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Irreparable Cuff Injuries: Treatment Options and Clinical Outcomes
Complex Regional Pain Syndrome
Wrist Immobilization after Surgical Decompression of the Median Nerve in Carpal Tunnel Syndrome: A Systematic Review
The Influence of High Physical Demand on the Occurrence of Major Muscle and Ligament Injuries in Professional Soccer Athletes: A Systematic Review
Histomorphometric Study of Non-critical Bone Defect Repair after Implantation of Magnesium-substituted Hydroxyapatite Microspheres
Electrical Stimulation Prevents Muscular Atrophy and the Decrease of Interleukin-6 in Paralyzed Muscles after Spinal Cord Injury in Rats
Comparison of Bone Graft Preparations to Treat a Critical Bone Defect on a Rodent Animal Model
Bicruciate Reconstruction with Bilateral Hamstring Autografts: Technique and Functional Results
Analysis of the Biomechanical Behavior of an Animal Model of Triple Hamstring Graft Configuration for Combined ACL and ALL Reconstruction with a Single Femoral Tunnel and a Single Strand for ALL Reconstruction
Evaluation of the Mechanical Behavior of the Patellar and Semitendinosus Tendons Using Supersonic Shear wave Imaging (SSI) Elastography and Tensile Tests
Conservative Treatment of Camptodactyly with Orthoses: A Retrospective Cohort
Surgical Rhizarthrosis Treatment: Trapezius Resection Arthroplasty Associated with Tendon Interposition *versus* the Kuhns Technique
Percutaneous Surgical Treatment of Trigger Finger
The COL5A1 Gene Allelic Combination and ACL Injury Risk in Team Sport: A Preliminary Report
Comparison of Manual Two-dimensional and Automated Three-dimensional Methods of Assessing Shoulder Joint Morphology through Computed Tomography Images
Osteopontin, WNT3A, and ABCB5 Biomarkers Expression in Osteosarcoma Patients
Radiographic Evaluation of the Surgical Treatment of Pediatric Supracondylar Humeral Fractures
Congenital Clubfoot: Difficulties in Maintaining the Use of the Dennis-Brown Orthosis by Caregivers
Evaluation of a Blood Reserve Protocol for Hip Fracture Surgery in the Elderly
Free Osteoarticular Metatarsal Autograft in the Reconstruction of Giant Cell Tumor of Metacarpal: Report of Two Cases and Description of a Technique
Systematization of Steps for Printing 3D Models of Orthopedic Deformities
Transfer of Second Toe for the Treatment of Traumatic Thumb Amputation in a Four-year-old Child: A Case Report
Retroperitoneal, Liver, and Lymph Node Metastasis from Proximal Tibial Osteosarcoma: A Case Report

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Volume 59, Number 4/2024

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Update Articles

Shoulder and Elbow

489 Irreparable Cuff Injuries: Treatment Options and Clinical Outcomes
José Carlos Souza Vilela, João Felipe de Medeiros Filho, Tadeu Fonseca Barbosa, Lucas de Castro Melo Deligne, and Thalles Leandro de Abreu Machado

Hand

497 Complex Regional Pain Syndrome
Giana Silveira Giostri, and Camila Deneka Arantes Souza

Systematic Review

Hand

504 Wrist Immobilization after Surgical Decompression of the Median Nerve in Carpal Tunnel Syndrome: A Systematic Review
Thiago Moreth da Silva Barbosa, and Ítalo Carvalho Ferraz

Sports Medicine

510 The Influence of High Physical Demand on the Occurrence of Major Muscle and Ligament Injuries in Professional Soccer Athletes: A Systematic Review
Matheus Martins Godoy, Lucas Ferreira Gonçalves, Thiago da Mata Martins, and Renato Ventura

Original Articles

Basic

519 Histomorphometric Study of Non-critical Bone Defect Repair after Implantation of Magnesium-substituted Hydroxyapatite Microspheres
Jacqueline de Azerêdo Silva, George Gonçalves dos Santos, Iorrana Índira dos Anjos Ribeiro, Ana Maria Guerreiro Braga da Silva, Isabela Cerqueira Barreto, Marcos Almeida Matos, Maurício Andrade Barreto, and Fúlvio Borges Miguel

Spine

526 Electrical Stimulation Prevents Muscular Atrophy and the Decrease of Interleukin-6 in Paralyzed Muscles after Spinal Cord Injury in Rats
Nicolas A. M. M. Machado-Pereira, Patrícia S. do Nascimento, Gabriel R. de Freitas, Franciane Bobinski, Caroline C. do Espírito Santo, and Jocemar Ilha

532 Comparison of Bone Graft Preparations to Treat a Critical Bone Defect on a Rodent Animal Model
Rian Souza Vieira, Renan Ernesto Reis Borges, Daniel Guimarães Tiezzi, Antonio Carlos Shimano, Ariane Zamarioli, and Helton Luiz Aparecido Defino

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Knee

542 Bicruciate Reconstruction with Bilateral Hamstring Autografts: Technique and Functional Results
Bruno Aspirino Ciancio, Marina Mayumi Azuma, João Victor Medeiros De Cerqueira, Gustavo Kenzo Miyashita, Jorge Liozi Yamashita, and Leonardo Addêo Ramos

549 Analysis of the Biomechanical Behavior of an Animal Model of Triple Hamstring Graft Configuration for Combined ACL and ALL Reconstruction with a Single Femoral Tunnel and a Single Strand for ALL Reconstruction
Maria Luzete Costa Cavalcante, Renata Clazzer, Camilo Partezani Helito, Rodrigo Nogueira de Codes, Lana Lacerda de Lima, and Diego Ariel de Lima

556 Evaluation of the Mechanical Behavior of the Patellar and Semitendinosus Tendons Using Supersonic Shear wave Imaging (SSI) Elastography and Tensile Tests
André Fontenelle, Pietro Mannarino, Liliam Fernandes de Oliveira, Luciano Luporini Menegaldo, Sérgio Augusto Lopes de Souza, and César Rubens da Costa Fontenelle

Hand

564 Conservative Treatment of Camptodactyly with Orthoses: A Retrospective Cohort
Maria da Conceição Soares de Oliveira, Diego Pinheiro Aguiar, and Felipe Soares Figueiredo

572 Surgical Rhizarthrosis Treatment: Trapezius Resection Arthroplasty Associated with Tendon Interposition *versus* the Kuhns Technique
Guilherme Henrique Teixeira Reis, Willker Galvão de Carvalho, Mauricio Foster Rodrigues, Jorge Raduan Neto, Aldo Okamura, and João Carlos Belloti

580 Percutaneous Surgical Treatment of Trigger Finger
Serdar Satılmış Orhan

Sports Medicine

584 The COL5A1 Gene Allelic Combination and ACL Injury Risk in Team Sport: A Preliminary Report
Carla Maria Calò, Myosotis Massidda, Roberto Sorge, Alessandra Tiloca, and Giovanni Monteleone

Shoulder and Elbow

590 Comparison of Manual Two-dimensional and Automated Three-dimensional Methods of Assessing Shoulder Joint Morphology through Computed Tomography Images
Geraldo da Rocha Motta Filho, Marcus Vinícius Amaral, Márcio Cohen, Marcio Schiefer de Sá Carvalho, Raphael Soares da Fonseca, and Ana Carolina Leal de Oliveira

Oncology

599 Osteopontin, WNT3A, and ABCB5 Biomarkers Expression in Osteosarcoma Patients
Glauco José Pauka Mello, Cleima Coltri Bittelbrunn, Glauco Vinicius Bittelbrunn Pauka Mello, Fernanda Pinto Garcia, Ana Valéria Brunetti Rigolino, and Pedro Reggiani Anzuatégui

Pediatric Orthopedics

607 Radiographic Evaluation of the Surgical Treatment of Pediatric Supracondylar Humeral Fractures
Gabriel Rigatti, Sérgio Roberto Canarim Danesi, Rafaela Dias Barbosa, and Douglas Backes Schreiner

613 Congenital Clubfoot: Difficulties in Maintaining the Use of the Dennis-Brown Orthosis by Caregivers
Fernando Minari Sassi, Filipe Augusto Shimanoe Nazario, Gabriela Bardelli, and Ana Carolina Pauleto

Trauma

617 Evaluation of a Blood Reserve Protocol for Hip Fracture Surgery in the Elderly
Maurício Rodrigues Miyasaki, Lucas de Quadros Marques, Thiago dos Santos Miranda, André Ruan Ruiz, Karen Barros Parron Fernandez, and Bruna Biglia

Technical Notes

Hand

622 Free Osteoarticular Metatarsal Autograft in the Reconstruction of Giant Cell Tumor of Metacarpal: Report of Two Cases and Description of a Technique
Luiz Fabiano Gomes Gularte

Pediatric Orthopedics

626 Systematization of Steps for Printing 3D Models of Orthopedic Deformities
Mariana Demétrio de Sousa Pontes, Carlos Henrique Ramos, and Luiz Antonio Munhoz da Cunha

Case Reports

Hand

632 Transfer of Second Toe for the Treatment of Traumatic Thumb Amputation in a 4-year-old Child: A Case Report
Hugo Alberto Nakamoto, Reinaldo Borges Gonçalves, João Carlos Nakamoto, Fernanda do Carmo Iwase, Mariana Miranda Nicolosi Pessa, and Marcelo Rosa de Rezende

Oncology

637 Retroperitoneal, Liver, and Lymph Node Metastasis from Proximal Tibial Osteosarcoma: A Case Report
Daniela Gutierrez, Carlos A. Sánchez, Francisco B. Linares, and Oscar Messa

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Irreparable Cuff Injuries: Treatment Options and Clinical Outcomes

Lesões irreparáveis do manguito: Opções de tratamento e desfechos clínicos

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Abstract

Rotator cuff tear is a common cause of shoulder pain and dysfunction. Its prevalence increases with age. Nonsurgical treatment is adequate for many patients; however, for those with no indication for surgical treatment, rotator cuff repair provides reliable pain relief and good functional outcomes. However, massive and irreparable tears due to tear size, tendon retraction, muscle atrophy, and fatty infiltration are significant challenges for surgeons. Reverse shoulder arthroplasty is the gold standard for irreparable tears coexisting with cartilage degeneration/arthritis (rotator cuff arthropathy). Surgeons prefer joint-sparing procedures, from debridement to muscle transfers, for young patients without arthritis. The literature does not establish well the most appropriate treatment, and each therapeutic modality has particular indications, advantages, and disadvantages.

Keywords
- outcome treatment
- rotator cuff tear
- shoulder

Resumo

A lesão do manguito rotador é uma fonte frequente de dor e incapacidade funcional na população em geral, e sua prevalência aumenta com o envelhecimento. O tratamento não cirúrgico é adequado para muitos pacientes, e, quando necessário, o reparo cirúrgico resulta em alívio da dor e bons resultados funcionais. Entretanto, lesões extensas e não reparáveis devido ao tamanho da lesão, grau de retração, atrofia muscular e substituição gordurosa apresentam desafios ao tratamento. Nos casos de lesões irreparáveis que coexistem com degeneração articular/osteoartrite (artropatia do manguito rotador), a indicação de artroplastia reversa é o padrão ouro. Porém, nos casos de pacientes mais jovens e sem osteoartrite, as indicações que preservam a

Palavras-chave
- lesões do manguito rotador
- ombro
- resultado do tratamento

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articulação, desde o debridamento até as transferências tendinosas, são preferíveis. A escolha do tratamento mais apropriado não está claramente estratificado na literatura e cada modalidade tem suas indicações, vantagens e desvantagens.

Introduction

The first mention of irreparable cuff injury in the literature might be from Wiley who, in 1991,[1] despite not providing a precise concept or adequate treatment, stated that: "large injuries may be irreparable surgically and under such circumstances, debridement of the cuff edges and bursa decompression can alleviate pain". Even today, the concept is not precise, and the treatment is not assertive. The concepts of irreparable injury, extensive injury, and tendon healing are confusing and, ultimately, determine the clinical outcome.

This paper does not aim to define the precise concepts of an extensive injury and an irreparable injury since they are not clear in the literature. Similarly, there is no definition of healing failure (pain, reoperation, decreased strength, etc.).

An extensive injury presents two or more ruptured tendons, a lesion over 5 cm in length, or both.

The concept of irreparability is more imprecise because it implies the impossibility of pulling the tendon and fixating it at its anatomical attachment site, or in a medialized position, immediately lateral to the articular cartilage, with no tension. However, in concrete terms, this perception only occurs perioperatively. The following parameters routinely infer this irreparability:

- an acromiohumeral height < 6 mm due to the cuff's lack of opposition to the deltoid muscle traction.
- torn edge of the tendon retracted at the level of the glenoid joint line (Pate III).
- significant muscular atrophy at the belly of the supraspinatus muscle (positive tangent sign).
- significant fatty infiltration at the belly of the affected muscle (Goutallier >2).[2]

Some patient-related factors negatively influence healing and deserve consideration, including age > 70, smoking, diabetes, hypercholesterolemia, multiple previous steroid infiltrations, cooperation and adherence to treatment, and secondary gains.[2,3]

In summary, preoperative factors indicating low or no possibility of functional repair are lesion size greater than 5 cm, fat replacement of the affected belly $> 50\%$ (Goutallier III or more), muscle atrophy $> 50\%$ at the supraspinatus muscle belly (tangent sign on magnetic resonance imaging in sagittal sequence), retraction of the ruptured tendon stump at the glenoid level (Patte III) and fixed superior subluxation of the humeral head, with acromiohumeral height < 6 mm (Hamada 2 or more). We believe these patients have irreparable injuries and present the existing treatment options in the next section.[2,3]

Treatments

- Clinical Treatments
- Surgical Treatments sparing the joint
- Surgical Treatments replacing the joint

Clinical Treatment

Non-surgical treatment is INITIALLY indicated for all symptomatic patients and continued for patients with low functional demand and comorbidities contraindicating surgical treatment. It encompasses physiotherapeutic rehabilitation focused on physical anti-inflammatory and analgesic measures, strengthening the remaining cuff, and strengthening the parascapular and deltoid muscles. The use of non-steroidal anti-inflammatory medications and corticosteroid infiltrations should occur sparingly. There is no scientific evidence to warrant using hyaluronic acid or platelet-rich plasma (PRP) injections.[2]

Debridement, Acromioplasty, and Tenotomy with or without Tenodesis

All these treatment modalities, combined or alone, resulted in immediate clinical improvement in around 95% of patients but with progressive deterioration in pain and function. Walch et al.[4] presented the first systematic multicenter report involving 283 patients with a mean age of 64.3 years and a mean follow-up period of 57 months. These authors observed that the initial gain was very satisfactory in 93% of patients. However, there was a decline in satisfaction and function in subsequent years, resulting in loss of external rotation, atrophy, weakness, and progression of cartilage degeneration. They also noted that tenotomy has an adverse effect on patients with an acromiohumeral distance > 7 mm, and that involvement of the teres minor has a poor prognostic value.

Pander et al.[5] retrospectively evaluated 39 patients with a mean age of 75.6 years who underwent debridement of irreparable injuries with or without tenotomy and a mean follow-up period of 6.5 years. Despite some limitations, like not including patients requiring an additional surgical procedure due to an unsatisfactory clinical outcome, these authors observed that it is possible to obtain favorable outcomes in the elderly population with low functional demand.

Boileau et al.[6] observed that biceps tenotomy promoted an average of 1.1 mm of head elevation but is not a risk factor for progression to rotator cuff arthropathy. These authors suggested that pseudoparalysis and rotator cuff arthropathy are contraindications for this procedure.

Checchia et al.[7] also demonstrated in 12 patients undergoing tenotomy, with an average follow-up period of 26 months, an improvement in satisfaction, range of motion (ROM; 30° of elevation, 1.7° of lateral rotation, and two vertebral levels of internal rotation). In their series, a single subject presented a characteristic Popeye deformity.[7]

Almeida et al. showed that only 35.1% of patients undergoing tenotomy complained of biceps deformity. These authors reported that age affected the side and biotype had no significant correlation with deformity complaints. In contrast, the male gender, dominant side, abdominal skinfold < 23.2, triceps skinfold < 14.5, and body mass index (BMI)< 30 were risk factors for deformity.[8]

In summary, it is better to reserve debridement, acromioplasty, and biceps tenotomy, whether or not associated with tenodesis, for elderly patients with low functional demands. As advantages, these are quick, simple techniques with few complications compared with other surgical procedures. More than a third (35.1%) of patients undergoing tenotomy complain of residual deformity (Popeye sign). These procedures, combined or alone, show immediate clinical improvement in 93% of patients, which deteriorates over time. Involvement of the teres minor muscle tendon, static superior subluxation with acromiohumeral distance < 6 mm, cartilaginous degeneration, and pseudoparalysis are contraindications.

Partial Repair and Margin Convergence

Burkhart was the first author to introduce the concepts of functional rotator cuff tear and partial repair. This implies that the "ties" or margins of the lesions can keep the cuff functional despite the central lesion as long as these residual forces are balanced/compensated (also known as "even forces"). This is the logical reasoning for partial repair, which creates a balanced moment of force in the shoulder. Often, this scenario is the repair of an acute over a chronic injury, when the chronic portion of the injury is irreparable due to poor tendon quality and great retraction, and the acute part is repairable. When the acute portion heals, it is possible to resume the pre-traumatic state of balance, and the cuff is functional because of the restoration of even strength. Despite being small, Burkhart's initial sample had 14 subjects (average age, 56 years; average follow-up period, 20 months) and showed important gains in ROM, strength, and patient satisfaction.[9]

In addition to partial repair, another surgical resource to biomechanically increase the repair of extensive injuries is margin convergence. After the partial repair, when the anterior and posterior edges of the cuff reach the footprint with acceptable tension and the central part does not, usually in "V" or "U" shaped injuries, the surgeon brings together the anterior and posterior edges and suture them side-to-side. This results in a significant reduction in the cuff pullout force (a six-fold reduction), minimizing fixation failure and improving clinical outcomes, which remain stable in the medium term.[10,11]

We concluded that the indication for partial repair, with or without margin convergence, is appropriate for extensive acute over chronic injuries (traumatic cases) sparing a portion of the subscapularis tendon. The best outcomes occur after repairing the subscapularis and infraspinatus tendons, restoring the force balance, and making the cuff functional, even with the persistent injury in its central part. In the medium term, 67% of patients present good and excellent outcomes. These outcomes are better than isolated debridement.[8,9,11]

Subacromial Balloon

The subacromial balloon/spacer is an inflatable device made from poly-DL-lactide and E-coprolactone that degrades within 12 months. The procedure is simple and involves placing the device between the humeral head and the acromion, either by arthroscopy or percutaneously. It aims to restore the painless ROM of the shoulder in the presence of an irreparable injury by reducing subacromial friction and improving the deltoid lever by lowering the humeral head.

Senekovic was one of the first to demonstrate good outcomes with this technique. He showed that in 24 patients followed up for 5 years, i.e., after complete balloon reabsorption, 84.6% showed improvement, and only 10% presented worsening. The procedure is simple and the average time for device placement is 4.3 minutes.[12]

The literature indicates an improvement in pain and functional disability in 46% to 84.6% of cases and a complication rate of 16.7%. The most frequent complications include anterior migration of the balloon, transient deficit of the lateral cutaneous nerve of the forearm, and infection. Irreparable damage to the subscapularis is a contraindication due to the risk of anterior extravasation.[13]

This procedure is suitable for patients with irreparable damage to the integrity of the subscapularis and teres minor, no osteoarthritis, and preferably with low demand. Another less classic indication is protecting the suture of a cuff injury. (►**Fig. 1**).[12,13]

Superior Capsule Reconstruction (SCR)

Mihata et al.[14] developed the concept of implanting the fascia lata in the glenoid and greater tubercle to stabilize the humeral head and prevent its upward ascension characterizing irreparable injuries to restore the rotation center of the humeral head. This concept was tested in vitro in multiple biomechanical studies and has been clinically reproduced since then.[14] Humeral head fixation to the glenoid with a fascia lata graft presents better resistance than the interposition of the tendon stump with other grafts. The most frequently interposed grafts are the fascia lata graft (autologous or homologous), acellular dermal graft, or the biceps tendon (long portion). The optimal procedure is to suture the remaining edges of the cuff to the graft (partial repair).[15]

The literature reports diverse clinical outcomes because there is a lot of heterogeneity between surgical procedures: number of fascia lata layers, graft types (fascia lata, biceps,

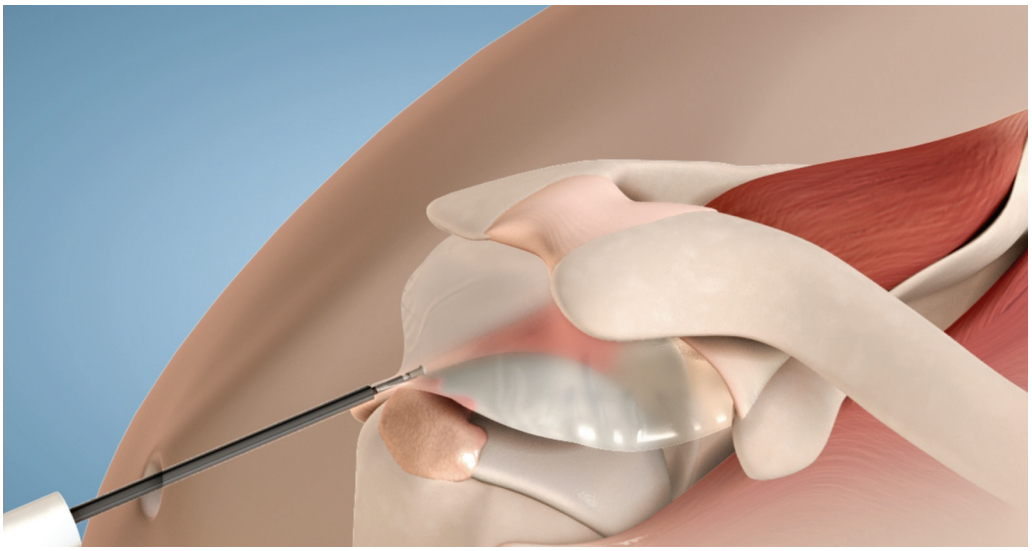


Fig. 1 Schematic drawing of the subacromial balloon.

etc.), fixation site method, and surgeon experience. While some authors do not present consistently good outcomes, Mihata described 31 shoulders from 23 patients with a mean age of 65.1 years presenting significant improvement of 64° in anterior elevation, 14° in external rotation, and two vertebral levels of internal rotation.[14–16]

Denard et al.[17] used dermal grafts and reported a surgical review rate of 18.6% in 59 patients. Despite observing complete healing in only 45% of patients, the procedure was successful in 74.6% of subjects.

This information warrants SCR indication for patients with irreparable cuff injuries, no cartilaginous degeneration, refractory to clinical treatment, intact or repairable subscapularis, and Hamada 1 or 2.

Tendon Transfer

The classic indication for tendon transfer is young patients presenting a relative contraindication for reverse arthroplasty, no cartilaginous degeneration, and irreparable damage to the rotator cuff. Tendon transfer can provide satisfactory and long-lasting functional outcomes in this subset of patients. Currently, arthroscopy can assist most transpositions. As a general rule, the transposed muscle provides force at a lower level than the native muscle under physiological conditions.[18,19]

When considering tendon transposition, there are important principles to follow:

1 - The transferred muscle must be expendable, with no compromise to the function of the donor limb.
2 - The donor and recipient muscles must have similar excursion and tension.
3 - The tension vector of the donor and recipient muscles must be similar.
4 - The transferred muscle must replace a function of the recipient's muscle.[18,19]

Posterosuperior Injuries

Historically, the latissimus dorsi has been the muscle of choice for this transfer. However, recently, the lower trapezius has grown in popularity due to ease, clinical outcome, and adherence to transfer principles.

Latissimus Dorsi

It is a large muscle acting in arm adduction, extension, and medial rotation. It originates from the thoracolumbar fascia, spinous processes from T2 to L5, the dorsal surface of the sacrum and iliac crest, and muscular fascicles from three or four lower ribs interdigitating with the external abdominal oblique muscle. Its attachment is a terminal tendon 7 to 10 cm long and 0.5 to 1.5 cm wide after axial torsion of 180° at the bottom of the bicipital canal of the humerus, between the pectoralis major anteriorly and the teres major posteriorly. The thoracodorsal nerve, a branch of the posterior cord of the brachial plexus, provides its motor innervation. Its primary vascularization comes from the thoracodorsal artery, a terminal branch of the subscapular artery together with the circumflex artery of the scapula. From an anatomical point of view, two structures are at risk when transferring this muscle: the axillary nerve, which is close to its attachment site and in the transposition path, and the radial nerve, which is medial to its attachment.

Careful patient selection is crucial to obtaining satisfactory and lasting outcomes. Indications for transposition include extensive lesions in young, active patients with no cartilaginous degeneration. Risk factors for poor prognosis, therefore contraindications, are irreparable injuries to the subscapularis tendon, limitation of passive movement, pseudoparalysis, osteoarthritis, Hamada 3 or more, and fatty infiltration at the teres minor.[18,19]

Gerber popularized the technique and showed excellent long-term outcomes, with 74% transfer viability and good

and excellent outcomes after 10 years. The Subjective Shoulder Value (SSV) score increased from 29% to 70%, with a significant increase in ROM and strength, and failure in 10% of cases.[20]

The attachment site is a source of controversy. Some believe that when it is more anterior (supraspinatus attachment), it increases the tenodesis effect; when it is more posterior (infraspinatus attachment), it produces better moments of force for abduction and external rotation.[18]

Simultaneous teres major and latissimus dorsi transposition did not significantly increase the clinical outcome, not warranting its recommendation.

The current technical and material improvements allowed fully arthroscopic or assisted transpositions presenting the same clinical outcomes and complications.[18]

Lower Trapezius

The trapezius muscle has three portions, i.e., upper, middle, and lower. These parts work together to elevate, retract, and laterally rotate the scapula. The muscle originates from the occipital bone and spinous processes from C7-T12. The upper portion attaches to the lateral third of the clavicle and the middle and lower portions attach to the medial part of the acromion and scapular spine. The lower trapezius receives irrigation from the transverse cervical artery and innervation from the spinal accessory nerve (XI cranial nerve).

The lower trapezius is a more anatomical alternative than the latissimus dorsi. It has a more cranial origin than the latissimus dorsi and is more medial than the infraspinatus fossa, maintaining the same force vector. As such, it provides a better moment of force in external rotation. One caveat of this technique described by Elhassan is that the length of the tendon is insufficient to reach the greater tubercle, requiring an autologous or homologous graft, which may be from the knee flexor or calcaneus tendon.

This transfer provides an improvement/increase in external rotation of 70°, thus prioritizing patients presenting a more significant loss of external rotation than elevation. (►**Fig. 2**).[18,19]

Anterosuperior Injuries

Pectoralis Major

The pectoralis major muscle adducts, flexes, and medially rotates the humerus. It has two portions, i.e., the clavicular and sternal portions. The clavicular portion originates from the medial aspect of the clavicle, and the sternal portion comes from the upper portion of the sternum and the second to fourth ribs. These portions attach to the lateral part of the intertubercular groove. Pectoralis major irrigation comes from the pectoral branch of the acromial thoracic trunk and the medial and lateral pectoral nerves provide its innervation.

Its transfer occurs most commonly for anterior superior injuries, to replace irreparable injuries to the subscapularis tendon. In its initial description by Wirth and Rockwood, the transposition was superficial to the conjoint tendon. Later, Resch revised the technique, and the transposition was deep to the conjoint tendon, increasing mechanical efficiency. Pay

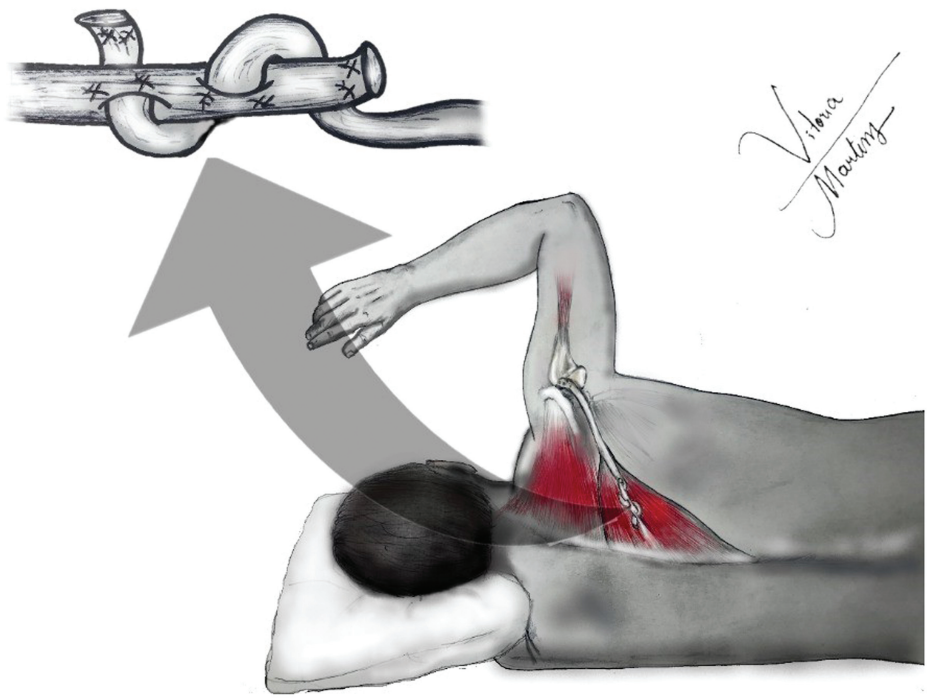


Fig. 2 Illustration of lower trapezius transfer.

special attention to the musculocutaneous nerve during the deep transposition to the conjoint tendon.

Clinical outcomes are predictable for pain relief and heterogeneous concerning functional gain (ROM and strength). Outcomes are better when sparing the supraspinatus muscle tendon and centering the head. In contrast, cases with humeral head subluxation present worse functional outcomes.[18]

A theoretical explanation for the non-reproducibility of the functional gain in transferring the pectoralis major is that in certain abduction positions, the force vector of the pectoralis is orthogonal to the vector of the subscapularis, even causing anterior subluxation of the humerus.[18,19]

Latissimus Dorsi

The approach to the latissimus dorsi occurs via the axillary fossa. Then, proceed to latissimus dorsi attachment, with or without the teres major, into the lesser tubercle, whether open or arthroscopically. This technique is less likely to cause iatrogenic nerve injury and better reproduces the subscapularis traction line.[15,16]

Reverse Prosthesis

The gold standard indication for reverse arthroplasty is rotator cuff arthropathy (RCA). This single procedure solves two issues: joint degeneration and rotator cuff insufficiency resulting from irreparable injury, the latter being difficult to treat with other surgical modalities.

While the indication for reverse prosthesis is well-established in RCA, it is not clear for irreparable injuries with no osteoarthritis. The indication must rely on individualized criteria.[21]

The ideal candidate must be over 65 years old and present pain and pseudoparalysis in a scenario of irreparable injury, and an anterior elevation lower than 90°. Additionally, elderly patients with other poor prognostic factors such as smoking and diabetes may be eligible for reverse arthroplasty, as well as patients who, even with no osteoarthritis, present leakage/instability of the humeral head. The literature shows that patients undergoing reverse arthroplasty at an age < 65 years have worse clinical outcomes and higher complication rates.[22]

Relative contraindications are patients younger than 65, with neurological dysfunction of the upper limb, and virtually normal function with an elevation higher than 90°, Simple Shoulder Test (SST) functional questionnaire score $>= 7$, or both, denoting satisfactory function.[22] Until recently, deltoid muscle dysfunction was also a contraindication. However, Elhassan et al. demonstrated good outcomes in reverse arthroplasties associated with pectoralis transposition in patients with deltoid paralysis.[23]

Frankle et al.[24] evaluated 60 patients for an average follow-up period of 33 months and showed a significant improvement in anterior elevation (55° to 105°), abduction (41° to 102°), lateral rotation (12° to 41°) and visual analog scale (VAS) for pain (6.2 to 2.2). Regarding complications, they observed 17% of scapular notching and 12% of revision due to failure of the glenoid platform. Multiple studies by many surgeons reproduced these outcomes. More recent studies, such as those from Groh and Groh, showed lower complication (7%) and reoperation (5.3%) rates.[25]

The biggest concern when placing a reverse prosthesis may be the prosthesis longevity, especially in younger patients. The literature shows 91% to 95% of prosthesis survival in 10 years. Unlike arthroplasty for other conditions, RCA and irreparable injuries show less functional deterioration after the fifth year of surgery (►**Fig. 3**).[26]

Final Considerations

Treatment of irreparable cuff tears in elderly patients with low functional demands and osteoarthritis (rotator cuff arthropathy) presents a predictably good outcome with the indication of a reverse prosthesis. However, there is a large subgroup of young and active patients who meet irreparability criteria. In this subgroup, despite the enormous advances in surgical treatment modalities in recent years, from partial repair using a subacromial balloon to superior capsule reconstruction and tendon transfers, the outcomes are less predictable despite the particularity of each patient and the injury (anterosuperior, posterosuperior, etc.), functional demand, adherence to treatment, comorbidities and, MAINLY, the experience of the attending physician with the respective techniques.[26]

In the literature, most studies present level III and IV evidence. Due to the lack of adequate comparative studies, there is no consensus regarding the superiority of one of these techniques over the others. Therefore, treatment must be individualized, weighing up the advantages and disadvantages of each modality for the patient.

In summary, considering the best available evidence, **partial repair** is indicated in acute-on-chronic injuries, given the reparable nature of the acute portion of the injury, and in patients with no osteoarthritis and low functional demand, with outcomes similar to more invasive methods. The **subacromial balloon** is a new method, without approval from many regulatory agencies, and indicated for patients without osteoarthritis, with preserved ROM, and intact subscapularis. However, the subacromial balloon requires more robust studies to confirm its indication. **RSC** presents excellent outcomes in the hands of surgeons experienced in this technique. RSC may treat pseudoparalysis but leads to frustrating outcomes in irreparable subscapularis injuries. **Tendon transfers of the latissimus dorsi and lower trapezius** for posterosuperior injuries and of the pectoralis major or latissimus dorsi for anterosuperior injuries are good indications for young patients with significant functional demands and no osteoarthritis. Finally, the reverse prosthesis is an excellent indication for elderly patients with low functional demands, with or without osteoarthritis. In patients under 60, with high functional scores, great functional demand,

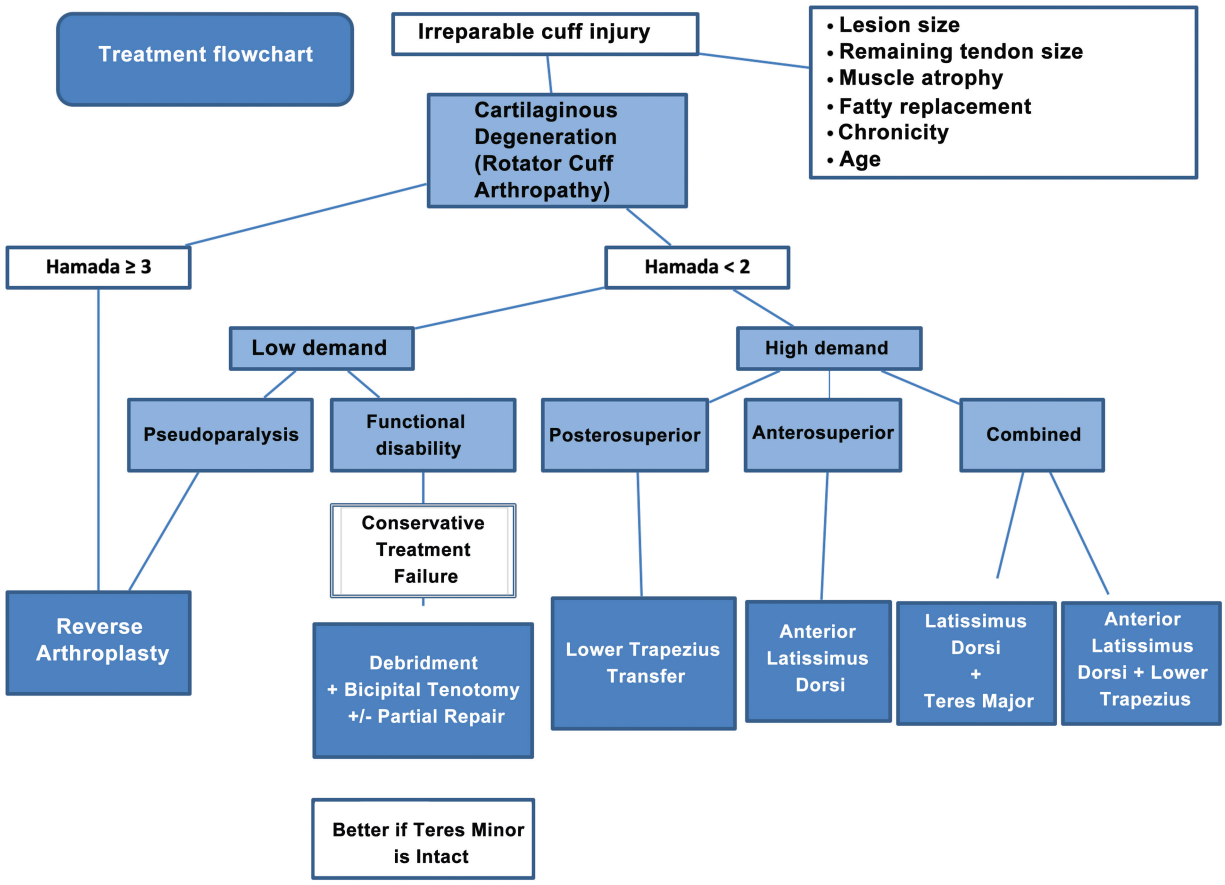


Fig. 3 Flowchart for treating irreparable cuff injuries.

neurological deficit, or any combination of these factors, clinical outcomes are worse.

