscular control, defined as muscle strength, power, coordination, or activation patterns, play an important role. The increased ligament laxity in females has been extensively studied, because more compliant tendon can lead to reduced performance in tasks requiring rapid force generation. There is evidence that estrogens can increase ligament laxity, but the changes across the menstrual cycle and the relationships with the incidence of ACL injuries show large individual differences. Recent research indicates that normal menstruating women release in small quantity the collagenolytic hormone relaxin, and that increased relaxin levels are associated to significant risk of ACL injury (4 time increase of tears incidence for serum concentrations > 6.0 pg/mL). Given the economic implications of lesions in top level players, these findings can help to better profile the female athletes at risk, and pave the way to the development of preventive and therapeutic procedures. Narrative Review

Anterior Cruciate Ligament (ACL) lesions are a common occurrence in high velocity, dynamic field and court sports, such as soccer, basketball and volleyball (1-3). Video analysis studies have shown that, in both sexes, the majority of injuries (70%) results from noncontact mechanism (landing, cutting, pivoting or decelerating) (4-6). Joint loads causing motions beyond the normal physiologic range in the sagittal, frontal and transverse planes potentially could lead to ACL injury (6). In particular, there is evidence that the predominant forces that increase strain in ACL are anterior-directed shear forces applied to the tibia, in combination with valgus loading, in external or internal knee rotation. In this condition, hamstrings and quadriceps co-contraction contributes substantially to dynamic knee stabilization. With the knee in near full extension, the contraction of quadriceps muscle produces an anterior-directed shear force on the proximal aspect of the tibia that strain the ACL, while co-contraction of the hamstring muscles reduces the ACL strain values (6).

Several epidemiologic studies have shown that the incidence of ACL injuries is higher in women practicing sport activities in comparison with the male counterpart (1-2). The Females/Males ratio ranges widely from 9 to 2; match play accounts for most of the risk increase in females, whereas training incidence is similar between males and females (1-3). These discrepancies can be explained by several reasons, such as different data source and collection modalities, subjects characteristics, lesions

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evaluation methods, injury occurrence modalities, and statistical methodology (3).

Several factors (anatomic, neuromuscular and biomechanical) contribute to explain the higher incidence of ACL ligaments and tendons injuries in females. Interestingly, differences in kinematics and, accordingly, the increase in the injury rate sex-related, become evident after the onset of puberty (7-8). This emphasizes the role of the hormonal factors in making manifest some physiologic characteristics, which are genetically determined.

Given the growing participation of women in sport, a more comprehensive understanding of the mechanisms associated with tendon and ligament injuries in female athletes is warranted.

Aim of this review was to evaluate these causal mechanisms, focusing on the role played by hormonal factors, which at present is not fully elucidated.

A search of English-language articles was performed in Pubmed, Web of Knowledge (WOK) and EMBASE using the key search terms “Anterior Cruciate Ligament”, “Knee injuries”, “Sex difference”, “Females athletes”, “Epidemiology”, “Biomechanics”, “Laxity”, “Menstrual cycle” “Hormones”, “Estrogens”, “Relaxin”, “Collagen”, independently and variously combined. Bibliographies were hand searched to include any applicable studies that were not captured by our search. Articles were eligible if they provided specific information related to the correlation between female sex, knee biomechanics and ACL injuries.

Anatomic and biomechanical factors

Anatomic differences might contribute to the higher rate of ACL tears in female athletes. First, there is evidence that ACL is smaller in women than in men when normalized by BMI (6). Moreover, women show deeper medial and lateral femoral condyles, as well as deeper medial tibial plateaus than men. Comparative studies show that subjects with deeper tibial plateaus have a higher incidence of ACL tears (9). In a study, involving 714 consecutive patients who underwent patellar tendon graft for ACL reconstructions, the relevance of intercondylar notch width was evaluated. Analysis showed that, controlling for height and weight as covariates, women had statistically significantly narrower notches than men and that patients with narrower notches had a higher incidence of tearing their contralateral ACL (10).

More importantly than structural characteristics, several physiologic differences sex-related must be taken into account. The tibiofemoral joint laxity, defined as the combined resistance of the ligament, muscles and capsule to a displacing load, is of paramount relevance to assure the stability of the knee. Joint laxity is an important contributing factor for ACL injuries as the odds of ACL injuries increase fourfold for every 1.3 mm increase in antero-posterior knee displacement and fivefold for positive knee hyperextension (11). It is well established by retrospective (12-15) and prospective (16-17) studies that females exhibit greater anterior knee laxity than males, and that it is even greater in those with ACL injuries compared with uninjured controls. The difference involves the sagittal plane as well as the frontal and transverse plane motion.

Genetic factors, linked to collagen metabolism genes, contribute to the increased joint laxity in females (18-21) but, as detailed in the following paragraph, hormonal factors are also of paramount relevance.

Moreover, neuromuscular control deficits, defined as muscle strength, power, coordination, or activation patterns, play an important role (9). In comparison to males, females show decreased potential for dynamic stabilization of the knee joint during landing, and decreased ability to safely attenuate large forces, recruiting muscular restraints (22).

Some studies have compared the knee kinetics in athletes of both sexes, performing forward, vertical, and backward stop-jump tasks (23). Three-dimensional videography and force plate data have been used to record the subjects’ performance. In the landing phase, the knee in females, compared to males, is in more extension and has higher quadriceps activation at initial contact with the ground. This combined situation produces an anterior-directed shear force and therefore more strain on ACL. On the other hand, females exhibit lower hamstrings to quadriceps torque ratios at high angular velocities, altered quadriceps and hamstrings activation strategies, that may increase dynamic knee abduction, and greater frontal plane motion (10). In conclusion, as proved by longitudinal observations (10), a combination of altered motor control strategies, with relative decreased hamstrings and high quadriceps strength, may be a risk factor for ACL injury in females athletes (24-25).

Finally, proprioception (balance and coordination) is important for neuromuscular control of the lower extremities, particularly during dynamic tasks. Proprioceptive deficits in control of the body's core predict knee injury with high sensitivity and specificity (26).

Coordination imbalances and lateral trunk displacements in the single leg stance, or after a sudden perturbation, have been shown greater in females than in males, and even more in the female athletes who subsequently had a knee injury (27).

Hormonal factors

Sex hormones

The onset of puberty is crucial for making evident the difference between sexes in knee biomechanics, and accordingly for explaining the increased rate of ACL injuries in females. Biomechanical and neuromuscular differences sex related are minimal before puberty (7-8), but after the onset of puberty an increase in knee abduction angles, knee abduction motion, joint laxity and active joint stiffness becomes evident.

