

# Management of Post-Traumatic Arthritis of the Ankle with Closed Technique of Arthrodesis Using Circular External Fixation

Redento Mora<sup>1\*</sup>, Luisella Pedrotti<sup>1</sup>, Barbara Bertani<sup>1</sup>, Gabriella Tuvo<sup>1</sup> and Nicoletta Mora<sup>2</sup>

<sup>1</sup>Orthopaedics and Trauma Section; Department of Surgical, Diagnostic and Pediatric Sciences, University of Pavia, “Città di Pavia Institute” University Hospital, School of Medicine, Pavia, Italy

<sup>2</sup>Veterinarian; Specialist in Public Health, Breeding and Livestock Production; Experimental Zooprophyllactic Institute of Lombardy, Cremona, Italy

**Received:** March 27, 2025; **Accepted:** April 03, 2025; **Published:** April 05, 2025

**Citation:** Mora R, Pedrotti L, Bertani B, Tuvo G, Mora N (2025) Management of Post-Traumatic Arthritis of the Ankle with Closed Technique of Arthrodesis Using Circular External Fixation. *Arc Orthop & Phy ther* 01(01): 1–9.

## Abstract

Ankle arthrodesis is indicated for multiple conditions, including post-traumatic arthritis. Circular external fixation represents an effective alternative to internal osteosynthesis for ankle fusion. Experimental investigations showed that continuous joint immobilization and overloading provoke cartilage destruction and a range of metabolic alterations to the matrix; as an alternative a closed procedure based on stable fixation combined with continuous compression, without resection of the joint surfaces, may obtain a solid fusion in selected cases of post-traumatic ankle arthritis where severe deformities are absent.

Between 2007 and 2015 12 patients (7 men and 5 women; average age 53 years) underwent this kind of surgery and were followed up for 4–12 years.

The Ilizarov device was employed for the fixation in all cases; no intraoperative complications were observed; mean duration of treatment with external fixator was 105 days (range: 90–125); in all cases consolidation in correct ankle orientation was obtained.

This main advantage of this technique is that you can preserve subchondral bone without shortening the length of the lower limb. Moreover, duration of surgical procedure is very short with no blood loss, and removal of the external device at the end of treatment is simple. Results obtained in this series show that closed arthrodesis is effective in cases with no significant angular deformities of the affected ankle.

**Keywords:** Ankle arthrodesis, cartilage destruction, joint immobilization, joint continuous compression, Ilizarov external fixation

## Introduction

Ankle fusion (or tibiotalar arthrodesis) is a surgical procedure indicated for multiple conditions including neuromuscular conditions, rheumatoid arthritis, primary or post-traumatic osteoarthritis, injury, osteonecrosis, infection, Charcot joint, failed ankle replacement.

After the first description performed by Albert [1], many surgical techniques have been proposed for ankle arthrodesis with varying fusion rates.

Open ankle fusions are generally performed through a two-incision (medial and lateral) large exposure; these techniques are based on a careful preparation of joint surfaces with flat cut osteotomies of distal tibia and

proximal talus (in order to remove residual cartilage and subchondral bone and obtain broad flat cancellous bone surfaces) [2–4]. Moreover, a wide variety of open minimally invasive procedures were also been proposed for cases of arthritic ankles with minimal deformity, including dowel arthrodesis, arthroscopy–assisted arthrodesis, arthrodesis with mini-arthrotomy approach [5–10].

Subsequent joint compression is obtained by means of internal fixation with screws, plate and screws or intramedullary rodding or by means of external fixation with axial or circular frames [11–14].

A particular technique of percutaneous ankle arthrodesis, proposed by Lauge-Pedersen [15], is based on fixation with percutaneous screws to obtain joint compression without resection of the articular surfaces. According to this Author, the advantages of performing a minimally invasive procedure and preserving the subchondral bone and the arch-shaped geometry contribute to the arthrodesis stability.