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Conflict of Interests

The authors declare no conflicts of interests.

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Complex Regional Pain Syndrome

Síndrome da dor complexa regional

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Abstract

Complex Regional Pain Syndrome is characterized by regional pain that is disproportionate to the triggering event, with no distribution to dermatomes, a tendency towards chronicity, and dysfunction. This narrative review proposes an update of criteria for diagnosis and management of the syndrome, providing information on epidemiology, etiology, and pathophysiology. We base our information on systematic and narrative reviews, as well as guidelines published in recent years, aiming to facilitate diagnostic suspicion and provide a broad overview of therapeutic possibilities.

Keywords
- chronic pain
- complex regional pain syndrome
- hyperalgesia

Resumo

A Síndrome da Dor Complexa Regional é caracterizada por dor regional desproporcional ao evento desencadeante, sem distribuição para dermátomos, com tendência a cronicidade e disfunção. Esta revisão narrativa propõe a atualização de critérios para o diagnóstico e condução da síndrome explicitando dados da epidemiologia, etiologia, fisiopatologia. Baseamo-nos em revisões sistemáticas, narrativas e diretrizes publicadas nos últimos anos, procurando facilitar a suspeição diagnóstica e proporcionando visão ampla de possibilidades terapêuticas.

Palavras-chave
- dor crônica
- hiperalgesia
- síndromes da dor regional complexa

Introduction

Complex Regional Pain Syndrome (CRPS) is a syndrome that represents a great challenge to diagnosis and especially management, made difficult by numerous interventions with little scientific basis and evidence. It is characterized by chronicity and progressive worsening of symptoms that can lead to significant functional disability in patients. The diagnosis is based on a careful history analysis and, more importantly, on a thorough physical examination.[1] In general, it differs from other conditions that determine chronic pain by presenting prominent autonomic and inflammatory changes in a segment or region, without following dermatomes.[2,3] More common in upper than lower limbs, it is more frequently unilateral.[4] Laboratory studies are irrelevant, although useful for differential diagnosis in certain circumstances. Radiographs may show signs of regional osteopenia. Early diagnosis and treatment are essential to minimize permanent loss of limb function.

From the beginning of the 1990s, the term Complex Regional Pain Syndrome was adopted from what previously received terms such as reflex sympathetic dystrophy.[5] The International Association for the Study of Pain (IASP) began to establish parameters, known as the Budapest criteria, which seek to assist in the diagnosis and categorization of

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Chart 1 Pain criteria for Complex Regional Pain Syndrome (CRPS) revised and adopted by the IASP (International Association for the Study of Pain) in 2012

Characteristics:
CRPS is a syndrome characterized by a continuing regional pain (spontaneous and/or evoked) that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.
Clinical Criteria for Diagnosis of CRPS
1. Continuing pain disproportionate to the inciting event 2. They should report at least one symptom in three of the four following categories: Sensory: Reports of hyperalgesia and/or allodynia, Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry, Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry, Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails) 3. they must display at least one sign* at the time of evaluation in two or more of the following categories: Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch or deep somatic pressure), Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry, Sudomotor/edema: Edema and/or sweating changes and/or sweating asymmetry, Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails). * A sign is only counted if it was observed at the time of diagnosis. 4. There is no other diagnosis that better explains the signs and symptoms

Source: Harden RN, McCabe CS, Goebel A, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 5th edition. Pain Med 2022;23(Suppl 1):S1-S53.[6]

the clinical picture (►**Chart 1**).[6] These parameters have been validated in guidelines seeking greater specificity, since useful clinical criteria may differ not only between patients, but over time in the same individual.

Types of CRPS

Classically, CRPS is presented in three subtypes. In type I, there is no specific involvement of the peripheral nerve, evidenced on clinical or electrophysiological examination, a relatively limited syndrome in which vasomotor signs predominate. In type II, previously called causalgia, there is involvement of identifiable nerve damage that determines neuropathic pain, a relatively limited syndrome in which neuropathic pain/sensory abnormalities predominate. Some authors refer to a third type that partially meets the criteria, however, they are not specified in the other two types, type III is defined as a very florid CRPS, although signs of motor/trophic changes were observed in all three groups, they doubled in frequency among Subgroup 3 patients.[3,4,7] Apart from the previously mentioned subtypes I, II, and III, there is reference to clinical differentiation of the syndrome into "hot" and "cold" patterns, respectively characterized by a hot, swollen, dry, and reddish extremity, and another by a cold extremity, less swollen, with sweating and a bluish hue. Harden et al. reported that the more common pattern is the "hot" pattern, which has a shorter duration of the syndrome compared to the "cold" pattern.[7]

Epidemiology

CRPS has a frequency of 5.46-26.2 per 100,000 people per year.[6,8] Women are three times more affected than men. The most prevalent age ranges between 46 and 53 years. Upper limbs are more involved than the lower limbs. Shim et al.[5] reported that there will be a greater risk of developing CRPS in women who suffer high-energy trauma to the upper limb. Bruehl[2] reports different incidence rates for types I and II of the syndrome, respectively 5.46 per 100 thousand people per year and 0.82 per 100 thousand people per year.

Etiology and Pathophysiology

Fractures are referred to as the main precipitating factor for CRPS in the upper and lower limbs, with fractures of the radius and ulna at their distal extremity being the region most affected by the syndrome.[1] CRPS is more likely to occur after distal radius fractures in patients treated with tight casts or after a nociceptive or neuropathic event such as median nerve compression, hyperdistraction, distal radioulnar joint instability, or ulna fracture.[1] Other traumas, surgeries and even inflammatory conditions can be manifesting factors. Urits et al.,[3] mentioned that in 7% of cases, type I syndrome develops usually within 8 weeks following the traumatic event. It is important to note the persistence of pain and edema after the first weeks of trauma as signs of the onset of the syndrome. There is a report of an incidence slightly higher than 8% in patients undergoing carpal tunnel release.[3] However, in a recent systematic review, which searched for available evidence on the occurrence of CRPS after surgical release of the carpal tunnel, our group found an incidence of 2 to 5%. And the following are listed as risk factors for the onset of the syndrome after surgery: female sex, age from the fifth decade, surgery on the dominant hand, tourniquet time and use of immobilization after surgical procedure.[8]

The pathophysiology of CRPS is uncertain. The exact mechanism that determines the onset and maintenance of pain remains unknown.[3] Theories tend to focus on why pain persists rather than how it arises. It is hypothesized that neuropeptides linked to the gene of chemical modulators, such as calcitonin, incite neurogenic inflammation and catecholamine sensitization. The persistent nature of pain in CRPS appears to be connected to autonomic characteristics of the sympathetic nervous system, such as upregulation of adrenoceptors and decreased density of cutaneous nerve fibers.[9] Pathological pain appears to come from changes in sensory and motor processing, that is, motor function, sensory feedback, body representation, proprioception and sensorimotor integration. However, there is very limited evidence that changes in this processing would actually lead to chronic pain.[10] The multifactorial theory is more accepted and includes aspects that interfere from the moment of the offending event, such as nervous system sensitization, autonomic dysfunction, inflammatory changes, in addition to a possible relationship with psychological factors and genetic predisposition.[5] Also, smoking was identified as a significant risk factor for the development of CRPS.[7]

Dysfunctions caused by CRPS may include loss of normal arteriovenous flow mechanisms and definitive changes in central neurological responses, resulting in segmental ischemia and cell death.[10] These, in turn, cause pain, edema, joint stiffness and atrophy of the segment. In summary, complex regional pain syndrome essentially brings exaggeration or abnormal prolongation of pathophysiological events expected after a certain traumatic episode, altering perception and subjecting the individual to a complex interaction of physiological and psychological factors.[10]

Diagnosis

The suspicion of the development of CRPS begins with the appearance of exacerbated pain, normally not expected after trauma or surgery. Other factors must be considered, such as unexpected maintenance of edema, slower than usual recovery, sleep disorders and lack of pain improvement with common analgesics.[11] The diagnosis can be aided by using the Budapest criteria (►**Chart 1**).[6]

It is distinguished from other painful syndromes by the presence of autonomic dysfunction, persistent regional inflammatory changes, and the absence of distribution following dermatomes.[5] Patients describe the pain as tearing or burning, often exacerbated by cold. In addition to difficulty sleeping, they also report anxiety and restlessness. Commonly found on physical examination are allodynia (painful response to normally non-painful stimuli), hyperalgesia and hyperpathy associated with edema. Trophic changes resulting from autonomic dysfunction may be present, such as abnormal sweating, changes in temperature and skin texture. The involved extremity is identified as "hot" and edematous or "cold" and atrophic. Over time, pain and swelling lead to joint stiffness, especially in the fingers, wrists and shoulders.[10]

Children and adolescents can be affected by CRPS. It is more common in the lower limbs of adolescent girls, around 12 years of age, who have had a traumatic event in the ankle and foot region.[1] The clinical picture includes pain, autonomic changes and heightened sensitivity to painful and even non-habitually painful stimuli (allodynia). As in adults, it can lead to motor disorders and trophic changes. The prognosis tends to be better compared to the occurrence in adults.[12]

In the face of intense pain that tends to become chronic, it is essential to rule out other pathologies in the absence of objective physical findings, such as trophic changes, edema and osteopenia. Pain and disability linked to CRPS point to psychological comorbidities that create a vicious cycle of pain, isolation and depression.[4]

Piñal (Enzine, 2019), in his true outburst published in the IFSSH (International Federation of Societies for Surgery of the Hand) magazine on the topic, casts doubt on the existence of types of the syndrome and exposes the controversy in diagnosis and treatment. It refers to the theory of stimulus amplification in a nerve that is being "irritated", even without an established mechanical injury, which would result in more comprehensive symptoms in the affected limb. The author recently published a study of 53 patients, on average 55 years of age, previously diagnosed as having CRPS, who presented atypical symptoms and signs of pain and dysesthesia in the upper limb. He emphasized the inability of individuals to completely flex their fingers (grip), and demonstrated improvement in symptoms after releasing the transverse carpal ligament. Only 6 of the 53 patients maintained their condition prior to surgery, assessed with a visual analogue pain scale and the DASH questionnaire (Disabilities of the Arm, Shoulder and Hand Questionnaire).[13] In this line of reasoning, Chang et al.[4] discussed the labeling psychosocial effects of syndromes. They started from the premise that CRPS can present a set of inconsistent and vague symptoms, easily addressed in the context of other diagnoses. They cited examples of articles that confirmed high percentages of the syndrome after a certain surgical procedure without patients even completing signs and symptoms such as those mentioned in the criteria presented in the table.[2] They highlighted the importance of a thorough clinical examination to identify possible sources of pain and avoid incorrect procedures that could have disastrous consequences for the patient.

Complementary imaging and laboratory tests will generally be unchanged and will be of little help in establishing the diagnosis of CRPS. Two weeks or more after the onset of the condition, radiographs may show signs of osteopenia and bone resorption, mainly subchondral and periarticular. It is estimated that up to 30% of patients will not present radiographic abnormalities at the time of diagnosis of the syndrome.[10] Although thermography, scintigraphy, electroneuromyography and ultrasound can demonstrate changes in the presence of CRPS, ultimately, there is no scientific evidence for their indiscriminate use in diagnosing the syndrome.[5]

Treatment

The difficulty in proposing treatment in CRPS goes in the same direction as establishing its diagnosis. Numerous therapies are suggested in isolated case series or in comparisons, narrative reviews, guidelines and data grouped in systematic reviews and meta-analysis attempts. In a simple search on one of the scientific search platforms, it is possible to capture more than four thousand articles published between the years 1945 and 2022, the majority being after the year 2000. The first publications are found with the names of causalgia, reflex pain, dystrophy sympathetic reflex, Sudeck's dystrophy, which express the same difficulties found in more recent studies, that is, the discussion in establishing diagnosis and management. This leads us to reflect, we are studying the cause of this supposed syndrome, trying to discover its prevention or exposing countless treatment options for poorly recognized or misdiagnosed symptoms.

Patients with type 2 CRPS have an identifiable or documented peripheral nerve injury. Surgical interventions that correct nerve damage or protect the nerve can decrease the incidence of nociceptive foci, lessen symptoms, and improve function. Similarly, patients with type 1 CRPS may have a non-neural or mechanical nociceptive focus, which, if corrected, will facilitate extremity recovery.[1]

The use of numerous drugs, neuraxial therapy, spinal cord and dorsal ganglion branch stimulation, intravenous regional and peripheral sympathetic blockade, adjuvant therapy, among others, are mentioned in the treatment of CRPS alone or together.[6,14] To present the current CRPS treatment options, we based ourselves on systematic reviews, narratives and guidelines from recent years. We seek to organize them into topics to facilitate understanding given the plethora of possibilities. However, studies suggest that high-quality randomized controlled trials are still needed to make solid recommendations regarding the treatment of CRPS.[1]

Drugs

- Bisphosphonates
  They can be administered orally or intravenously; seek to inhibit bone reabsorption that accompanies CRPS. Research states that bisphosphonates have clear benefits in the treatment of the syndrome.[14,15] There are reports of significant improvement in allodynia, hyperalgia, edema and joint mobility. Pamidronate infusions are well tolerated and easy to administer. Several patients have reported minor infusion site reactions and mild symptoms that resolved within 6 to 24 hours after administration. The mechanism of the analgesic effect of bisphosphonates remains speculative. They are potent inhibitors of osteoclastic activity and may play a role in modifying inflammatory cytokines (such as interleukin-1) and other systemic factors (such as prostaglandin E2) involved in the sensitization of pain nociceptors and low-threshold mechanoreceptors.[15]
- Corticosteroids
  Christensen et al.[16] compared oral prednisone and placebo in the treatment of CRPS and achieved improvement in pain, edema, palmar sweat, pinching ability and fingering with the use of corticosteroids. These mediate the inhibition of inflammation and analgesia. Also, other authors reported better control of pain and edema with the use of oral prednisone when compared to non-hormonal anti-inflammatory drugs.[17]
- Calcitonin
  When compared to placebo or other therapies, such as physical therapy, it showed insignificant benefits in the treatment of CRPS.[14] Believing that its action would determine inhibition of bone resorption and analgesia mediated by beta endorphin.
- Non-steroidal anti-inflammatory drugs
  Breuer et al.[18] found no significant difference in terms of improvement in pain and edema in patients diagnosed with the syndrome, when comparing the use of intravenous parecoxib and saline solution. Its use was increased due to its function of promoting COX2 inhibition, tending to reduce peripheral sensitization and normalize the local pressure pain threshold.
- Vitamin C
  The systematic review carried out by Giusta et al.,[19] evaluated the effectiveness of vitamin C in preventing type I CRPS in fractures or surgeries of the upper and lower extremities. Five of the six studies analyzed were in favor of the prophylactic use of a daily dose of 500-1000 mg of vitamin C for 45-50 days after orthopedic or traumatological care to prevent CRPS type I. Only one study did not find any benefit in vitamin C supplementation compared to placebo in the prevention of CRPS. Therefore, in this analysis of the literature, it is suggested that daily supplementation of 500-1000 mg of VC can reduce the appearance of type I CRPS in upper/lower extremity trauma and orthopedic surgery.
- N-Methyl-D-Aspartate (NMDA) receptor antagonist
  Due to its action on peripheral and central sensitization mechanisms, specifically on the neuronal sensitization cascade, which leads to the activation and release of substances in the central nervous system (CNS) such as glutamate, increasing the efficiency of synaptic transmission of the pain signal. However, some articles reported no significant improvement with the use of NMDA antagonists or placebo.[18,20,21]
  Ketamine acts in the CNS as a non-competitive receptor blocker. Authors report a reduction in allodynia/hyperalgia with topical use of ketamine compared to placebo.[22] Good results were also reported with intravenous use. Attention should be paid to the short duration of intravenous treatment, avoiding undesirable symptoms such as nausea, vomiting and psychomimetic effects.[23,24]
- Botulinum toxin A
  As botulinum toxin tends to decrease peripheral sensitization and central pain perception by inhibiting both superficial and deep pain neurotransmission and blocking retrograde axonal transport, its action was evaluated in

the treatment of CRPS. However, there is reference to intense pain during the application of the toxin and little or no difference in the results when compared to placebo.[25]

- Lenalidomide
  It is a thalidomide derivative with reduced toxicity potential. The high plasma levels of pre- and anti-inflammatory cytokines suggest that the use of non-steroidal immunomodulatory agents contributes to the reduction of symptoms of the syndrome. However, like other drugs mentioned, there appears to be no significant benefit when compared to the use of placebo.[26]
- Immunoglobulin
  Used intravenously, it points to evidence of reducing peripheral and central neuroimmune activation, acting positively in reducing pain in CRPS when compared to placebo.[27]
- Isosorbide dinitrate (ISDN)
  This medication determines endothelium-derived vasodilation, which would benefit the changes in microcirculation and decrease in limb temperature that occur in chronic CRPS. Groeneweg et al.[28] cited no difference when compared to placebo.
- Other pharmacological agents
  Sahin et al.[29] reported the use of gabapentin in neuropathic pain compared to placebo. Although its anticonvulsant action interferes with analgesia, there was no significant difference in the condition of patients in the two groups. Those who reported improved pain control also experienced more adverse events, such as dizziness, drowsiness and lethargy. Tadalafil is a vasodilator, which acts to inhibit phosphodiesterase.[6] It is used in CRPS to resolve changes in chronic microcirculation that lead to metabolic acidosis and tissue hypoxia. Groeneweg et al.,[28] reported a large reduction in pain in the tadalafia group compared to placebo, but without improvement in other markers such as improvement in the sensation of changes in limb temperature and muscle strength.

Neuraxial Therapy

Alpha 2 adrenergic agonists administered into the epidural space can reduce pain by decreasing sympathetic system activity. Rauck et al.[30] also mentioned clonidine applied epidurally, associated with adenosine used intrathecally. The improvement in pain seemed to be similar to the use of placebo, and the association with adenosine led to inconvenient arterial hypotension after its application.

Baclofen, an alpha-aminobutyric acid type b receptor agonist (inhibitor of sensory input to the spinal cord) is indicated in cases of irresponsive dystonia. Authors report improvement in dystonia and discuss its intrathecal infusion, whether slowly or quickly. More adverse effects such as headache, nausea and chorea are associated with rapid infusion. Glycine, a glycinergic neurotransmitter, acts to inhibit the process of motor and sensory information, also being useful in the treatment of dystonias. Corticosteroids, such as methylprednisolone, were used intrathecally to treat the syndrome, however, they differed little from the results with intravenous use.[14]

Stimulation of the Medulla and Dorsal Ganglion Branch

Performed by implanting an epidural electrode in the root that innervates the painful area. The electrical current induces the inhibition of the hyper-excited central neural circuit, a decrease in the sympathetic efferent response and the activation of vasoactive substances. Deer et al.[31] compared stimulation of the spinal cord with stimulation of the dorsal ganglion, with the second method resulting in better results in the pain assessment score. Although there was no difference in patient satisfaction and incidence of adverse events in the two groups studied. Kemler et al.,[32] reported good results in the use of stimulation associated with physiotherapy in the first 2 years when compared to the physiotherapy group alone. There is a hypothesis of neuronal adaptation with loss of long-term analgesic effect.[32,33]

Regional EV Block and Peripheral Sympathetic Block

Although intravenous regional block is a popular practice in the treatment of CRPS, Tran et al.,[14] reviewed eleven clinical trials using different substances in the blockade, such as guanethidine, reserpine, droperidol, ketanserin, atropine, lidocaine associated with methylprednisolone, and found no consistent benefit in this recommendation. Other authors also reported this same evidence.[14,34,35]

Peripheral sympathetic blockade, of the thoracic stellate ganglion, aims at chemical neurolysis through radiofrequency or the use of anesthetic substances. Several authors have presented more satisfactory results than intravenous blockade.[36–39]

Adjuvant Therapy

Physiotherapy, occupational therapy, aerobic exercise, transcutaneous electrical nerve stimulation (TENS) and mirror therapy are the adjuvant procedures most cited in the literature for the treatment of CRPS. Several physical therapy protocols using stretching exercises, muscle strengthening, associated or not with aerobic exercises, edema drainage, temperature contrast baths, ice, heat and TENS, have been reported in series of clinical cases with and without comparison between them. The latter would promote vasodilation and release of endogenous opioids, tending to reduce edema, pain and showing functional benefits when associated with physiotherapy.[40] Although results are promising in some studies, there is no evidence of significant improvement with these methods, especially if used alone.[14,41–44]

Mirror therapy proposes the recognition of the laterality of the hand through constant training in observing the reflection of the unaffected limb in the mirror. According to Moseley et al.[45] constant visualization of the reflex simulating the possibility of using the affected hand would have a positive impact on improving pain and function. Other authors also reported favorable results, with significant reduction in pain, allodynia and improvement in global hand function.[44,46–48]

Final Considerations

Complex Regional Pain Syndrome is considered a complicated pathology. Commonly manifested in scientific literature by studies of clinical series with small samples. Patients diagnosed early with the syndrome, between 6 and 18 months of clinical evolution, respond to treatment differently from those with persistent symptoms. The evolution of the condition can be modified through rapid and specific measures, such as the use of specific medications, nerve blocks and adjuvant therapies that will alter the natural history of CRPS. It is estimated that 15% of patients diagnosed at the onset of signs and symptoms of the syndrome will fail to recover satisfactorily. Early observation of a cold extremity tends to mean a poor prognosis.[6]

It is emphasized that the available treatment methods help control symptoms and not specifically cure the syndrome. The constant use of medications leads to analgesic tolerance, developed in most patients with CRPS. Also consider the persistence of side effects due to prolonged use of drugs used during treatment. An individualized and coherent therapeutic plan must be established, considering cost and including different classes of medications and procedures that meet other possible needs of the patient. As an example, use of effective tricyclic antidepressants for neuropathic pain and to control anxiety, depression and insomnia.[6] It is suggested that a daily supplementation of 500-1000 mg of Vitamin C can reduce the appearance of CRPS type I in upper/lower extremity trauma and orthopedic surgery.[19]

Self-awareness and patient education in the face of a condition compatible with CRPS can lead to the possibility of autonomy in the early use of measures and medications when faced with daily situations and events that could trigger symptom exacerbation. The establishment of reasonable goals during the course of the disease aims to objectively measure symptom improvement or worsening, leading to consequent adjustments in therapeutic measures. This should be developed collaboratively among a multidisciplinary team, the patient, and their family, and it is essential for the quality of treatment. It is crucial to empathetically clarify that the therapeutic approach aims to assist in symptom control. Currently, there is no proven cure for the syndrome, nor are there measures that can alleviate symptoms in all patients.

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Conflict of Interests
The authors declare that there is no conflict of interest.

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Wrist Immobilization after Surgical Decompression of the Median Nerve in Carpal Tunnel Syndrome: A Systematic Review

Imobilização do punho após a descompressão cirúrgica do nervo mediano na síndrome do túnel do carpo: Uma revisão sistemática

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Abstract

Objective The most common compressive neuropathy of the upper limbs is carpal tunnel syndrome (CTS). Historically, there has been a tendency to apply immobilization in the postoperative period, a practice that has decreased in recent years. This review aims to assess whether there is scientific evidence to justify the use of immobilization in the postoperative care of CTS decompression.

Methods The following databases were used: Biblioteca Virtual em Saúde (BVS), PubMed National Library of Medicine – (NLM), Cochrane Library, Scientific Electronic Library Online (SciELO), and EMBASE. The following inclusion criteria were used: 1) discussion of the postoperative period of median nerve decompression surgery in CTS; 2) comparison of results after surgical decompression in CTS between wrist immobilization or local dressing; 3) all languages, regardless of the year of publication; and 4) all types of publications. The following exclusion criteria were used: 1) studies that did not evaluate the postoperative period of CTS decompression; 2) lack of evaluation of the outcome related to the application of local dressing or some form of wrist immobilization after the surgical decompression procedure; and 3) repeated publications.

Results The literature search resulted in 336 relevant publications. In the end, 18 publications were chosen. Systematic reviews, randomized clinical trials, and cross-sectional studies were found.

Conclusions Due to the scarcity of evidence supporting the use of immobilization coupled with the higher costs associated with the practice, it has become less and less frequent in recent decades.

Keywords

- carpal tunnel syndrome
- median nerve
- peripheral nerve trauma
- wrist injuries

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Clinical relevance In the literature, two approaches to postoperative care for CTS decompression are described: immobilization or just local dressing. According to the available scientific evidence, it is worth evaluating which one is better.

Resumo

Objetivo A neuropatia compressiva mais comum dos membros superiores é a síndrome do túnel do carpo (STC). Historicamente, houve uma tendência à aplicação de imobilização no pós-operatório, prática que tem diminuído nos últimos anos. O objetivo desta revisão é avaliar se existem evidências científicas que justifiquem o uso da imobilização nos cuidados pós-operatórios de descompressão da STC.

Métodos Foram utilizadas as seguintes bases de dados: Biblioteca Virtual em Saúde (BVS), PubMed National Library of Medicine (NLM), Cochrane Library, Scientific Electronic Library Online (SciELO), e EMBASE. Foram utilizados os seguintes critérios de inclusão: 1) discussão do pós-operatório de cirurgias de descompressão do nervo mediano na STC; 2) comparação dos resultados, após descompressão cirúrgica, na STC entre imobilização do punho ou apenas curativo local; 3) todos os idiomas, independentemente do ano de publicação; e 4) todos os tipos de publicações. Foram utilizados os seguintes critérios de exclusão: 1) estudos que não avaliaram o pós-operatório de descompressão da STC; 2) falta de avaliação do resultado relacionado à conduta de aplicação de curativo local e/ou alguma forma de imobilização do punho após o procedimento cirúrgico de descompressão; e 3) publicações repetidas

Resultados A busca bibliográfica resultou em 336 publicações relevantes. Ao final, foram escolhidas 18 publicações. Foram encontradas revisões sistemáticas, ensaios clínicos randomizados e estudos transversais.

Conclusões Devido à escassez de evidências que apoiem o uso da imobilização, associada aos custos mais elevados relacionados com a prática, nas últimas décadas, essa tem se tornado cada vez menos frequente.

Relevância clínica Na literatura há descrições de duas abordagens nos cuidados pós-operatórios de descompressão da STC: imobilização ou apenas curativo local. Vale a pena avaliar qual é a melhor entre as duas de acordo com as evidências científicas disponíveis.

Palavras-chave
- nervo mediano
- síndrome do túnel carpal
- traumatismos do punho
- traumatismos dos nervos periféricos

Introduction

The most common compressive neuropathy of the upper limbs is carpal tunnel syndrome (CTS). The most frequent symptom is paresthesia, especially at night, in the region innervated by the median nerve. Surgical treatment is preferable in cases in which conservative therapy fails. Surgical decompression can be open or endoscopic.[1] Historically, there was a tendency to apply immobilization in the postoperative period, a practice that has decreased in recent years.[2–4] Immobilization would theoretically have the advantage of avoiding the bowstring effect of the flexor tendons and promoting analgesia.[5] However, more recent studies do not support this idea.

The literature describes two courses of action in the postoperative period of CTS decompression: immobilization or local dressing only. According to the available scientific evidence, it is worth evaluating which one is better.

The aim of the present study is to evaluate the outcomes after CTS decompression surgery when the wrist is immobilized and when only a bandage is applied and to compare them.

Material and Methods

Research Strategy

An active search for articles in the literature was carried out on May 6, 2023. The search used the following databases: Virtual Health Library (VHL), PubMed National Library of Medicine (NLM), Cochrane Library, Scientific Electronic Library Online (SciELO), and EMBASE. The descriptors used, together with the Boolean operators, were: "*Carpal Tunnel Syndrome* [Mesh] OR *carpal tunnel syndrome* [tw] OR *carpal tunnel release* [tw] AND *Postoperative Care* [Mesh] OR *postoperative* [tw] OR *postoperative care* [tw] AND *Restraint, Physical* [Mesh] OR *immobilization* [tw] OR *splint** [tw] AND *Bandages* [Mesh] OR *dress** [tw] OR *bandage** [tw]. A cross-reference search was also done in the databases to find articles not initially identified.

The search strategy for each database is detailed in the appendices at the end of the paper.

Selection Criteria

The following criteria were used to include the studies: 1) discussion of the postoperative period of median nerve decompression surgeries in CTS; 2) comparison of outcomes after surgical decompression in CTS between wrist immobilization or local dressing alone; 3) all languages, regardless of the year of publication; and 4) all types of publications.

The following exclusion criteria were listed: 1) studies that did not evaluate the postoperative period of CTS decompression; 2) absence of an evaluation of the outcome related to the conduct of local dressing or some form of wrist immobilization after the surgical procedure; and 3) repeated publications.

Data collection

Two researchers carried out the data collection process. Initially, the titles and abstracts of each publication were analyzed independently, after which any inconsistencies were discussed, and a consensus was reached. Subsequently, each publication was read in full independently, and meetings were held to decide which studies should be included and excluded, reaching a mutual consensus.

Level of Evidence

The studies were classified from I to V according to the hierarchical level of evidence.[6] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this review for the search, data extraction, and analysis of results.[7]

Results

The literature search resulted in 336 relevant publications. After removing duplicates, 210 articles were obtained. Subsequently, after analyzing the titles and abstracts, 179 studies were excluded, resulting in 31 eligible articles. After a complete reading of the text, four articles were eliminated due to the availability of only the title on digital platforms, and another five were excluded due to the availability of only the abstract. Two articles were eliminated because they did not present the results (only the body of the work was available, as it had not been finalized). Two other studies were excluded after a complete reading of the text because they did not fit the study's objective. In the end, 18 publications were listed. ►**Fig. 1** illustrates the research process.

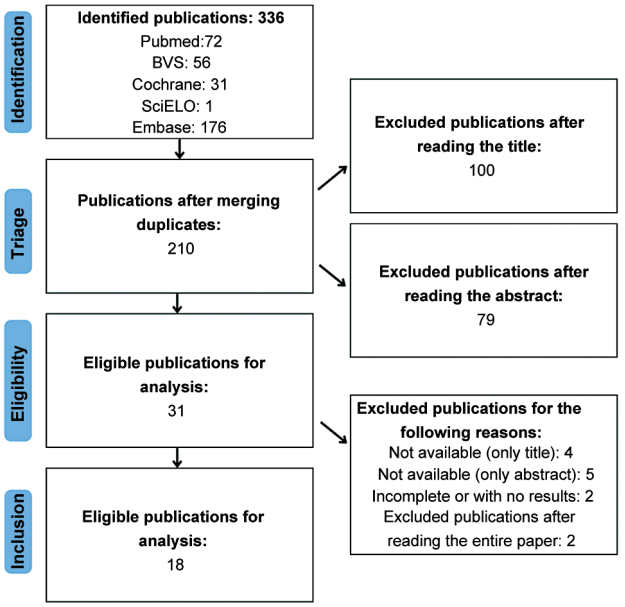


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram to illustrate the search process according to this study's inclusion and exclusion criteria.

Systematic Reviews - Level of Evidence I

A systematic review by Ashworth found randomized clinical trials (RCTs) comparing immobilization versus non-immobilization groups after CTS decompression. At 6 months, no differences were found in grip and pinch strength between patients in the 2 groups. Another RCT showed that return to work was slower in the immobilized group (27 days versus 17), and there were higher rates of pillar pain and scar tenderness after 1 month.[8]

Similarly, Huisstede et al.[9] found five RCTs that showed no evidence of benefit from immobilization. Grip and pinch strength, analgesia, and functionality were comparable in both groups.

A systematic review by Peters et al.,[10] which included 20 trials with 1,445 participants, found little scientific evidence in favor of using postoperative immobilization. Later, in 2015, Peters et al.[11] updated the previous review from 2013. They included 22 trials and 1,521 patients. The results remained the same.

►**Table 1** shows the systematic review articles found.

RCT - Level of Evidence II

An RCT evaluated 40 patients and 43 open CTS decompressions, comparing the 2-week postoperative period between a

Table 1 Level I evidence studies

Authors	Title	Level of evidence
Ashworth 2010	Carpal tunnel syndrome	RS (I)
Huissttede et al. 2010	Carpal tunnel syndrome. Part II: effectiveness of surgical treatments-a systematic review	RS (I)
Peters et al. 2013	Rehabilitation following carpal tunnel release	RS (I)
Peters et al. 2016	Rehabilitation following carpal tunnel release	RS (I)

group of 26 who received a splint and a group of 17 who received only a bulky dressing. No beneficial effect was observed in that group when evaluating the objective parameters of grip strength, pinch strength, complications, range of motion in the hand and fingers, and the subjective parameter of personal satisfaction.[5]

Another RCT evaluated 50 patients, divided equally into 2 groups. One group received a splint after the decompression procedure for CTS, while the other group was allowed free range of motion in the immediate postoperative period. In the immobilized group, higher rates of pain, scar tenderness, stiffness, and longer recovery time were observed.[12]

In one publication, Finsen et al.[13] analyzed 82 wrists that had undergone CTS decompression and were randomly divided into a group without immobilization and a group with postoperative immobilization for 4 weeks. No benefits or harm related to the practice were found. In another publication, 52 patients were divided equally into 2 groups: 26 who received immobilization for 2 weeks after CTS decompression and 26 patients without postoperative immobilization. Both groups had similar outcomes, including two-point discrimination. It was concluded that the immobilized group was not superior to the control group.[14]

Bhatia et al.[15] showed, from an RCT with 102 patients, that using a volar splint in the postoperative period was not correlated with any analgesic effect compared to the control group. After 50 open CTS decompressions, half received only a dressing, and the other half received a volar splint for 2 days. These patients were followed up for 3 months after surgery. No differences were found when analyzing functional parameters and electrophysiological tests, and both groups obtained good analgesia.[16]

Like the previous study, Cebesoy et al.[17] divided 40 patients into 2 groups. The non-immobilized group was allowed immediate mobility, while the other group was only allowed movement after 10 days when the immobilization was removed. Levine's Carpal Tunnel Questionnaire (CTQ) was applied preoperatively and in the 1st and 3rd months after surgery. The Symptom Severity Scale (SSS) and the Functional Status Scale (FSS) were applied for this assessment. In the observation after 3 months, it was identified that the group that received only the dressing had lower SSS values. This superiority was attributed to early rehabilitation. Furthermore, 16 patients (80%) complained of discomfort associated with using the splint in the immobilized group.[17]

Tinfhofer's group evaluated 63 wrists of 60 patients, comparing dorsal immobilization for 1 week versus a 2-day dressing in the postoperative period of CTS decompression. Follow-up occurred after 3 and 6 months, assessing pain parameters, 2-point discrimination, grip and pinch strength, and electrophysiological studies. The follow-up showed that the individuals in the 2nd group had better grip and pinch strength results at 6 months.[18]

Similarly, Shalimar et al.[19] studied 30 patients. Sixteen received immobilization for 1 week, and 14 patients only received bandages. They were evaluated after 1 week, 2 months, and 6 months. The following parameters were observed: visual analog scale (VAS), 2-point discrimination, grip and pinch strength, abductor pollicis brevis strength, and the Boston questionnaire. The two groups had no significant difference in any of the parameters assessed.