Boys and girls land from a stop jump with a similar amount of knee flexion and valgus at age 11 and 12, but women begin to land with straighter knees, and to show impaired motor control strategies, with decreased hamstrings/quadriceps strength ratio, progressively up to age 16.

Indeed, there is growing evidence that estrogens influence ligaments and tendons metabolism. Estrogen receptors have been localized in these structures (28), and experimental data obtained in vitro suggest that estrogens can depress collagen synthesis and fibroblast proliferation (29-31), which could be the biochemical feature underlying the increased joint laxity observed in the clinical setting. In human ACL's cultures, these effects increase with estradiol concentrations in the medium, are more pronounced immediately after hormone exposure (1-2 days), are attenuated with maintained exposure (7 days), and seem independent from progesterone concentration (32). Recent research on cultured rat Achilles tendon fibroblasts suggests that raloxifene, a selective estrogen receptors modulator, increases type III collagen and elastin expression, which are considered to govern tendon elastic properties. Based on the fact that type III collagen fibers are thinner and more compliant than type I, the increased type III collagen content may weaken the tensile strength of tendons (33). However, these findings are challenged by other studies, which have shown no effect (34), or paradoxically a stimulating effect of estrogens on collagen synthesis and fibroblast proliferation (35).

The limitations of experimental research are obvious: supraphysiologic hormone concentrations are often used, the differences between animal species can be a confounding factor, and, most importantly, the tissue culture model does not take into account the number of environmental factors which, in the intact individual, can largely influence tendon mechanical properties, overcoming the effects of estrogen. Therefore, given these limitations and the non univocal results, care must be taken to apply the experimental findings in the clinical setting.

Better information about the role of estrogens could be obtained studying the changes of the ligaments and tendons biomechanical properties, and the tendon injury risk, across the phases of the menstrual cycle. Unfortunately, these studies have lead to conflicting results. In several reports no consistent variations of knee joint laxity have been observed (36-41). Burgess et al. (41) evaluated the functional properties of the patellar muscle-tendon unit in normally menstruating healthy females. Dynamometry, ultrasonography, electromyography and biochemical assessment of circulating levels of estradiol and progesterone were performed. No significant differences were seen in tendon mechanical properties among the three phases of the menstrual cycle. Pollard et al. (40) measured knee laxity in female and males subjects prior and following an exercise protocol. In females, serum estrogen levels were also evaluated at specific times to represent three menstrual cycle phases. Exercise induced equivalent increases in knee laxity in males and females. Knee laxity was greater in females than in males both pre- and post-exercise, but was not influenced by estrogen fluctuations across the menstrual cycle.

In contrast with these findings, more recent and accurate experiments have shown changes in anterior knee laxity, general joint laxity, and genu recurvatum across the menstrual cycle in recreationally active eumenorrhoic women (42). On average, at the group level, consistent increases between days in the early follicular to days in the early luteal phase occurred simultaneously in these parameters, and were of sufficient magnitude to influence collagen metabolism, studied by means of serum markers of collagen production and degradation. Moreover, the variations of anterior knee joint laxity across the cycle were consensual to joint biomechanics changes, as shown by comparative measures performed during the knee transition from non-weight bearing to weight bearing conditions (42-43). This finding is important, because ACL's role is relevant in maintaining normal knee biomechanics during weight acceptance, and injuries most often occur during sudden deceleration or changes of direction, with the knee relatively extended (44-45). However, in these studies, not only the magnitude of the changes varied considerably among females and could not always be confined to the periovulatory and early luteal phases, but also several participants did not experience cyclic variations in their laxity values (42).

The discrepancies arising from the studies performed across the menstrual cycle could result from several factors. The physiologic hormonal pattern exhibits individual differences and erratic perturbations in cycle phase length. Moreover, subtle menstrual disturbances, such as anovulation and luteal phase defects, are frequently associated with exercise and may occur in physically active women (46), mainly in athletes. The prevalence of these disorders ranges from 12% to 48%, and often goes undetected because menstrual bleeding may still occur at regular intervals, that is, every 26 to 35 days. Both anovulation and luteal phase defects are associated with alterations in sex steroid hormone profiles. So, the studies which identified the phases of the menstrual cycle by questionnaire, or by the determination of sex steroid hormones from just a single day, can be misleading. Moreover, it is reasonable that the effects of sex hormones on ligaments and tendons are not immediate, but occur with just some days delay (34). Finally, it must be considered that other factors across the menstrual cycle, independent or interacting with sex hormones, may influence laxity measures: among them, water retention, muscle strength and musculotendinous stiffness.

On the basis of these results, it seems likely that changes of tendon laxity occur across the menstrual cycle, but with very large individual differences. Moreover, it remains unknown what magnitude of laxity change may be relevant to modify the individual risk profile (42). Finally, from the pathogenetic point of view, it may be questioned whether the reduced stiffness in females is mainly due to the serum estrogen levels, or to the intrinsic characteristics of collagen metabolism sex-related (47).

The discrepancies observed in biomechanical parameters are also reflected by the observations about the incidence of lesions in the different phases of the menstrual cycle. The majority of studies show a higher proportion of ACL injuries in the follicular (both early and late) compared to the luteal phase (48-50), but other studies report a higher incidence just before or at the onset of menses (51-52) or no correlation with the phases of the cycle (53).

To add complexity, the effects of the pill must be taken into account. A lower rate of lesions in women who use the pill has been observed in some studies (49, 51, 54), but not in others (48, 53). However, the composition and the dosage of estrogens and progesterone vary widely among oral contraceptives and, as a consequence, the endogenous hormonal levels vary accordingly. Therefore there is no conclusive evidence that contraceptives have a protective effect against ACL injuries.

Relaxin

Relaxin is a small peptide hormone in the insulin superfamily, first described in pregnant animals and women, which can be detected also during both the follicular and the luteal phases of the menstrual cycle. Relaxin is provided of collagenolytic effects, that are believed to be mediated by the release of collagenases, matrix metalloproteinases, and plasminogen activator (55). Specific receptors for relaxin have been found in females but not in males (56).

The potential to affect the mechanical properties of connective tissues has been proven: in an animal model (guinea pig), following 21 days of treatment with relaxin, the females' ACL was significantly weaker during load to failure testing than untreated control ligaments (57).