Among surgical procedures aimed to arthrodesis stabilization, circular external fixation is considered an effective alternative to internal fixation methods, on the basis of non-traumatic application, stable fixation, early weight bearing and simple removal of the device at the end of treatment [16–19]. Revision of the literature shows that in the majority of reported series of post-traumatic ankle fusion performed by means of external fixation methods, open techniques are usually employed for the preparation of joint surfaces, an external device instead of an internal one is employed in order to obtain adequate stabilization, and a tibial corticotomy, followed by internal lengthening, is performed, if needed, to regain the limb length [20–25]. However, in a few series of ankle arthrodesis performed employing external fixation methods, sporadic cases are described where fusion was obtained using only compression by means of an external device without any preparation of the joint surfaces [26–28].

Moderate mechanical loading on joints plays a favorable role in normal tissue remodeling, but on the contrary no physiological mechanical stimuli lead to a process of joint cartilage degradation: continuous joints immobilization and overloading causes increasing damage and destruction of the cartilage and a range of metabolic alterations to the matrix [29–31].

With regard to the morphological alterations, much relevant information have been obtained from experimental studies performed “in vivo” in various species of animals. Salter and Field [32] evaluated the effects of continuous compression on articular cartilage of monkeys and rabbits, observing that compression (produced by a clamp or by simple immobilization of a joint in a forced position) caused in a few days articular lesions called “pressure necrosis”.

Trias [33] also described in rabbits severe degenerative changes caused at the cartilage level by persistent pressure, including death of chondrocytes, fibrillation of cartilage, eburnation of joint surfaces, and sclerosis of bone and production of bone cysts.

Gritzka et al [34] studied by means of light and electron microscopy the progressive joint deterioration following the continuous compression in rabbit joints and concluded that severity of the damage correlated with the duration of compression, and that the most evident morphologic lesion was pyknosis of the chondrocytes.

Chondrocytes respond to excessive mechanical signals by disrupting the composition and structure of the extracellular matrix, which reduces the biomechanical integrity of cartilage [35,36].

Shevtsov and Asonova [37] showed the ultra-structural findings of the degenerative and destructive changes of articular cartilage in dog’s joints under the effect of immobilization and compression.

Loening et al [38] demonstrated in bovine cartilage explants that continuous compression causes pressure necrosis with chondrocyte apoptosis, degradation of collagen fibril network, glycosaminoglycans release and increase of nitrile levels.

An ultra-structural study performed by Patwari et al [39] on bovine calf articular cartilage under the effect of compression showed a significant increase (from 7 to 62 %) in cell apoptosis.

It was also observed that the application of static load, equivalent to a compressive strain of 50%, decreased the synthesis of both collagen type II and proteoglycans in bovine cartilage explants [29].

About the biochemical alterations, an increase of NO (nitric oxide) production and NOS (NO synthase)

activity was interpreted by Fermor et al [40] as an effect of compression on porcine articular cartilage.

Lin et al [41] demonstrated that, in load-injured bovine joint cartilage, mechanical load causes cell death, increased MMP-3 and proteoglycan degradation and collagen damage starting from the articular surface and increasing in depth with loading time.

In an experimental study on mice, Koike et al [42] showed that mechanical overloading causes mitochondrial Superoxide overproduction and selective Superoxide Dismutase 2 downregulation in chondrocytes, resulting in cartilage degeneration.

In vitro studies [43–45] demonstrated that mechanical loading, representing an injurious or traumatic response, activates the integrin receptors, which stimulate stress-induced intracellular pathways, finally leading to the production of proinflammatory cytokines such as Interleukin-1 (IL-1) and Tumour Necrosis Factor- $\alpha$  (TNF $\alpha$ ). These cytokines disturb the normal remodeling activities of chondrocytes by increasing production of proteolytic enzymes such as Matrix Metallo Proteinases (MMPs). This process is mediated by Nitric Oxide (NO), Prostaglandin E2 (PGE2) and Reactive Oxygen Species (ROS).

The enhanced levels of proteinase enzymes cleave both collagens and proteoglycans, resulting in an increase in matrix fragments, which stimulate abnormal integrin signals. Accumulation of matrix fragments enhance catabolic protease-driven pathways that override anabolic events and contribute to loss of matrix components and structural damage [46,47].