A total of 249 patients were divided into three groups: 80 without orthoses, 83 with removable orthoses, and 86 with non-removable orthoses. The following criteria were assessed: Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH); SSS, and FSS; grip and pinch strength; wrist flexion and extension; and measurement of pain at rest and in action, using the Numerical Pain Rating Scale (NPRS). The outcomes were assessed at 10 to 14 days, 6 weeks, and 3, 6, and 12 months after surgery. The only difference observed was that in the non-removable orthosis group, the pinch strength was lower after 6 and 12 months than that of patients in the other groups. The most common complication was hypersensitivity in the scar area.[20]

More recently, in 2023, a published study evaluated 24 patients who underwent endoscopic decompression of CTS. Two groups were randomized, with 12 patients each. In one group, immobilization was used for 2 weeks; in the other, immediate mobilization was allowed. The following parameters were assessed: two-point discrimination test, Semmes-Weinstein monofilament test; occurrence of pain in the pillar; the range of motion of the wrist; Visual Analog Scale (VAS); Boston Carpal Tunnel Questionnaire (BCTQ) score; DASH score; grip and pinch strength; and occurrence of complications. These outcomes were observed 2 weeks and, 1, 2, 3, and 6 months after surgery.[21]

Two weeks postoperatively, the immobilized group showed better results regarding VAS, grip strength, and pinch, and a lower occurrence of pillar pain. In subsequent comparisons, these differences were not maintained. In two patients in the non-immobilized group, hypersensitivity was observed in the scar in the immediate postoperative period, but this disappeared after 1 month of follow-up. It was, therefore, concluded that in the early follow-up, the immobilized group had better analgesia and grip and pinch strength. However, the two groups were similar at subsequent follow-ups.[21]

►**Table 2** shows the RCT articles found.

Cross-Sectional Studies - Level of Evidence IV

A survey of members of the American Society for Surgery of the Hand (ASSH) in 1987, by Duncan et al. apud Henry et al.[2] showed that 82% of surgeons immobilized the wrist in the postoperative period of CTS decompression. In 2008, an assessment of 1,091 members of the ASSH showed that this percentage had fallen to 53%. The number of days varied greatly among those interviewed (1–42 days).

Two other evaluations were carried out with ASSH members. In 2012, Leinberry et al.[3] showed that 247 of 659 respondents (around 37%) used postoperative immobilization. In 2014, Munns et al.[4] found that 193 of 710 respondents (around 27%) had this routine.

►**Table 3** shows the cross-sectional study articles found.

Table 2 Level II evidence studies

Authors	Title	Level of evidence
Finsen et al. 1999	No advantage from splinting the wrist after open carpal tunnel release. A randomized study of 82 wrists	ECR (II)
Bhatia et al. 2000	Does splintage help pain after carpal tunnel release?	ECR (II)
Martins et al. 2006	Wrist immobilization after carpal tunnel release: a prospective study	ECR (II)
Huemer et al. 2007	Postoperative splinting after open carpal tunnel release does not improve functional and neurological outcome	ECR (II)
Cebesoy et al. 2007	Use of a splint following open carpal tunnel release: a comparative study	ECR (II)
Tinhofer et al. 2013	Postoperative care and rehabilitation after open carpal tunnel surgery	ECR (II)
Shalimar et al. 2015	Splinting after Carpal Tunnel Release: Does it really Matter?	ECR (II)
Logli et al. 2018	A Prospective, Randomized Trial of Splinting After Minicarpal Tunnel Release.	ECR (II)
Zhang et al. 2023	The significance of wrist immobilization for endoscopic carpal tunnel release	ECR (II)

Table 3 Level IV evidence studies

Authors	Title	Level of evidence
Henry et al. 2008	Splinting after carpal tunnel release: current practice, scientific evidence, and trends	ET (IV)
Leinberry et al. 2012	Treatment of carpal tunnel syndrome by members of the American Society for Surgery of the Hand: a 25-year perspective	ET (IV)
Munns et al. 2015	Trends in carpal tunnel surgery: an online survey of members of the American Society for Surgery of the Hand	ET (IV)

Discussion

In the mid-1980s, it was estimated that more than 80% of ASSH members wore a splint postoperatively after open decompression of CTS. Immobilization would theoretically have the advantage of avoiding the bowstring effect on the flexor tendons, wound dehiscence, and median nerve entrapment in the scar, as well as increasing grip and pinch strength and promoting analgesia. However, this practice was already correlated with a longer time to return to daily activities and work.[5,12]

In 1978, McDonald et al. apud Henry et al.[2] observed the bowstring effect in 2 patients out of 186 who underwent decompression. Interestingly, in this study, these patients received immobilization in the postoperative period. Another reason would be to avoid prolapse of the median nerve out of the carpal tunnel after sectioning the transverse ligament, observed in 2 cases in 1980 by Inglis. However, early mobility is the best way to prevent friction between the nerve and the overlying skin scar.[2]

Due to the scarcity of evidence supporting the use of immobilization, associated with the higher costs related to the practice,[15] it has been observed in recent decades that it has become less and less frequent. Cebesoy et al.[17] showed that it is related to more significant discomfort and making the procedure more expensive without offering any benefits. Other comparative studies advocate early mobility, as it gives a faster recovery in the range of movement. Tinhofer et al.[18] showed the superiority of unrestricted mobility in the immediate postoperative period when analyzing grip strength and pinch parameters in the late postoperative period. On the other hand, much of the evidence also shows that there are no differences between one practice and another.[9–11]

Among the studies evaluated in this systematic review, only Zhang et al.[21] showed that immobilization conferred greater grip and pinch strength and better analgesia in the early postoperative period. However, even in this study, later follow-up showed no difference between applying immobilization or allowing early mobility.

The limitations of this study include the fact that the number of studies with a higher level of evidence (systematic reviews and RCTs) on the subject is still small.

Conclusion

Most of the evidence currently available indicates that the use of immobilization after decompression of CTS is not necessary. However, it is worthwhile carrying out more studies on the subject, as not many publications elucidate this issue.

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Conflict of Interest

The authors declare that there are no conflicts of interest in this study.

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The Influence of High Physical Demand on the Occurrence of Major Muscle and Ligament Injuries in Professional Soccer Athletes: A Systematic Review

A influência da alta demanda física na ocorrência das principais lesões musculares e ligamentares em atletas profissionais de futebol: Uma revisão sistemática

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Abstract

Objective The present systematic review aimed to investigate the influence of high physical demand on the increase in muscle and ligament injuries in professional soccer athletes.

Methods We analyzed scientific publications to determine the incidences of the main injuries, their causes and mechanisms, and their association with high physical demand. We compared amateur and professional players and assessed the effectiveness of FIFA11+ as a prevention alternative. Searches occurred on Scielo, Pubmed, and Google Scholar databases. The filters were the topic, publication date (last 5 years), and study relevance. The indexing terms were the following: *Overuse*, *Calendar*, *Injuries*, *Muscular*, *Ligament*, *Athletes*, *Soccer*, *Football*. We described the main data obtained to compare and analyze the results. This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.

Results The query resulted in 24 articles published from 2019 to 2023. The high physical demand increased the risk of injuries. Most injuries occurred in the lower limbs. The most common injuries were strains, sprains, contractures, and ligament ruptures. FIFA11+ presented itself as a viable prevention alternative.

Conclusion We concluded that high physical demand increases the most frequent muscle and ligament injuries in professional soccer players, that is, strains, sprains, contractures, and ligament rupture, suggesting the FIFA11+ program as a prevention alternative.

Keywords
- athletes
- knee injuries
- muscle, skeletal
- soccer/injuries

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Resumo

Objetivo Esta é uma revisão sistemática que objetivou investigar a influência da alta demanda física no aumento de lesões musculares e ligamentares em atletas profissionais de futebol.

Métodos Tratou-se de buscar, por meio da análise de publicações em meios científicos, as incidências das principais lesões, abordando suas causas e mecanismos, bem como sua relação com a alta demanda física. Comparamos jogadores amadores (categorias de base) com jogadores profissionais e avaliamos a eficácia do FIFA11+ como alternativa de prevenção. As buscas foram realizadas nas plataformas Scielo, Pubmed e Google Scholar. Os filtros foram de acordo com o tema, data de publicação (últimos 5 anos) e relevância para o estudo. Foram utilizados os seguintes termos de indexação: *Overuse, Calendar,Injuries, Muscular, Ligament, Athletes, Soccer, Football*. Os principais dados obtidos foram descritos, objetivando a comparação e análise dos resultados. Foram aderidas as recomendações da declaração de Principais Itens para Relatar Revisões Sistemáticas e Metanálises *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses*, PRISMA).

Resultados A pesquisa resultou em 24 artigos, publicados entre 2019 e 2023. Quanto à influência da alta demanda física, observou-se o aumento do risco de lesões. Em relação à incidência, constatou-se a prevalência de lesões nos membros inferiores. Quanto aos tipos de lesões, nota-se que as mais comuns são estiramento, entorse, contratura e rompimento ligamentar. Quanto ao FIFA11+, apresentou-se como alternativa viável de prevenção.

Conclusão Concluiu-se que a alta demanda física aumenta a ocorrência das lesões musculares e ligamentares mais frequentes em futebolistas profissionais, que são estiramento, entorse, contratura e rompimento ligamentar, sugerindo-se o programa FIFA11+ como prevenção.

Palavras-chave

- atletas
- futebol/lesões
- músculo esquelético
- traumatismos do joelho

Introduction

Soccer is one of the most popular sports worldwide. It is played in several countries by individuals from all age groups and both genders. However, professional soccer players present a high incidence of injuries due to the intense physical demand in training and matches throughout the year.[1,2]

The incidence of sports injuries and their risk factors is a subject of intense debate. The search for good performance and success in sports causes many players to undergo threshold physical effort or beyond their physiological limits, resulting in overload-related injuries.[3] Soccer requires a lot of impact from physical contact, short, fast, and discontinuous movements such as acceleration and deceleration, jumps, and sudden directional changes.[1,4]

It is estimated that soccer accounts for 50 to 60% of sports injuries affecting different muscle groups, mainly in the lower limbs.[2] Injuries often negatively impact not only the player's quality of life but the team's performance, resulting in strategic and economic losses to the club due to the absence in training and matches.[5]

Taking care of the athlete's health and implementing injury prevention strategies are critical to maximize the team's chance of success and the player's professional growth. Therefore, knowledge of injuries emerges as a strategy for developing plans to prevent or minimize them in sports, reducing the losses and unhappiness resulting from players' absence.[6,7]

The growth of national and international competitions, especially with the increase in the number of official matches, makes it critical to know about the different types of injuries that affect soccer players the most with the goal of prophylaxis as well as taking care of the athlete's health and safety.[6] Therefore, this study aimed to investigate and address the influence of high physical demand on the incidence of the main muscle and ligament injuries in professional soccer players.

Materials and Methods

We conducted this study according to the guidelines for systematic reviews, whose goal is to examine and discuss articles published on a determined topic.[8] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

The present study is a systematic review. The review had six stages: 1) identification of the topic and selection of the research question; 2) establishment of criteria for literature search and study inclusion and exclusion; 3) definition of the information to be extracted from the selected studies; 4) study categorization; 5) evaluation of studies included in the integrative review and their interpretation; and 6) review presentation.

The first stage used the Patient, Intervention, Comparison, and Outcome (PICO) strategy to define the following research question: "Does high physical demand have an influence in the increase of major muscle and ligament injuries occurrence in professional soccer players?" In this question, P refers to professional soccer players, I is high physical demand, C is regular physical demand, and O refers to increased occurrence.

We searched for articles about the intended outcome to answer this question using the terminologies registered in the Health Sciences Descriptors (DeCS) created by the Virtual Health Library and developed by the Medical Subject Headings of the U.S. National Library of Medicine, allowing the use of common terminology in Portuguese, English, and Spanish. The descriptors included *Overuse*, *Calendar*, *Injuries*, *Ligament*, *Muscular*, *Athletes*, *Football*, and *Soccer*. Keyword crossing used the Boolean operators *and*, *or*, and *not*.

The bibliographic survey occurred through electronic searches in the following databases: Scientific Electronic Library Online (SciELO), National Library of Medicine (PubMed), and Google Scholar.

The search took place in September 2023. For inclusion criteria, there was no language limitation, considering articles in English and Portuguese published in the last 5 years (from 2019–2023) about the topic and available electronically in its full format. Articles that did not meet the inclusion criteria were excluded.

Results

We identified a total of 315 studies. The time interval filter (2019–2023) application resulted in 157 articles for further investigation, according to the established exclusion criteria, generating a sample of 54 publications for complete reading. Of these 54 studies, we excluded 30 because they were irrelevant to the present study. The final sample for this review consisted of 24 articles. The flowchart (►**Fig. 1**) demonstrates this paper selection process.

We tabulated the selected studies (►**Table 1**)[5,6,8–29] including authors' names and year of publication, type of article, title, study objective, and main findings.

Of the 24 articles selected, 16 were systematic reviews, 3 were field research, 3 were prospective studies, 1 was a systematic review and meta-analysis, and 1 was a clinical trial. However, they all address the main theme: the occurrence of sports injuries in soccer players. The authors' main objectives included investigating the prevalence of different types of injuries (looking for the most common ones), the different incidences of injuries in amateur (base categories) and professional players, the effectiveness of the FIFA11+ program as a preventive alternative and understanding the influence of risk factors and mechanisms for the occurrence of certain types of injury.

Discussion

Influence of High Physical Demand

Functional Capacity

The functional capacity of the player is paramount because of the significant difference between professional and amateur athletes. Each age group requires different training strategies, with distinct loads, intensity of physical activity, exercise duration, and appropriate selection for each category.

The stratification of the sport modality and the variables from each athlete provide indications, such as ball techniques

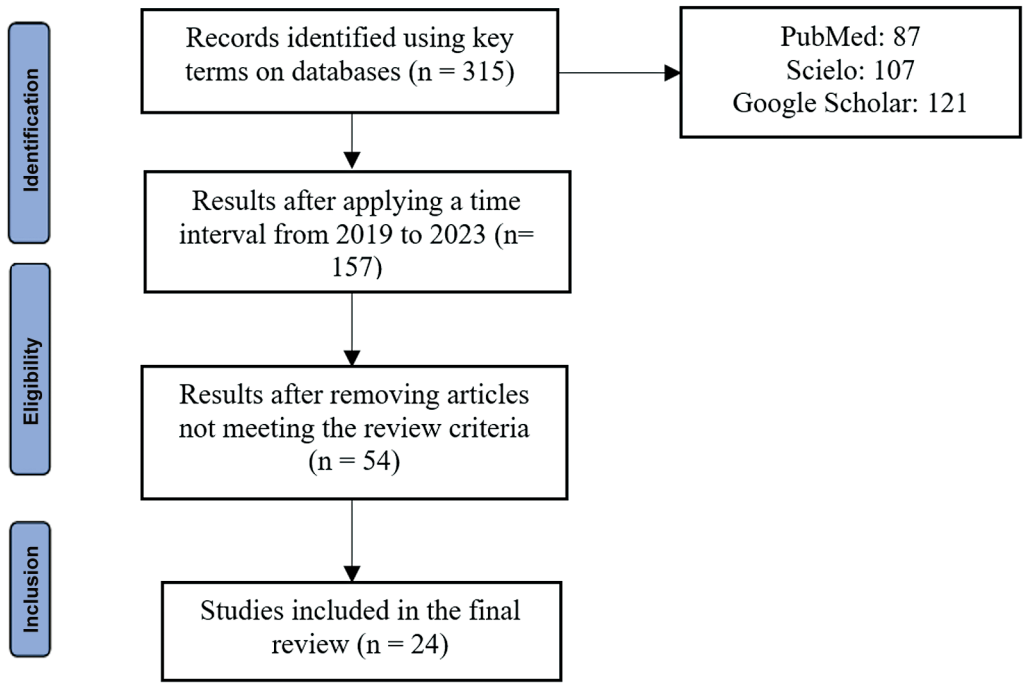


Fig. 1 Study selection flowchart.

Table 1 Articles included in the systematic review

#	Author and year	Article type	Title	Main findings
1	Drummond et al.,[6] 2021	Prospective study	Incidence of injuries in soccer players – mapping foot: a prospective cohort study	In a soccer tournament, 86.9% of injuries in male players occurred in the lower limbs. Stretch injuries were the most common and mainly affected the semitendinosus, biceps femoris, and gastrocnemius muscles.
2	Marques,[5] 2021	Systematic review	Injuries in Portuguese female soccer athletes	In female soccer athletes, 85.5% of injuries affected the lower limbs.
3	Lima et al.,[8] 2022	Systematic review	Injuries in soccer athletes: a theoretical study	Lower limb injuries are more frequent in soccer due to the demands imposed on this anatomical region.
4	Castelo et al.,[9] 2022	Systematic review	Injuries in professional soccer: a systematic review	Stretch injuries are the most common and mainly affect the semitendinosus, biceps femoris, and gastrocnemius muscles. Muscle contracture damages the semitendinosus, semimembranosus, and biceps femoris muscles. Fatigue is the main cause of muscle contracture, which greatly affects elite soccer players.
5	Silva et al.,[10] 2019	Systematic review	Incidence of musculoskeletal injuries in professional soccer players in Brazil	Stretch injuries are the most common and affect the semitendinosus, biceps femoris, and gastrocnemius muscles. Stretching refers to an excessive fiber elongation and occurs during sudden acceleration, deceleration, or sprints.
6	Teixeira et al.,[11] 2021	Field research	Epidemiological analysis of injuries in professional football athletes in two football clubs in Goiânia, Goiás, Brazil	Stretch injuries are the most common and affect the semitendinosus, biceps femoris, and gastrocnemius muscles.
7	Allah,[12] 2022	Systematic review	Physical therapy for ankle sprain injuries in soccer players: a literature review	A sprain is an injury to joint ligaments, and it commonly affects the ankle, with potential partial or complete rupture. It results from sudden movements, such as plantar flexion with foot inversion.
8	Ribeiro et al.,[13] 2022	Systematic review	The physiotherapeutic approach to lateral ankle sprain: a literature review.	A sprain is an injury to joint ligaments, and it commonly affects the ankle, with potential partial or complete rupture. It results from sudden movements, such as plantar flexion with foot inversion.
9	Meneses,[14] 2021	Systematic review	Sports injuries in futsal athletes: a systematic review of the literature	In soccer, knee sprains frequently result from a sudden directional change in the knee with the foot in a fixed position. Capsuloligamentous and meniscal injuries stand out.
10	Feitoza Neto et al.,[15] 2021	Systematic review	Injuries to knee structures in soccer players	In soccer, knee sprains frequently result from a sudden directional change in the knee with the foot in a fixed position. Capsuloligamentous and meniscal injuries stand out.
11	Farias,[16] 2021	Systematic review	Applicability of strength exercises in the prevention and rehabilitation of grade I and II muscle injuries in elite soccer players	Contracture results from incorrect muscle contraction with no return to the regular relaxed state. The overload of anaerobic respiration

(*Continued*)

Table 1 (*Continued*)

#	Author and year	Article type	Title	Main findings
				leads to lactic acid accumulation, causing this phenomenon. Muscle contracture mainly damages the semitendinosus, semimembranosus, and biceps femoris muscles. Fatigue is its main cause, explaining why these injuries are common in elite soccer players.
12	Zhang and Wanh,[17] 2023	Field research	Sports injuries in professional soccer players	Muscle contracture damages the semitendinosus, semimembranosus, and biceps femoris muscles. Fatigue is its main cause, explaining why these injuries are common in elite soccer players.
13	Silva et al.,[18] 2020	Systematic review	Physical therapist's role with players with anterior cruciate ligament injuries	Ligament tears depend on the performed movement. Athletes frequently present anterior cruciate ligament injuries due to excessive force during knee rotation.
14	Borba,[19] 2021	Systematic review	Criteria for return to soccer after anterior ligament reconstruction surgery: a literature review	Ligament tears depend on the performed movement. Athletes frequently present anterior cruciate ligament injuries due to excessive force during knee rotation.
15	Sousa,[20] 2021	Systematic review	Plyometrics in the prevention of anterior cruciate ligament injuries in soccer athletes: an integrative literature review	Knee ligament injuries can cause loss of integrity and functionality in the short and long term and be irreversible, resulting in the retirement of soccer players.
16	Choriyev,[21] 2021	Field research	Planning and organizing training of football players	We must consider the relatively low functional capacity of children aged 8 to 11. These children required training in age-specific ball techniques and game tactics. For teenagers aged 12 to 17, the focus changes to individual preparation, with more elaborate exercises emphasizing movement speed, resistance, agility, and flexibility in different age groups. Therefore, we must select proper exercises based on the match, their influence on the body's functions, and their duration and intensity.
17	Jones et al.,[22] 2019	Systematic review	Injury incidence, prevalence, and severity in high-level male youth football: a systematic review	Age influences the total incidence of injuries in athletes. Older players have higher injury incidence rates. One-fifth of injuries are severe and can cause the athlete to stop playing for at least 28 days, which harms the subject and the team, as both lose out in seasonal development.
18	Pfirrmann et al.,[23] 2016	Systematic review	Analysis of injury incidences in male professional adult and elite youth soccer players: a systematic review	Injury rates were higher in matches than in training both for young and adult players. Youth athletes had a higher incidence of training injuries than professional players.
19	Cezarino et al.,[24] 2020	Prospective study	Injury profile in a Brazilian first-division youth soccer team: a prospective study	The injury incidence was higher in matches than in training, and the oldest age group (sub-20) had the

Table 1 (*Continued*)

#	Author and year	Article type	Title	Main findings
				highest injury incidence rate in games, while the sub-17 group had the highest injury incidence rate in matches. Injury incidence rates for players under 20 years old are close to professional players.
20	Yang et al.,[25] 2022	Systematic review and meta-analysis	Effects of the "FIFA11+ Kids" program on injury prevention in children: a systematic review and meta-analysis	FIFA11+ significantly decreased the risk of overall injuries compared to regular warm-up training. Soccer players aged under 15 are at the highest risk of injuries among all age groups analyzed as they have a lower level of physical development. FIFA11+ Kids is effective in preventing soccer-related injuries in young players. The program can significantly reduce the risk of ankle, knee, and lower limb injuries.
21	Al Attar et al.,[26] 2022	Clinical trial	The FIFA 11+ kids injury prevention program reduces injury rates among male children soccer players: a clustered randomized controlled trial	FIFA11+ significantly reduced knee, leg, and ankle injuries, the likelihood of a player becoming injured, and the rates of contact, non-contact, and overuse injuries. Therefore, this study confirms the critical role of implementing the program in younger players to prevent injuries.
22	Pinto et al.,[27] 2021	Systematic review	FIFA 11+ for injury prevention in soccer players: a systematic review	In addition to all the indications from Al Attar's study, the prevention effect is higher when all team players adhere to the program. When targeted at high-competition athletes, outcomes are less significant due to periodization and competition calendar. Furthermore, the arrival of players from other clubs in midseason reduces the program's effectiveness, as do players who fail to complete the protocols due to injury or illness. The program also improves performance variables, causing significant improvements in dynamic postural control.
23	Materne et al.,[28] 2020	Prospective study	Injury incidence and burden in a youth elite football academy: a four-season prospective study of 551 players aged from under 9 to under 19 years	Compared to other age groups, sub-16 and sub-18 players had higher incidence rates of overuse injuries. In the remaining players, bruises, sprains, and growth-related injuries were the most common. Meniscus/cartilage injuries were the most severe lesions.
24	Aiello et al.,[29] 2022	Systematic review	Injury-inciting activities in male and female football players: a systematic review	High-intensity running and kicking activities may be the main triggers for thigh and groin injuries, while contacts may be the most common triggers for ankle injuries. Contact and pressure may be the most common inciting activities leading to anterior cruciate ligament injuries, but there is no consensus in the literature.

and game tactics, for players aged 8 to 11 years old, and individual preparation with an emphasis on movement speed, resistance, agility, and flexibility for players aged 12 to 17. This stratification highlights the role of grading intensity as age advances to preserve the athlete's physical health up to the professional level. Otherwise, the lack of planning, with exaggerated demands, may expose these players to greater chances of injuries.[21]

Comparison of Amateur and Professional Players

Analyzing the incidence rate of injuries in high-level youth soccer, we noted an influence of advancing age, as older athletes have higher incidence rates. Among these injuries, 20% are severe, and result in absence for at least 28 days.[22]

This analysis is consistent with the fact that professional match calendars are more competitive and require greater physical demand compared with base (amateur) athletes. The higher frequency of short breaks between official matches, training intensity, time zone variation affecting rest, and the distinct climates from different locations, among other details, generate a set of factors contributing to higher physical wear and tear in professional players.

Younger athletes from base categories have a less intense calendar, with greater chances of preventing overload-related muscle and ligament injuries, partially explaining the different injury incidences. However, when comparing younger players from sub-9 and sub-19 categories, the latter presented high injury incidence rates due to the increasing training intensity and frequency of championship matches. Therefore, we infer that the higher intensity and match frequency, with no proper physical preparation, are risk factors for injuries even in young athletes.[28]

Furthermore, this data demonstrates that the transition from amateur (base categories) to professional category, following the same notion of advancing age, could be a risk factor for the higher incidence rate in these athletes.

Training and Matches

The high physical demand for high-performance athletes increases the chance of injuries, more so in matches than in training sessions. Meanwhile, younger (amateur) players presented a higher incidence of injuries in training than in official matches.[23] Moreover, groups with an age range closer to the professional category suffered more injuries than the others. For instance, a sub-20 player group had injury rates similar to professional players, especially in matches than in training, while the sub-17 group had a higher injury rate during training.[24] This relationship is justified by the higher number of matches in the calendars of older age groups, which also happens in the transition from youth categories to professional soccer.

This information demonstrates that the load evolution during the athlete's progress to the professional category, if not balanced, has a strong relationship with the occurrence of injuries caused by the high physical demand in their training routine and matches.

Main Injuries

Injuries in soccer players, whether amateurs or professionals, mainly occur in the lower limbs. A study with male athletes competing in a regional soccer tournament investigated the incidence and prevalence of injuries and found that the lower limbs are more affected than other parts of the body, representing 86.9% of injuries.[6] Another author had consistent results, noting that 85.5% of the identified injuries affected the same anatomical region.[5] The lower limbs are the most required in soccer, explaining the higher frequency of injuries in this area.[8]

The most common injury type includes muscular strains, mostly affecting the semitendinosus, biceps femoris, and gastrocnemius.[6,9–11] Strain results from fiber stretching beyond the physiological limits. It occurs during extravagant muscle contractions, such as rapid acceleration and deceleration, predisposing the player to an increased injury rate, with excess muscle tone as a major risk factor.[10]

Although with a lower incidence, studies also mentioned other injuries, including sprains, contractures, and ligament ruptures. A sprain is a traumatic ligament injury affecting joint ligaments, particularly the ankle. In this injury, the main ligaments involved include the deltoid, anterior talofibular, and posterior talofibular. This type of trauma results from sudden movements, as small, repetitive injuries due to excessive activity can increase ligament fragility. The mechanism of this injury mainly results from plantar flexion during foot inversion, leading to a complete or partial rupture of the lateral ligaments.[12,13] Knee sprains are also common in soccer due to valgus torsion, that is, when the knee is directed sharply to the inside and the foot remains fixed. In this case, in addition to ligament lesions, meniscus injuries may occur.[14,15]

Contracture results from an incorrect muscle contraction with no return to its regular relaxation state. Contractures occur due to lactic acid accumulation from anaerobic respiration after excessive overload.[16] Muscles damaged by this injury include the semitendinosus, semimembranosus, and biceps femoris. Soccer players are more susceptible to contractures, especially in the quadriceps, posterior thigh, gastrocnemius, and soleus, mainly from fatigue.[9,16,17,29]

Ligament tears depend on the performed movement and mainly affect the anterior and posterior cruciate ligament. Anterior cruciate ligament injury, for instance, is common in athletes due to knee rotation with a fixed foot (facilitated by shoe cleats) and valgus stress in a deceleration movement, abrupt directional change, or both.[18,19] This injury can disrupt knee integrity and functionality in the long term and be irreversible; therefore, it accounts for many early retirements of soccer players.[20] The anterior talofibular ligament suffers injuries by excessive lateralization when walking on uneven surfaces.

FIFA11+ Prevention Program

The FIFA11+ prevention program had significantly better outcomes than the regular warm-up. As functional capacity influences the risk of injuries, athletes under 15 years old are more susceptible to them because of their lower physical

development; as a result, a high physical demand can overload these players.[25]

FIFA11+ considerably reduced injuries in commonly affected areas, including the knee, leg, and ankle. A special reduction occurred in contact, non-contact, and excessive use injuries.[26]

As for professional players, FIFA11+ led to less impressive outcomes due to the competition calendar, short breaks between matches, and the highly physically demanding routine. However, it improved variables critical for good performance, such as the athlete's dynamic postural control.[27]

Final Considerations

The high physical demand influences an increase in the occurrence of muscle and ligament injuries in professional soccer players. Considering functional capacity, the increased intensity in the transition between base and professional categories, and the amount of training and competition calendars of official matches in professional soccer are relevant factors. The lower limbs are the most affected, and the most prevalent injuries include strains, sprains, contractures, and ligament ruptures.

Given the propensity for soccer injuries, it is critical to implement preventive interventions to care for the athletes' health. In this sense, we recommend FIFA 11+ or another customized method developed by the medical department of each club, taking into account individual features. These programs may reduce collective performance losses and health expenses.

Further studies are required to address the effects of the exacerbated routine of professional athletes and improve the performance and physical health of each player to increase the success in preventing injuries.

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Conflict of Interests
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Histomorphometric Study of Non-critical Bone Defect Repair after Implantation of Magnesium-substituted Hydroxyapatite Microspheres

Estudo histomorfométrico do reparo de defeito ósseo não crítico após implantaç ão de microesferas de hidroxiapatita substituída por magnésio

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Abstract

Objective The present study aims to analyze histomorphometrically the repair of a non-critical bone defect after implantation of hydroxyapatite (HA) microspheres substituted by magnesium (Mg).

Methods Thirty rats were distributed into 3 experimental groups, evaluated at 15 and 45 days postoperatively: HAG (bone defect filled with HA microspheres); HAMgG (bone defect filled with HA microspheres replaced with 1 mol% Mg), and CG (bone defect without implantation of biomaterials).

Results After 15 days, the biomaterials filled the entire defect extent, forming a new osteoid matrix between the microspheres. In the CG, this neoformation was restricted to the edges with the deposition of loose connective tissue with reduced thickness. At 45 days, new bone formation filled almost the entire extension of the bone defect in the 3 groups, with statistically significant osteoid deposition in the CG despite the reduced thickness compared with the HAG and HAMgG. The groups with biomaterial implantation displayed a more abundant osteoid matrix than at 15 days.

Keywords
- biomaterials
- bone and bones
- bone regeneration
- hydroxyapatite
- magnesium

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Conclusion The biomaterials studied showed biocompatibility, osteoconductivity, and bioactivity. The Mg concentration in the substituted HA did not stimulate more significant bone formation than HA without this ion.

Resumo

Objetivo O presente estudo teve como objetivo fazer uma análise histomorfométrica do reparo de um defeito ósseo não crítico após a implantação de microesferas de hidroxiapatita (HA) com substituição por magnésio (Mg).

Métodos Trinta ratos foram distribuídos em 3 grupos experimentais, avaliados aos 15 e 45 dias após a cirurgia: GHA (defeito ósseo preenchido com microesferas de HA); GHAMg (defeito ósseo preenchido com microesferas de HA com substituição por 1 mol % de Mg) e GC (defeito ósseo sem implantação de biomateriais).

Resultados Aos 15 dias, evidenciou-se que os biomateriais preencheram toda a extensão do defeito, com neoformação de matriz osteoide de permeio às microesferas. No GC, essa neoformação ficou restrita às bordas, com deposição de tecido conjuntivo frouxo de espessura reduzida. Aos 45 dias, a neoformação óssea preencheu quase toda a extensão do defeito ósseo nos 3 grupos, com deposição osteoide estatisticamente significativa no GC, apesar da espessura reduzida em comparação ao GHA e o GHAMg. Os grupos com implantação de biomaterial apresentaram matriz osteoide mais abundante do que aos 15 dias.

Conclusão Os biomateriais estudados apresentaram biocompatibilidade, osteocondutividade e bioatividade. A concentração de Mg na HA com substituição não estimulou a formação óssea mais significativa do que a HA sem este íon.

Palavras-chave
- biomateriais
- hidroxiapatitas
- magnésio
- osso e ossos
- regeneração óssea

Introduction

Bone tissue bioengineering, an emerging, interdisciplinary, and multidisciplinary area, has gained prominence in recent years due to the technical-scientific advances achieved and the increasingly growing biomedical and socioeconomic demands in today's society. Researchers in this area have applied the principles of biological and health sciences, chemistry, physics, and engineering to developing and improving regenerative techniques and biomaterials capable of restoring or improving the function and aesthetics of compromised tissues and organs.[1–4]

To define the applicability of these biomaterials, they shall present physical-chemical, biological, and morphological properties similar and compatible with living tissues to act as three-dimensional (3D) scaffolds assisting tissue regeneration or working as suitable replacements for damaged or lost tissues and organs. Among the various biomaterials currently available, calcium phosphate bioceramics (CaP) represent a widely researched and used class in bone regenerative techniques.[1] Among these materials, synthetic hydroxyapatite (HA) has stood out in recent decades due to its biocompatibility, similarity with biological apatite, bioactivity, osteoconductivity, non-immunogenicity, and enabling cellular events observed during tissue regeneration, such as angiogenesis and osteogenesis.[1–4] However, this ceramic presents slow biodegradation and bioresorption rates after *in vivo* implantation, asynchronous to the bone regeneration mechanism.[1–4] Furthermore, it is a rigid and brittle material, which can remain in the implantation site for months and even years, depending on the synthesis and processing method.[4,5]

Given this, one of the main objectives of researchers in this area has been to improve the properties of synthetic HA and modify the characteristics of this material to enhance the tissue response after *in vivo* implantation. Among the different methods available to carry out these modifications, HA-hexagonal-structure isomorphic substitutions have shown satisfactory results[3,6] due to the effects on the physical properties of the material, observed by changes in network parameters, crystalline structure, morphology, solubility, and thermal stability compared to unsubstituted HA.[7]

In these cases, other metals, such as zinc (Zn), strontium (Sr), fluorine (F), manganese (Mn), and magnesium (Mg), can replace calcium (Ca).[3,4,6] Magnesium has attracted great scientific interest, considering that, among other properties, it participates in the homeostasis of bone tissue and, together with other minerals, is fundamental to the mechanism of bone regeneration, stimulating bone formation, through the activation of osteoblasts and inhibiting resorption, through action on osteoclasts.[8–11]

Despite these possibilities, the physicochemical properties, biological behavior, and regenerative capacity of CaP substituted with Mg still require further studies to ensure the effectiveness of the techniques used during the synthesis and processing of these biomaterials. Therefore, this study evaluated the repair of non-critical bone defects after implantation of Mg-substituted HA microspheres in the rats' calvaria.