In a study aimed to determine the interactions between relaxin levels and tendon stiffness, in normal menstruating women, Pearson et al. (56) found that serum relaxin levels were negatively associated with patellar tendon, but not with Achilles tendon stiffness or with the cross sectional area of either of the two tendons. The conclusion was that there is a selectivity in the impact of relaxin on tendon tissues, which appears to be related on the intrinsic properties rather on the dimensions of the tendon. Differences in relaxin receptors density, or in their sensitivity to the hormone, or in metabolic characteristic of different tendons were hypothesized.

Serum relaxin concentrations usually peak in the mid-luteal phase, but the differences are small across the cycle. So, it seems unlikely that ACL collagen remodeling keeps pace with the monthly relaxin variations. More plausibly, there is likely a long-term exposure effect, and those with higher levels of relaxin levels experience increased activation of relaxin receptors on the ACL over time, which ultimately leads to decreased ligament integrity and increased risk of ACL tears compared with those who do not have chronic exposure to relaxin (55-57).

In a study (58), performed in 128 female athletes from two american universities, participating in sports at high risk for ACL tears (basketball, hockey, soccer, gymnastics, and volleyball), the serum levels of sex hormones, as well as those of relaxin, were evaluated at regular intervals. Moreover, the cumulative incidence of complete ACL tears was monitored over 4 years of their athletic career. Serum relaxin resulted detectable in 46 (35.9%) and undetectable in 82 (64.1%). In the subset with detectable levels, the mean serum relaxin values resulted significantly higher in athletes with ACL tears, compared to those without ACL tears (12.1 ± 7.7 pg/mL *vs* 5.7 ± 3.6 pg/mL, p= 0.002). When 6.0 pg/mL was set as cut-off value for screening athletes at risk, the positive predictive value was 52%, the negative predictive value 88%, and the relative risk of 4.4. This study suggest that females with high relaxin serum levels are at increased risk for ACL tears.

CONCLUSIVE REMARKS

The mechanisms underlying the higher incidence of ACL tears in female athletes are yet incompletely known, but recent research adds new perspectives for profiling the subjects at higher risk, and therefore for suggesting preventive measures.

Anatomical and neuromuscular factors account for the sex difference. The increased laxity of knee ligaments in women is an important risk factor. More compliant ligaments and tendons can expose to injuries when performing tasks requiring rapid force generation. Changes of knee laxity and biomechanics occur across the menstrual cycle, but their amount and timing show large individual variability (42). The estrogens profile with regard to the phasing and amplitude of serum levels varies among subjects, and it is not clear whether the increased laxity may depend exclusively on estrogens. Therefore it is possible that some women may experience greater effects on ligaments than others. Relaxin levels could be more important than estrogens to explain the increased knee laxity and risk of ACL injuries in females.

Identifying at-risk athletes is of paramount relevance. At this regard, reliable clinical assessment tools have been developed; they include techniques of neuromuscular evaluation and the study of changes of knee laxity across the menstrual cycle (6, 59)

The dosage of relaxin serum levels could be envisaged as a new perspective to assess the individual risk of ACL injuries.

Athletes at risk can benefit from appropriate injury prevention programs. Interventions that integrate biomechanical, proprioceptive, and strength training techniques, not only enhance the athletic performance, but also can significantly lower ACL injury risk (10, 60). On the contrary, protocols targeting single-components training approaches are of limited value. Emphasis is placed on improving landing technique, increasing hamstring strength and power, reducing hamstring to quadriceps and side-to-side strength imbalances. Females categorized as high risk receive more benefit from neuromuscular protocols than teammates who do not exhibit high risk measures (6, 10). In the future, the block of relaxin receptors with a binding protein antagonist medication could be considered.

The substantial increase in the number of women participating in sports, resulting in a corresponding increase in ACL injuries, strongly suggest to better profile the athletes at risk, to extend screening programs and to develop preventive procedures.

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REVIEW ARTICLE

COMPLEX FRACTURES OF TIBIAL PLATEAU: ANYTHING NEW?

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The purpose of this article is to highlight some controversial aspects in the diagnosis and treatment of these severe skeletal lesions. The use of a spanning external fixator should be adopted by all emergency departments. It is a method which allows immediate fracture stabilization and better imaging studies. Recent CT studies have shown the importance of the anatomo-pathological study of fractures on both sagittal (slope)and coronal planes to highlight the fragments position. This allows us to determine the best surgical access and osteosynthesis techniques to obtain the most stable, anatomical synthesis. The correlation among these aspects becomes clear at the end of this work as well as how they affect treatment decisions. Narrative Review

Temporary external fixation

Complex fractures of the tibial plateau are usually caused by high-energy trauma.

After being evaluated in the emergency department, the patient must undergo an X-ray examination of his knee with an appropriate series which includes anteroposterior (AP, AP with 10 degrees angulation) and laterolateral views (LL).

The clinical and radiographic parameters published by Watson in 1994 still have a general prognostic value: 5 mm step-off, meta-diaphyseal dissociation, diastase of the condyles, soft tissue lesions. They are signs of absorbed energy by the traumatized segment and indicate the initial biological damage.

After these initial steps, we have to decide whether or not to use a temporary external fixator.

The spanning external fixator is a very common technique in American and English trauma centers. Some authors consider it an essential step in their therapeutic protocol (1-5).

The use of a spanning external fixator presents some advantages:

- immediate fracture stabilization;
- deformity correction at least in the frontal plane;
- improvement of patient's mobility;
- better nursing care;
- improvement of CT scan examination.

Several authors point out the importance of applying at least two femoral pins and two tibial pins connected by two different bars. Pins should be placed as far away from the planned incision site as possible.

There are two possible complications associated with femoral pin position:

- anterior pin insertion may injure the quadriceps with possible muscle calcifications. However, it is a very rare complication (6);
- lateral pin position may predispose to infections if the pins are near the planned incision site.

Recent research clearly shows it is a concern not supported by clinical findings (7).

Key words: tibial plateau, complex fracture

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A controversial point is how much time needs to pass until the definitive treatment. Apart from particular cases, it is recommended to wait 7-10 days. The device gets removed during the planned osteosynthesis.

Imaging

The sensitivity and specificity of MRI in making diagnosis for associated capsular and ligament lesions is high (8). However, a CT provides more information about bone damage and, as MRI is not always available in every hospital, it cannot be considered a standard diagnostic test. In 40% of cases, the CT study, in particular three-dimensional reconstructions, leads to modification of the initial treatment decision based only on X-rays imaging. Careful radiographic evaluation is essential to define fracture characteristics and treatment decisions.