MMPs are regulated in their function by a family of proteins called TIMPs (Tissue Inhibitors of Metalloproteinases) [48].

MMPs and TIMPs are secreted in joints by both synovial cells and chondrocytes; TIMPs should contribute to the regulation of MMPs expression and should play an important pro-homeostatic role in joints, as suggested by the results of a pathological and immunohistochemical study on equine fetlock performed by Mora et al [49].

On the basis of these morphological and biochemical data, we have started since 2007 to use a completely closed procedure (application of a circular external fixator, gradual correction of residual deformities, joint compression), without any resection of joint surfaces, to

gradually obtain ankle arthrodesis in selected cases of post-traumatic ankle arthritis with preoperative alignment not severely deformed.

## Materials and Methods

### Operative Technique and Post-Operative Management

The patient was positioned supine on the operating table under general anesthesia, with a support under the hip of the operated leg; pneumatic tourniquet was not employed (Figure 1 A,B). After removal of the hardware if present, an Ilizarov circular external fixator (Sintea - Plustek, Assago, Italy) was applied (two-ring frame on the tibia and a foot ring on the foot, preferably connected to the bone with crossed wires instead of half pins, in order to maintain the elasticity of the device) (Figure 2 A,B).

If a joint deformity has been diagnosed, gradual correction was performed during the following days until the deformity was eliminated, then only adequate compression was applied. The final post-operative orientation of the ankle was approximately 0° flexion, 0° to 5° hindfoot valgus, 5° external rotation. This position allows for the greatest compensatory motion at the foot and places the least strain on the knee [50].

Gradual weight bearing was allowed after 3 days. Patients were evaluated every 2 weeks; assessment of the fusion was made by means of periodical AP and lateral X-rays (Figure 3 A,B).

After Radiographic Evidence Of Fusion, Removal Of The External Device Was Performed Under Short Sedation In The Operating Room (Figure 4 A,B). The Ankle Was Then Protected In A Below-Knee Plaster With Partial Weight-Bearing For 3 Weeks; After This Time, Gradual Increasing Weight-Bearing Without Protection Was Allowed (Figure 5 A,B).

### Patients and Methods

Technique of completely closed procedure of ankle fusion was employed in 12 cases between 2007 and 2015, with a follow-up of 4–12 years. There were 7 men and 5 women with a mean age of 53 years (range: 35–68 years). All of them had a diagnosis of post-traumatic arthritis with minor ankle deformity.

Figure 1: A,B: Anteroposterior and lateral X-ray pictures of a 65 year-old male with post-traumatic arthritis of the left ankle.



Figure 2: A,B: Anteroposterior and lateral X-ray pictures of the left ankle at the end of the surgical procedure (removal of the hardware and application of an Ilizarov external fixator).