Materials and Methods

Biomaterials

The biomaterials evaluated in this study have been synthesized, processed, and sterilized in the Biomaterials Laboratory (LABIOMAT, in the Portuguese acronym) of the Brazilian Center for Physical Research (Centro Brasileiro de Pesquisas Físicas, CBPF). The synthesis, processing, and characterization are described in Santos et al.[4]

Surgical Procedures

This study was performed in the bioterium of Universidade Estadual de Feira de Santana (UEFS) after approval by the Ethics Committee on Animal Use (CEUA, in the Portuguese acronym) of Escola Bahiana de Medicina e Saúde Pública, protocol 02/2013. Thirty adults male *Wistar* rats, with body weight between 350 and 400g, were randomly distributed to form 3 experimental groups, with 5 animals each: HAG (defect filled with HA microspheres group); HAMgG (bone defect filled with MgHA microspheres group), CG – control group (bone defect without biomaterial), evaluated 15 and 45 days after surgery. The surgical technique used was the same as described by Miguel et al.[12] and illustrated by Santos et al.[2] However, it is worth highlighting that in these studies, the bone defect was approximately 8.0 mm in diameter, while in this study, it was about 5.0 mm[13] (►**Fig. 1**).

Histological Processing and Histomorphological Analysis

At the biological points of 15 and 45 days, the animals have been euthanized with a lethal ketamine and xylazine dose. Then, the upper portion of the calvaria was removed, the soft tissues were discarded, and the specimens were fixed in 4% buffered formaldehyde for 7 days. After this step, they were decalcified in 5% nitric acid for 2 hours, embedded in paraffin, and cut into 5.0-µm thick slices. The histological sections obtained were stained with hematoxylin-eosin (HE) and subsequently examined by standard light microscopy (DM1000–Leica Microsystems, Wetzlar, Germany) for histomorphological and morphometric analysis. A digital camera (DFC 310 FX – Leica Camera AG, Wetzlar, Germany) coupled to a standard light microscope (DM1000–Leica) and the software QWin 3.1 (Leica) measured the area of the newly formed mineralized matrix in the 3 experimental groups. Subsequently, statistical analysis was carried out based on the mean and standard deviation to obtain the *p*-value, with a significance level of 5% ($p < 0.05$), using the analysis of variance (ANOVA).

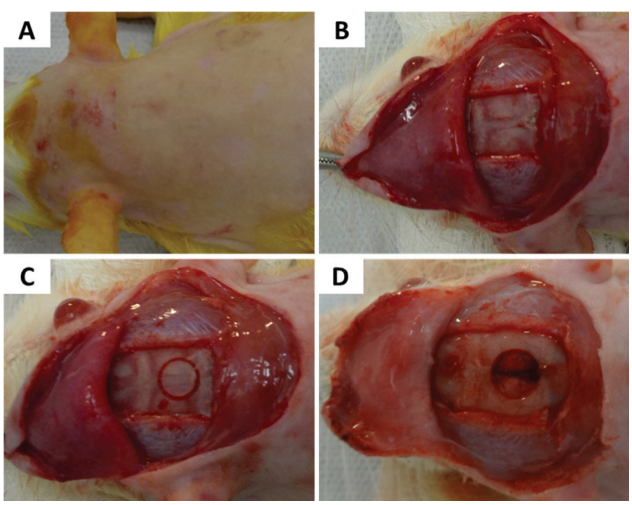


Fig. 1 Surgical steps for creating a non-critical bone defect. (**A**) Calvarial region after trichotomy and antisepsis; (**B**) flap reflected after a semilunar bi-coronal skin incision to expose the bone tissue; (**C**) demarcation of the bone defect in the median portion of the calvaria; and (**D**) non-critical bone defect created.

Results

Histomorphological Analysis

At 15 days, in the HAG, neoformation of an osteoid matrix was observed associated with the bone edges and surrounding some microspheres, which were predominantly organized in a monolayer and occupied the entire extension of the bone defect, maintaining the thickness proportional to the edges (►**Fig. 2A**). Active osteocytes and osteoblasts were observed associated with this matrix. The formation of connective tissue and mild chronic inflammation with mononuclear inflammatory infiltrate and multinucleated giant cells, mainly around the microspheres, was noted between the mineralized areas and the microspheres (►**Fig. 2B**).

At the biological point of 45 days, the microspheres in the HAG were mainly distributed in multilayers. The newly formed osteoid matrix was more evident than at 15 days and filled, on average, 4/5 of the bone defect in a centripetal direction, surrounded by the biomaterial (►**Fig. 2C**). The microspheres near the edges were surrounded by the newly

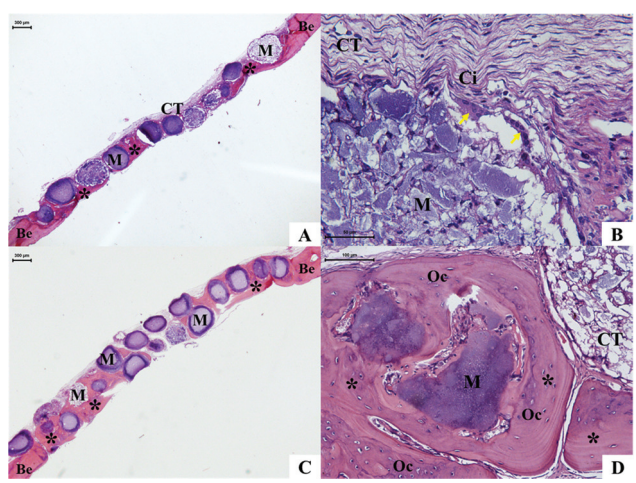


Fig. 2 Photomicrograph of HAG – 15 and 45 days. Note microspheres (M) distributed in a mono or double layer, with the formation of an osteoid matrix (*), in almost the entire extension of the defect, with the presence of osteocytes (OCs) and organized in concentric bone lamellae; loose connective tissue (CT) in the residual area of the bone defect, with the presence of mononuclear inflammatory cells (Ci) and multinucleated giant cells (yellow arrow). Abbreviations: Be, bone edge; HE, hematoxylin and eosin. 15 days (**A**,**B**). 45 days (**C**,**D**).

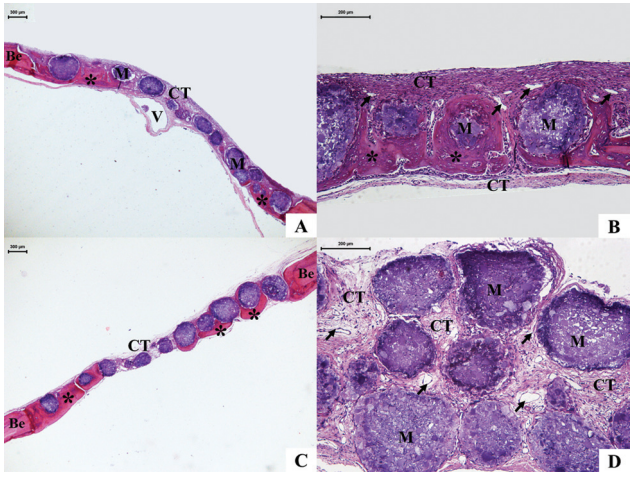


Fig. 3 Photomicrograph of HAMgG – 15 days and 45 days. Microspheres (M) are observed distributed in a monolayer, permeated by a newly formed osteoid matrix (*), in a centripetal direction, and by connective tissue (CT), rich in blood vessels (black arrow). Abbreviations: Be, bone edge; V, central vein; HE, hematoxylin and eosin. 15 days (**A**,**B**). 45 days (**C**,**D**).

formed osteoid matrix, with many active osteoblasts, osteocytes, and some concentric lamellae (►**Fig. 2D**). In the residual area, the formation of connective tissue with a denser appearance than the previous biological point was noted, with the presence of blood vessels and a mild chronic granulomatous inflammatory response.

In the HAMgG, at 15 days, with the biomaterials, neoformation of the osteoid matrix was noted in a centripetal direction, more evident in the peripheral region of the defect (►**Fig. 3A**). Like HA, the biomaterials filled the entire bone defect, with a thickness proportional to the edges, and arranged in a monolayer. Active osteoblasts and numerous osteocytes were observed in association with the osteoid matrix. The remaining areas were filled with loose connective tissue full of blood vessels (►**Fig. 3B**) and chronic granulomatous inflammatory infiltrate of moderate appearance, mainly surrounding the microspheres.

At the biological point of 45 days, in the HAMgG, the new bone formation permeated by the microspheres extended centripetally and confluently, filling approximately 2/3 of the linear extension of the defect (►**Fig. 3C**). Furthermore, it was noted that the microspheres located close to the edges were surrounded by osteoid neoformation rich in osteocytes. In the residual area, there was a new formation of connective tissue, more organized than at 15 days, and a large number of blood capillaries (►**Fig. 3D**).

The CG, at 15 days, displayed bone neoformation with a reactional appearance associated with the edges, presenting active osteoblasts and osteocytes. The remaining area showed deposition of loose connective tissue, with reduced thickness, abundant in spindle cells and blood vessels (►**Fig. 4A**). At 45 days, new bone formation extended beyond the edge in a centripetal direction, more evidently than at 15 days (►**Fig. 4B**). The chronic inflammation observed was discreet and scarce. Tissue repair was completed with the formation of connective tissue in the region and no mineralization.

Histomorphometric Analysis

The histomorphometric study displayed no statistically significant differences among the three groups evaluated at 15 days when analyzing the newly formed osteoid matrix area. At the biological point of 45 days, statistical significance was noted when comparing the HAMgG and HAG with the CG, with the latter group having a higher average of newly formed osteoid matrix (►**Table 1**).

Discussion

Experimental models in vivo have been referenced for many decades in different types of studies in various knowledge areas. To evaluate biomaterials designed for bone regeneration, these models must present anatomical and physiological characteristics that enable an understanding of natural phenomena to determine the osteogenic potential of the materials investigated. Thus, among the different possibilities for studies, the

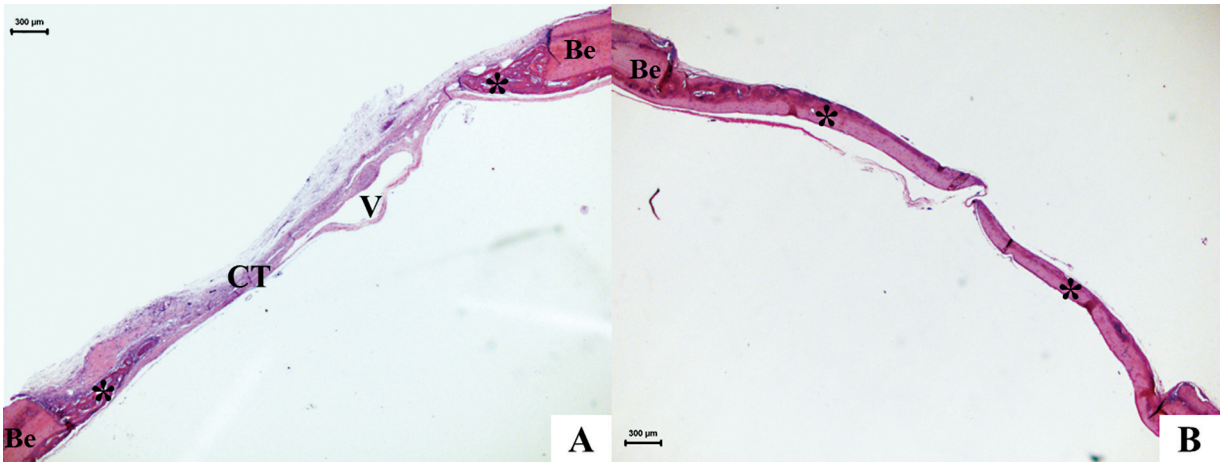


Fig. 4 Photomicrograph of CG – 15 and 45 days. Note the neoformation of the osteoid matrix (*) in a centripetal direction, with reduced thickness about the bone edges (Be), with a residual area filled with connective tissue (CT). HE, hematoxylin and eosin. 15 days (**A**) and 45 days (**B**).

Table 1 Percentage of the newly formed mineralized area in relation to the total area of the defect at the 15- and 45-days biological points, in the 3 experimental groups

Group / Period	HAMgG	HAG	CG	*P-value* (between-group)	Comparison HAMgG x HAG	Comparison of CG with HAMgG and HAG
15 days	25% (±29)	12% (±7)	20% (±38)	$p = 0.58$ NS	$p = 0.55$ NS	HAMgG: $p = 0.89$ NS HAG: $p = 0.82$ NS
45 days	20% (±13)	25% (±11)	61% (±21)	$p = 0.01$ S	$p = 0.92$ NS	HAMgG: $p = 0.01$ S HAG: $p = 0.02$ S

Abbreviations: CG, control group; HAG, group with defect filled with hydroxyapatite microspheres; HAMgG, group with bone defect filled with magnesium-substituted hydroxyapatite microspheres group; NS, not statistically significant; S, statistically significant.

bone defect created in the calvaria of a rat stands out, which presents easy access and surgical manipulation, low cost, good predictability, and reproducibility.[14] Therefore, this study evaluated the repair of non-critical bone defects after implantation of HA microspheres substituted with Mg.

The surgical procedure to create this defect promoted tissue damage and, consequently, vascular rupture that resulted in blood leakage and clot formation, followed by release of cytokines that triggered an inflammatory response. This inflammation, chronic granulomatous, discrete, and regressive throughout the study, agreed with what occurs when a biomaterial is implanted *in vivo*.[15,16] These findings are in line with what was observed by Santos et al.,[2] Santos et al.,[4] Miguel et al.,[12] Daltro et al.,[13] Almeida et al.[17] and Ribeiro et al.[18] These authors evaluated different types of biomaterials for bone regeneration, in rat calvaria, and described the same tissue response.

During the physiological events that occur in bone regeneration, besides the release of cytokines and chemical mediators, there is the secretion of growth, cellular differentiation, and angiogenic factors, which stimulate the formation of connective tissue rich in new blood vessels, with consequent development of granulation tissue, as well as deposition of the osteoid matrix, which subsequently becomes mineralized. At all biological points, such histomorphological characteristics were observed in the three groups evaluated in our study. At 45 days, in the CG, the neoformation of mineralized tissue was approximately 60%. However, in HAG and HAMgG this percentage was 25 and 20%, respectively. This difference in bone neoformation in the two groups with biomaterial implantation, as compared to the CG, derives from the presence of microspheres in the bone defect since these were sintered and, consequently, not reabsorbed due to the sintering of the material – a procedure that promotes changes in the HA crystal lattice with crystal fusion.[19] Thus, in HAG and HAMgG, the microspheres occupied a large part of the sectional area of the defect and, thus, formed a three-dimensional framework throughout the linear extension and height of the bone defect.

It is worth highlighting that although some authors suggest and defend some methodologies as standard, there is still no consensus in the literature on which bone defect exact diameter shall be considered non-critical or critical. A "critical" bone defect has been defined as a bone defect that does not regenerate throughout the life of the animal[20] or of the study.[21] In these cases, the repair is completed by fibrosis, and new bone formation is restricted to the edges.[4,12,17,18] This situation was not observed in the present study, in which new mineralized tissue formed centripetally along the biological points, with regeneration of almost the entire defect area in the CG at 45 days. These findings contrast with the results obtained by authors who classify this 5.0-mm bone defect as critical.[22–24]

Concerning bone regeneration, a 3D scaffold is essential for the cellular and vascular events observed during this mechanism. Therefore, ceramic biomaterials have been widely studied for this purpose in different forms of presentation and composition. Scientific and technological advances experienced in recent decades have increasingly enabled the development of materials with biomimetic physicochemical characteristics to stimulate new bone formation. Among these materials, HA has been extensively researched due to its biocompatibility, similarity with natural components of the mineral phase of bone tissue, osteoconductivity, bioactivity,[1,3] and lack of toxicity and immunogenicity. Our study observed such characteristics in the two groups in which biomaterials were implanted, in the three biological points, which allowed the formation of an osteoid matrix and connective tissue between and surrounding the microspheres.

The HA hexagonal structure performs ionic exchanges at the Ca^{2+} and HPO_4^{3-} sites with elements or functional groups that are naturally part of the bone composition to promote changes in crystallinity, solubility, biodegradation, and, consequently, in biological properties of the biomaterial after in vivo implantation.[4,25,26] Mg stands out, playing a critical role in bone metabolism and growth: the deficiency of this element inhibits the osteoblasts' activity, favoring the osteoclasts' survival and performance.[27,28] Furthermore, the presence of Mg contributes to biomineralization, mainly in the initial phase of osteogenesis: it increases the kinetics of HA nucleation, delays its crystallization, and can interfere with qualitative changes in the bone matrix.[29] This is probably why the average bone formation at 15 days was higher in HAMgG compared to HAG, however, without statistically significant differences. Despite this, this pattern did not repeat after 45 days, and the average osteoid matrix formation was similar between these groups.

Mg also has an essential effect on promoting angiogenesis, stimulating endothelial cells, and the production of vascular growth factors,[30] which may justify the presence of more evident blood vessels in HAMgG than in the other groups throughout the study. Furthermore, incorporating this metal into the HA structure promoted a slight decrease in the

biomaterial crystallinity without hampering the ceramic biodegradation, probably due to sintering.

The biocompatibility and bioactivity of the biomaterials studied here demonstrate that these materials have future clinical applications, especially as filler biomaterials. Given the results obtained in this work, new studies shall analyze these biomaterials without heat treatment (sintering) and with other variations in Mg concentration in critical (8.0 mm) and non-critical defects (5.0 mm) to better characterize the osteogenic potential of these ceramics replaced with this metal.

Conclusions

The biomaterials evaluated in this study are biocompatible, osteoconductive, and bioactive. The Mg substituted in HA stimulated a higher bone formation only in the initial phase of bone repair (15 days), forming the osteoid matrix similarly between ceramics in the final stage of the study.

Authors' Contributions

The authors contributed individually and significantly to the development of this article: JAS: Study conception and design; manuscript preparation; and surgical procedures. GGS: Manuscript preparation; and surgical and technical procedures. IIAR: Manuscript preparation; and surgical and technical procedures. AMGBS: Manuscript preparation and english text review. ICB: Surgical and technical procedures and histopathological analysis. MAM: Study conception and design; and histopathological analysis. MAB: Study conception and design; and histopathological analysis. FBM: Study conception and design; surgical and technical procedures; and critical review.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Electrical Stimulation Prevents Muscular Atrophy and the Decrease of Interleukin-6 in Paralyzed Muscles after Spinal Cord Injury in Rats

A estimulação elétrica previne a atrofia muscular e a diminuição da interleucina-6 em músculos paralisados após lesão da medula espinal em ratos

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Abstract

Objective To analyze the muscle trophism and expression of interleukin-6 in the biceps brachii muscle of rats with incomplete cervical spinal cord injury treated with neuromuscular electrical stimulation (NMES).

Methods Adult rats underwent C5-C7 spinal cord hemisection and a 5-week NMES protocol. Trophism of the biceps brachii was assessed using muscle weight/body weight ratio and histological analysis. Interleukin-6 expression from biceps brachii was measured using the enzyme-linked immunosorbent assay technique.

Results Preservation of the biceps brachii muscle trophism was found in the NMES treated group, along with prevention of interleukin-6 level reduction.

Conclusion Spinal cord injury causes muscle atrophy and decreases interleukin-6 levels. These alterations are partially prevented by NMES. The results suggest a possible NMES action mechanism and underscore the clinical use of this therapeutic tool.

Keywords
- electric stimulation therapy
- interleukin-6
- muscular atrophy
- paralysis
- rehabilitation
- spinal cord injury

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Resumo

Objetivo Analisar o trofismo muscular e a de interleucina-6 no músculo bíceps braquial de ratas com lesão medular cervical incompleta tratados com estimulação elétrica neuromuscular (EENM).

Métodos Ratas adultas foram submetidas à hemissecção da medula espinal em C5-C7 e a um protocolo de EENM de 5 semanas. O trofismo do bíceps braquial foi avaliado pela relação peso muscular/peso corporal e análise histológica. A expressão de interleucina-6 no bíceps braquial foi medida usando ensaio de imunoabsorção enzimática.

Resultados O grupo tratado com EENM apresentou preservação do trofismo muscular, assim como prevenção da redução dos níveis de interleucina-6.

Conclusão A lesão da medula espinal causa atrofia muscular e diminui a expressão de interleucina-6. Essas alterações são parcialmente prevenidas pela EENM. Os resultados sugerem um possível mecanismo de ação da EENM. e ressaltam o uso clínico desta ferramenta terapêutica.

Palavras-chave

- atrofia muscular
- interleucina-6
- paralisia
- reabilitação
- terapia por estimulação elétrica
- traumatismos da medula espinal

Introduction

Spinal cord injury (SCI) is a clinical condition resulting mainly from trauma.[1] It disrupts the neural inputs between the spinal cord's upper and lower regions, impairing motor, sensory, and autonomous function below the injury level. Muscular paresis/paralysis is the most pronounced motor impairment after a SCI, being able to provoke an imbalance between anabolism and catabolism of several proteins, leading to protein breakdown or poor protein synthesis.[2]

This protein breakdown may lead to several health concerns, such as hormonal changes, cardiovascular diseases, overweight and muscle loss.[3,4] Moreover, the protein imbalance causes changes in muscle fiber type,[5] promoting the reduction of fatigue resistance and reduced ability to generate force,[6] cross-sectional area and muscle weight due to loss of myofibrillar proteins, organelles, and cytoplasmic content.[7–9]

The atrophy grade was pronounced in humans 1 to 4 months after SCI, with preferential type II muscle fibers atrophy. Additionally, a predominant type I fiber atrophy was seen in the later stage of the SCI (7–10 months).[10,11] Muscle atrophy and transformation of type I and II muscle fibers into type IIx leads to increased fatigue of these muscles.[12]

Similarly, animal models have shown muscle atrophy after induced SCI.[13,14] In rats, 5 days after SCI, there is a decreased muscle fiber cross-sectional area of the soleus and extensor digitorum longus muscles.[11] The cross-sectional area continues to decrease for about 3 months after injury.[12] Additionally, there is reduced muscle strength 2 days after SCI, analyzed by grip test.[15]

There is a range of strength and muscle mass gain treatments is available in clinical practice. Even so, neuromuscular electrical stimulation (NMES) is the treatment with the highest level of evidence for paralyzed and partially paralyzed muscles. Some studies have shown the benefits of electrically-induced involuntary muscle contraction in trophism and pointed out possible biological mechanisms underlying NMES in individuals with SCI[16,17] and animal models.[15,18] Recently, Freitas et al.[15] reported that in rats with SCI, the protein kinase B (Akt) pathway could be activated during involuntary muscle contraction by early application of NMES.

It is well established that the activation of Akt is the main pathway that leads to protein synthesis and hypertrophy after voluntary and functional electrical stimulation-induced muscle contraction, inducing muscle growth.[15–17] However, the involvement of the other molecules still needs to be investigated, such as the interleukin-6 (IL-6).

During and after active muscle contraction/voluntary exercise, the IL-6 is produced and released locally in muscle fiber and also released into the bloodstream, acting on muscle metabolism, glucose uptake, body heat production, promoting lipolysis and acting on the increase of muscle mass,[19] by activation of the phosphatidylinositol 3-kinase and possible activation of the Akt pathway contributing with muscle hypertrophy.[5]

Within this context, IL-6 can be considered a stimulation factor of muscular trophism. However, it is unknown if involuntary electrically-induced repeated contractions of skeletal muscle can release IL-6 and prevent atrophy following a cervical SCI. Therefore, this study aims to analyze the muscular trophism and expression of IL-6 in the biceps brachii muscle of rats with cervical SCI treated early with NMES.

Materials and Methods

Adult female Wistar rats aged 3 months were divided into the following groups: a) surgical simulation (sham; $n = 5$); b) untreated SCI ($n = 5$); and c) SCI treated with NMES ($n = 5$). The rats were anaesthetized with ketamine (87 mg/kg) and xylazine (12 mg/kg). Then, a laminectomy of the C5-C7 vertebrae and right-side spinal cord hemisection was performed using microscissors, except for the sham animals.[15,20]

In this study, we had a mortality rate of 40% for all causes. There were 8 animals lost during the surgical procedure (32%) under anesthesia, mainly due to uncontrolled hemorrhages or respiratory failure, and 2 animals were lost during the 5-week intervention (8%) due to excessive sedation and respiratory fail. Procedures have been approved by the Committee for Care and Use of Animals of the local institution (protocol: PP00745).

After the surgical procedure, the animals were kept in clean, temperature-controlled boxes with water and food. They were evaluated twice daily to identify any suffering/pain or signs of urinary infection. The manual bladder emptying procedure was performed two or three times a day, and intraperitoneal antibiotics (Baytril 65 mg/kg) were administered to prevent and treat any possible infection in the first few days after the induced SCI until the animals recovered their bladder capacity.

For treatment protocol, the Neurodyn portable device (Ibramed, Amparo, SP, Brazil) was used with animals under 5% isoflurane inhalation anesthesia, starting 48 hours after the SCI. The protocol followed a regimen of 10 minutes per session, once a day, 5 days a week, with a total therapy time of 5 weeks.[15] A trichotomy of the anterosuperior part of the right forelimb was performed to place the electrodes on the skin, aiming for the biceps brachii muscle stimulation. The electrical stimulation parameters were asymmetric biphasic pulses, pulse duration of 150 µs and stimulation frequency of 50 Hz. The intensity was regularly adjusted to produce effective muscle contraction of visualizing complete elbow flexion.

Evaluation of Muscular Trophism

After 5 weeks of treatment, the animals were euthanized, and the right biceps brachii muscle was dissected and weighed on a FA-2104 N precision scale –(Bioprecisa, Curitiba, PR, Brazil) to calculate muscle trophism measured by the ratio: muscle weight/animal weight. The muscle was sectioned longitudinally in the middle, and one part was frozen in liquid nitrogen and stored at -70°C for later biochemical analysis. The other part was separated for histological analysis.

Histological Analysis

The muscle samples were immersed in 0.1 M phosphate buffered saline (PBS) containing 4% paraformaldehyde for 18 hours. Then, the muscle was immersed in 30% nitric acid for 48 hours and transferred to a 50% glycerol solution.[7] After that, four muscle fibers from each animal were placed on histological gelatinized slides, dehydrated in increasing series of ethanol concentrations (70, 90, and 100%, for 2 minutes each), immersed in xylol for 30 seconds and covered with Permount (Fisher Chemical, Pittsburgh, PA, USA) and coverslip.

Images of the fibers were captured with a Biological O400S 17MBO500RS (Opticam, São José dos Campos, SP, Brazil) optical microscope, with 1,000x magnification coupled with a HD212, 1920 × 1080p camera (AmScope, Irvine, CA, USA) and the AmScope software (AmScope), v3.7.9229. For the qualitative analysis, three images of each fiber were randomly selected from at least two animals per group. A blind evaluator performed the descriptive analysis of these images regarding the diameter of the fibers and the length of the sarcomeres.

Biochemical Analysis

The IL-6 levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (DuoSet ELISA R&D Systems, Minneapolis, MN, USA). Muscle protein levels were estimated by interpolation from a standard curve using colorimetric measurements at 450 nm (wavelength correction = 540 nm) on an Apollo-8 LB 912 ELISA plate reader (Berthold Technologies GmbH & Co KG, Bad Wildbad, Germany). All results were expressed as pg/mg protein.

Statistical Analysis

Results of the muscle weight/animal weight ratio and IL-6 levels were analyzed by one-way analysis of variance (ANOVA). The Tukey post hoc test was used for comparisons between groups. The significance level was 95% ($p < 0.05$). All analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) software, version 20.0.

Results

NMES Prevents Muscle Atrophy

The untreated SCI group showed a reduction in muscle trophism (0.051 ± 0.002 g) when compared to the sham group (0.061 ± 0.001 g; $p < 0.05$). However, the NMES treated group (0.062 ± 0.001 g) showed similar values to the sham group, both being higher than the untreated group ($p < 0.05$; ►**Fig. 1**).

Furthermore, according to the observational analysis of the muscle fibers under the light microscope, the transverse striations of all groups are presented in series and in an organized way. However, it is possible to verify that there is a decrease in the diameter and length of the sarcomeres of the muscle fibers in both untreated and NMES treated SCI groups compared to the sham group. On the other hand, there was a

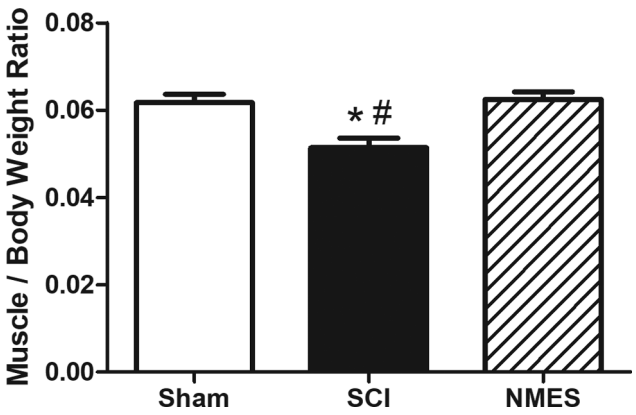


Fig. 1 Effects of NMES for 5 weeks on the biceps brachii muscle trophism after 36 days of SCI. *$p < 0.05$ compared to the sham group; and #$p < 0.05$ compared to the treated group. Values are expressed as the mean and standard error of the mean.

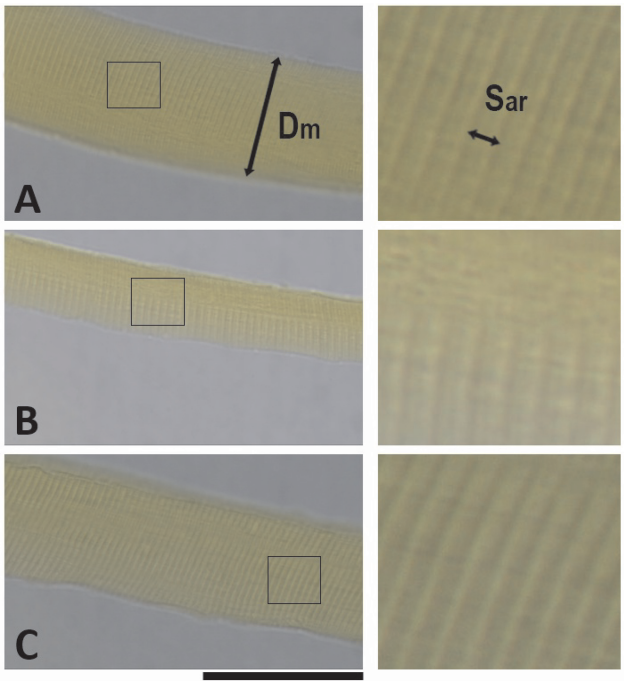


Fig. 2 Histological images from the biceps brachii muscle. (**A**) Sham group, (**B**) untreated group, (**C**) NMES treated group, (Dm) diameter, (Sar) sarcomere. The black square is shown zoomed on the side. The black bar represents a space of 10μm.

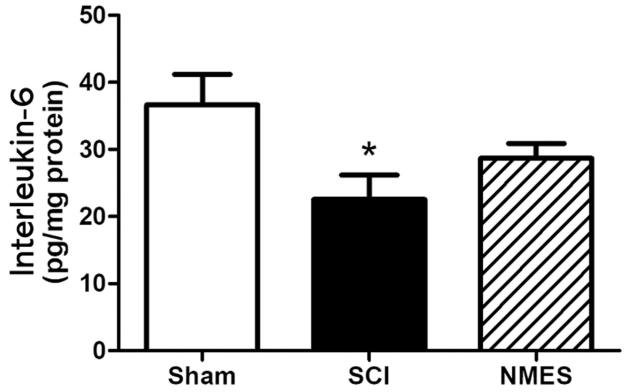


Fig. 3 Effects of 5 weeks NMES on the expression levels of the Interleukin-6 from the biceps brachii muscle after 36 days of SCI. $^{*}p < 0.05$ compared to the sham group. Values are expressed as the mean and standard error of the mean.

partial recovery in the NMES treated group, which is not as evident in the untreated group. It was observed that the diameter and length of the sarcomere in the NMES treated group were similar to the fibers of the sham group, evidencing a reduction in the loss of muscular trophism (►**Fig. 2**).

NMES Prevents the Decrease of IL-6

There was a decrease in expression of IL-6 in the untreated group (22.5 ± 3.6) compared to the sham group (36.6 ± 4.5; $p < 0.05$). However, the values of the NMES treated group (28.6 ± 2.2) were similar to both sham and untreated groups, evidencing partial preservation of the IL-6 expression in the NMES treated SCI group (►**Fig. 3**).

Discussion

This study showed that applying NMES for 5 weeks prevents biceps brachii muscle atrophy after incomplete cervical SCI. Additionally, this therapy prevents loss in IL-6 levels, a potential stimulation factor of muscular trophism. Few studies assessed muscle trophism in rodents with SCI treated with NMES.[15,18] Additionally, no other study investigated the release and role of myokines, such as IL-6, in paralyzed muscles following NMES in a SCI model.

However, previous studies have shown the effects of NMES on muscle trophism after a complete or incomplete SCI model. Butezloff et al.[18] showed that the treated group (NMES for 4 weeks) had 54% more muscle mass in gastrocnemius than the untreated group. Additionally, this same study showed a decrease in the number and size of muscle fibers in rats with complete SCI by surgical transection of the spinal cord at the T10 level. Hayashi et al.[21] showed that 4 weeks of daily percutaneous electrical muscle stimulation promoted a significant improvement in motor function and an increase of brain-derived neurotrophic factor (BDNF) levels in both muscles and in the injury site in an incomplete SCI model, with contusion injury at the T9 level in rats. Moreover, de Freitas et al.[15] evidenced an increase of about 15% in muscle trophism of the biceps brachii muscle after 5 weeks of electrical stimulation in rats in a model of incomplete SCI by a spinal cord hemisection at the C5-C7 level in rats. Our data corroborate these results, showing about 17% more muscle mass in the treated injured animals than the untreated ones.

Our study also showed a reduction in the size of sarcomeres from both untreated and treated SCI groups. However, NMES partially recovered these characteristics once they were similar to sham animals. These findings indicate that electrically induced muscle contraction can prevent muscle atrophy caused by SCI and maintain the architectural features of muscle fibers.

Several studies have shown that IL-6 released during active exercise stimulates the activation of satellite cells, leading to increased muscle mass and consequent muscle hypertrophy.[6,22] Thus, during strength training, IL-6 is produced in large amounts at the local level, being considered an essential regulator in muscle satellite cell proliferation and myonuclear agglomeration, characterizing a biochemical-signaling pattern that stimulates muscle hypertrophy.[22,23]

In our study, a decrease in local levels of IL-6 expression was found in paralyzed muscle after SCI, and involuntary muscle contraction elicited by electrostimulation for a short period could prevent this reduction. Bustamante et al.[24] showed that depolarization of skeletal muscle cells induces not only expression of IL-6 mediated by adenosine triphosphate (ATP) signaling but also cytokine secretion to the extracellular medium. Furthermore, this expression depends on an IP3-derived Ca signal,[2] acting as an early step to promote a positive IL-6 loop via the Janus kinase 2/signal

transducer and activator of transcription 3 (JAK2/STAT3) pathway.

Additionally, several studies have reported that IL-6 can interact with the Akt pathway and regulate glycogen synthesis, thus acting in muscle trophism.[8,25] Moreover, IL-6 is released within the muscle with low glycogen levels. Therefore, muscle contraction and energy consumption are essential for its regulation, which arises by activating Ca^{2+} nuclear factor of activated T cells (NFAT) and glycogen-P38 mitogen-activated protein kinase (MAPK) pathways.