The presence of a spanning external fixator improves the evaluation of the topography of the fragments.

In recent studies two factors have sparked interest as conditioning factors in therapeutic choices:

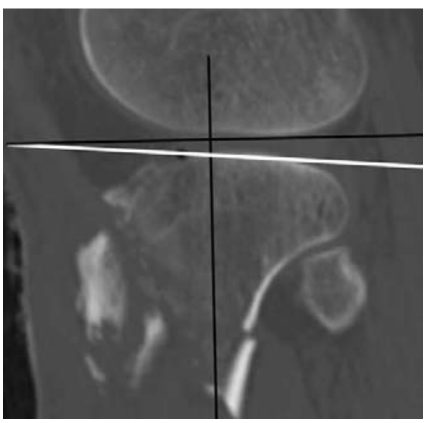

Fig. 1. *Slope measuring technique described by Hudek in 2009 (10).*

• modification of the tibial slope in the sagittal plane;

• The presence of posterior fragments, especially posteromedial fragments, in the coronal plane.

Slope Modification

The slope has been considered just an anatomical aspect of proximal tibia metaphys for a long time. On the contrary, recent studies have shown (9-10):

1. possible difference in slope between internal and external plateau in the same person;

2. difference in slope among subjects with sex-dependent Gaussian curve.

It is known that tibial slope is biomechanically relevant and that, in stable and controlled fractures such as tibial osteotomies, it can change. For both of these issues, a group of traumatologists from Toronto decided to study how the plateau slope changes when metaphyseal dissociation occurs in complex proximal tibial fractures.

In 2004 (11) Barei et al. published a research report which highlighted the problem of sagittal plane and pointed out that a quarter of the patients treated for complex tibial plateau fractures had a sagittal plane deformity. This outcome was common among authors, whatever the surgical technique used. In another research report published in 2011 (12) Barei et al. studied slope modification in complex tibial plateau fractures and used Hudek's studies (10) as a reference to define normal human anatomy.

Measurements were made on CT images of patients stabilized in Emergency Room with a spanning external fixator (no definitive osteosynthesis)(Fig. 1).

The results were amazing (Table I):

➢ more than half of the tibial plateaus exceeded the limits of physiological variability;

➢ the external tibial plateau tended to increase its slope in about two-thirds of cases, while the internal plateau inverted its slope with an anterior tilt in

Table I *Slope modification on both sides of a tibial plateau after a fracture (4).*

LATERAL SIDE	MEDIAL SIDE
MEDIUM SLOOP +9,8°	MEDIUM SLOOP +4,1°
RANGE -37°/+17°	RANGE -31°/+16°
57% > 5°	58% > 5°
76% POST; 24% ANT	47% POST ; 53% ANT

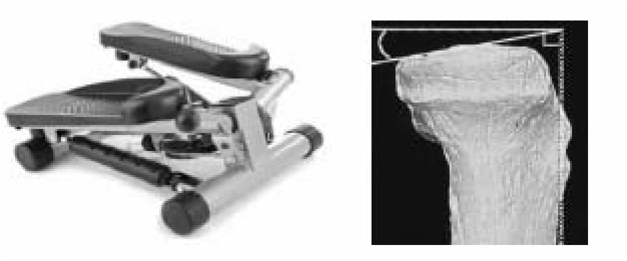

Fig. 2. *Comparison between a mini stepper and a tibia.*

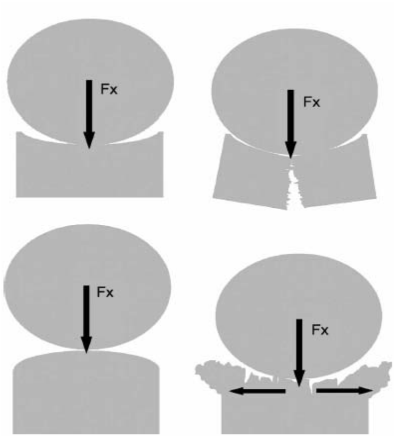

Fig. 3. *The different behavior between the tibial plateaus (16).*

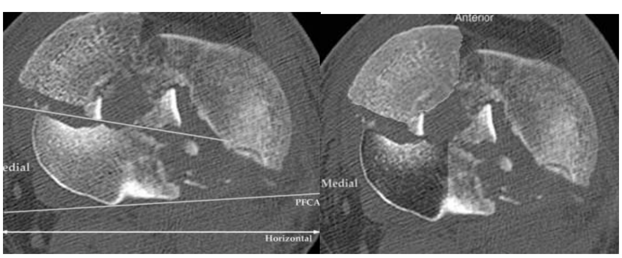

Fig. 4. *Barei's measurement technique (17).*

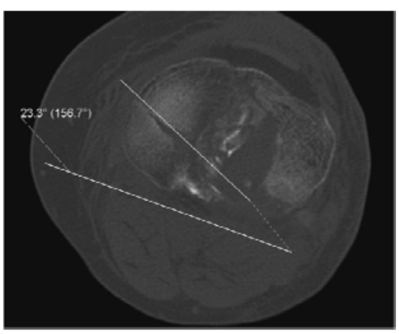

Fig. 5. *Posteromedial fragment in extra-rotation position (18).*

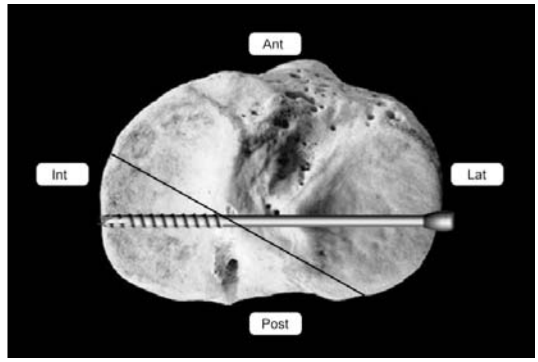

Fig. 6. *Posteromedial fragment in extra-rotation position. Starting from the lateral plate, the screw can stabilize the fragment.*

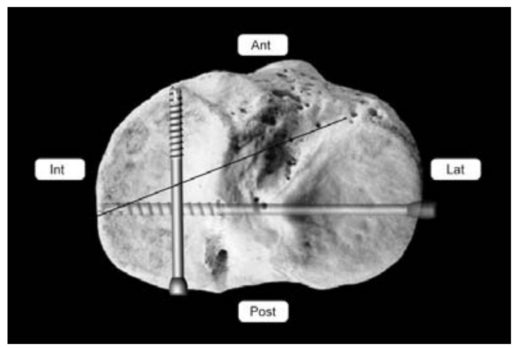

Fig. 7. *Posteromedial fragment in intra-rotation position. Only a screw inserted in a posterior-anterior direction can stabilize the fragment.*

more than half of the cases;

➢ as among patients the slope modification went from 0 degrees to 31 degrees, it is possible to compare a post-traumatic image of proximal meta-epiphysis of the tibia with a mini stepper with its pedals placed on two different planes (Fig. 2);

➢ No other anatomopathological element can be associated with such a sagittal plane deformity;

➢ The use of a spanning external fixator does not correct the deformity.