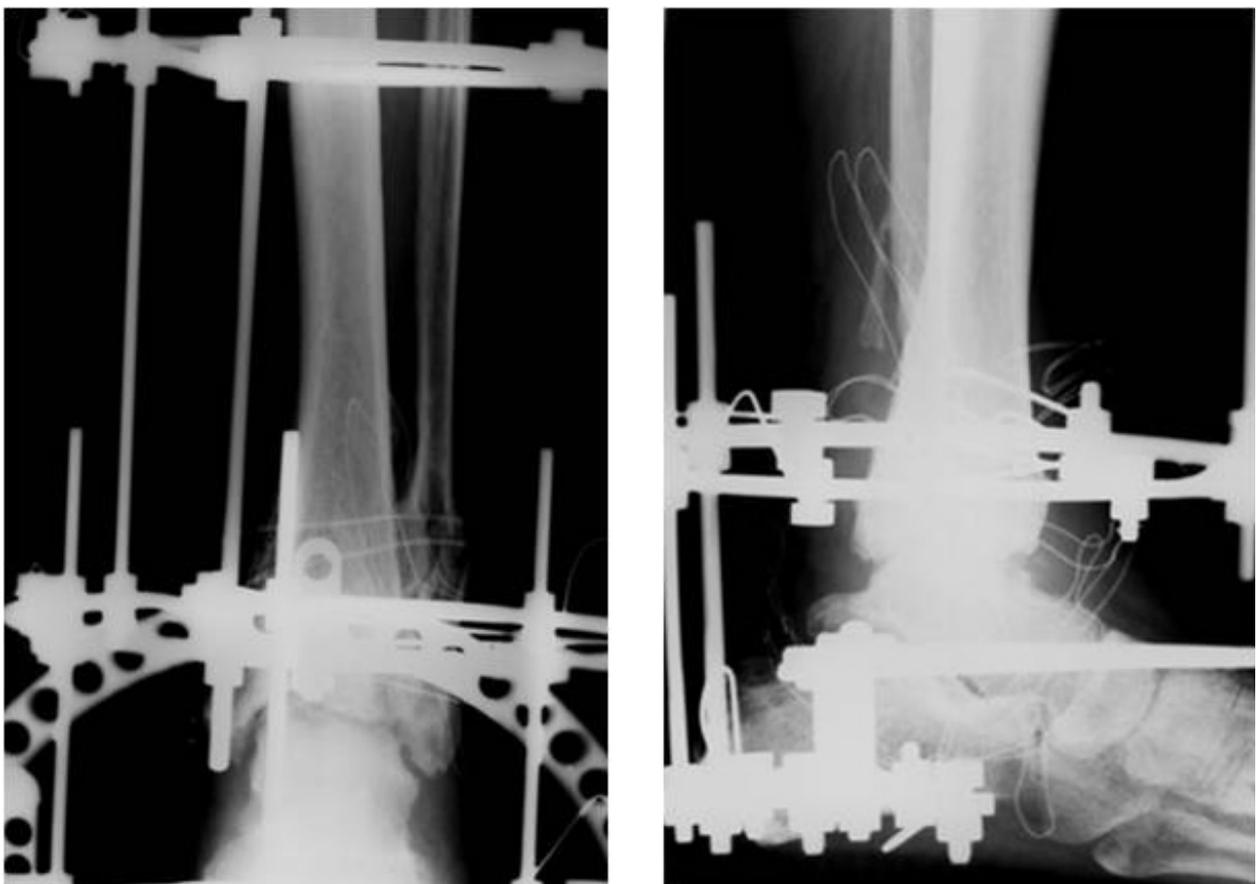


Figure 3: A,B: Anteroposterior and lateral X-ray pictures 2 months after the beginning of treatment.