It is known that type I muscle fibers are converted to type II after SCI.[12] This process has been reported within weeks in rats, and NMES can partially prevent this in the hindlimbs.[26] Our findings indicate that this prevention may have occurred in the forelimbs of rats with IL-6 participating in this process. However, some gaps remain, like the possibility of IL-6 being released by electrically induced muscle contraction inhibiting the catabolic pathway of trophism, whether there is an association between IL-6 levels and the number of type I muscle fibers, or whether another myosin participates in the process of maintaining muscle trophism and the characteristics of muscle fibers and their underlying mechanisms.

Liang et al.[27] showed that ex-vivo IL-6 released from skeletal muscles is type-specific, meaning treatment with a cytokine secretion stimulant cocktail induces a robust IL-6 release from the soleus, a typical slow oxidative muscle, and the same treatment was not able to cause a detectable release from the extender digitorum longus (a typical fast glycolytic muscle). However, as previously reported in SCI,[12] the type I muscle fibers are converted into type II, corroborating with the decreasing IL-6 in those fast glycolytic muscles. As expected, in the current study, we showed decreasing muscle IL-6 in SCI rats, and the NMES could prevent this decrease.

Additionally, other interleukins may be involved in muscle trophism beside IL-6, such as the leukemia inhibitory factor (LIF), a member of the IL–6 cytokine superfamily that has multiple biological functions. The LIF protein is secreted from human-cultured myotubes. When electrically stimulated, it causes satellite cell proliferation. It has been demonstrated that both IL-6 and LIF activate myotube mammalian target of rapamycin complex 1 (mTORC1) signaling in a time- and dose-dependent fashion.[28]

Conclusion

This study indicates that early NMES can prevent muscle atrophy and preserve the characteristics of muscle fibers in the biceps brachii after an incomplete SCI model. Moreover, the NMES partially maintained the reduction of IL-6 levels after injury in this muscle. We suggest that the NMES induced IL-6 release, possibly activating the satellite cells and increasing the phosphorylated Akt levels. However, further studies are required to elucidate the subsequent mechanisms of NMES on paralyzed muscles after SCI.

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Conflict of Interests
The authors have no conflict of interest to declare.

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Comparison of Bone Graft Preparations to Treat a Critical Bone Defect on a Rodent Animal Model

Comparação de preparações de enxertos ósseos para tratamento de defeitos ósseos críticos em um modelo animal roedor

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Abstract

Objective Although autologous bone grafting is the most widely used treatment for bone defects, the most effective preparation remains unclear. This animal study aimed to compare different autologous bone grafting preparation for the treatment of rat́s calvaria critical bone defect.

Methods 122 rats were randomly allocated into three groups: Sham, Macerated and Chopped. The specimens underwent craniotomies at the top center of their calvarias with a 7mm diameter circumferential cutter drill. The critical bone defect produced was treated or not according to the group the specimen wasallocated. The rats were euthanized at 3, 6 or 12 weeks post-op and its calvarias were analyzed by histomorphometry, bone densitometry, nanocomputed tomography (nCT), and biomechanical tests.

Results The histomorphometry analysis showed the highest percentage of fulfillment of the critical bone defect in the chopped and macerated group when compared to sham. The densitometry assessment evidenced higher bone mass at all endpoints analysis ($p < 0.05$) in the chopped group. The nCT data exhibited an expressive increase of bone in the chopped group when compared with the sham and macerated groups. The biomechanical tests exhibited highest values of deformation, maximum force, and relative stiffness in the chopped group at any time of euthanasia ($p < 0.05$).

Conclusions Our experimental work showed that chopped bone grafting preparation exhibited significant better outcomes than macerated in the treatment of a critical bone defect in rat́s calvaria.

Keywords
- bone and bones
- bone regeneration
- bone transplantation
- models, animal

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Resumo

Objetivo Embora enxertos ósseos autólogos sejam o tratamento mais utilizado para defeitos ósseos, a preparação mais eficaz ainda é obscura. Este estudo animal teve como objetivo comparar diferentes preparações de enxerto ósseo autólogo para o tratamento de defeito ósseo crítico no crânio de ratos.

Métodos No total, 122 ratos foram alocados aleatoriamente em três grupos: Simulado, enxerto macerado e enxerto picado. Os espécimes foram submetidos a craniotomias no centro superior do crânio com broca de corte circunferencial de 7 mm de diâmetro. O defeito ósseo crítico produzido foi tratado ou não de acordo com o grupo de alocação do animal. Os ratos foram eutanasiados às 3, 6 ou 12 semanas após a cirurgia e seus crânios foram analisados por histomorfometria, densitometria óssea, nanotomografia computadorizada (nTC) e testes biomecânicos.

Resultados A análise histomorfométrica mostrou maior percentual de preenchimento do defeito ósseo crítico no grupo picado e macerado em comparação ao simulado. A avaliação densitométrica evidenciou maior massa óssea em todos os desfechos de análise ($p < 0,05$) no grupo picado. Os dados de nTC revelaram um aumento ósseo expressivo no grupo picado em comparação aos grupos simulado e macerado. Os testes biomecânicos mostraram maiores valores de deformação, resistência máxima e rigidez relativa no grupo picado em qualquer momento da eutanásia ($p < 0,05$).

Conclusões Nosso estudo mostrou que a preparação de enxerto ósseo picado gerou resultados significativamente melhores do que os enxertos macerados no tratamento de defeitos ósseos críticos no crânio de ratos.

Palavras-chave

- modelos animais
- osso e ossos
- regenaração óssea
- transplante ósseo

Introduction

The incidence of bone defects is increasing and demanding solutions.[1–3] These injuries have profound economic and clinical impacts, treatment outcomes are limited by high rates of complications.[4–6] Autologous bone grafting is the most widely used treatment for bone defects as it is easy to obtain, combines properties and does not induce immune responses nor transmit infections.[7–9] However, the most effective autologous bone graft technique is uncertain.[10,11]

A critical size bone defect is an orthotopic defect that will not heal without intervention[12,13] or the smallest size of tissue defect that will not completely heal over a lifetime.[12,14] In the rat calvaria model, defects larger than five millimeters are considered critical.[15–17]

The keystone to the preclinical development of translational technologies is the reliable reproducibility, analogues to the clinical condition they are investigating in animal models.[12,18] We developed an animal based on a rat calvaria critical bone defect treated with different bone graft techniques. Bone regeneration was evaluated in different endpoint periods by histomorphometry, nCT, bone densitometry and biomechanical tests.

This study compared distinct autologous local bone graft treatment techniques used to treat a rat calvaria critical bone defect.

Materials and Methods

The work was approved by our institution's animal ethics committee under protocol number CEUA: 120/2019

Seven-week-old male Wistar rats weighing 200 g ($\pm$ 10 g) were obtained from the central animal facility of our institution and housed in individual cages with environmental enrichment in a room with controlled conditions of humidity (55-60%), temperature (23 $\pm$ 1°C), and an artificial light/dark cycle of 12 hours. The experimental procedures started after the specimens reached maturity with 300 g ($\pm$ 10g) and ten-weeks of age.

One hundred and eight (108) rats were randomly divided into three groups ($n = 36$ per group): (1) Sham: rats with calvaria critical bone defect (7mm in diameter); (2) Macerated: rats with calvaria critical bone defect treated with macerated local autologous bone graft; (3) Chopped: rats with calvaria critical bone defect treated with chopped local autologous bone graft. The experimental procedures (initial surgeries and euthanasia surgeries) were carried out at the same time, surgeon and conditions to minimize biases.

All surgical instruments were sterilized and cooled down to room temperature (23°C). The operating table and instruments were sterilized with ethanol at a 70% concentration.

All rats were anesthetized by intramuscular (IM) injection of Cetamin® by Syntec (Ketamine hydrochloride 10%, 60 mg/kg) and Xylazin® by Syntec (Xylazine hydrochloride 2%,

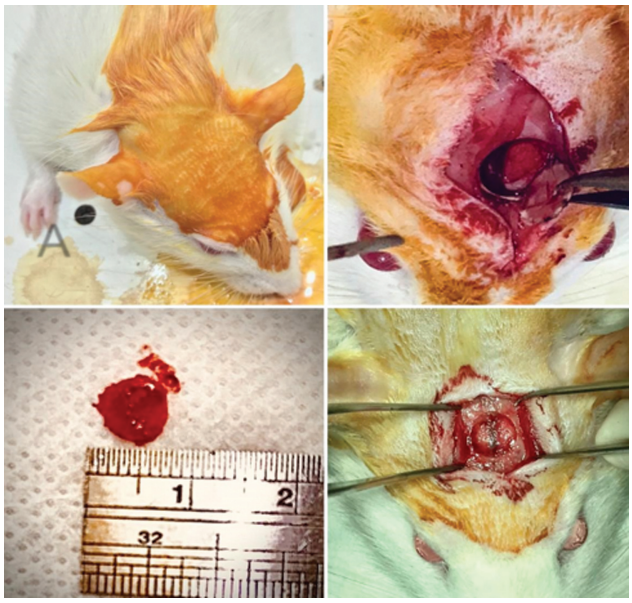


Fig. 1 Technical steps of the initial surgery.

7.5 mg/kg) and shaved from the bridge of the snout to the distal end of the calvaria. A swab was used to remove hair trimmings and Lacrilube® by Allergan

Inc. applied to each eye. The calvaria was painted with iodine. A sterile surgical field was placed over with a round opening above the calvaria.

A 1.5cm longitudinal incision from superficial skin down to the periosteum over the calvaria, from the nasal bone to caudal to the middle sagittal crest or bregma. The periosteum was divided in half with the scalpel through a sagittal midline elevating it from the skull. A self-retaining retractor spreads the soft tissues and exposes the underlying bone.

A targeted area centered at the intersection of the two calvaria midlines anteroposterior, side to side was drawn. The drill Strong® Micro Motor 210/105L and Zipperer® trephine (7mm total diameter) attached scores the top of the calvaria at 1500 rpm, with sterile saline drops (1 every 2 seconds) to prevent thermal injury. The drill was handled with gentle pressure against the skull surface to produce the defect. An elevator was used into the osteotomy margin completing the defect. The same elevator was used to lift the cylinder of the bone, releasing the dura from the underside of it and pulling the bone out (►**Fig. 1**).

The defect was washed with saline to remove debris before grafting (►**Figs. 2** and **3**). The periosteum was closed using a running suture and subsequently the skin using simple gut suture. The rats were placed under observation for any sign of purposeful movement and then transferred to normal husbandry cages.

The daily postoperative care was composed of a health assessment including wound examination, prevention of distress, neurological observation and optimized analgesia. All specimens were treated with tramadol (25 mg/kg) subcutaneously twice daily for 3 days for postoperative pain. The cages were cleaned, and water / food changed three times a week. Rats had their body masses registered routinely once a week. The groups were followed postoperatively and each of them were separated into three subgroups according to the endpoint analysis: 3, 6 and 12 weeks post-surgery.

The rats in all the three groups were sacrificed in three different moments: 3, 6 and 12 weeks post operatively. The euthanasia method used was intramuscular injection of anesthetic overdose of Cetamin® and Xylazin®.

Similar initial procedure steps were taken with a slightly longer (2.5cm) surgical access centered in the previous incision. A rectangular segment of the rat calvaria was delimited and cut with a serrated disc SDT® fine granulometry 19/0.15mm at 9000 rpm attached to the same Strong® Micro Motor 210/105L. The calvaria fragments were collected containing the critical bone defect surrounded by original skull bone sized average 15.01 × 11.85 mm (►**Fig. 4**).

A total of 58 samples were designated to histology and were fixed in cold 4% paraformaldehyde while the other 57 samples were embedded in alcohol 70% recipients for bone densitometry assessment, ntomography and mechanical tests.

The routine of decalcification with cold 10% EDTA, progressive dehydration with crescent alcohol concentrations, clearing in xylene with its 3 exchanges and framing in paraffin were performed at the Histology Lab of our

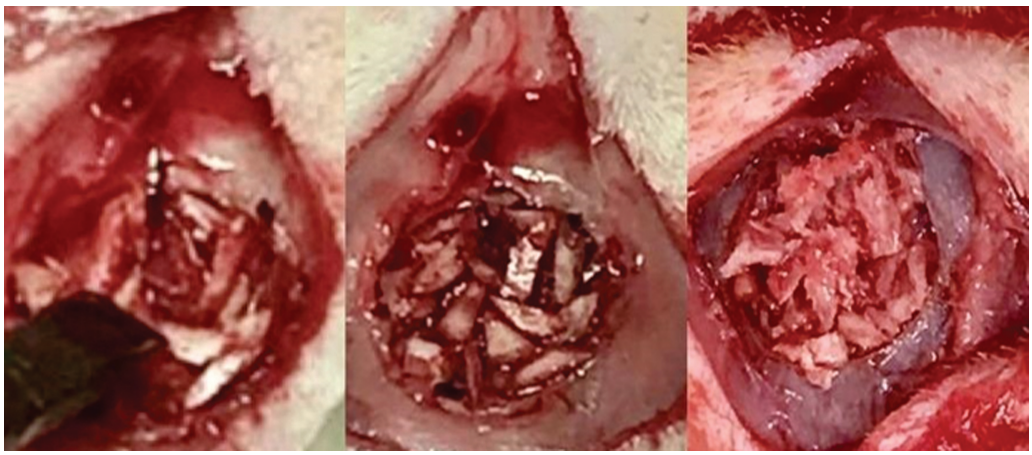


Fig. 2 Macerated bone graft preparation filling the critical defect.

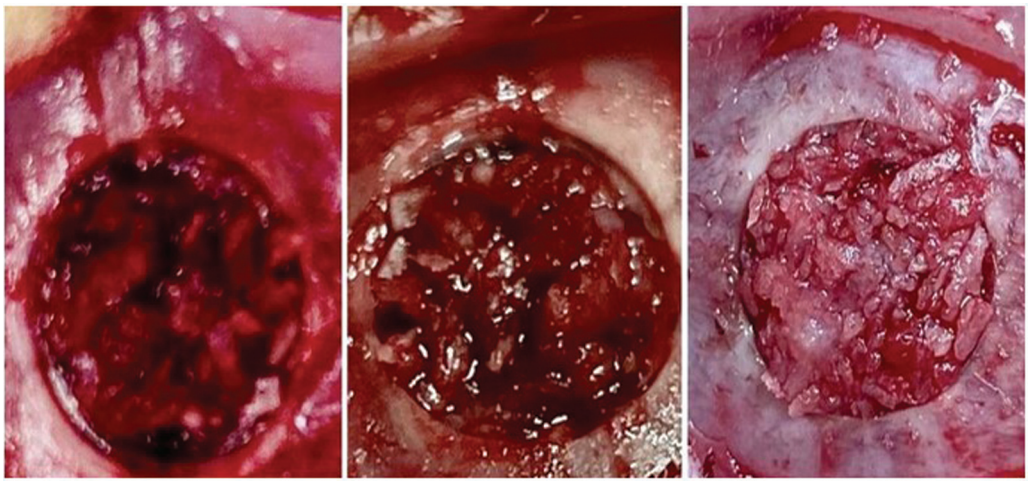


Fig. 3 Chopped bone graft preparation filling the critical defect.

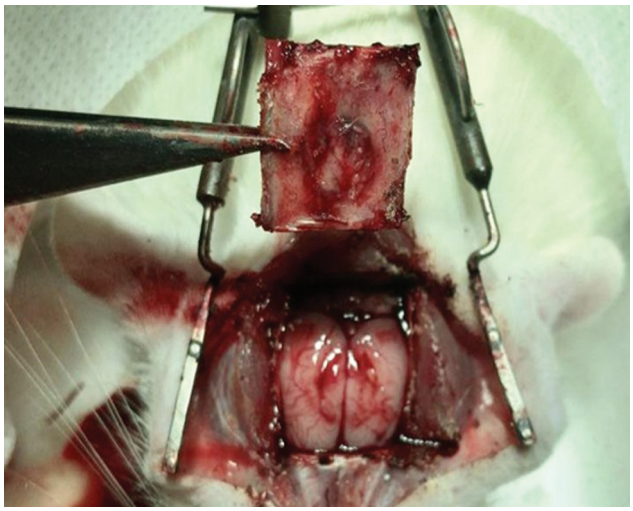


Fig. 4 Calvarial rectangle obtained after euthanasia.

Institution. When embedded in paraffin, 5mm sections were obtained and placed on charged histology laminas (Manco Inc., USA). Staining was performed with hematoxylin and eosin (HE) on coronal sections. A bright field microscopy (Axiovert; Carl Zeiss®, Germany) was used to explore those laminas. A CCD camera (AxioCam MRc; Carl Zeiss®, Germany) captured images with many different magnifications for posterior analysis (►**Fig. 5**). A total of 500 histology laminas were produced with these 58 samples.

Bone densitometry analysis was performed at the calvaria samples containing the critical bone defect (total of 57 samples) by Dual-energy X-ray absorptiometry (DXA) using a Lunar® DPX-IQ densitometer (Lunar®; software version 4.7e, GE Healthcare®, United Kingdom). A ROI (region of interest) of approximately 49 mm^2 was used to assess the new bone formation. Bone mineral density (BMD, g/cm^2) and bone mineral content (BMC, g) were measured as protocol.

The DXA samples were then organized and scanned by the *Nano tomograph Phoenix v|tome|x s – General Electric®* (►**Fig. 6**). Images of each specimen were reconstructed with specific software (*Dataviewer 1.5.1.2 64bit - SkyScan® Bruker®*) and analyzed by CTAn (*CTAn v.1.15.4.0 64bit - SkyScan® Bruker®*) to determine morphometric parameters in selected regions of interest (ROI). All morphometric parameters are in accordance with the ASBMR nomenclature: Bone Volume (BV), Percent Bone Volume (BV/TV), Bone surface / Volume ratio (BS/BV), Structure model index (SMI), Trabecular Thickness (Tb.Th), Trabecular number (Tb.N), Trabecular separation (Tb.Sp), Total porosity percent (Po tot) and Connectivity density (Conn.Dn).

The 57 calvaria samples were mechanically stressed in a perforation pushout test. A universal testing machine was used for critical bone defect stress tests with a 50N load cell

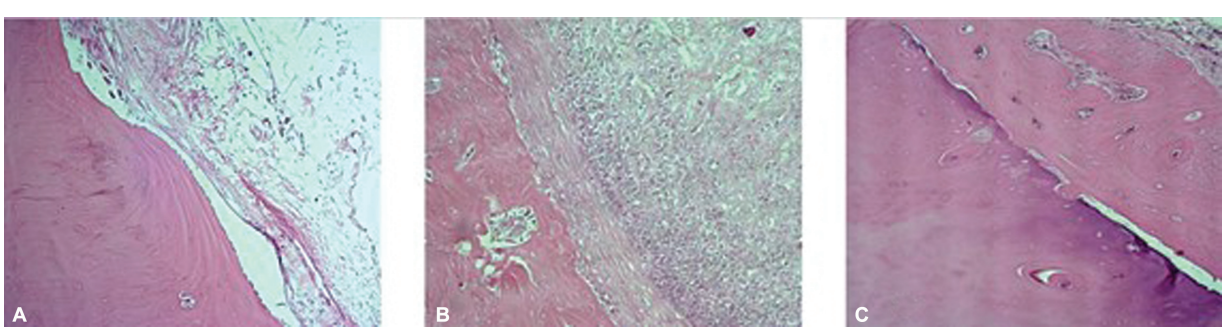


Fig. 5 Photomicrographs: 1A sham, 1B Macerated e 1C Chopped (12 weeks post-op).

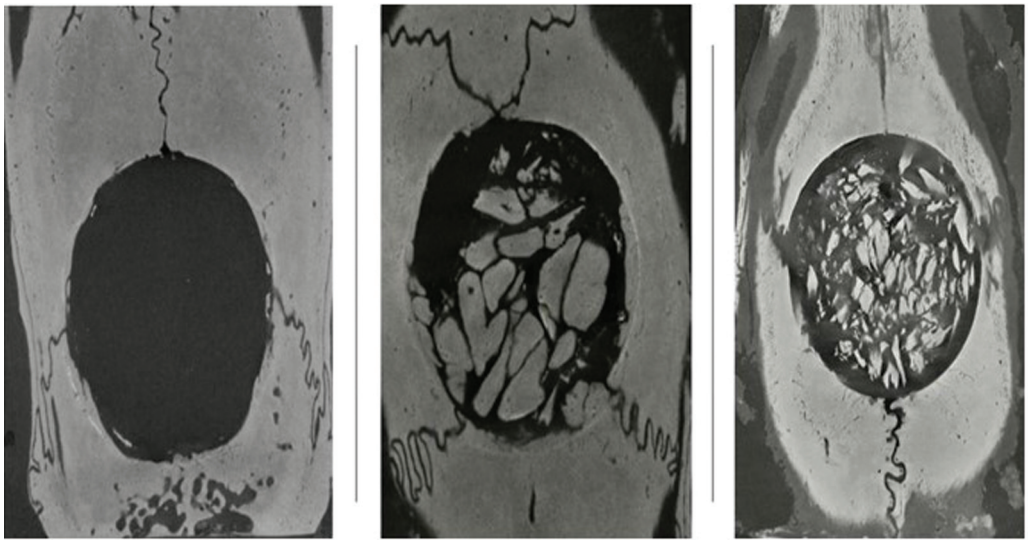


Fig. 6 Nanotomographic appearance of the sham, chopped and macerated groups.

(Trd 28–EMIC DL 10000®). The settings of the tests were: 1mm/min progression speed, 1N pre-load and 30s accommodation time. The bone sample was positioned on a custom-made metallic support with an 8mm diameter circumferential hole centered and aligned with the critical bone defect center. A cylindrical metal pusher with 7mm diameter also centered and aligned with the bone defect and the support circumferential hole center gradually descended to contact the samples, preload and then gradually stress the with or without graft until complete disruption (►**Fig. 7**). Using the Tesc 3.04 software script, raw data were filtered and measured maximum force, deformation, relative stiffness and elasticity maximum strength. The samples were hydrated with saline during the tests.

Hypothesis tests were performed to analyze the variation on bone regeneration across different bone engraftment techniques compared to the sham group. All variables were tested for normality based on visual histogram and the Shapiro-Wilks test. Descriptive statistics used the median and median absolute deviation (MAD) as measures of central tendency and dispersion, respectively. We applied the nonparametric KruskalWallis test followed by the post hoc Dunn for Kruskal-Wallis multiple comparison. The Spearman rank correlation index was calculated to analyze the relationship between multiple parameters obtained by nCT, bone densitometry and the stress test. All statistical analyses were performed in R for Linux/GNU version 4.1.0 and the p value < 0.05 was considered statistically significant.

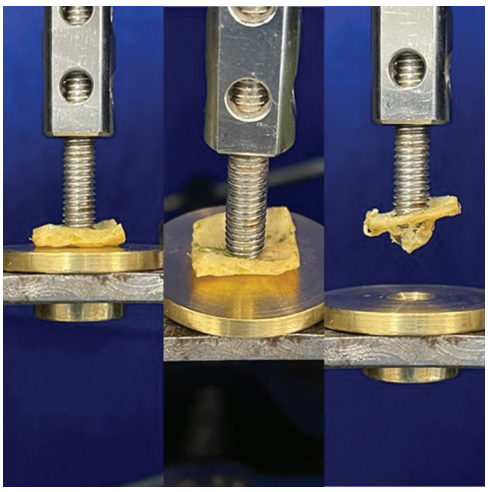


Fig. 7 Mechanical testing from different angles and in detail.

Results

A qualitative histological analysis evidenced a higher proportion of new bone formation in the critical bone defect of the grafted groups when compared to the shams. Furthermore, the chopped group is suggested to induce the uppermost new bone formation of all under bright field microscopy qualitative analysis.

In accordance, our quantitative analysis proved a higher percentage of new bone formed in the Chopped and Macerated groups when compared to Sham ($p = 0.008$). Although the Chopped group showed the highest percentages of new bone formation, the difference with the Macerate group was not statistically relevant ($p = 0.1$) (►**Fig. 4**). We understand this observed trend deserves attention.

We observed a significant overall increase in BMD by comparing the different endpoint periods ($p < 0.001$) (►**Table 1**). At 3 weeks after the procedure, the median BMD was 0.01 in the sham group (MAD = 0.001), 0.026 (MAD = 0.001) in the macerated group, and 0.041 (MAD = 0.0007) in the chopped group ($p = 0.0004$). The differences persisted at 6 and 12 weeks ($p = 0.0004$ and $p = 0.0002$, respectively). In the sham group the median BMD was 0.0085 (MAD = 0.0007) and 0.03 (MAD = 0.001) at 6 and 12 weeks, respectively. In the macerated group the median BMD was 0.0185 (MAD = 0.0007) and 0.04 (MAD = 0.001), and in the chopped group the median BMD was 0.031 (MAD = 0.002) and 0.054 (MAD = 0.001) at 6 and 12 weeks, respectively (►**Fig. 8**). The post hoc test for pairwise

Table 1 Densitometry statistics summary

Variable	Weeks	Groups	Median	MAD	P Value
BMC	3w				0.00038150651248
		Sham	0.002	0	
		Chopped	0.009	0.0007413	
		Macerated	0.005	0	
BMC	6w				0.00067991117923
		Sham	0.0015	0.0007413	
		Chopped	0.0055	0.0007413	
		Macerated	0.003	0	
BMC	12w				0.00019298618864
		Sham	0.003	0	
		Chopped	0.015	0.0014826	
		Macerated	0.008	0.0014826	
BMD	3w				0.00048367583690
		Sham	0.0105	0.0014826	
		Chopped	0.0415	0.0007413	
		Macerated	0.026	0.0014826	
BMD	6w				0.00046850172588
		Sham	0.0085	0.0007413	
		Chopped	0.0315	0.0022239	
		Macerated	0.0185	0.0007413	
BMD	12w				0.00020323763567
		Sham	0.03	0.0014826	
		Chopped	0.054	0.0014826	
		Macerated	0.04	0.0014826	

BMC, Bone mass content; BMD, Bone mineral content.

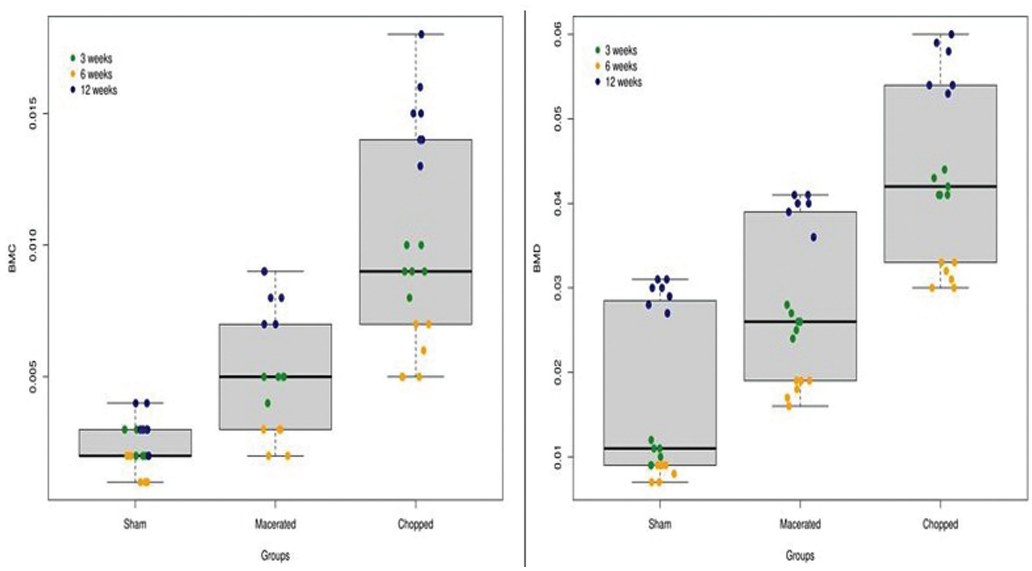


Fig. 8 Bone mineral concentration (BMC) and bone mineral density (DMO) in groups and times.

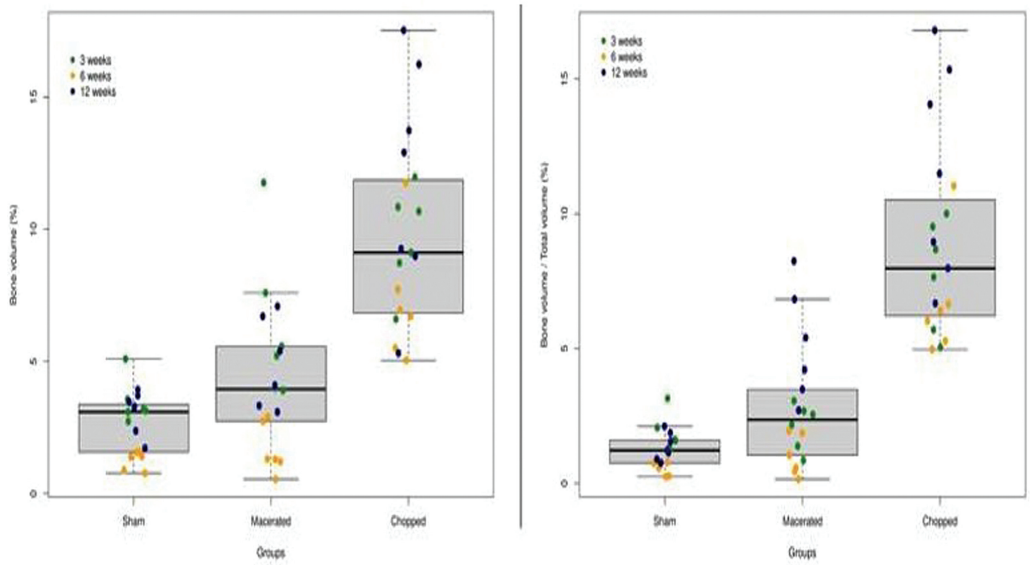


Fig. 9 Bone Volume (BV) and Bone Volume by Total Volume (BV/TV).

comparison has demonstrated the increment in bone regeneration comparing the chopped group with the sham.

We analyzed the nCT parameters across the experimental groups. The BV and BV/TV estimate the volume of bone regenerated in the critical bone defect area. We observed a significant overall bone regeneration in chopped and macerated groups compared to the sham group ($p < 0.0001$) (►**Fig. 9**). The median BV in the sham group at 3, 6 and 12 weeks were 1.4 (MAD= 0.2), 3.1 (MAD= 0.35) and 3.3 (MAD= 0.6), respectively. In the macerated group the median BV at 3, 6 and 12 weeks were 1.3 (MAD= 0.6), 5.4 (MAD= 2.1) and 4.7 (MAD= 2.3) (►**Table 2**).

We analyzed the correlation between the BMD and microstructural parameters obtained by nCT and detected a high positive correlation with BV, BV/TV and Tb.N (rho= 0.77, rho= 0.82 and rh0= 0.81, respectively), and a strong anti-correlation with trabecular separation and total porosity (rho= -0.73 and rho= -0.82, respectively).

The biomechanical analysis was performed to infer the behavior of the new bone formation under a stress test. We measured the maximum force, the deformation, the relative stiffness and the elasticity maximum strength for every calvaria specimen. We observed that the calvaria specimens from rats subjected to the engraftment with chopped bone were significantly more resistant to the stress (►**Table 3**) ($p < 0.0001$ for all variables). The overall median (MAD) maximum force, the deformation, the relative stiffness and the elasticity maximum strength in the chopped group was 36 (19.9), 2.6 (0.8), 12.5 (5.5) and 39.1 (20.5), respectively, compared to 10.1 (4), 1.39 (0.3), 6.8 (3) and 6.8 (2.8) in sham and 13.1 (9.2), 1.9 (1), 4.7 (3) and 14.6 (11) in macerated groups (►**Fig. 10**).

Discussion

Bone defects represent relevant challenges to Orthopedists.[1–4,19,20] The treatments for critical bone defects often result in complications.[4–6] There is also an association with prolonged recovery decreasing quality of life.[21]

The success of bone grafting is limited by many factors such as remodeling capacities of the host, material itself, surgical technique[22] and even how the graft is handled.[23,24] Autografting is the most widely used treatment for bone defects, but it remains unclear what preparation technique will induce the greater regeneration.[8,24,25] It is well stablished that graft dimensions influence the outcome of treatment[26–28] and the calvaria has already been described as a donor site[29] but, to the best of our knowledge, there was not a study comparing macerated and chopped local autologous bone graft preparations.

From macroscopic and clinical to microstructural level, our data demonstrated the higher efficiency of chopped bone graft preparation at inducing bone regeneration.

Macroscopically, we detected higher bone mass (density and content) in the Chopped group when compared to the Sham and Macerated at all endpoints: three, six and twelve-weeks following surgery. Likewise, our mechanical tests also confirmed the higher effectiveness of chopped bone graft at inducing bone regeneration with stronger properties. As of note, the chopped group exhibited newly formed bone with higher maximum force, stiffness, and deformation, which demands heavier loads prior to failure and has a higher modulus of elasticity. Histologically, our qualitative analysis suggests a much higher percentage of woven bone formation and critical bone defect fulfillment in the Chopped samples than in the Macerated group, which could be confirmed microscopically by our nCT assessment. The Chopped group exhibited a remarkable osteogenic effect at increasing the bone formation-related parameters of bone volume and fraction, connectivity density, trabecular thickness and number, concomitant with decreases in resorption-related parameter; bone surface/volume ratio, structure model index, trabecular separation and porosity.

Table 2 Nano tomography statistics summary

Variable	Weeks	Group	Median	P Value
BV	3w			0,002338
		Sham	3,166115	
		Chopped	9,8977	
		Macerated	5,39414	
BV	6w			0,0033992
		Sham	1,39563	
		Chopped	6,83119	
		Macerated	1,30313	
BV	12w			0,0013393
		Sham	3,29243	
		Chopped	12,90203	
		Macerated	4,74866	
BV/TV	3w			0,0030956
		Sham	1,60475	
		Chopped	8,1638	
		Macerated	2,360649	
BV/TV	6w			0,0029369
		Sham	0,622355	
		Chopped	6,21231	
		Macerated	0,812585	
BV/TV	12w			0,0003588
		Sham	1,22118	
		Chopped	11,49151	
		Macerated	4,80795	

BV, Bone Volume; TV, Toal Volume.

Table 3 Biomechanical test statistics summary

Variable	Weeks	Grupo	Median	P Value
Maximum strenght	3w			0,002338
		Sham	8,375	
		Chopped	34,54	
		Macerated	13,06	
Maximum strenght	6w			0,006104
		Sham	11	
		Chopped	36,77	
		Macerated	10,92	
Maximum strenght	12w			0,003498
		Sham	10,56	
		Chopped	35,99	
		Macerated	14,075	

(*Continued*)

Table 3 (*Continued*)

Variable	Weeks	Grupo	Median	P Value
Deformation	3w			0,041776
		Sham	1,44	
		Chopped	2,415	
		Macerated	2,965	
Deformation	6w			0,010158
		Sham	1,32	
		Chopped	2,565	
		Macerated	1,39	
Deformation	12w			0,014718
		Sham	1,13	
		Chopped	2,64	
		Macerated	2,185	

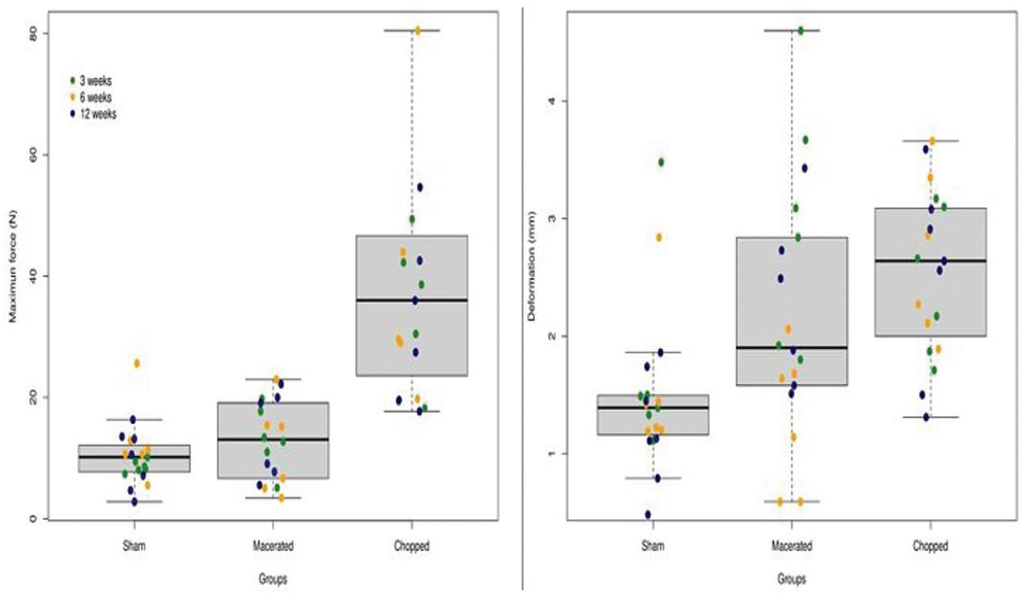


Fig. 10 Maximum force (N) and deformation (mm).