In their conclusions the authors underlined, on the one hand, the limitations of their study, on the other hand, the undeniable interest of their results which will lead to another research. The new study will focus on two main aspects:

Table II. *Comparison between Barei and Higgins's results (17-18).*

BAREI (17)	RESULTS	HIGGINS (18)
40%	% CASES	59%
58%	% ARTICULAR SURFACE	NOT REPORTED
23%	% TOTAL SURFACE	25%
-9° (23°/- 41°)	ANGLE FRACTURE	-21° (52°/-87°)
42MM	POSTERIOR HEIGHT	45MM
81°	SAGITTAL ANGLE	73°

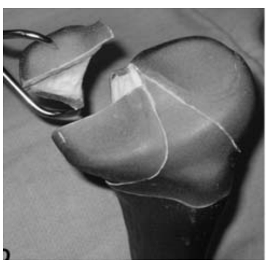

Fig. 8. *Experiments on a synthetic bone (19).*

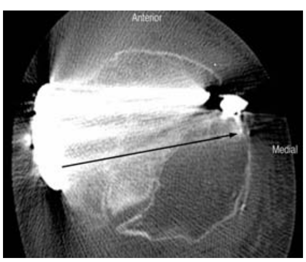

Fig. 9. *Only one screw can reach the posteromedial fragment (17).*

• the quality of correction obtained through open synthesis;

• the importance of the sagittal deformity in the outcome of the fracture.

Fig. 10. *Barei's two incision method of (11).*

Posteromedial Fragments

We have already stated that establishing the exact pathological anatomy of the fracture is essential in deciding about surgical access and type of osteosynthesis (13). Both the A.O. and Schatzker classifications are widely used as common language for scientific studies. However, it is no longer possible to use these one-dimensional classifications as a main system to decide treatment options such as surgical access and osteosynthesis material. We should either update these two systems or to introduce a new classification system, also considering that decisions are made on tridimensional imaging (14-15).

We have already spoken about the sagittal plane. X-rays are undoubtedly effective in studying the frontal plane. CT evaluates diastasis and the cupping of tibial plateau precisely and is the most effective tool to study the coronal plane. With these scans, you must consider above all the anteroposterior topography of fragments. It is important to understand the tight bond between this evaluation and the surgical access choice, in order to master the surgical treatment.

The presence and the position of posterior fragments seem conditioned by the two tibial plateaus anatomy (16). Thanks to its convexity, the external tibial plateau dissipates the trauma energy in the sub-condral cancellous bone. The consequence is a multidirectional fragmentation and spongiosa compression with apparent bone loss. The internal tibial plateau has a concave shape, which, due to the position of its trabeculars, leads to a division in the sagittal plane which often causes detachment of a big posterior fragment (Fig. 3).

The CT studies by Barei and Higgins (17-18) showed that the posteromedial fragment affects more than 50% of complex fractures, with the following anatomopathological aspect result:

- the fragment is about the 50% of the internal tibial plateau surface;
- its height of the posterior cortex is proportional to its size in the coronal plane.

The two CT studies have shown another important characteristic of posteromedial fragment. The inclination axis of its main fracture surface can be measured with a reproducible method. In fact, if we consider the posterior bicondylar femoral axis as a fixed reference (Fig. 4), the anteroposterior axis of the fragment shows a more frequent extra-rotation orientation (posteroanterior and lateromedial direction) than an intra-rotation one (posteroanterior and mediolateral direction). The angular values are reported in Table II. This measure is important to decide surgical access and osteosynthesis type and stability. If the fragment presents an extra-rotation degree, it will still be possible to stabilize it through one or more screws coming from the lateral side. On the contrary, in case of intra-rotation it is almost impossible to stabilize it with lateromedial screws, whatever the type of plate.

As other authors had shown the reliability of this method, Barei et al. performed a study using synthetic bone (19). They used a simulated bicondylar tibial fracture with a posteromedial fragment designed according the behavior reported in the previous work (Fig. 5). The experiment showed that an external plate with angular-stable screws does not give a stable synthesis of the posteromedial fragment. Only a plate placed in the posterior tibial metaphysis side can ensure a durable synthesis which won’t collapse (Fig. 6).

These considerations lead into our next topic.

Surgical Access

In 1995 the American Academy of Orthopaedic Surgeon (AAOS) still suggested the use of a single median access to treat complex tibial plateau fractures (20). The study of the pertinent literature show a high incidence of skin complications and infections when a very invasive and traumatizing incision is used. This surgical access has been gradually abandoned thanks to the new angular-stable fixation technique and a more careful evaluation of the anatomopathological characteristics of the fracture.

When a surgical access to both tibial plateaus is necessary (4), the majority of fractures can be managed through a standard anterolateral access and a posteromedial approach passing behind the hamstrings tendons (Fig. 7). This incision placement permits having enough space to avoid soft tissue damage and an adequate view of the fracture fragments.

Different kinds of lateral or posterior surgical access to proximal tibia have been described and can be used in relation to the synthesis system required by the fracture pathological anatomy (21-25). It is evident that the tissue sparing surgery respects the anatomical structure, soft tissue in particular, and this strategy should be extended to the entire orthopedic surgical behavior.

Osteosynthesis Material

The main objectives of fracture treatment are anatomical reconstruction, stable synthesis, quick patient mobilization, especially with articular fractures.

Generally, the pertinent literature aims to define the state of the art in a disease treatment and how orthopedic research tries to achieve the above goals (1, 3, 5, 20, 26).

In 1995 the American Academy of Orthopaedic Surgeons (AAOS) suggested the use of opposite lateral plates with large-fragment screws to reconstruct and stabilize complex tibial plateau fractures. This method was later renamed "dead-bone sandwich" also for excessive soft tissue complications. High incidence of major complications such as infections, dehiscence, bad reduction or loss of reduction led some traumatologists to abandon open osteosynthesis and prefer the use of external fixation as main technique (2, 27-30).