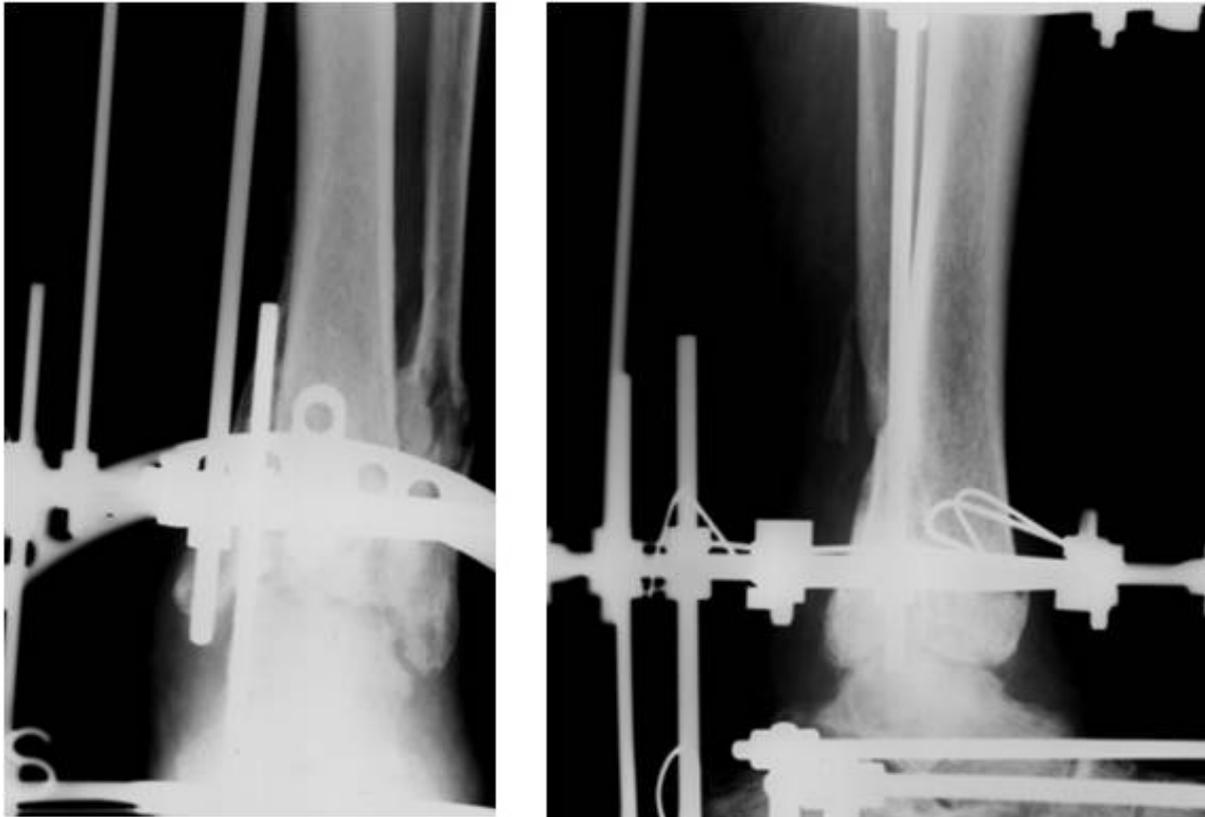


Figure 4: A,B: Anteroposterior and lateral X-ray pictures after external fixator removal at the end of treatment (120 days after external fixator application).



Figure 5: A,B: Anteroposterior and lateral X-ray pictures 3 years after the removal of the external fixator.



They had severe weight-bearing pain and limited and painful ankle range of motion, with a mean preoperative duration of symptoms of 4 years (range: 2–5 years), without relief using conservative measures.

Evaluation with American Orthopaedic Foot and Ankle Society (AOFAS) rating system, developed with the aim to estimate clinical problems of the ankle with regard to pain, function and range of motion [51], allowed to assess the preoperative clinical situation and the surgical outcome.

Ankle preoperative radiographs showed subchondral sclerosis, narrowing of the joint space with joint destruction, absence of significant misalignment (more than 15° of varus or valgus of the affected ankles).

## Results

Mean operative time was 45 minutes (range: 35 – 65).

No intra-operative complications were observed; neither vascular nor neurological injuries were observed. The following minor complications have occurred during treatment: wires broke, requiring wire substitution, in 5 cases; superficial infection at some wire tracts in 3 patients, treated with local dressing and targeted antibiotic therapy.

Ankle deformity correction and fusion were obtained in all patients and the removal of the external device was performed after an average of 105 days (range: 85 – 135 days).

Because the AOFAS score rating system was modified by eliminating the range of motion component, patients were also postoperatively evaluated, as suggested by Wroslawski et al [10], with the non-numeric rating system proposed by Paley, divided into clinical and functional outcome components [52].

Clinical outcomes are evaluated on the presence or absence of union, infection, deformity and limb-length discrepancy, while functional outcomes are evaluated on the basis of the following four criteria: pain, gait abnormality, daily activity, walking distance. In this classification both outcomes can be defined as excellent, good, fair or poor.

Analysis of the AOFAS scale (Student t-test) showed a significant difference ( $P$  value  $< 0.001$ ) between the mean pre-operative score of 36 points (range: 32 – 47) and the mean postoperative score of 73 points (range: 63 – 79).

According to the Paley score, the clinical status resulted excellent in 8 cases and good in 4; the functional outcome proved to be excellent in 9 patients and good in the others.

## Discussion

This kind of treatment has been developed because the results of some experimental studies had showed that continuous immobilization and compression on the joint cause a damage to the cartilage, consisting of morphological and biochemical alterations.