It is important to highlight that models of rat calvaria critical bone defect can be used for the study of bone regeneration and biomaterials before considering larger animals or future potential human applications.[30] The first rat calvaria model of a bone defect was described in 1973 by Freeman and Turnbull but only accomplished by Takagi and Urist in 1982. We confirmed the efficacy of our model as no spontaneous bone regeneration occurred in the Sham group at any endpoint.

Among the limitations of our study, we may include a lack in elucidating the mechanisms leading to a better bone regeneration due to chopped bone graft preparation. Although it was not the purpose of our study, future studies should include molecular assessment to expand our critical capacity and data scientific production, as well as to target potent pharmacological therapies to further induce regeneration. The comparison among local autologous bone graft, distant autologous bone graft, bone substitutes adjuvants should be further investigated in the bone healing processes to reach the best available critical bone defect treatment.

Conclusion

This study evidenced that different techniques to prepare and locally treat bone defects may play an important role at inducing bone regeneration. We used an animal model of bone defect that did not spontaneously heal throughout the experiment. Conversely, our protocols for local autologous bone graft induced bone regeneration in this animal model. The chopped bone graft exhibited newly formed bone with higher mass, improved microarchitecture and better mechanical integrity than the newly formed bone followed by macerated bone graft.

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Conflict of Interests
The authors declare no conflict of interest.

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Bicruciate Reconstruction with Bilateral Hamstring Autografts: Technique and Functional Results

Reconstrução dos ligamentos cruzados anterior e posterior com autoenxertos bilaterais dos isquiotibiais: Técnica e resultados funcionais

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Abstract

Objective The purpose of this study was to evaluate the clinical and functional results of simultaneous reconstruction of the ACL and PCL with bilateral hamstring autografts. We hypothesized that this reconstruction technique results in less morbidity and has similar results to the ones published in the previous literature.

Methods Eighteen patients with bicruciate lesions were selected and treated by arthroscopic surgery with autologous hamstring tendons in a single-stage procedure. The thicker semitendinosus tendon (ST) and the two gracilis tendons (G) were used for a 6-strand PCL reconstruction. The thinner ST was used for a 3-strand ACL reconstruction. The average patient age at surgery was 31 years, and the minimum follow-up was 2 years. Function of the operated knee was evaluated according to the Lysholm scale. Anterior knee laxity was examined with a KT-1000 arthrometer. Posterior laxity was evaluated using stress radiographies.

Results Statistically significant improvements were found for all three measurements ($p < 0.001$). Knee function by the Lysholm score increased from 43.8 ± 4.1 to 89.9 ± 3.8 post-surgery. The average anterior knee laxity improved from 5.2 +-0.8 mm initially to 2.4 +- 0.5 mm post-surgery. The posterior translation of the tibia relative to the femur decreased from 10 ± 3.4 mm to 3 ± 1.6 mm post-surgery. No patient showed loss of motion in extension or knee flexion.

Conclusion The simultaneous bicruciate reconstruction with bilateral hamstring autograft is a valuable option to achieve good functional outcomes and ligamentous stability.

Keywords
- anterior cruciate ligament
- anterior cruciate ligament reconstruction
- hamstring tendon
- joint instability
- knee dislocation
- posterior cruciate ligament
- posterior cruciate ligament reconstruction

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Resumo

Objetivo O objetivo deste estudo foi avaliar os resultados clínicos e funcionais da reconstrução simultânea do ligamento cruzado anterior (LCA) e ligamento cruzado posterior (LCP) com autoenxertos bilaterais de isquiotibiais. Nossa hipótese é que esta técnica de reconstrução gera menor morbidade e tem resultados semelhantes aos publicados na literatura anterior.

Métodos Dezoito pacientes com lesões em LCA e LCP foram selecionados e tratados por cirurgia artroscópica com tendões isquiotibiais autólogos em procedimento único. O tendão semitendinoso (ST) mais espesso e os dois tendões do músculo grácil (G) foram usados para a reconstrução do LCP com seis fios. O ST mais fino foi usado para reconstrução do LCA com três fios. A média de idade dos pacientes à cirurgia foi de 31 anos e o acompanhamento mínimo foi de 2 anos. A função do joelho operado foi avaliada de acordo com a escala de Lysholm. A lassidão anterior do joelho foi examinada com um artrômetro KT-1000. A lassidão posterior foi determinada por meio de radiografias de estresse.

Resultados Melhoras estatisticamente significativas foram observadas nas três medidas ($p < 0{,}001$). A função do joelho pelo escore de Lysholm aumentou de $43{,}8 \pm 4{,}1$ para $89{,}9 \pm 3{,}8$ após a cirurgia. A lassidão anterior média do joelho melhorou de $5{,}2 \pm 0{,}8$ mm para $2{,}4 \pm 0{,}5$ mm após a cirurgia. A translação posterior da tíbia em relação ao fêmur diminuiu de $10 \pm 3{,}4$ mm para $3 \pm 1{,}6$ mm no período pós-operatório. Nenhum paciente apresentou perda de movimento em extensão ou flexão do joelho.

Conclusão A reconstrução simultânea do LCA e do LCP com autoenxerto bilateral dos isquiotibiais é uma opção valiosa para obtenção de bons resultados funcionais e estabilidade ligamentar.

Palavras-chave

- instabilidade articular
- ligamento cruzado anterior
- ligamento cruzado posterior
- luxação do joelho
- reconstrução do ligamento cruzado anterior
- reconstrução do ligamento cruzado posterior
- tendões dos músculos isquiotibiais

Introduction

The term "bicruciate" simultaneously refers to the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) of the knee. Bicruciate lesions (BL) are rare and associated with knee dislocation.[1] Most of these injuries occur as a result of a high-energy mechanism, such o motor vehicle accidents and animal tramplings.[2] Knee dislocations can also occur as a result of a low-energy mechanism, such as hyperextension in a sports-related trauma.

Although the ACL has a poor biological potential for healing, the PCL has a more favorable environment for healing due to a well vascularized environment that allows to improve the regenerative process and restore its functional stability.[3] Other anatomical differences between the ACL and the PCL are morphological aspects, such as width and thickness between the intact PCL (13 mm) and ACL (10 mm), which can be associated with functional impairments after BL.

The best choice for treatment after BL remains unclear, but surgical procedures appear to provide more favorable clinical benefits.[4] Despite the availability of several operative options, some controversies remain unclear, such as time for surgery, single versus double-stage, open versus arthroscopic surgery, single versus double tunnel, and graft choice.

For simultaneous ACL and PCL reconstruction, different graft types may be considered, such as allografts, autografts, synthetics, or any combination thereof. There is no consensus about the best graft type.[5,6] However, autografts have been recommended for high-demand sports athletes and young patients. Meanwhile, the hamstring autograft has gained popularity for ACL reconstruction. The small diameter size of the hamstring autograft has been deemed a risk factor for early failure after ACL reconstruction.[7] One study with 20 patients with chronic ACL and PCL deficiency who underwent simultaneous single-stage arthroscopic reconstruction showed good knee joint function after the initial follow-up period at 24-month.[8]

We conducted this study using the thinnest semitendinosus tendon (ST) for a 3-strand ACL graft and the two gracilis tendons (G) and the thickest ST for a 6-strand PCL graft to simultaneous ACL/PCL arthroscopic reconstruction. We prefer to use autografts because we do not have easy access to allografts. The purpose of this study was to evaluate the clinical and functional results of simultaneous reconstruction of the ACL and PCL with bilateral hamstring autografts. We hypothesized that this reconstruction technique results in less morbidity and has similar results to the ones published in the previous literature.

Materials and Methods

This prospective study was conducted from May 2016 to May 2019 after approval by the ethics committee of our institution. During this period, there were 166 cases of multiligament knee injuries. Of these, eighteen patients were classified with complete bicruciate injury. After

diagnosis, all participants used non-articulated braces for 6 weeks and underwent a rehabilitation protocol for at least 3 months for functional improvement and range of motion gain.

The diagnosis was made by an experienced single orthopedic surgeon knee specialist and confirmed with magnetic resonance by an experienced musculoskeletal radiologist. The preoperative outpatient evaluation consisted of instability tests[9] and X-rays under stress. For PCL injury, these X-rays were taken while the patient kneeled on the affected limb[10] to evaluate the posterior displacement of the tibia relative to the femur. We considered complete PCL injuries where the distance of the line drawn parallel from the posterior cortex of the tibia to the most posterior point of the Blumensaat line was greater than or equal to 8 mm.[11]

The inclusion criteria for participants were: complete bicruciate injury, symptomatic functional instability. The exclusion criteria were: associated fractures, presence of symptomatic peripheral instability, confirmed by physical examination and stress X-rays, patients with flexion contracture $>$10 degrees and flexion $<$90 degrees, presence of angular deviation in the coronal plane, and presence of knee osteoarthritis greater than Ahlbäch grade 2.[12] All included patients agreed to participate and authorized the publication of surgery photographs, if necessary.

Patients were followed for at least 24 months. Knee function was assessed by the Lysholm scale and return to sports activities. Anterior stability was assessed using the KT-1000 arthrometer. Posterior translation was assessed by stress radiographs pre and with 24 months postoperative. Additionally, we evaluated the thickness graft, and complications related to the surgical procedure and postoperative.

Its important to note that when calibrating the KT-1000, we used the "*step off*" of the contralateral knee joint line as a reference.

The procedure began by arthroscopy through the anteromedial (AM) and anterolateral (AL) portals. A leg holder was used, keeping the popliteal fossa free from compression. The surgeon confirmed complete bicruciate injury. The integrity of both collateral ligaments was confirmed through dynamic maneuvers.

After the confirmed diagnosis, the surgeon continued with the hamstring harvest of the ST and G bilaterally. To make a thicker PCL than the ACLThe two grafts were prepared as follows: After measured, the thicker ST tendon and the two G tendons were separated and doubled up once, yielding a 6-strand graft for PCL reconstruction (►**Fig. 1**); the remaining ST was folded 2 times onto itself, leaving a 3-strand graft for ACL reconstruction (►**Fig. 2**).

The arthroscopy continued by treating possible chondral and meniscal injuries. The ACL and PCL anatomical femoral points were determined at their respective femoral condyles and tibial origins.[13,14] Whenever possible, the original footprints were used for the tunnel position. With the camera through the AM portal in the intercondylar background under direct visualization, the posteromedial (PM) portal was made 2 cm above the joint line. With this technique, we captured a better view of the posterior aspect of the proximal tibia.

The surgeon drilled the PCL and ACL tunnels backward so that the leakage of saline solution through them did not obscure the intra-articular view due to the pressure decrease.

With the camera through the PM portal and the PCL tibial guide through the AM portal, the tibial tunnel was drilled

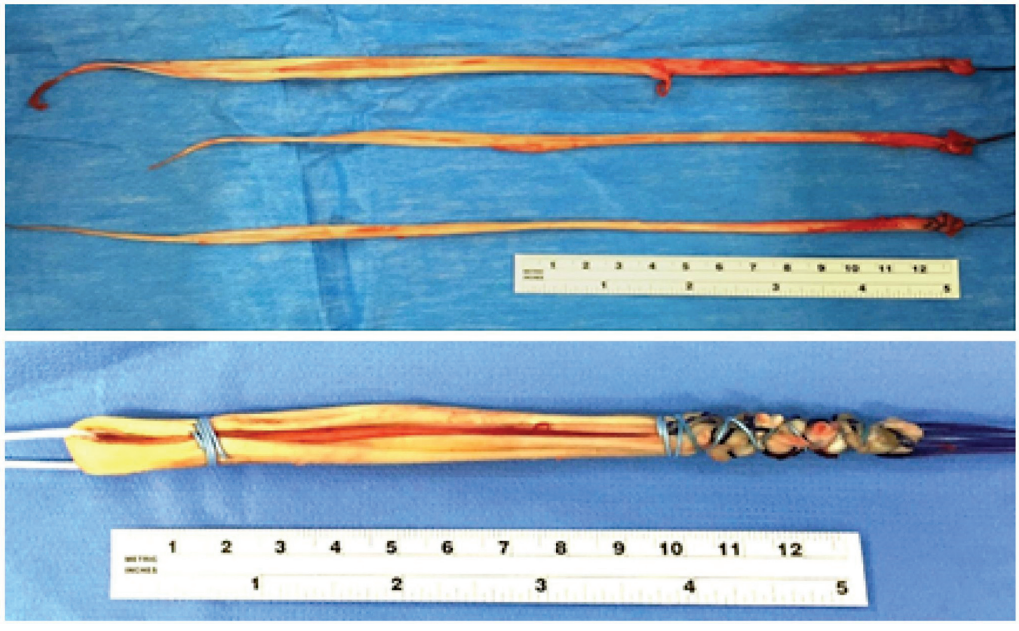


Fig. 1 The 6-strand PCL graft with the thicker semitendinosus tendon and two gracilis tendons.

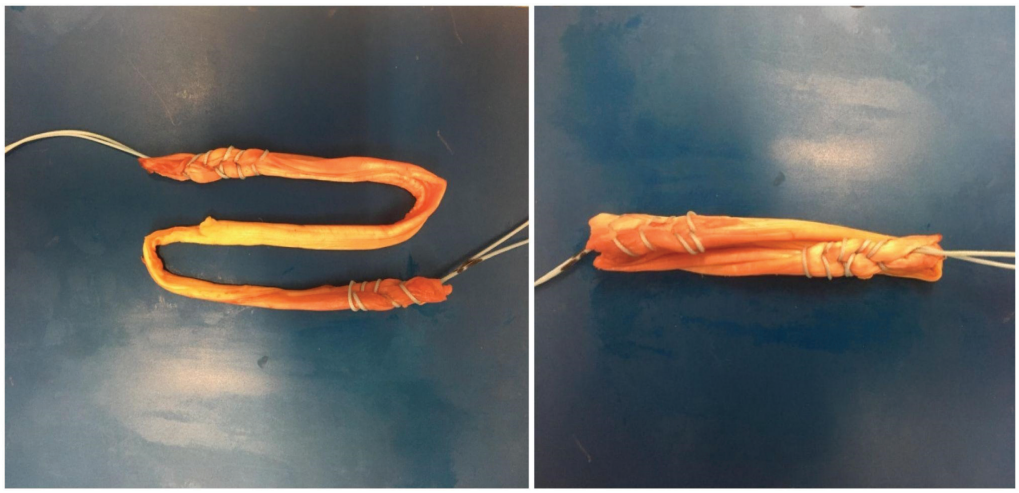


Fig. 2 The 3-strand ACL graft with a thinner semitendinosus tendon.

using the Flipcutter® (Arthrex), which provided greater security of the neurovascular structures at the popliteal fossa and eliminated the need of drilling a larger diameter or the chance of guidewire migration at the time of drilling.

The camera was exchanged for the AL portal to drill the femoral ACL tunnel through the AM portal. To avoid a very short tunnel (<30mm) the knee was bent to 110 degrees at the time of drilling. We again exchanged the portals to drill the femoral PCL tunnel through the AL portal.

The surgeon then proceeded to the tibial ACL tunnel.

When the tunnels were ready, the PCL graft was first raised up and fixed with a bio-interference screw (BIS) at the femur. Then, the ACL graft was raised up and fixed with a RetroButton® (Arthrex) at the femur.

The final fixation of each graft at the tibia was performed with a BIS: first the PCL with the knee at 70 degrees of flexion and then the ACL with 20 degrees of flexion. Before fixing the screws, with the help of the thumb on the joint line, we checked and maintained the knee reduction.

All participants were prescribed the same postoperative management: functional immobilization for 6 weeks. Complete range of motion gain is recommended after this period. Partial weight bearing is started after four weeks. The rehabilitation protocol is started in the second week after surgery and continued for at least 8 months.

At 24 months post-surgery, the functional outcomes were assessed by the Lysholm Knee Scoring Scale,[15] the KT-1000 arthrometer, and the stress X-ray.[16]

Statistical analysis was performed by the paired *t*-test. The significance level of 0.05 was adopted in all statistical tests, and the statistical program SPSS version 18.0 was used for all statistical analyses.

Results

The average age of these 18 patients was 31 years (range: 17–49), and 17 were men. Regarding the mechanism of injury, 12 patients were injured in car acidentes, and 6 in sports practice. Four reported to be sedentary, while 14 practiced regular physical activity at different levels and modalities (►**Table 1**). Two patients (11%) lost the knee bending motion and one (5.5%) presented anterior knee pain. There were no infection complications. The mean thicknesses of the grafts for the ACL and PCL were 7.55 and 8.5 mm, respectively (►**Table 1**). The statistical analysis suggested significant improvements for the following variables: the Lysholm score (►**Table 2**), posterior displacement of the tibia through stress X-rays (►**Table 3**), and use of the KT-1000 arthrometer (►**Table 4**).

The Lysholm scale was used to analyze subjective symptoms. The mean preoperative Lysholm score was 43.8 ± 4.1 (range: 38–52). The mean postoperative Lysholm score was 89.9 ± 3.8 (range: 82–98). After the two-year follow-up, according to this scale, 16 of 18 (88%) patients displayed excellent results, and 2 (12%) patients displayed good results. A significant improvement in the Lysholm score from preoperative to the final follow-up was observed ($p < 0.001$) (►**Table 2**).

Stress X-rays were used to analyze PCL function. The mean preoperative value was 10 ± 3.4 mm (range: 6–20). After the two-year follow-up, this value fell to 3 ± 1.6 mm (range: 1–6), showing a significant improvement in posterior tibial displacement (►**Table 3**).

Although the selected cases did not present symptomatic peripheral lesions, we observed values of tibial posteriorization on stress radiographs above 12 mm. We believe that the injury of other knee restrictors such as the posterior capsule and menisci may have contributed to these.

The KT-1000 arthrometer examination showed that the mean side-to-side difference of anterior-posterior laxity was 5.2 ± 0.8 mm before surgery. After the two-year follow-up, this mean difference fell to 2.4 ± 0.5 mm (►**Table 4**).

Fourteen patients declared regular sports activity before their injury (►**Table 1**). After surgery, 8 (57%) were able to return to their sports activities. We did not consider their sports levels before and after surgery.

Table 1 Individual outcomes of each study participant

Patient number	Age (y)	Trauma	Sport	Lysholm score		KT-1000 arthrometer (mm)		Stress X-ray (mm)		Graft thickness (mm)	
				Pre	Post	Pre	Post	Pre	Post	ACL	PCL
01	36	E	Soccer	44	90	6	2.8	8	3	8	9
02	28	E	Soccer	44	90	4	2	10	3	7	8
03	27	A	Motocross	40	96	5	3	20	4	8	8
04	19	E	Judo	52	90	6	2	8	2	7	8
05	47	A	–	42	88	6	3	14	5	8	9
06	35	A	–	44	86	4	2	8	6	7	8
07	29	A	Soccer	42	86	6	3	10	6	8	8
08	42	A	–	40	82	6	3	8	2	8	9
09	29	E	Soccer	38	90	5	2.5	14	5	7	9
10	23	A	Soccer	40	90	6	2	12	4	8	10
11	46	A	Running	38	98	5	2	8	2	7	7
12	25	E	Skate	52	90	4	2	8	2	8	9
13	19	A	Motocross	48	88	5	2	6	2	7	9
14	30	A	Soccer	44	90	5	2.5	8	1	7	8
15	32	A	Soccer	44	84	6	2	10	1	8	9
16	29	E	Soccer	48	90	6	2	12	2	7	8
17	35	A	Running	44	92	4	2	8	3	8	9
18	26	E	–	44	86	5	3	8	1	8	8

Abbreviations: A, automotive injury; E, sports injury.

Table 2 Changes in the Lysholm score from pre- to postoperative evaluation

Evaluation	Lysholm score				
	Average	d.p.	Median	Low	High
Pre	43.8	4.1	44	38	52
Post	89.2	3.8	90	82	98
Variation (post-pre)	45.4	6.0	45	38	60
Paired *t*-test	$p < 0.001$				

Table 3 Changes in the posterior displacement of the tibia on stress X-ray from pre- to postoperative evaluation

Evaluation	Posterior displacement of the tibia on X-ray (mm)				
	Average	d.p.	Median	Low	High
Pre	10.0	3.4	8.0	6	20
Post	3.0	1.6	2.5	1	6
Variation (post-pre)	−7.0	3.0	−6.5	−16	−2
Paired *t*-test	$p < 0.001$				

Discussion

The most important finding in this study was the improvement in the functional outcomes after bicruciate reconstruction with bilateral hamstring autografts. Bicruciate lesions are rare and are associated with knee dislocation. Some studies have shown that primary surgical reconstruction yields better results than conservative treatment with regard

Table 4 Changes in anterior knee laxity by KT-1000 arthrometer from pre- to postoperative evaluation

Evaluation	Anterior knee laxity by arthrometer (mm)				
	Average	d.p.	Median	Low	High
Pre	5.2	0.8	5	4	6
Post	2.4	0.5	2	2	3
Variation (post-pre)	−2.8	0.8	−3	−4	−2
Paired *t*-test	$p < 0.001$				

to the objective stability and motion of the joints. Simultaneous ACL and PCL reconstruction through open procedures have also been reported with good results.[7–10] Previous techniques have used one or two stages with different graft types.[5,6]

Literature has discussed the best time to operate as well as the number of procedures. The systematic review for multiple ligament knee injuries, Mook et al.[17] reported that acute surgery is highly associated with range of motion deficits and that staged procedures may produce better subjective outcomes and lower rates of range of motion deficits. Chuang et al.[18] described a rehabilitation protocol of a 3-stage program in which after 12 weeks the full range of motion was achieved. Then, the 1-stage reconstruction of the ACL and PCL was performed. A single-stage procedure was chosen for better stabilization of the knee, thus reducing the chance of ligament loosening.

The issue of single or double bundles are also discussed in ACL and PCL reconstruction. While the literature has shown some evidence that double-bundle have superior results in objective measures of knee stability, no results of clinical function have shown significant differences between both reconstructions.[19] In a recent systematic review, Shin et al.[20] found no clinically important differences between the transtibial and tibial inlay approach for PCL reconstruction. Fanelli et al.[21] reported their technique of a simultaneous arthroscopic reconstruction of the ACL and PCL in 1996 and the 2- to 10-year follow-up results in 2002.[22]

La Prade et al.[23] demonstrated that single-staged multiple-ligament reconstruction with immediate post operative rehabilitation improved outcomes, including ROM, with low complication rates.

In 2006, Zhao et al.[24] published their ACL/PCL single-stage reconstruction technique with autogenous hamstring tendons. They used the ST tendon and the G tendon from the uninjured leg for a 6- to 8-strand PCL graft and the ST of the injured leg for a 4-strand ACL graft. Their results showed a KT-1000 side-to-side difference of anterior laxity at 25 degrees of flexion of 0 to 2 mm in 8 patients, 3 to 5 mm in 3 patients, and 7 mm in 1 patient. The Lysholm score post-surgery was 91.8 ± 4.6, similar to our present study. This is the closest technique to ours and had similar results. The main difference between them was in the preparation of the graft.

In 2015, Denti el al.[8] described a simultaneous arthroscopic reconstruction of BL comparing allograft tendons versus bone-patellar tibial-bone autograft for PCL and hamstring for ACL. They reported a mean Lysholm score of 93.9 ± 3.9 for the allograft and 89.1 ± 7.6 for the autograft. No significant strength deficit was found in both groups.

Inada and Piedade[25] published in 2021 a retrospective analysis of 25 patients treated by a two-stage technique. PCl inlay with patellar tendon and three months later an Acl reconstruction with hamstring tendons. They reported that 60% of the patients scored zero or + at the posterior drawer test, while 40% scored ++; 60% of patients were evaluated as good/excellent according to the Lysholm scale. Only one patient reached the pre-injury Tegner activity level. Injury duration had a negative influence on functional limitation.

For our technique, we chose the hamstring tendon due to less anterior knee pain, extension loss, and donor site morbidity.[26] By combining it with an extra gracilis tendon, we were able to enlarge the graft thickness for the PCL reconstruction. The maximum strength for a quadruple ST/G tendon was measured at ∼4.000 N in a study by Horner et al.[27] While a 4-strand graft appears to be sufficient for PCL reconstruction, it is our opinion that a 6-strand graft with an extra double gracilis, increasing graft thickness, produces a stronger graft.

As described in the papers above, different grafts bring similar results. The choice depends on the surgeon's preference. In knees with peripheral injuries, we choose the hamstrings for reconstruction of these and grafts of the extensor mechanism to the central pivot.

Moatshe et al.[28] conducted a biomechanical study in 2018 in which a better result was observed by first tensioning the PCL, then the ACL and then the posterolateral corner. Franciozi et al.[29] used a simultaneous tensioning protocol in BL. They found a better tibiofemoral orientation in the group that ACL fixation was made first. Based in our and others authors experiences[21,22,30] we prefer first to fix the PCL at 70 degrees of flexion, keeping the knee reduced and then the ACL with 20 degrees of flexion.

In a retrospective study of open complete single-stage reconstruction of complex ligament knee lesions, Hirschmann et al.[31] found that 79% of the patients were able to return to their previous sports practice, but only 33% reached their identical preinjury sport activity level. We believe that the different findings in our study are due to the lower level of athletes evaluated, assuming that elite athletes adhere to a more intensive rehabilitation protocol.

There were no infection. Two pacients had arhtrofibrosis and received manipulation 3 months after surgery. One

patient had thrombosis despite the use of anticoagulant and was treated with a higher dose with a good outcome

The weaknesses of this study were the small number of patients, the absence of a control group, and the lack of a second observer to evaluate the results.

Conclusion

The bicruciate reconstruction with bilateral hamstring autograft is a valuable option to achieve good functional outcomes and joint stability.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Analysis of the Biomechanical Behavior of an Animal Model of Triple Hamstring Graft Configuration for Combined ACL and ALL Reconstruction with a Single Femoral Tunnel and a Single Strand for ALL Reconstruction

Análise do comportamento biomecânico de um modelo animal de configuração de enxerto de trança tripla de isquiotibiais para reconstrução combinada de LCA e LAL para túnel único femoral

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Abstract

Objective To describe and biomechanically test a configuration, in an animal model that simulates the triple hamstring graft for combined anterior cruciate ligament (ACL) and anterolateral ligament (ALL) reconstruction, with a single femoral tunnel and a single strand for ALL reconstruction.

Methods Deep flexor porcine tendons were used as the graft and fixed with titanium interference screws in a polyurethane block. The samples were divided into 3 groups: group 1 (control) – with a quadruple graft; group 2–with a simple triple graft; and group 3–with a braided triple graft. The tests were conducted using an EMIC DL 10000 (Instron Brasil Equipamentos Científicos Ltda., São José dos Pinhais, PR, Brazil) electromechanical universal testing machine.

Results The samples in groups 1, 2, and 3 obtained mean peak forces of 816.28 ± 78.78 N, 506.95 ± 151.30 N, and 723.16 ± 316.15 N, respectively. In Group

Keywords
- anterior cruciate ligament
- anterior cruciate ligament reconstruction
- knee joint
- ligaments, articular

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3, braiding increased graft diameter by 9% to 14%, and caused a shortening of 4% to 8% compared with group 1, with an average peak force increase of $\sim$ 200 N ($p < 0.05$). Regarding peak forces, there was no statistically significant difference between groups 1 and 3, indicating that quadruple and braided triple grafts showed similar strength results.

Conclusion The triple-braided hamstring graft configuration for combined ACL and ALL reconstruction with a single femoral tunnel and a single strand for ALL reconstruction may become a biomechanically viable solution, with potential clinical application.

Resumo

Objetivo Descrever e testar biomecanicamente uma configuração, num modelo animal que simula o enxerto triplo de isquiotibiais para a reconstrução combinada do ligamento cruzado anterior (LCA) e do ligamento anterolateral (LAL), com apenas um túnel femoral e somente uma "perna" para a reconstrução do LAL.

Métodos Tendões flexores profundos de suínos foram utilizados como enxerto e fixados com parafusos de interferência de titânio num bloco de poliuretano. As amostras foram divididas em 3 grupos: grupo 1 (controle) – com enxerto quádruplo; grupo 2–com enxerto triplo simples; e grupo 3–com enxerto triplo trançado. Os testes foram realizados com uma máquina universal de ensaios eletromecânica EMIC DL 10000 (Instron Brasil Equipamentos Científicos Ltda., São José dos Pinhais, PR, Brasil).

Resultados As amostras dos grupos 1, 2 e 3 alcançaram forças de pico médias de 816,28 $\pm$ 78,78 N, 506,95 $\pm$ 151,30 N e 723,16 $\pm$ 316,15 N, respetivamente. No Grupo 3, o trançado aumentou o diâmetro do enxerto entre 9% e 14%, e causou um encurtamento de 4% a 8% em comparação ao grupo 1, com um aumento médio da força de pico de $\sim$ 200 N ($p < 0,05$). Não houve diferença estatisticamente significativa entre os grupos 1 e 3 com relação às forças de pico, o que indica que os enxertos quádruplos e triplos trançados apresentaram resultados de força semelhantes.

Conclusão A configuração do enxerto de isquiotibiais com trança tripla para a reconstrução combinada do LCA e do LAL com um só túnel femoral e uma só "perna" para a reconstrução do LAL pode se tornar uma solução biomecanicamente viável, com potencial aplicação clínica.

Palavras-chave
- articulação do joelho
- ligamento cruzado anterior
- ligamentos articular
- reconstrução do ligamento cruzado anterior

Introduction

Combined reconstruction of the anterior cruciate ligament (ACL) and the anterolateral ligament (ALL) of the knee has shown excellent results in specific patient groups.[1–4] It may reduce graft failure and improve outcomes in high-risk patients. There are several surgical techniques described, with quadrupled hamstring grafts being the most commonly used for this type of reconstruction.[5]

Many techniques have been described for combined ACL and ALL reconstruction.[6–13] Many of them use one single strand of the gracilis tendon (GT) for ALL reconstruction and the remainder for the ACL.[14] However, using a single strand of the hamstring for ALL reconstruction leaves only a "triple" graft for ACL reconstruction, which could make it weaker since it would be thinner. Studies on isolated intra-articular ACL reconstruction show that hamstring grafts smaller than 8 mm may present a higher risk of failure, but this is not as well-established when combined with extra-articular reconstruction. Helito et al.[15] showed that grafts of 7 mm or less, when combined with ALL reconstruction, can have similar results to those of isolated intra-articular grafts of 8 mm or more. In other words, theoretically, the ideal scenario would be to create a model/technique that enables ALL reconstruction while still providing a graft thick enough for ACL reconstruction.

Therefore, the objective of the present study is to describe and biomechanically test a configuration in an animal model that simulates the triple-braided hamstring graft for combined ACL and ALL reconstruction with a single femoral tunnel and a single strand for ALL reconstruction (►**Figs. 1**–**2**). Our hypothesis is that a triple braid provides a graft thick enough for ACL reconstruction and leaves a single strand of the GT "free" for ALL reconstruction.

Materials and Methods

Test Samples

To prepare the test samples, a simulated surgery was performed, in which a hole was opened in the polyurethane block, representing the "bone tunnel," to enable graft insertion and fixation with an interference screw, as would occur in practice.

According to Brazilian standard (*norma brasileira*, NBR, in Portuguese) 15678:2020 of Associação Brasileira de Normas

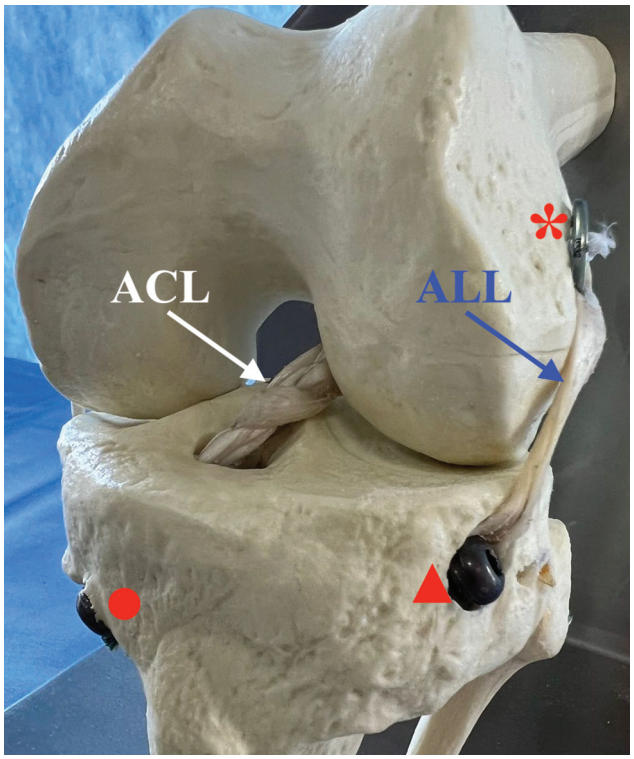


Fig. 1 Model demonstrating the technique for anterior cruciate ligament (ACL) and anterolateral ligament (ALL) reconstruction using a triple-braided hamstring graft for the ACL and a single strand for ALL reconstruction. *Endobutton (Smith & Nephew Ltd) securing the triple-braided graft in the femoral tunnel; ▲ interference screw securing the single strand for ALL reconstruction at its tibial insertion, between Gerdy tubercle and the head of the fibula; • interference screw securing the triple-braided graft in the tibial tunnel.

Técnicas (Brazilian Association of Technical Standards, ABNT, in Portuguese), which regulates the standard material for the mechanical testing of implants and orthopedic instruments, rigid unicellular polyurethane foam with the following characteristics was applied:

- Dimensions: 100 mm × 100 mm × 30 mm;
- Color: brown;
- Density: 40 pounds per cubic foot (PCF; 0.96 g/cm^3);
- Hole/tunnel: length of 30 mm on the central axis of the 100 mm × 100 mm surface, over the entire height of the block, and a diameter equal to that of the graft.

Graft

Similarly to what has been described in the biomechanical study by Moré et al.,[16] we used recently-frozen Landrace pig legs in the experiments. The tendons were collected from a slaughterhouse. A total of 8 legs were stored at −20°C and thawed 12 hours before the test. Each tibia was dissected and the deep flexor tendon, measuring ~ 8 mm in width and 9 cm in length, was extracted to be used as graft.