From these considerations, we can take out two aspects which have marked the technical evolution since the beginning of the 21st century. The first aspect concerns some principles of external fixation clearly reported in the angular-stable fixation. This new technology uses materials which give substantial rigidity to the synthesis systems as well as tools which allow to reduce surgical access extension. It is a method which has given new force to open synthesis supporters.

Smaller incisions and great mechanical stability appeared to be the main principles to treat injuries of proximal metaepiphysis of the tibia with this new technique. First clinical works and biomechanics studies to compare the synthesis methods seemed to support the initial enthusiasm (31-34). But after some years of use, even the angular-stable fixation showed its limitations, in particular when its use was not appropriate.

The right decision chain in fracture treatment has not changed over time:

- knowledge of normal anatomy;
- anatomopathological fracture pattern study;
- choice of surgical access and synthesis material.

The limits of angular-stable fixation are known and three of them in particular have to be considered here:

- constrained direction of screw position. We have seen how the stabilization of posteromedial fragments is often impossible due to the presence of an external plate;
- absence of interfragmentary compression. The joint surface reduction must be made and stabilized before applying an angular-stable fixation which, generally, does not use compression screws;
- screw dimension. Recently there has been a tendency to use smaller screws (3.5 mm) which provides good mechanical stability and respect the bone biology more.

As a perfect synthesis system does not exist, the orthopedic surgeon has to choose the most suitable one for the fracture he/she is treating.

The synthesis system consists in two main functions:

- preserving the reduction over time resisting stress during rehabilitation;
- protecting the phase of consolidation.

Depending on the surgeon's knowledge and experience, different synthesis techniques can be mixed together if biomechanically appropriate.

Literature has shown that, if properly used, the different osteosynthesis techniques have the same mid-term and long-term results.

CONCLUSIONS

Complex tibial plateau fractures are very difficult to treat. Some authors still invite orthopedic surgeons to evaluate their experience and the suitability of the hospital before facing a similar operation. It is important to inform the patient about the seriousness of the lesion and the chance to develop early arthrosis even after an initial satisfactory result.

An in-depth study of the anatomopathological characteristics of the fracture is essential to get good results as well as choosing the right surgical access to obtain the anatomical reduction of the fragments. We need to adopt a flexible approach to synthesis materials as a material suitable for all cases does not exist.

The preoperative study and a right surgical technique help prevent complications or failures which leave little hope for a second operation. This way we could make decisions which will combine to form a perfect jigsaw puzzle and to give the result we look for.

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BASIC SCIENCE AND RESEARCH

BIOACTIVE MATERIALS FOR CARTILAGE TISSUE ENGINEERING

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This study is focused on the development of a biomaterial that could mimic cartilage tissue, using only natural substances, gelatin and/or collagen, crosslinked with genipin (GP). These materials are cheap and easy to handle, and in particular collagen, represents a chemo-attractor factor that may help cellular colonization. The optimal genipin concentration was decided primarily assuring that it was not cytotoxic, measuring its release in aqueous environment. Elastic moduli of scaffolds prepared with different GP concentrations, were then measured taking into account that scaffolds had to present mechanical properties suited to the implant site. Biocompatibility tests, preliminary *in vitro* and *in vivo* tests, were performed using respectively murine primary cells and Wistar rats. Laboratory Study

Cartilage injuries occur for several reasons including degenerative, surgical and traumatic processes which significantly compromise the quality of life and for this reason they have long presented a challenge to physicians (1-2). Cartilage is a tissue that has a low self-repair capacity due to its particular and unique features (3-4). Following an injury which does not penetrate to the subchondral bone, intrinsic cartilage repair has different barriers: it is avascular, meaning that the nutrients required for energetic repair processes and the removal of metabolic waste products are limited by diffusion to / from surrounding tissues. It is relatively acellular; therefore few cells are available to affect repair (5). These obstacles work together to limit repair of defects to a fibrocartilaginous substitute tissue with a different molecular composition (more type I collagen, less proteoglycan) and biomechanical behaviour (less proteoglycan and collagen type II, more collagen type I), compared to the original hyaline tissue (6-7). Many techniques have been used to treat articular cartilage defect, such as microfracture, multiple drilling and arthroscopic lavage with or without corticosteroids (8). However, only a few of these approaches were able to achieve satisfactory clinical results in comparison to autografts or allografts (9). There is still no universally accepted and successful therapeutic approach for damaged cartilage. The common strategies for cartilage repair were short-lived, they presented many side effects and were limited to small lesions (10). Tissue Engineering represents a potential alternative therapeutic process to treat severely injured patients with minimally invasive techniques (11).

We developed a biomaterial made of gelatin and collagen, natural substances, which are biocompatible, biodegradable and chemo-attractor (12-14). The main problem with the use of hydrogel is its rapid dissolution in an aqueous environment (15), so a crosslinking agent was necessary. Recently,

Key words: Genipin (GP), gelatin, collagen, cartilage.

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there has been increasing interest in the biomedical applications of a naturally occurring cross-linking reagent, Genipin (GP) (16-17). It is extracted from the fruits of *Gardenia jasminoides Ellis* and it is able to efficiently cross-link cellular tissues and biomaterials containing primary amino groups (18-20). It is much less toxic than the other crosslinkers commonly used (21).

The aim of this study was to develop a biomaterial using natural substances, gelatin and/or collagen crosslinked with GP, that could mimic cartilage tissue.

MATERIALS AND METHODS

Materials

Gelatin type A from porcine skin was purchased from Sigma Aldrich, Italy. Collagen type I (acetic acid solution) was extracted from Wistar rat tail (22) with a 4 mg/ml concentration. Genipin (98% by HPLC) was purchased from Challenge Bioproducts Co., Ltd (CBC, Taiwan).

Scaffold preparation

5% w/v gelatin solution was obtained by dissolving gelatin in phosphate buffered saline (PBS); it was heated and mixed to 70°C on a stirrer for 1h until the solute was totally dissolved. Samples were prepared mixing 5% gelatin and 2 mg/ml collagen solutions in a 1:1 weight ratio (i.e. 1g of gelatin with 1g of collagen) in a water bath at 40°C, and then GP at different concentration 0.1%, 0.2%, 0.5% and 2.5% w/w respect to the total weight of solution was added. The mixture was stirred till the reaction started, blue appeared. After 48 hours of casting, all samples were uniform and mechanically stable.