Closed technique of ankle fusion using circular external fixation provides many advantages: removal of cartilage and subchondral bone by means of osteotomes or power instrumentation is not needed, thus reducing the damage of viable bone cells; moreover, the morbidity degree associated with this technique is very low, because pneumatic tourniquet is not employed, blood loss is absent, operative time is extremely short. Nevertheless, this minimally invasive technique is not indicated in cases of severe angular deformities that require osteotomies to realign the joint.

In the reported series any preparation of the ankle joint by means of resection of articular surfaces proved to be unnecessary to perform because the damage of the cartilage, following the immobilization and continuous

compression performed by means of the external device, caused an increasing cartilage degeneration and disappearance, with gradual fusion of the tibial and talar bones. In cases of arthritic ankles with minimal deformity, the resection of the joint surfaces to produce tibial and talar flat surfaces is not needed; on the contrary, the maintaining of the subchondral bone and of the arch – shaped geometry of the joint allows for better post-operative stability.

Surgical procedure is simple and very rapid, with no blood loss; complications are rare and the removal of the external device at the end of treatment is very simple.

The choice to use as classic circular fixator instead of a hexapod fixator mainly depended on the fact that procedure is simple and alignment corrections during the treatment period are rarely needed so even it could be easily performed.

Moreover, length of the lower leg is not or just minimally reduced and a concurrent or further treatment such as secondary leg lengthening is not required.

## Conclusion

The completely closed technique of ankle fusion by circular external fixation is based on the results of several experimental studies that demonstrated the high risk of severe damage of the articular cartilage in cases of immobilization and continuous compression, and on the results of clinical and experimental studies of Lauge-Pedersen [15], who suggested the possibility of achieving arthrodesis performing a stable fixation, without the removal of residual cartilage and subchondral bone.

This result is better obtained by means of circular external fixation, which offers the main advantage of the high stability of the mounting, in addition to other advantages such as nontraumatic application, possibility of early functional weight bearing, easy correction of residual postoperative deformities, simple removal at the end of treatment.

Results achieved in this series demonstrate that ankle arthrodesis performed by closed technique is effective in obtaining solid arthrodesis with correct ankle orientation in selected cases of post-traumatic ankle arthritis with preoperative alignment not severely deformed.