Sample Preparation

The samples were divided into three groups (►**Fig. 3**):

- **Group 1–control Group:** the graft was joined in a quadruple manner and fixed at its ends to the polyurethane blocks with interference screws (made of ASTM F136 titanium alloy, Traumédica Instrumentais e Implantes, Campinas, SP, Brazil); each screw had a length of 30 mm and a diameter equal to that of the graft.
- **Group 2–simple triple:** the graft was joined in a triple parallel manner and fixed at its ends to the polyurethane blocks with interference screws (made of ASTM F136

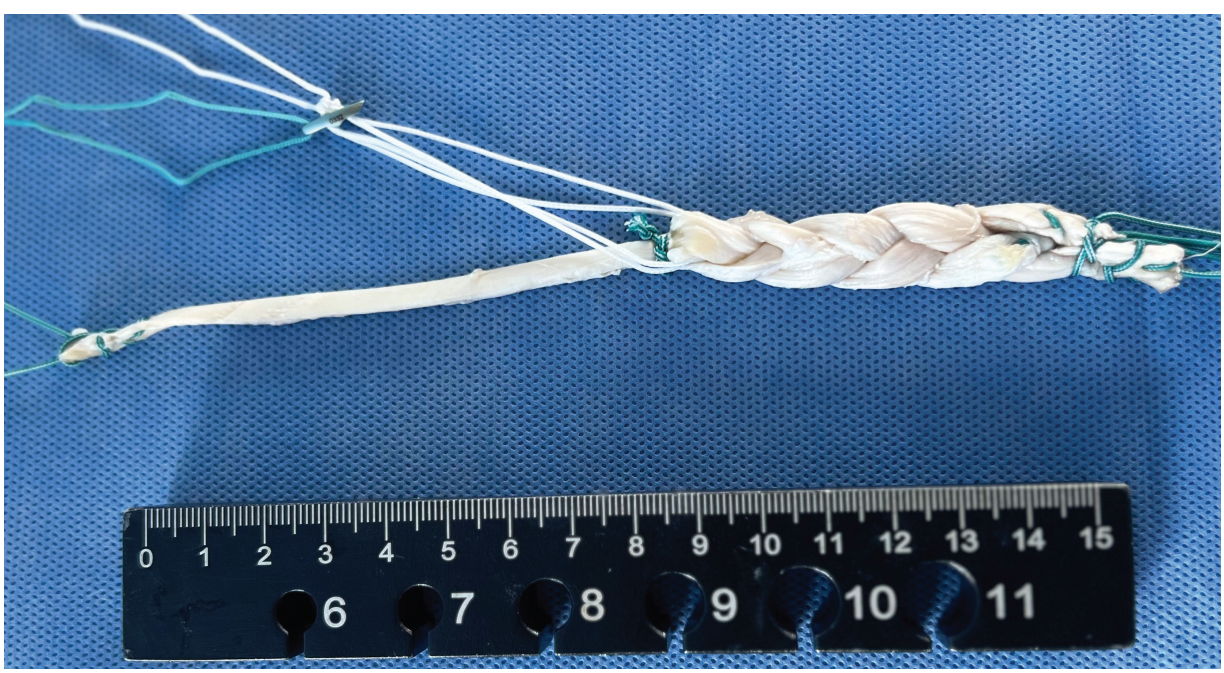


Fig. 2 Triple-braided hamstring graft for the ACL with a single strand for ALL reconstruction.

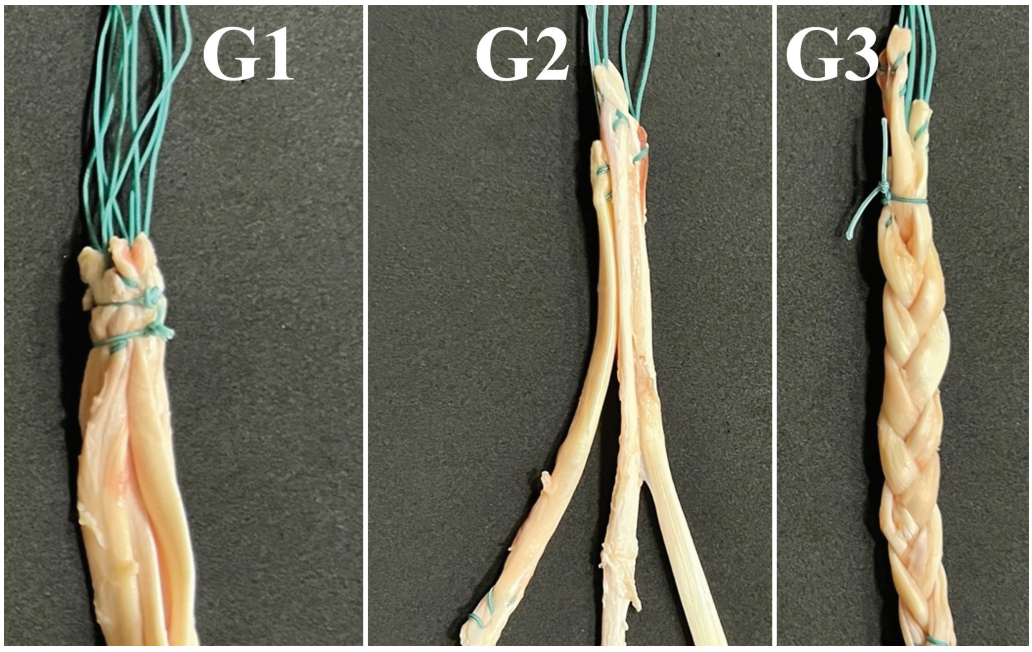


Fig. 3 The samples were divided into three groups: group 1–quadruple control group; group 2–simple triple; and group 3–triple-braided.

titanium alloy, Traumédica Instrumentais e Implantes); each screw had a length of 30 mm and a diameter equal to that of the graft diameter.

- **Group 3–triple-braided:** the graft was joined in a triple manner and braided in a "pure" form: (σ1σ2 – 1)3n, with n being a positive integer, meaning the sequence of concatenations σ1σ2 – 1 σ1σ2 – 1 σ1σ2 – 1 repeated an integer number of times (►**Fig. 4**). The basic sequence (σ1σ2 – 1)3n can be correlated with permutations of points (p1, p2, p3) in the following order: (p1, p2, p3), (p2, p1, p3), (p2, p3, p1), (p3, p2, p1), (p3, p1, p2), (p1, p3, p2), and (p1, p2, p3).[17] The braided graft was fixed at its ends to the polyurethane blocks with interference screws (made of ASTM F136 titanium alloy, Traumédica Instrumentais e Implantes); screw had a length of 30 mm and a diameter equal to that of the graft.

The average graft length was of 9 cm, 3 cm inside each block and 3 cm "free" between the blocks. The fixation procedures were performed by a trained orthopedic surgeon. All polyurethane blocks had a tunnel with a diameter equal to that of the graft, which was drilled by the surgeon. The screw was implanted with the aid of a Kirschner wire to avoid divergence and false trajectory. At the end, the test specimens displayed the following configuration: screw – block – graft – block – screw.

Performance of the Tests

The tests were performed on an EMIC DL 10000 (Instron Brasil Equipamentos Científicos Ltda., São José dos Pinhais, PR, Brazil) electromechanical universal testing machine, using its axial traction to determine the efficiency of graft fixation with interference screws, and a computer to register the data obtained.

In the tests, the experimental length of the sample was correlated by deformation (mm) in relation to time (seconds), stipulated as $10mm^{-2}/s$, with traction applied until graft rupture or slippage of the screw/graft assembly.[18] Nine tests were conducted for each group.

Methodology and Data Analysis

The categorical and numerical variables were tabulated and analyzed using the R (R Foundation for Statistical Computing, Vienna, Austria) software for Mac OS, which provided measures of central tendency, percentile values, and dispersion.

Data normality was assessed using the Shapiro-Wilk test. The homogeneity of variables among the groups was verified using the Levene test. A comparison of group means, to either reject or accept a null hypothesis, was performed using the *t*-test. The presence of outliers was examined through the development of boxplots. Homoscedasticity was tested through the development of a linear regression model between variables.

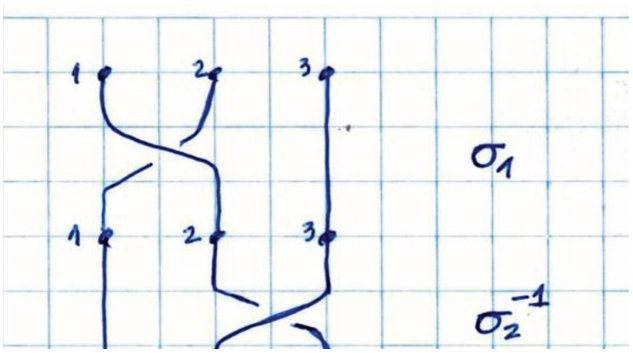


Fig. 4 Braiding in a "pure" manner.

Analyses with a 95% confidence interval (95%CI) and a *p*-value lower than 0.05 were considered statistically significant.

Results

The data obtained from the tests included time (s), deformation (mm), and force (N) to which the samples were subjected. With these data, graphs were drawn of the force (N)/deformation (mm) ratio suffered by the samples fixed with the titanium screws.

In group 1 (quadruple control), the samples achieved a mean peak force of 816.28 ± 78.78 N. As the graft deformation progressed, the force decreased until the graft ruptured, with a mean of approximately 41.30 ± 10.01 mm of deformation relative to the initial length.

In group 2 (simple triple), the samples achieved a mean peak force of 506.95 ± 151.30 N. As the graft deformation advanced, the force decreased until the graft ruptured, with a mean of approximately 36.28 ± 3.25 mm of deformation relative to the initial length.

In group 3 (triple-braided), the samples achieved a mean peak force of 723.16 ± 316.15 N. As the graft deformation advanced, the force decreased until the graft ruptured, with a mean of approximately 52.38 ± 17.35 mm of deformation relative to the initial length.

When comparing the diameter and length of groups 2 and 3, creating a braid in a triple graft increased its diameter by $\sim$ 9% to 14%. However, this led to a shortening of the graft by $\sim$ 4% to 8% of its length, with an average peak force increase of $\sim$ 200 N ($p < 0.05$), representing an approximate 40% increase in its peak force.

Regarding the peak forces in group 1 (quadruple control) and group 2 (simple triple), the *t*-test showed a statistically significant difference between them ($t = 3.1452$; *p*-value $= 0.03467$) (►**Fig. 5**). This assessment yielded $p < 0.05$, rejecting the null hypothesis (H0) of no difference between the two groups. In other words, in the study, quadruple and simple triple grafts exhibited different peak forces.

Concerning the peak forces in group 1 (quadruple control) and group 3 (triple-braided), the *t*-test showed no statistically significant difference between them ($t = 0.49722$; *p*-value $= 0.6451$) (►**Fig. 5**). This assessment yielded $p > 0.05$, confirming the null hypothesis (H0) of no difference between the two groups. In other words, in the study, quadruple and triple-braided grafts exhibited similar peak forces.

The titanium screw provided secure fixation of the graft in the polyurethane block, without any apparent slippage or deformation. In all samples, the test culminated in graft rupture.

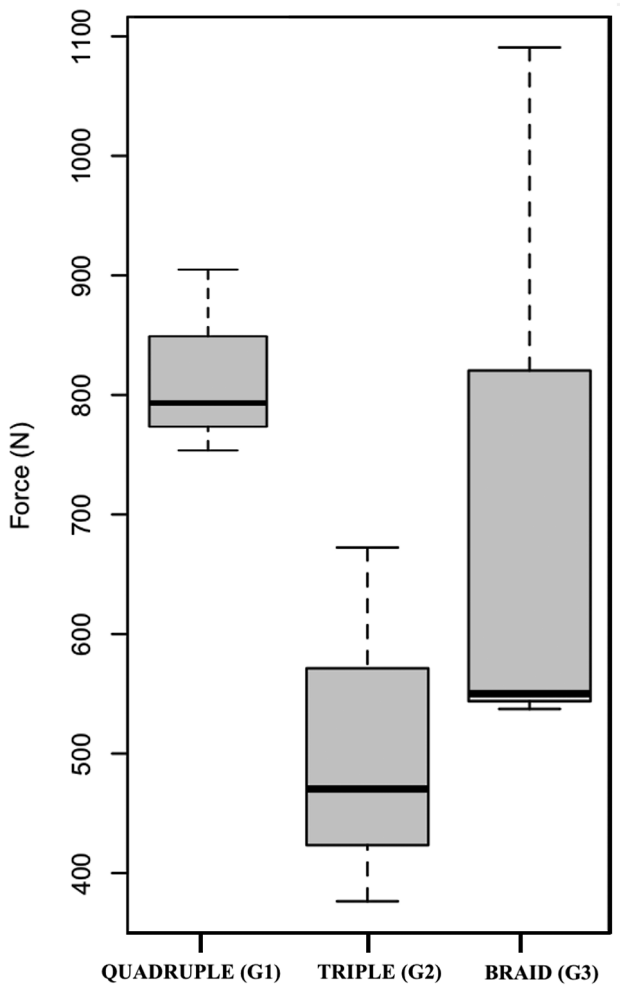


Fig. 5 *t*-test regarding peak forces (N) in group 1–(quadruple control), group 2 (simple triple), and group 3 (triple-braided).

Discussion

The main finding of the present study demonstrates that the triple-braided graft can be a biomechanically viable alternative when compared with the quadruple graft. The present study opens up new possibilities for multiligament reconstructions, especially for combined reconstructions of the ACL and ALL.

In many medical centers, especially those without access to tissue banks, a significant challenge in ligament reconstructions is graft availability. With a braided configuration, a triple graft can present strength similar to that of a quadruple graft and still leave one single strand available for another reconstruction, such as that of the ALL, for example. From a technical standpoint, braiding is not difficult and only requires a short learning curve.

When three parallel threads are braided, they create a structure that is more resistant and capable of withstanding a variety of forces and conditions, making it a stronger option than individual threads. Braiding improves essential characteristics such as load distribution, torsional resistance, increased contact area, impact absorption, and flexibility. This is frequently used in cables and ropes, and in many other instances in which strength is crucial.[17]

When grafts are braided, the load or tension exerted on them is distributed more evenly along the structure. This means that each graft bears a smaller portion of the total load, reducing the risk of rupture. Braiding creates a structure that is more resistant to twisting and bending. If a single graft is bent or twisted, it can break more easily. However, when grafts are braided, they support each other, making the structure more resistant to these forces. Braided grafts have

more points of contact with each other than simple parallel threads. This increases the surface area of contact between them, helping distribute stress more effectively and reducing the likelihood of rupture. Braiding also enables the structure to better absorb impacts. When a force is applied to it, the grafts can move within the braid, dissipating the impact energy across the structure rather than concentrating it at a single point.[19]

Braiding can provide a certain degree of flexibility to the structure, enabling it to adapt to different conditions and movements without breaking. This is especially useful in applications involving movement or vibrations. However, this is a point that should be noted. In the present study, regarding the peak forces in group 1 (quadruple control) and group 3 (triple-braided), there was no statistically significant difference between them. However, the distribution of peak forces in the samples in group 3 was not as uniform, with some cases exceeding those in group 1 and some approaching those in group 2. Since the braids in group 3 were made manually, we did not standardize their tightness. The tighter the braid, the thicker the graft, providing greater strength but at the cost of greater shortening of its length.[17,19]

Graft insufficiency represents one of the main factors determining adverse outcomes in ACL reconstruction.[20] However, there is no solid evidence demonstrating the superiority of autologous grafts compared with other types of grafts. Each graft variety has specific advantages and considerations to consider. Supporters of hamstring tendon grafts have reported a lower incidence of complications in the donor area but increased weakness in hip extension and maximal knee flexion, as well as variable results related to graft size and length, such as a graft diameter shorter than 8 mm, which increases the risk of failure.[21] In many cases, the only available grafts are hamstring tendons, and depending on the patient's body type, the ideal thickness of 8 mm may not be achieved.[20,21]

There are numerous studies on graft preparation techniques for ACL reconstruction. Conte et al.[21] suggest that grafts smaller than 8 mm in diameter have high failure rates, and according to Figueroa et al.,[22] an increase in graft diameter of just 0.5 mm can lead to statistically significant improvements in graft success and longevity.

Authors like Park et al.[23] and Samitier and Vinagre[24] have reported a technique involving the braiding of four strands of hamstring autograft. According to these authors, braiding a 4-strand hamstring autograft can increase graft diameter by around 1 mm to 1.5 mm, but may result in a shortening of $\sim$ 5 mm to 10 mm. Therefore, this technique is not recommended for very short grafts.

Other theoretical advantages of the hamstring autograft braiding technique include obtaining a uniform graft strip that appears to mimic the native shape of the ACL and replicate its mechanical behavior,[25] as well as compensate for the intrinsic viscoelasticity associated with soft tissue grafts, minimizing postreconstruction stretching that can lead to laxity and reruptures.[24]

Regarding techniques for ACL and ALL reconstruction, Helito et al.[14] used a quadruple graft, combining three strands of the semitendinosus tendon (ST) and one of the gracilis tendon for the ACL and a single strand of the GT for the ALL; tibial fixation was performed with anchors. Sonnery-Cottet et al.[26] used a triple ST graft for the ACL and a double GT graft for the ALL, with two tibial tunnels for ALL reconstruction.

Ferreira et al.[11] employed a graft preparation method that creates a suspension effect similar to that of the Endobutton (Smith & Nephew Ltd., London, United Kingdom), adding a suture to reinforce this union, and including an interference screw. This enables the end of the ST graft to remain close to the femoral joint point, and it does not need to occupy the entire tunnel, which will be completed by the GT graft, facilitating the procedure for short grafts. This technique is similar to what has been described in the present study, with the exception of the triple braid.

Therefore, it is essential to master various graft preparation techniques to obtain an individualized graft with the appropriate diameter and length that match the patient's anatomy, height, and physical demands. The triple-braided hamstring autograft technique is a reliable graft configuration, relatively easy to prepare, and reproducible, providing a stronger and more uniform hamstring graft.

Limitations

The major limitation of the present study was the choice of graft for testing. Due to the ease of obtaining it, we used animal tissue as the graft; however, pig grafts do not have the same strength as young human grafts. Thus, we could not test the full capacity of the screw-polyurethane-graft complex. Nevertheless, the methodology followed in the present study is a useful model for future research. Another limitation was that the braids were made manually, meaning there was no standardization in terms of their tightness. Despite these limitations, our results are consistent with those obtained in other similar studies. Overall, the results indicate that the proposed configuration results in acceptable biomechanical performance. However, more research is needed to determine the clinical relevance of these findings.

Conclusion

The triple-braided hamstring graft configuration for combined ACL and ALL reconstruction with a single femoral tunnel and a single strand for ALL reconstruction may become a biomechanically viable solution, with potential clinical application.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Evaluation of the Mechanical Behavior of the Patellar and Semitendinosus Tendons Using Supersonic Shear-wave Imaging (SSI) Elastography and Tensile Tests

Avaliação do comportamento mecânico dos tendões patelar e semitendinoso utilizando a elastografia por ondas de cisalhamento (SSI) e testes de tração

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Abstract

Objective To analyze the mechanical properties of the patellar (PT) and semitendinosus (ST) tendons from fresh-frozen human cadavers from a tissue bank using supersonic shear-wave imaging (SSI) elastography and tensile tests.

Methods We tested seven PT and five ST samples on a traction machine and performed their simultaneous assessment through SSI. The measurements enabled the comparison of the mechanical behavior of the tendons using the stress x strain curve and shear modulus (μ) at rest. In addition, we analyzed the stress x μ relationship under tension and tested the relationship between these parameters. The statistical analysis of the results used unpaired *t*-tests with Welch correction, the Pearson correlation, and linear regression for the Young modulus (E) estimation.

Results The μ values for the PT and ST at rest were of 58.86 ± 5.226 kPa and 124.3 ± 7.231 kPa respectively, and this difference was statistically significant. The correlation coefficient between stress and μ for the PT and ST was very strong. The calculated E for the PT and ST was of 19.97 kPa and 124.8 kPa respectively, with a statistically significant difference.

Keywords
- elasticity imaging techniques
- patellar tendon
- Young's modulus

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Conclusion The ST was stiffer than the PT in the traction tests and SSI evaluations. The μ value was directly related to the stress imposed on the tendon.
Clinical relevance The present is an evaluation of the mechanical properties of the tendons most used as grafts in knee ligament reconstruction surgeries.

Resumo

Objetivo Analisar as propriedades mecânicas dos tendões patelar (TP) e semitendinoso (ST) obtidos de cadáveres humanos congelados enquanto ainda frescos, provenientes de banco de tecidos, utilizando elastografia por ondas de cisalhamento (*supersonic shear-wave imaging*, SSI, em inglês) e testes de tração.
Métodos Sete amostras de TP e cinco de ST foram testadas em máquina de tração e simultaneamente avaliadas por SSI. As medidas geradas possibilitaram comparar o comportamento mecânico dos tendões por curva *stress* x *strain* e módulo de cisalhamento (μ) em repouso. Também foi analisada a relação *stress* x μ sob tensão, e testada a relação entre esses parâmetros. Os resultados foram submetidos a análise estatística pelos testes *t* não-pareado com correção de Welch, correlação de Pearson e regressão linear para estimativa do módulo de Young (E).
Resultados O μ dos TP e ST em repouso foi, respectivamente, de 58,86 ± 5,226 kPa e 124,3 ± 7,231 kPa, com diferença estatisticamente significativa. O coeficiente de correlação entre *stress* e μ dos TP e ST foi classificado como muito forte. O E calculado dos TP e ST foi, respectivamente, de 19,97 kPa e 124,8 kPa, com diferença estatisticamente significativa.
Conclusão O ST foi mais rígido do que o TP nos testes de tração e nas avaliações por SSI. O μ esteve diretamente relacionado com o *stress* a que o tendão é submetido.
Relevância clínica Avaliar as propriedades mecânicas dos tendões mais utilizados como enxerto nas cirurgias de reconstrução ligamentar do joelho.

Palavras-chave
- módulo de Young
- técnicas de imagem por elasticidade
- tendão patelar

Introduction

In recent decades, the mechanical properties of tendons have been widely studied, providing knowledge about their behavior.[1–4] Recently, the evaluation of the elastic modulus (E) and resistance to failure (RF) of tendon tissues gained importance in the literature.[5] In 2013, LaCroix et al.[5] showed an intimate relationship between these properties despite their conceptual distinction.

Publications on the matter employed several methods to measure these properties, but most carry biases.[3,6–14] The results of in-vivo studies are usually obtained indirectly from calculations combining magnetic resonance imaging and ultrasound with data provided by a dynamometer.[10,13] Several authors[2,3,6,9,11,12,14] have performed ex-vivo analyses of tendons from human and animal cadavers. However, the reliability of these studies is questionable due to the protocol preparation of cadaveric tissues.[10,15]

We need new analysis methods including in-vivo studies and direct evaluation. Recently, ultrasound with elastography has been widely applied to evaluate tissue stiffness and measure it non-invasively, in real-time, and with less dependency on the operator's skill.[7,16–20]

There are different elastography modalities, and the most recent is supersonic shear-wave imaging (SSI).[17,20,21] In this method, an acoustic radiation force generates shear waves in the tissue for detection by the ultrasound transducer.[14,17,21] The system provides the speed of these waves and the shear modulus (μ) of the tissue, expressing its stiffness.[12,14,17,19,21]

The SSI is well-established in the evaluation of isotropic media, such as breast, liver, and thyroid tissues.[22–24] Despite requiring more robust validation, SSI has been used in musculoskeletal tissue, an anisotropic tissue, since the beginning of the last decade, with encouraging results.[1,6–8,16,18–20,25–27] Due to its anisotropic characteristic, the μ value of the tendon does not present the expected mathematical relationship with E.[14,17,21] Even so, recent studies[8,9,11,12,14,25] have demonstrated a strong correlation between the μ of the tendon obtained by SSI and its E calculated by the linear phase of the stress x strain graph. However, most of these tests used tendons from other animal species, with low scientific evidence.[9,11,12,14]

There are two studies[8,25] in the literature comparing ex-vivo mechanical behaviors of human tendons using SSI elastographic analysis. The present study aims to evaluate the mechanical properties of the patellar (PT) and semitendinosus (ST) tendons due to their great relevance and use as grafts in knee ligament reconstruction surgeries[28] using SSI and dynamometry.

The main objective was to obtain and compare the E value from PT and ST at stress by evaluating the stress x strain curve recorded by the traction machine. The secondary

objectives were to obtain and compare the μ values of PT and ST in the ultrasound assessment at rest carried out with SSI and to evaluate the influence of tissue stress in SSI-based evaluation, analyzing the correlation between μ values and the stress imposed on these tendons.

Materials and Methods

Ethical approval and study design

The institutional Ethics in Research Committee approved the present cross-sectional study under consubstantiated opinion 1,674,064 (CAAE: 26828914.3.0000.5257). The study was conducted at the Biomechanics Laboratory from 2019 to 2022.

The initial sample was composed of 14 PT and 19 ST samples from fresh-frozen human cadavers provided by the Brazilian Ministry of Health (MH) tissue bank. We received these tendons after they were considered unsuitable for surgical use, mainly due to contamination at some processing stage in the tissue bank. For the most part, the organism detected was *Staphylococcus epidermidis*, a bacterium that commonly colonizes human skin.

►**Tables 1** and **2** show the demographic distribution of the samples.

The fact that tissues preserved in formaldehyde lose their mechanical properties warrants using fresh-frozen human tendons.[2,15] As such, we asked for samples from the MH since its protocol for preparing musculoskeletal tissues does not involve irradiation, avoiding damage to their biomechanical characteristics.

The inclusion criteria were tendons from fresh-frozen human cadavers aged between 20 and 35 years at the date of death and preserved in a freezer at -80° C at the tissue bank.

The exclusion criteria were signs of degenerative tendon disease, storage time longer than 2 years, presence of macroscopic ruptures, tendon irradiation during preparation by the tissue bank, and inadequate biomechanical or elastographic recording.

After applying the exclusion criteria and the occurrence of accidental damage to the tendons during the pretest preparation, we lost 7 PT and 14 ST samples, and 7 PT and 5 ST samples remained for the final analysis.

Table 1 Patellar tendon: demographic distribution

Gender	N	Mean age (years)
Male	5	28.2 (22–35)
Female	2	28 (26–30)

Table 2 Semitendinosus tendon: demographic distribution

Gender	N	Mean age (years)
Male	4	27.5 (22–35)
Female	1	22

Sample preparation

We kept the samples in a freezer at -20° C at the Immunology Laboratory. For testing, the tendons were thawed one hour before at room temperature.

Preparation of the PT started after thawing the anatomical piece provided by the MH, which consisted of the entire knee extensor apparatus, with the quadriceps tendon, patella, patellar tendon, and tibial tuberosity. The pieces for testing were prepared with bone plugs in both PT attachments, with approximately 1.0 cm in each dimension. The intermediate tendinous part was approximately 1.0 cm wide (►**Fig. 1**). Each bone plug was drilled with a 2.5-mm drill, generating holes for passing Ethibond 5 wire (Ethicon, Inc., Raritan, NJ, United States).

Processing of the ST occurred before freezing in the tissue bank. Its length was standardized from the myotendinous junction to its tibial attachment. After thawing, we performed a Krakow suture with Ethibond 5 at both ends to optimize anchorage.

Both tendons were placed in the fixation system of the universal testing machine using metal claws (►**Fig. 2**).

For the ST, we made two attempts before the definitive fixation to the metal claws. In the first attempt, the tendons were attached directly to the claws, which caused macroscopic structural damage in the first samples and loosening of their ends at the interface with the claws when the tensile test was still beginning. As a result, we abandoned this method. In the second attempt, we anchored the tendons by tying Ethibond 5 directly to plastic tubes attached to the claws. Once again, there were losses due to structural damage to the tissues and the generation of inadequate elastographic or biomechanical readings, so thbis method was also abandoned. After test failures with these two anchoring prototypes, we unfortunately lost 14 ST samples. Finally, to generate more effective fixation between the claw and the ST, we inserted them into plastic tubes, fixated them

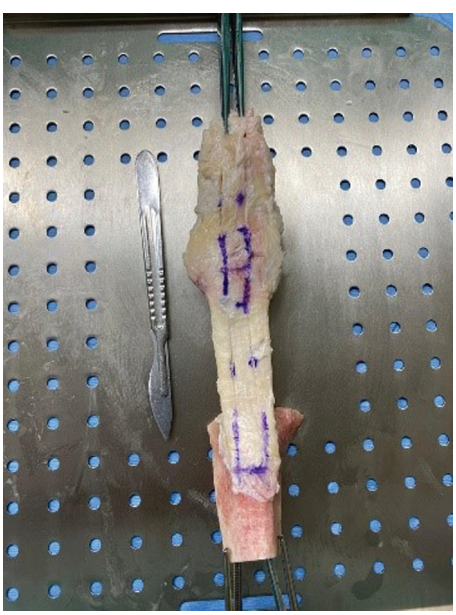


Fig. 1 Patellar tendon (PT) prepared for the test.

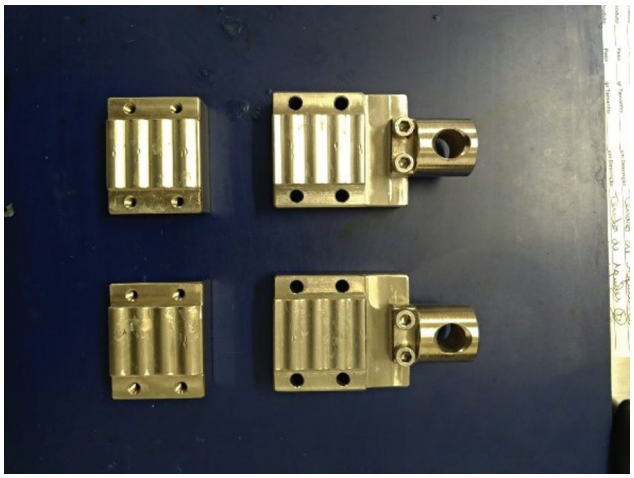


Fig. 2 Metal fixing claws.

with Ethibond 5 threads, and attached them with conventional screws to a framework (►**Figs. 3**–**4**). This last method, deemed ideal and definitive, did not cause any damage or interference in data acquisition.

Elastography

We used the Aixplorer equipment (SuperSonic Imagine, Aix-en-Provence, France) to acquire elastographic images with a linear transducer operating at frequencies ranging from 6 to 20 MHz. Before each test, we carefully aligned the transducer in the same direction as the tendon fibers using B-mode ultrasound (►**Fig. 5A**), ensuring µ value determination in the same direction as that of the longitudinal traction.

We activated the elastographic mode using the adapted musculoskeletal (MSK) preset, whose scale ranges from 0 to 800 kPa. The mapping area had a rectangular shape, enabling tendon delimitation. The test started after 10 seconds to stabilize the color mapping of the elastographic images (►**Fig. 5B**).

We used an AUBO i5 robotic arm (AUDO Robotics, Beijing, China) (►**Figs. 6**–**7**) to collect the images, keeping the transducer fixed and immobile over the region of interest (ROI). A gel (Ultrex-gel, Farmativa Indústria e Comércio Ltda., Rio de Janeiro, RJ, Brazil) was used for the acoustic coupling on the tendon surface.

The µ analysis employed a specific routine developed by the Biomechanics Laboratory (trough the Matlab R2013a software, The MathWorks, Inc., Natick, MA, United States). We acquired elastography images until mapping saturation. At that moment, we terminated the video and stress.

Biomechanical testing

We used a BioPDI (São Carlos, SP, Brazil) tensile testing machine with a 5-kN load cell to perform tensioning tests. The temperature and relative humidity in the laboratory during the tests were standardized and kept constant at 23° C and 50% respectively. We attached the ends of the PT and ST samples to the metal claws from the tensioning machine. One end remained fixed, while the other end was progressively pulled at a 1-mm/minute speed on a uniaxial longitudinal axis.

The testing machine values consist of position (mm) and force (N). Using the Matlab software, data underwent a sixth-order Butterworth filtering. We performed an exponential third-order adjustment, ending with 0.5 splines. After the process, we calculated the stress and strain using the previously-measured initial length and cross-sectional area.

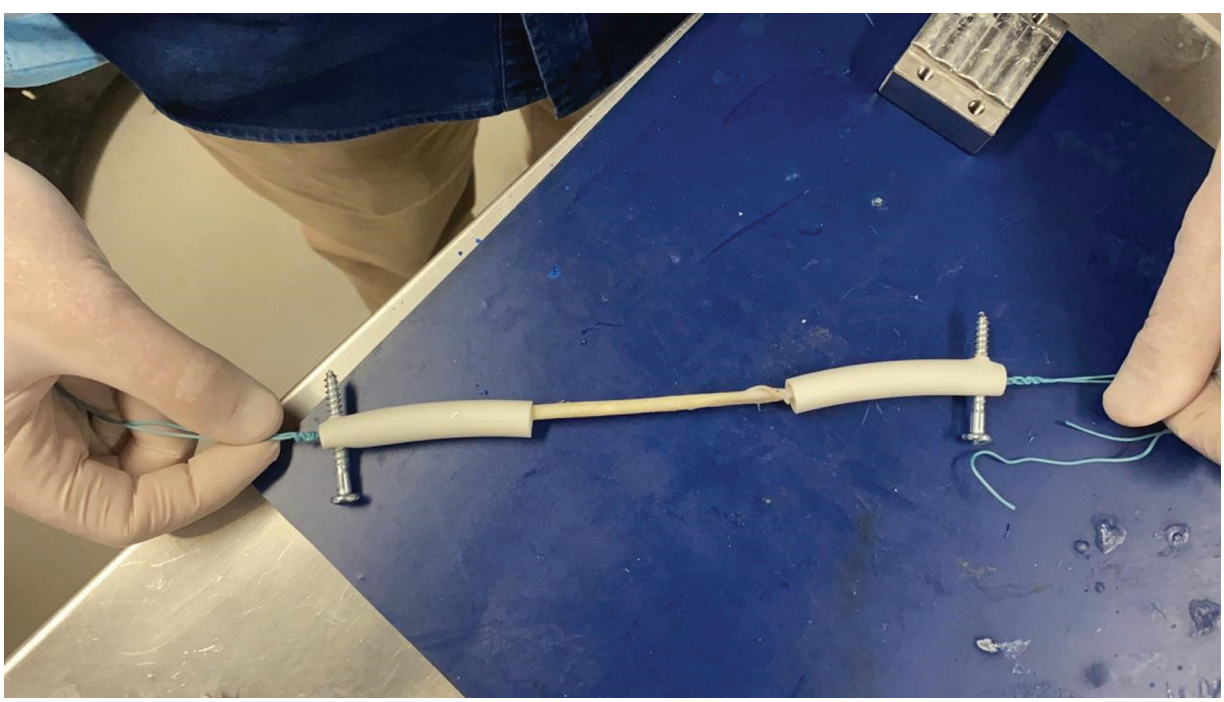


Fig. 3 Semitendinosus tendon (ST) inserted into tubes and fixated to the framework with screws.