Mechanical testing

Tests were performed using Zwick/Roell mod. Z005 (Zwick GmbH & Co, Germany) with controlled positioning. The realized samples maintained in PBS were subjected to a compressive load with the following settings:

- strain rate: 0.07 mm/s;
- end of loading phase: 10% strain (respect of the initial sample length).

Elastic moduli were then calculated from the first linear tract of the stress-strain curve.

Cell culture and seeding

A vial of cryopreserved fibroblast primary murine cells was thawed, plated and cultured with Dulbecco's modified Eagle's medium 4.5 g/l glucose (Lonza, Milan, Italy) supplemented with 10% fatal bovine serum (FBS), 1% L- glutamine (Lonza, Milan, Italy), and 1% Penicillin-Streptomycin-Amphotericin B Mixture (Lonza, Milan, Italy).

They were grown in a controlled atmosphere (5% CO2; T=37°C) and at confluence they were split 1:6 and used at fifth passage. Cells were detached using 0.25% trypsin (Lonza, Milan, Italy) and seeded (in triplicate) onto scaffolds and in wells coated with a mixture 1:1 of 5% gelatin+ 2mg/ml collagen as controls at a density of $1x10^4$ cells/cm^2. Scaffolds (in triplicate) only with media culture, without cells, were used as blank. They were cultured for 3 days. The cell viability assay, (The CellTiter-Blue®, Promega, Italy) was performed every day to asses cartilage scaffold biocompatibility. At the end of third day, cells were immediately fixed in 10% formaldehyde in PBS for ten minutes and stained with DAPI (4', 6-diamino-2-phenyldione) (Sigma, Milan, Italy) for 5 minutes and observed under a fluorescence microscope.

In vivo implantation procedure

The procedure was performed in accordance with the guidelines for animal testing of the Italian High Institute of Health and with the approval of the Local Ethical Committee as well as in accordance with the Directive of 24 November 1986 (86/609/EEC) of the European Communities Council. Surgery was carried out on Wistar rats under deep anaesthesia. The patella of left leg was dislocated medially and an osteochondral knee defect was created on femoral epiphysis using the tip of tweezers. The cartilage substitute was prepared in sterile conditions and injected when the solution turned blue.

μCT *analysis*

After 100 days, rats were deeply re-anesthetized, euthanized and a high-resolution μCT was performed on explanted femurs, using the Xalt scanner (X-ray Animal Tomograph). It is a dedicated *in vivo* cone beam μCT for small animals designed to provide flexible geometry setup and scanning modality. It was built within the collaboration framework between the Institute of Clinical Physiology (IFC-CNR) and the Functional Imaging and Instrumentation Group (FIIG) of the University of Pisa.

Histology

Femurs were fixed in phosphate-buffered 4% formaldehyde solution for more than 24h. After fixation, samples were decalcified in 10 ml of electrolytic decalcifying solution (Bio-Optica, Milan, Italy) containing hydrochloric acid and formic acid, for two days. Bone was sectioned orthogonally respect to its major axis and longitudinally through the center of the trochlea to obtain a half lesion for each sample. They were embedded in paraffin, and serial coronal sections 5 μmthick were performed. Sections were stained with eosin and haematoxylin.

RESULTS

Elastic moduli

Young's moduli of gelatin/collagen samples with

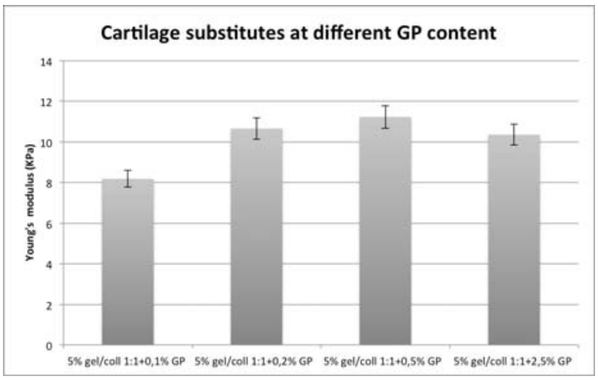

Fig. 1. *Young's moduli of gelatin/collagen samples with different GP content.*

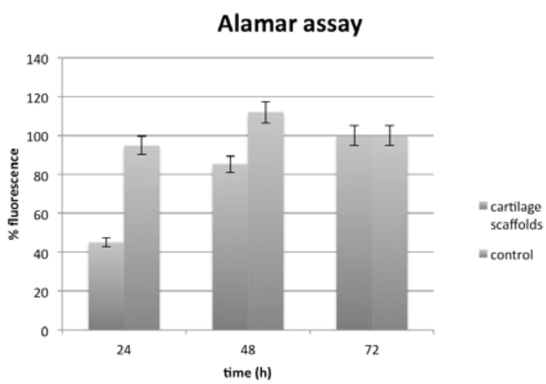

Fig. 2. *Fibroblasts viability seeded on cartilage scaffolds with respect to controls.*

0.2% and 0.5% w/w GP content were almost equal to 2.5% w/w GP samples, while 0.1% GP samples had a lower modulus value as shown in the graph (Fig.1).

Cell viability

In Fig. 2 fibroblast viability after 3 days is shown.

Viability of fibroblasts seeded on scaffolds, expressed as percent fluorescence with respect to fibroblasts seeded on well coated gelatin collagen (control), was inferior to 50% during the first day, but then it rose during the second day to reach the control value at the end of experiment. During the third day there was a small decrease in control viability due to confluence. Initially cells needed a period to adapt to a new substrate, this causes a low viability during the first day of the experiment. Similar cellular density on the third day was confirmed by DAPI staining (Fig. 3). There are no differences between cells on scaffolds and control cells.

Ex vivo µCT

Ex vivo images, clearly showed the lesion on the femoral epiphysis even after 100 days from the application of the cartilage substitute (Fig. 4).

Histology

Lesion of the femoral epiphysis at a macroscopic level was evident in the center of the trochlea (Fig. 5). At a microscopic level, cartilage had damage, with a triangular form involving also cancellous bone. Bone damage was totally filled with fibrous tissue and osteoclasts were rare at this level (Fig. 6). The histology techniques used did not make it possible to identify the remaining biomaterials.