## References

1. Albert E (1879) Zur Resektion des Kniegelenkes. *Wien Med. Press* 20: 705–708.
2. CHARNLEY J (1951) Compression arthrodesis of the ankle and shoulder. *J Bone Joint Surg Br* 33B: 180–191. [View]
3. Abidi NA, Gruen GS, Conti SF (2000) Ankle arthrodesis: indications and techniques. *J Am Acad Orthop Surg* 8: 200–209. [View]
4. Ahmad J, Raikin RS (2009) Minimally invasive ankle arthrodesis. In: Scuderi GR, Tria AJ editors. Minimally invasive surgery in orthopedics. New York: Springer; Pg No: 387–394.
5. Yasui Y, Hannon C, Seow D, Kennedy JG (2016) Ankle arthrodesis: a systematic approach and review of the literature. *WJO* 7: 700–708.
6. Myerson MS, Quill G (1991) Ankle arthrodesis. A comparison of an arthroscopic and an open method of treatment. *Clin Orthop Relat Res* 84–95. [View]
7. Paremain GD, Miller SD, Myerson MS (1996) Ankle arthrodesis: results after the miniarthrotomy technique. *Foot Ankle Int* 17: 247–252.
8. Belt EA, Maenpaa H, Lehto M (2001) Outcome of ankle arthrodesis performed by dowel technique in patients with rheumatic disease. *Foot Ankle Int* 22: 666–669.
9. Stone JW (2002) Arthroscopic ankle arthrodesis. *Techniques Foot Ankle Surg* 1: 2–7.
10. Wroslavsky P, Giorgini R, Japour C, Emmanuel J (2006) The mini-arthrotomy ankle arthrodesis: a review of nine cases. *J Foot Ankle Surg* 45: 424–430. [View]
11. Ilizarov GA, Okulov GV (1976) Compression arthrodesis of the ankle joint and adjacent foot joints. *Ortop Travmatol Protez* 11: 54–57.
12. Newman A (1980) Ankle fusion with the Hoffmann external fixation device. *Foot Ankle* 1: 102–109.
13. Alvarez RG, Barbour TM, Perkins TD (1994) Tibiocalcaneal arthrodesis for nonbraceable neuropathic ankle deformity. *Foot Ankle Int* 15: 354–359.
14. Slater GL, Sayres SC, O'Malley MJ (2014) Anterior ankle arthrodesis. *World J Orthop* 5: 1–5. [View]
15. Lauge-Pedersen H (2003) Percutaneous arthrodesis. *Acta Orthop Scand (Suppl)* 74: 1–30.
16. Paley D (2002) Principles of deformity correction. New York: Springer.
17. Mora R, Bertani B, Tuvo G, Galli GB (2006) Compression-distraction systems. In Mora R, editor. Nonunion of the long bones. Heidelberg: Springer; Pg No: 77–87.
18. Rozbruch SR, Ilizarov S (2007) Limb lengthening and reconstruction surgery. New York: Informa.
19. Solomin LN (2012) The basic principles of external skeletal fixation using the Ilizarov and other devices. Heidelberg: Springer.
20. Johnson EE, Weltmer J, Lian GJ, Cracchiolo A 3rd (1992) Ilizarov ankle arthrodesis. *Clin Orthop Relat Res* 160–169. [View]
21. Feibel RJ, Uthoff HK (2005) Primary Ilizarov ankle fusion for nonreconstructable tibial plafond fractures. *Oper Orthop Traumatol* 17: 457–480.
22. Easley M, Looney C, Wellman S, Wilson J (2006) Ankle arthrodesis using ring external fixation. *Techniques Foot Ankle Surg* 5: 150–163.
23. Salem KH, Kinzl L, Schmelz A (2006) Ankle arthrodesis using Ilizarov ring fixators: a review of 22 cases. *Foot Ankle Int* 27: 764–770.
24. Eylon S, Porat S, Bor N, Leibner ED (2007) Outcome of Ilizarov ankle arthrodesis. *Foot Ankle Int* 28: 873–879. [View]
25. Thiryayi WA, Naqui Z, Khan SA (2010) Use of the Taylor Spatial Frame in compression arthrodesis of the ankle. A study of 10 cases. *J Foot Ankle Surg* 49: 182–187.
26. Raschke M (2007) Arthrodesis of the ankle. *ASAMI Int Bull* 8: 3–4.
27. El-Alfy B (2010) Arthrodesis of the ankle joint by Ilizarov external fixator in patients with infection or poor bone stock. *Foot Ankle Surg* 16: 96–100. [View]
28. Kugan R, Aslam N, Bose D, McNally MA (2013) Outcome of arthrodesis of the hindfoot as a salvage procedure for complex ankle pathology using the Ilizarov technique. *Bone Joint J* 95-B: 371–377.
29. Bader DL, Salter DM, Chowdury TT (2011) Biomechanical influence of cartilage homeostasis in health and disease. *Arthritis*, ID 979032.
30. Musumeci G (2016) The effect of mechanical loading on articular cartilage. *J Funct Morphol Kinesiol* 1: 154–161.
31. Hogle T, Geurts J (2016) What drives osteoarthritis? Synovial versus subchondral bone pathology. *Rheumatology* 56: 1461–1471.
32. Salter R, Field P (1960) The effects of continuous compression on living articular cartilage. An experimental investigation. *J Bone Joint Surg* 42: 31–90.
33. Trias A (1961) Effect of persistent pressure on the articular cartilage. *J Bone Joint Surg Am* 43-B: 376–386.
34. Gritzka TL, Fry LR, Cheesman RL, Lavigne A (1973) Deterioration of articular cartilage caused by continuous compression in a moving rabbit joint. *J Bone Joint Surg* 55-A: 1698–1709.