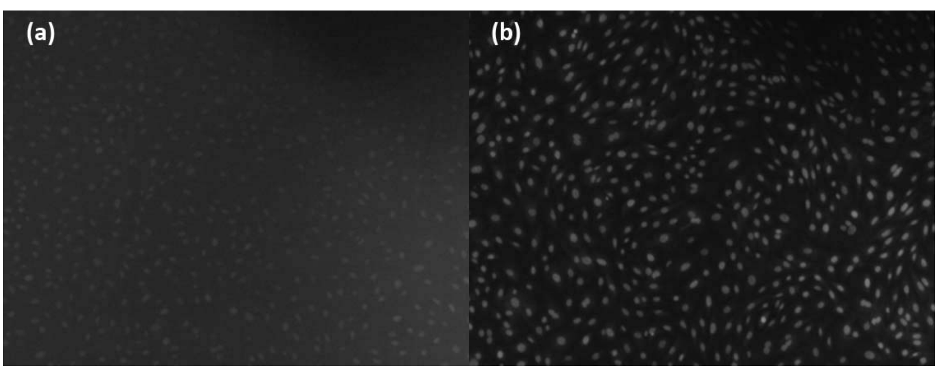

Fig. 3. *Dapi staining for (**a**) fibroblasts on cartilage scaffolds and (**b**) on gelatin/collagen coating (control) on the third day.*

Fig. 4. *Ex vivo high resolution image of cartilage damage 100 days after biomaterial implant.*

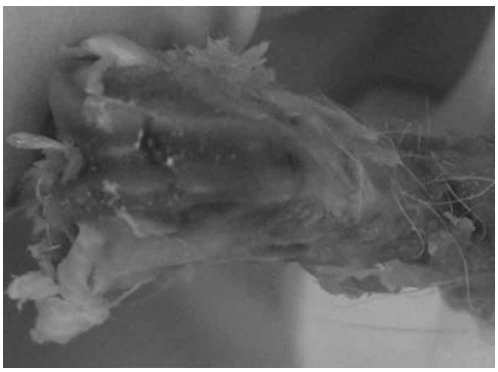

Fig. 5. *Macroscopic identification of the lesion of the femoral epiphysis .*

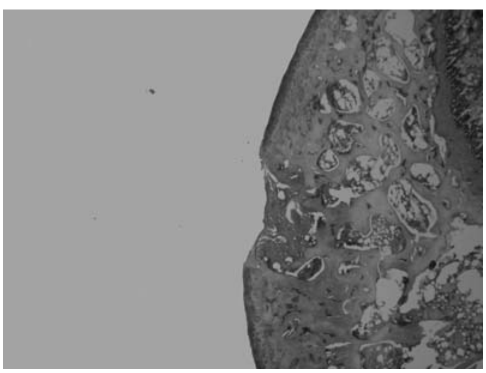

Fig. 6. *Cartilage damage and cancellous bone replaced with fibrous tissue.*

DISCUSSION

Similar values of Young's moduli could be explained by supposing that even with 0.2% GP content all amino groups were cross-linked. So by increasing the GP concentration Young's modulus does not change but GP could be only toxic for cells, considering that the genipin toxic concentration tested on osteoblast cultures was established to be 80 μg/ml (23). Cartilage biomaterials showed a good biocompatibility, even if cells required a period to adapt to the new substrate before reaching control value at the end of experiment. Micro-CT and histology confirmed that cartilage damage after 100 days from implantation of biomaterial was still present. One explanation could be that cartilage biomaterial was ineffective, or simply it did not remain in contact with the lesion enough time to be colonized by cells. An important finding was the absence of inflammation. Furthermore, because of the non invasive surgery technique utilized to create the cartilage lesion, it was not possible to assess the initial damage and to follow the progression of the regeneration. From histology performed at 100 days, we could state that the damage involved also the bone tissue and that the physiological cartilage repair process had started with the formation of fibrous tissue instead of hyaline cartilage.

CONCLUSION

All experimental results suggested that gelatin/collagen + 0.2% GP constructs could be used as an innovative hydrogel for cartilage repair. The elastic modulus of the constructs does not mimic that of natural tissue (0.5-0.9 MPa), but their high biocompatibility and the presence of chemo-attractors within them, may enhance fast cell colonization. Biomaterials could not be labeled as ineffective, as it was not possible to detect them after 100 days by μCT and histology. Biomaterials formulated and tested in this study show promising mechanical properties but more *in vivo* investigations are still needed.

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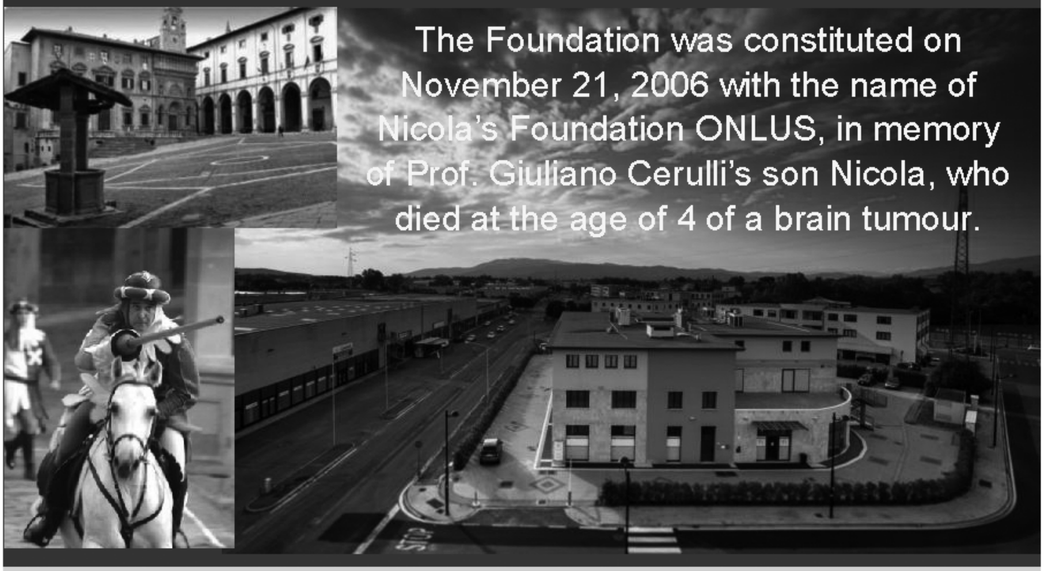

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- To promote research and training for a health service focused on the individual's needs and therefore more humane and humanizing
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- Entheses
- Tissue Regeneration: Stem Cells, PRP
- Tendon and Ligament Tissue Engineering
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