35. Sah RLY, Kim YJ, Doong WH, Grudzensky AJ, Plaas AH, et al. (1989) Biosynthetic response of cartilage explants to dynamic compression. *J Orthop Res* 7: 619–636.
  36. Kim YJ, Grodzinsky AJ, Plaas HK (1996) Compression of cartilage results in differential effects on biosynthetic pathways for aggrecan, link protein and hyaluronan. *Arch Biochem Biophys* 328: 331–340.
  37. Shevtsov VI, Asonova SN (1995) Ultrastructural changes of articular cartilage following joint immobilization with the Ilizarov apparatus. *Bull Hosp Jt Dis* 54: 69–75.
  38. Loening AM, James IE, Levenston ME, Badger AM, Frank EH, et al. (2000) Injurious mechanical compression of bovine articular cartilage induces chondrocyte apoptosis. *Arch Biochem Biophys* 381: 205–212.
  39. Patwari P, Gaschen V, James IE, Berger E, Blake SM, et al. (2004) Ultrastructural quantification of cell death after injurious compression of bovine calf articular cartilage. *Osteoarthritis Cartilage* 12: 245–252.
  40. Fermor B, Weinberg JB, Pisetsky DS, Misukoris MA, Banes AJ, et al. (2001) The effect of static and intermittent compression on nitric oxide production in articular cartilage explants. *J Orthop Res* 19: 729–737.
  41. Lin PM, Chen C, Torzilli P (2004) Increased stromelysin-1 (MMP-3), proteoglycan degradation (3B3 and 7D4) and collagen damage in cyclically load-injured articular cartilage. *Osteoarthritis Cartilage* 12: 485–496.
  42. Koike M, Nojiri H, Ozawa Y, Watanabe K, Muramatsu Y, et al (2015) Mechanical overloading causes mitochondrial superoxide and SOD2 imbalance in chondrocytes resulting in cartilage degeneration. *Sci Rep* 5: 11722.
  43. Fernandes JC, Martel-Pelletier J, Pelletier JP (2002) The role of cytokines in osteoarthritis pathophysiology. *Biorheology* 39: 237–246.
  44. Henrotin YE, Bruckner P, Pujol JPL (2003) The role of reactive oxygen species in homeostasis and degradation of cartilage. *Osteoarthritis and cartilage* 11: 747–755.
  45. Leong DJ, Gu XJ, Li Y, Lee J (2010) Matrix metalloproteinase-3 in articular cartilage is upregulated by joint immobilization and suppressed by passive joint motion. *Matrix Biol* 29 (5): 420–426.
  46. Del Carlo M, Schwartz D, Erickson EA, Loeser RF (2007) Endogenous production of reactive oxygen species is required for stimulation of human articular chondrocyte matrix metalloproteinase production by fibronectin fragments. *Free Radical Biology and Medicine* 42: 1350–1358.
  47. Guo D, Ding L, Homandberg GA (2009) Telopeptides of type II collagen-binding fragment upregulate proteinases and damage cartilage but are less effective than highly active fibronectin fragments. *Inflammation Research* 58: 161–169.
  48. Burrage PS, KS Mix, CE Brinckerhoff (2006) Matrix metalloproteinases: role in arthritis. *Frontiers in Bioscience* 11: 529–543.
  49. Mora R, Binanti D, Mora N, Fantinato E, Ferrante V, et al (2015) Pathological findings and immunohistochemical evaluation of MMP-2 and TIMPs in equine fetlock affected by degenerative joint disease. *Am J Clin Exper Med* 3: 172–177.
  50. Buck P, Morrey BF, Chao EY (1987) The optimum position of arthrodesis of the ankle. A gait study of the knee and ankle. *J Bone Joint Surg Am* 69: 1052–1062. [View]
  51. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, et al. (1994) Clinical Rating System for the ankle-hindfoot, midfoot, hallux and lesser toes. *Foot Ankle Int* 15: 349–353.
  52. Paley D (1993) The correction of complex foot deformities using Ilizarov's distraction osteotomies. *Clin Orthop Relat Res* 293: 97–111.
- \*Corresponding author:** Prof. Redento Mora, Past President, Italian Society of External Fixation (SIFE), Via Pusterla 13, 27100 Pavia, Italy, Città di Pavia Institute” University Hospital, Via Parco Vecchio, 27 – 27100 Pavia, Italy;
- Tel:** +39 0382 433611;
- Fax:** +39 0382 576821;
- Email:** tinomora@hotmail.com