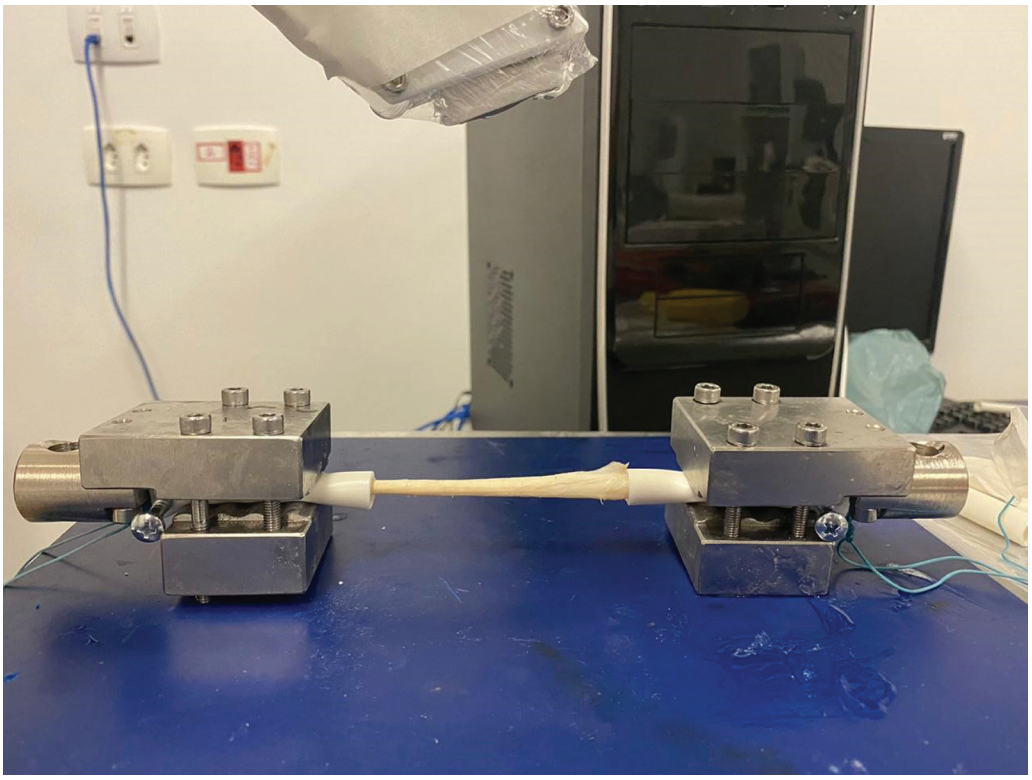


Fig. 4 Final assembly of the ST.

Statistical analysis

We calculated descriptive data, such as mean and standard deviation (SD). The Shapiro-Wilk test determined the distribution normality. The *t*-test for independent groups with Welch correction compared μ values at rest in the PT and ST samples. The Pearson correlation coefficient defined the relationship between μ under stress and tendon stress at moments of the stress x strain curve. Linear regression was performed on the distributions to measure the slope of the curve. E calculation used the slope^{-1} formula, since stress was selected as the independent variable on the x-axis. Values of $p < 0.05$ were considered significant. The analyses were performed using the GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, United States) software, version 7.0.

Results

Shear modulus at rest

The initial μ value (with no stress) of the ST was higher compared with that of the PT, which was statistically significant (ST = 124.3 ± 7.231 kPa; and PT = 58.86 ± 5.226; $p = 0.0059$) (►**Fig. 8**).

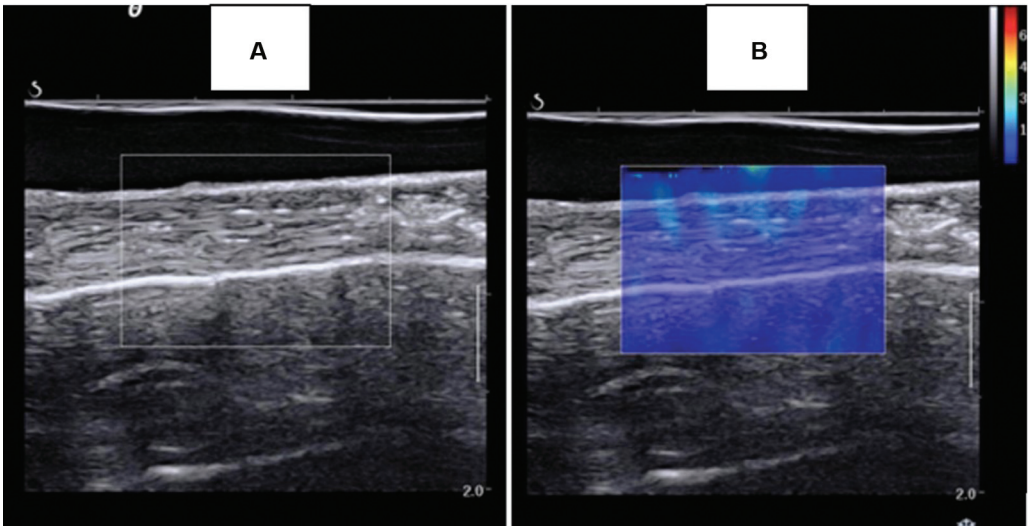


Fig. 5 . (**A**) Tendon aligned in ultrasound (US) mode B. (**B**) Region of interest (ROI) in the elastography mode.



Fig. 6. Robotic arm maintaining linear transducer positioning.

Correlation between shear modulus and stress

The μ value presented a very strong correlation with stress for both tendons (PT: $R = 0.9507$; $p < 0.0001$; and ST: $R = 0.9528$; $p < 0.0001$) (►**Table 3**).

Variation of shear modulus under stress

The variation in μ values from ST and TP under stress presented no statistically significant difference (ST: slope of 0.664 ± 0.063 kPa; and PT: 0.872 ± 0.085 kPa; $p = 0.065$). However, there was a statistically significant difference regarding the μ values of the tendons, especially noted at lower stresses (ST: an increase of 116.8–133.3 kPa; and PT: an increase of 47.14–69.31 kPa; $p < 0.0001$) (►**Fig. 9**).

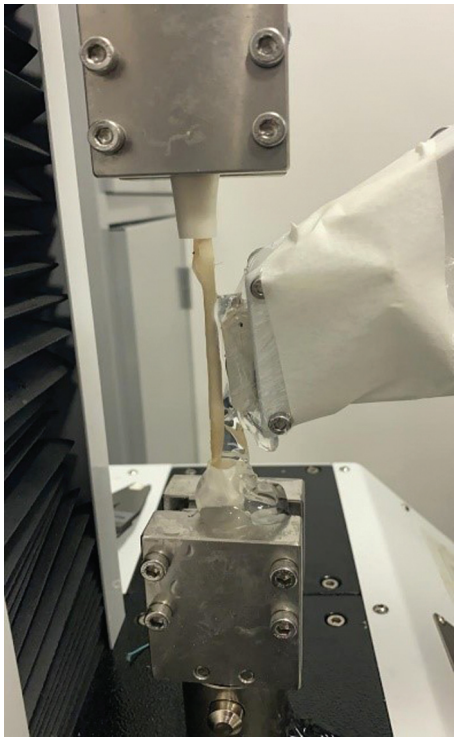


Fig. 7 Transducer positioning during testing on the traction machine.

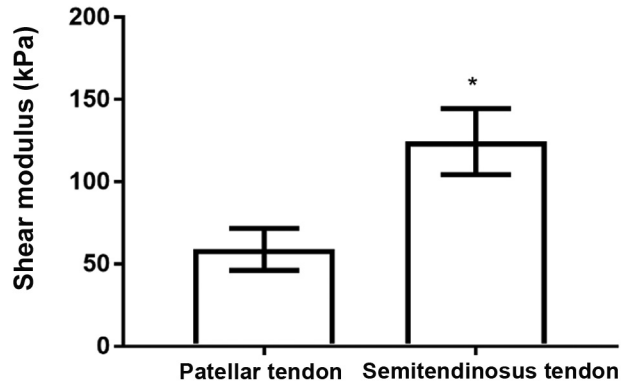


Fig. 8 Shear modulus (μ) of the PT and ST at rest. **Note:** $^{*}p < 0.05$.

Percentage of strain under stress and Young modulus

The ST showed significantly higher resistance to deformation than PT (ST: slope of 0.05 ± 0.005; and PT: slope of 0.008 ± 0.0002; $p < 0.0001$). There was a statistically significant difference between the calculated E of the tendons (ST = 124.8 kPa; and PT = 19.97 kPa; $p < 0.0001$) (►**Fig. 10**).

Discussion

Studying the mechanical properties of tendons provides information about their function and disease prevention and treatment.[1,3,18,26,27,29] In this context, the ST and PT are critical due to their wide use as grafts in surgeries for ligament reconstruction.[28]

The present study used tendons from fresh-frozen cadavers provided by the MH, not damaged by formaldehyde or ionizing radiation, enabling the evaluation of the stress x strain curve and computation of the relationship between the stress and the strain. The ST showed significantly higher resistance to strain under stress than the PT ($p < 0.0001$). We also observed a significant difference for the calculated E, showing a much higher value in the ST (ST = 124.8 Kpa; and PT = 19.97 Kpa; $0 < 0.0001$). We compared μ values from the PT and ST obtained through ultrasound with SSI assessment at rest. Again, the ST was stiffer than the PT ($ST = 124.3 \pm 7.231$ kPa; and $PT = 58.86 \pm 5.226$ Kpa; $p = 0.0059$), showing agreement between the results

Table 3 Shear modulus (μ) x stress correlation

Correlation coefficient (R)	N	μ x *stress*	*p*
Patellar tendon	7	0.9507 (0.839–0.985)	< 0.0001
Semitendinosus tendon	5	0.9528 (0.845–0.986)	< 0.0001

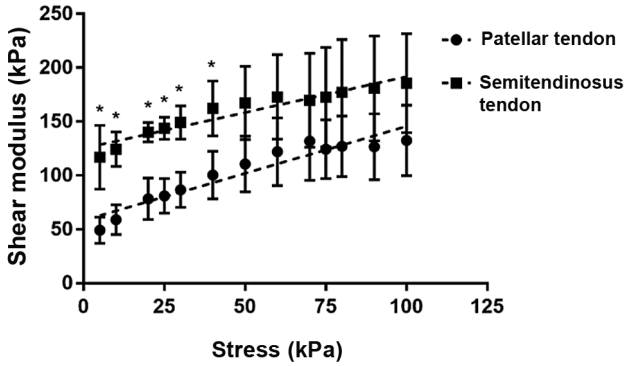


Fig. 9 Stress x shear modulus (μ) relationship. **Note:** $^{*}p < 0.05$.

obtained with SSI and those from the tensile tests. We also recorded the influence of tissue stress on the SSI assessment, showing that the greater the stress applied, the greater the μ recorded in both tendons, with a very strong correlation between the parameters (PT: $R = 0.9507$; $p < 0.0001$; and ST: $R = 0.9528$; $p < 0.0001$).

In the last decades the relevance of the SSI in real-time in-vivo tendon evaluation has been demonstrated.[7,18–20,26,27,29] A series of studies[19,29,30] have drawn attention to the importance of standardizing image acquisition, especially regarding the position of the limb examined. In 2019, for the first time, a study[8] showed the intimate relationship between the μ recorded using SSI and the stress imposed on a non-formolized human tendon; however, this work used a single specimen, presenting a low level of evidence. In the present study, we repeated this testing with two types of tendons (PT and ST), using 12 samples, showing a very strong and statistically significant correlation between these two variables. This sheds new light on the use of tendon assessment with SSI. From this moment on, it becomes critical to control the muscular action over the tendon studied, as this can significantly affect the elastographic record.

The current literature[9,12] consistently demonstrates the relationship between E and μ, although not respecting the classic mathematical estimate. Recently, in 2023, Brandão et al.[25] studied 5 PTs and 11 calcaneus tendons from fresh-frozen human cadavers, finding a strong correlation between the variation in μ recorded by SSI with the E calculated by the stress x strain curve in the biomechanical test. In the present study, stiffness was higher in the ST than in the PT, both in the SSI and the traction test, with statistical significance. This suggests that SSI can reliably measure the mechanical properties of tendons in a way comparable to the gold standard.

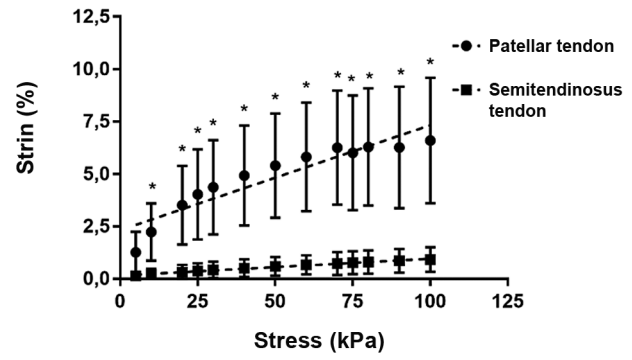


Fig. 10 Stress x strain relationship. **Note:** $^{*}p < 0.05$.

In the context of using the PT and ST as grafts for ligament reconstruction, it is interesting that these tendons not only present high RF but also elastic characteristics similar to those of the native ligament. Previous studies[5,11] have revealed a statistically significant correlation between μ and RF in normal animal tendons. Likewise, a reduction in μ and RF has been described in diseased or chemically-damaged tendons.[11,14] Therefore, SSI may be particularly useful in assessing tendons and decision-making for graft selection. However, none of these studies performed such tests on human tendons.

The findings of the present study are consistent with those of Fontenelle et al.[19] who, in 2018, reported that the in-vivo μ value of the ST was higher than that of the PT in relaxed and stressed states. This may suggest the choice of the ST when reconstructing a more rigid structure.

It is worth highlighting certain limitations of the present study. Although we obtained consistent E values by calculating the slope of the stress x strain curve,[19] the trendons were not brought to failure. The tests were interrupted when the SSI reached saturation, and the region of elastic strain of the tendon may not have been reached, which would compromise the E estimate. Furthermore, despite all care, tendon fixation to the metal claws of the traction machine was particularly difficult when there was no bone plug. This difficulty can generate micromovements at the tendon-claw interface, underestimating the deformation record obtained. Future studies must consider this.

Finally, the most appropriate graft depends on the mechanical behavior not only of the tendon, but also of the ligaments for replacement. Future research in this field should pay particular attention to the biomechanical analysis of these ligaments.

Conclusion

The ST was stiffer than the PT both in the traction test and SSI evaluation at rest and under stress, with μ values revealing a direct relationship with the stress imposed on the tendon during its assessment.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Conservative Treatment of Camptodactyly with use of Orthoses: A Retrospective Cohort

Tratamento conservador da camptodactilia com órteses: Coorte retrospectiva

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Abstract

Objective To evaluate the outcomes of conservative treatment using static orthoses manufactured by the Occupational Therapy Sector of our institution in participants with camptodactyly types I, II, and III in their rigid or flexible forms, to describe the demographic and clinical data, and to analyze the number of dropouts during the treatment period.

Methods The Ethics in Human Research Committee approved the project under protocol number CAAE 20300419.3.0000.5273. All medical records used in the research were made available by our institution. In the present retrospective study, we did not use the informed consent form due to the impossibility of contacting the high number of participants. The study included medical records of 38 participants treated at the Occupational Therapy Outpatient Clinic from 2013 to 2019.

Results Of the 54 fingers treated with orthoses, 38 were completely corrected. The rates of correction were as follows: type I in its rigid form – 100% type I in its flexible form – 81.2%; type II in its rigid form – 0%; type II in its flexible form – 100%; type III in its rigid form – 47.6%; and type III in its flexible form – 100%. Of the 93 fingers included in this study, 42% abandoned the treatment.

Conclusion Static orthoses are a safe alternative to surgical procedures, with low execution complexity for camptodactyly treatment.

Keywords
- finger joint
- hand deformities, congenital
- occupational therapy
- orthosis
- rehabilitation

Resumo

Objetivo Avaliar os resultados do tratamento conservador com o uso de órteses estáticas confeccionadas pelo Setor de Terapia Ocupacional da nossa instituição em

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participantes com camptodactilia dos tipos I, II e III, em suas formas rígida ou flexível, descrever os dados demográficos e clínicos, e avaliar o número de abandonos no período do tratamento.

Métodos O projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos, com número de protocolo CAAE 20300419.3.0000.5273. Todos os prontuários utilizados na pesquisa foram disponibilizados pela nossa instituição. Não foi feito o uso de termo de consentimento livre e esclarecido (TCLE) para este estudo retrospectivo devido à impossibilidade de contactar o elevado número de participantes. Foram incluídos os prontuários de 38 participantes atendidos no Ambulatório de Terapia Ocupacional de 2013 a 2019.

Resultados Dos 54 dedos tratados com órteses, 38 foram totalmente corrigidos. As taxas de correção foram as seguintes: tipo I na forma rígida –100%; tipo I na forma flexível –81,2%; tipo II na forma rígida – 0%; tipo II na forma flexível – 100%; tipo III na forma rígida –47,6%; e tipo III na forma flexível –100%. Do total de 93 dedos incluídos, 42% abandonaram o tratamento.

Conclusão O uso de órteses estáticas é uma alternativa segura ao procedimento cirúrgico e de baixa complexidade de execução para o tratamento da camptodactilia.

Palavras-chave

- articulações dos dedos
- deformidades congênitas da mão
- órteses
- reabilitação
- terapia ocupacional

Introduction

Camptodactyly is a permanent flexion deformity of the proximal interphalangeal (PIP) joint in one or more fingers, except the thumb, of non-traumatic cause.[1] The fifth finger is generally the most affected, and it may present hyperextension of the metacarpophalangeal joint (MCP).[2,3] For Monteiro and Almeida,[4] camptodactyly is a flexion deformity in the anteroposterior plane (►**Fig. 1**).

According to the classification by Benson et al.,[5] camptodactyly consists of the following types: Type I – children's camptodactyly, the most common form, which often affects the little finger alone (►**Fig. 2A**); type II – adolescent camptodactyly, which predominates in females and presents clinically as type-I (►**Fig. 2B**); type III – it is present since birth, affects several fingers, and is often bilateral and associated with syndromes and other malformations; in addition, it features rigid and accentuated shapes (►**Fig. 2C**).

Camptodactyly is painless and affects approximately 1% of the population.[6] Some families present an autosomal dominant trait with variable penetrance.[7] In other cases, the deformity appears casually. Approximately 75% of the cases are bilateral and progress during the skeletal growth spurt, mainly in the age groups ranging from 1 to 4 and 10 to 14 years.[4]

The fingers of camptodactyly subjects present several abnormal structures. Numerous abnormalities have been implicated as the primary cause, but with no consensus.[8] It can manifest as changes in various structures responsible for joint balance.

The patient may present shortening of the superficial flexor tendon of the finger, of the skin, of the PIP joint capsule, and aponeurosis, in addition to abnormalities in lumbrical muscle attachment, or intrinsic muscle insufficiency. All of these structures have been related to camptodactyly, but none of them has been proven to be an etiological factor.[1,2,8–14]

Goffin et al.[15] reported that hand function is not affected in patients with up to 30° of flexion, with functional compromise above 60°. The most common complication of the surgical treatment for camptodactyly correction is the loss of total flexion of the finger. Almeida et al.[16] stated that incomplete extension is more desirable than deficient flexion. Patients must use orthoses even after the surgical treatment.[17–19] The use of orthoses (►**Figs. 3A-D**, **4A-C**, and **5A-D**) for camptodactyly treatment is based on the principle of soft tissue remodeling, a fundamental concept for the theory and technique of immobilization known empirically since ancient times. Slow, gentle, prolonged stress causes soft tissues to remodel or grow.[20]

The primary reason to select an orthosis is the biological principle of connective tissue remodeling. This remodeling is a response to time and stress inflicted on the connective tissue, and it consists of a physical rearrangement of the



Fig. 1 Clinical presentation of a patient with camptodactyly. Flexion of the proximal interphalangeal (PIP) joint of the fifth finger.



Fig. 2 Types of camptodactyly according to the Benson et al.[5] classification. (**A**) Type I: PIP joint flexion in the middle and little fingers. (**B**) Type II: PIP joint flexion of the little finger. (**C**) Type III: PIP joint flexion in the middle, ring, and little fingers.

tissue's extracellular matrix. It is not a quick process, and it is directly associated with the frequency of use and total time of daily use.[21] Joint contracture correction requires a constant and low-load force applied for a sufficient period to cause stretching and the creation of new tissue. Adjustments are also necessary to accommodate the changes achieved and maintain the alignment of mechanical force. Despite controversies regarding the mechanism of action on soft tissue, the result is an adaptation to the presence or absence of force, increasing or decreasing in size and remodeling to accommodate the stress received.[22] Living tissues have mechanical sensors to detect pressure, direct force changes, touch, and stretching. The key is to establish the amount of stimulus needed to promote cellular tissue modification and remodeling. Although the first observations of the influence of forces on the shape and function of tissues occurred around 150 years ago, there is still much to uncover.[23]

The present study is relevant due to several camptodactyly types and structures potentially involved. In addition, the alternative of surgical treatment often results in the loss of complete flexion in the treated finger.

We aimed to evaluate the conservative treatment with static orthoses for all types of camptodactyly in patients treated at our service.

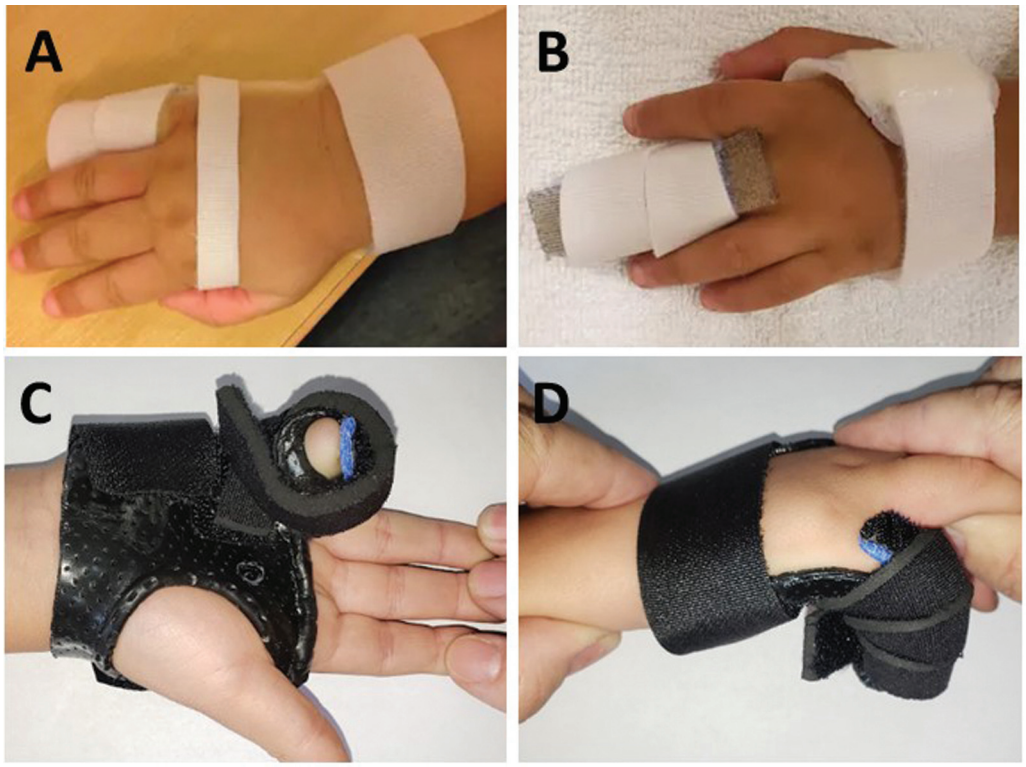


Fig. 3 Models of static orthoses with dorsal support used for type-I camptodactyly. (**A**) Static orthosis for flexible camptodactyly on the little finger; (**B**) static orthosis for flexible camptodactyly in the middle finger; (**C**) static orthosis for rigid camptodactyly in the little finger with flexed metacarpophalangeal (MCP) joint, volar view; and (**D**) static orthosis for rigid camptodactyly in the little finger with flexed MCP joint, lateral view.



Fig. 4 Models of static orthoses with dorsal support for rigid type-II camptodactyly. (**A**) Bilateral rigid type-II camptodactyly: PIP joint flexion in the little finger; (**B**) static orthosis for rigid camptodactyly in the little finger with flexed MCP joint, dorsal view; and (**C**) short static orthoses for daytime use.

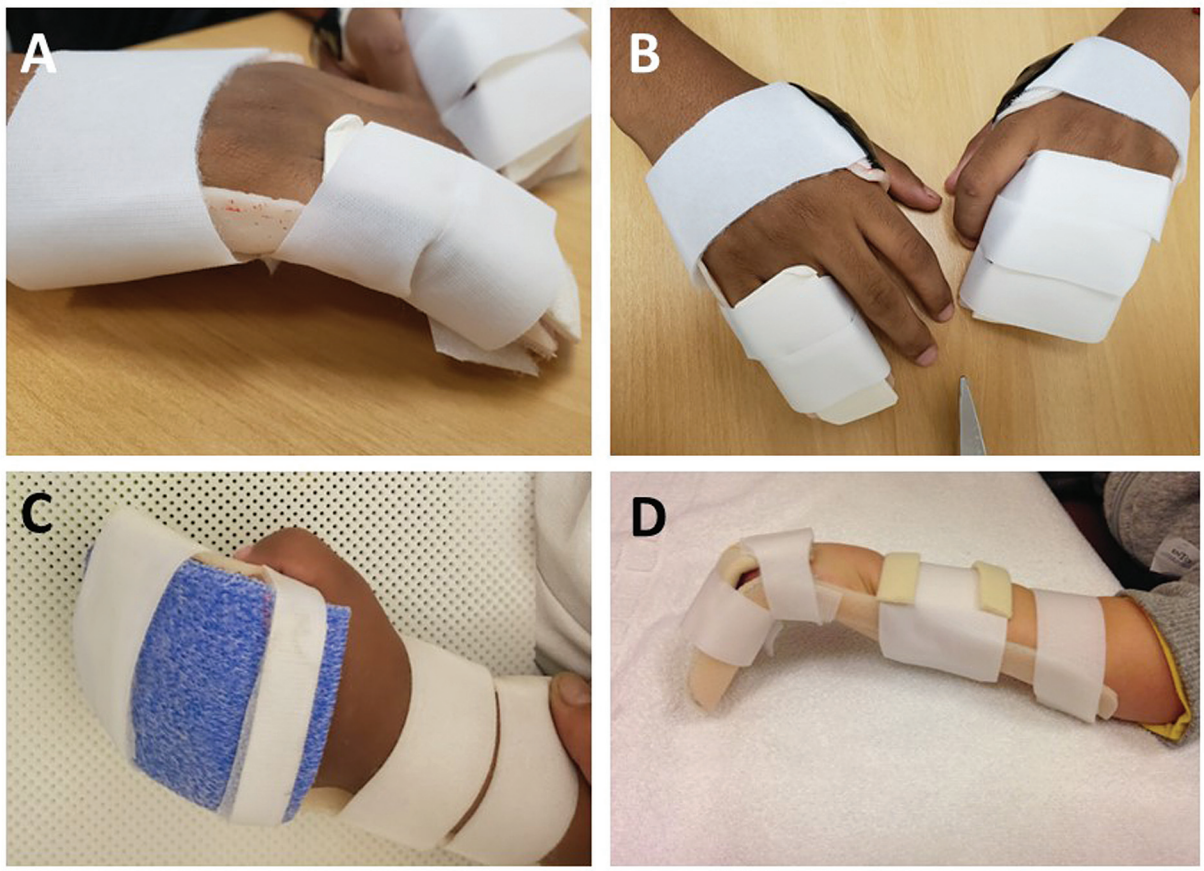


Fig. 5 Models of static orthoses with dorsal support used for rigid type-III camptodactyly. (**A**) Static orthosis for rigid camptodactyly in the little and ring fingers, lateral view; (**B**) static orthoses for rigid camptodactyly in the little and ring fingers of the right hand, and the little, ring and middle fingers of the left hand; (**C**) static orthosis for camptodactyly encompassing all fingers, with flexed MCP joint; and (**D**) static orthosis for camptodactyly encompassing all fingers and flexed MCP joint.

Materials and Methods

The Ethics in Human Research Committee approved the project of the present study under protocol number CAAE 20300419.3.0000.5273. All medical records used in the research were made available by our institution. The present retrospective study did not use the informed consent form due to the impossibility of contacting the high number of participants.

Study Design

The present observational retrospective cohort study included six cohorts, one for each type of camptodactyly (I, II, or III) with rigid or flexible presentation according to the Benson et al. classification.[5] For each of the six cohorts, we evaluated the proportion of patients achieving correction and the average time to correct the type and form of camptodactyly. We also assessed the frequency of affected fingers and the dropout rate from the conservative treatment. We

Table 1 Distribution of the participants according to sex and camptodactyly type

Type		I	II	III	Total	p^*
Sex	Male	10	1	6	17	0.124
	Female	12	6	3	21	

Note: *Fisher exact test.

considered camptodactyly correction as complete extension of the finger without loss of flexion.

Sample Composition

The present study included medical records from participants diagnosed by the Specialized Care Center (SCC) of the Hand with camptodactyly of types I, II, and III in their rigid or flexible forms. All medical records from patients undergoing surgery for other associated deformities or with another type of congenital deformity not related to camptodactyly were excluded.

Data Collection

We used the Epi Info (Centers for Disease Control and Prevention, Atlanta, GA, United States) software, version 7.2.3.1, and developed a form-type instrument specifically for the present research. Data collection followed the protocol created for the current study. We collected the demographic data of the 38 patients, in addition to camptodactyly data (affected finger, type and form of camptodactyly), as well as data on corrections and dropouts, and treatment time (date of birth, dates of the beginning and end of the follow-up, date when the camptodactyly correction was recorded, and date of dropout, if applicable).

Outcome

Deformity correction implies complete extension of the finger, with no loss of flexion. We calculated the correction proportion using the fingers of participants who adhered to the treatment and achieved correction of their type and form of camptodactyly. The dropout rate consisted of the fingers of participants who did not adhere to treatment for the time established in this cohort.

Statistical Analysis

The descriptive analysis used proportions for the categorical variables, and mean, standard deviation, median, minimum, maximum, and quartile values for the quantitative variables. Due to the low sample size, all comparative analyses consisted of non-parametric tests, such as the Wilcoxon-Mann-Whitney test. In addition, we presented the median and interquartile range of the six cohorts. Categorical variables were correlated in contingency tables and evaluated with the Fisher exact test.

Results

The current study analyzed data from the medical records of 38 participants and a total of 93 affected fingers. ►**Table 1** describes the sociodemographic characteristics. There was no association between sex and camptodactyly types according to the Fisher exact test ($p = 0.124$).

►**Table 2** shows the distributions of camptodactyly types and forms in each of the six cohorts. The rigid form prevailed in our sample, affecting 60 fingers ($n = 93$; $0 = 0.007$). Considering each camptodactyly type, the rigid and flexible forms did not present the same proportions ($p = 0.003$) For type III, the prevalence of the rigid and flexible forms was different ($p < 0.001$), and the rigid form occurred in 85% of the affected fingers. Considering each finger (►**Table 2**), type II presented an association between the form and the affected finger ($p = 0.005$). The little finger demonstrates a greater prevalence of the rigid than the flexible form ($p = 0.027$).

Table 2 Prevalence of types and forms of camptodactyly per affected finger

Type	Form	N	Index	Middle	Ring	Little	p^*
I	Rigid	22	0	7	5	10	0.926
	Flexible	23	0	6	5	12	
	Total	45	0	13	10	22	
II	Rigid	9	0	0	0	9	0.005
	Flexible	5	0	2	2	1	
	Total	14	0	2	2	10	
III	Rigid	29	2	8	10	9	> 0.99
	Flexible	5	0	1	2	2	
	Total	34	2	9	12	11	

Note: *Fisher exact test.

Table 3 Occurrence of camptodactyly in the affected fingers

Type	N	Index: n (%)	Middle: n (%)	Ring: n (%)	Little: n (%)	p^*
I	45	0 (0.0)	13 (28.9)	10 (22.2)	22 (48.9)	< 0.001
II	14	0 (0.0)	2 (14.3)	2 (14.3)	10 (71.4)	< 0.001
III	34	2 (5.9)	9 (26.5)	12 (35.4)	11 (32.4)	0.023
Total	93	2 (2.2)	24 (25.8)	24 (25.8)	43 (46.2)	< 0.001

Note: *Proportion test.

Table 4 Distribution of frequencies of the fingers of participants who dropped out of the treatment before achieving correction

Type	Form	N	Dropout: n (%)	p^*
I	Rigid	22	13 (59.1)	0.075
	Flexible	23	7 (30.4)	
	Total	45	20 (44.4)	
II	Rigid	9	7 (77.8)	> 0.99
	Flexible	5	4 (80.0)	
	Total	14	11 (78.6)	
III	Rigid	29	8 (27.6)	0.309
	Flexible	5	0 (0.0)	
	Total	34	8 (23.5)	

Note: *Fisher exact test.

►**Table 3** shows that the little finger was the most affected ($p < 0.001$), representing 46% of the fingers with camptodactyly. The middle and ring fingers were equally affected (26%). The least affected finger was the index finger, representing 2% of the total. A total of 20 participants had unilateral involvement: 6 subjects had multiple fingers affected, and 14 had a single finger with camptodactyly. And 18 participants presented bilateral involvement, 10 of them with multiple fingers affected. One participant presented both forms, rigid and flexible, simultaneously.

►**Table 4** shows the dropout frequency. From the 93 fingers included, 39 abandoned the treatment. Type II had the highest (78.6%) dropout frequency, whereas type III had the lowest (23.5%). The proportion of dropouts among participants with type-III in the flexible form was of zero. Despite this, there was no association between camptodactyly form and dropout (type I: $p = 0.075$; type II: $p > 0.99$; and type III: $p = 0.309$).

►**Table 5** shows the proportion of camptodactyly correction with static orthoses. Of the total of 54 fingers of participants adhering to the treatment, 38 (71.7%) presented complete correction. The correction rate was of 59% for fingers with rigid camptodactyly, and of 86% for fingers with flexible camptodactyly. There was no

Table 5 Distribution of frequencies of the fingers of participants who adhered to treatment and achieved camptodactyly correction

Type	Form	N	Correction: n (%)	p^*
I	Rigid	9	9 (100.0)	0.280
	Flexible	16	13 (81.2)	
	Total	25	22 (88.0)	
II	Rigid	2	0 (0.0)	0.333
	Flexible	1	1 (100.0)	
	Total	3	1 (33.3)	
III	Rigid	21	10 (47.6)	0.053
	Flexible	5	5 (100.0)	
	Total	26	15 (57.7)	

Note: *Fisher exact test.

Table 6 Distribution of the time in months until correction of camptodactyly with static orthoses

Type	Form	N	Mean	SD	Min.	Max.	Median	Q1	Q3	p^*
I	Rigid	9	7	±9	1	22	4	1	11	0.705
	Flexible	13	3	±4	1	15	2	2	4	
	Total	22	5	±6	1	22	2	1	4	
II	Rigid	0	0	±0	0	0	0	0	0	NA
	Flexible	1	7	NA	7	7	7	7	7	
	Total	1	7	NA	7	7	7	7	7	
III	Rigid	10	18	±8	9	24	24	9	24	0.006
	Flexible	5	6	±3	4	9	4	4	9	
	Total	15	14	±9	4	24	9	9	24	

Abbreviations: Max, maximum; Min, minimum; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Notes: *Mann-Whitney test. The values of mean ± SD, minimum, maximum, median, Q1, and Q3 refer to the months until correction.

association between camptodactyly form and correction, but there was a trend favoring type III in the flexible form ($p = 0.053$).

►**Table 6** shows the time required for correction. Type-I camptodactyly presented the shortest median time until correction (two months). Type-III rigid camptodactyly presented the longest median time until correction (24 months). There was no association regarding the time until correction between the rigid and flexible forms in type I ($p = 0.705$). We could not calculate this association for type II because there was no correction for the rigid form. Type III presented an association between the time until correction and the rigid or flexible forms. Correction of the flexible form occurred in sooner ($p = 0.006$).

Discussion

Consistent with the literature,[16,24,25] the little finger was the most affected in the sample of the present study. In contrast, the literature reported a bilaterality rate of 75%,[4] but this rate was lower than 50% in our patients. In a systematic review, Wang et al.[8] could not determine the best treatment for camptodactyly. However, there was consensus among the authors regarding the inaccuracy of the surgical outcome and the need to use orthoses before and after surgery.

The use of orthoses would be the way to maintain the correction achieved or even start it. Most of the articles in the literature agreed that the conservative approach with orthoses should be the first-line treatment, restricting surgery to severe cases that could not be corrected with the use of these devices.[5,8,9,14,15,17,18,24,26–30]

The most common postoperative complications reported by Almeida et al.[16] were vascular structure injury, scar tension, and loss of full flexion of the treated finger. However, functionally, incomplete extension is better than loss of flexion.[16]

The results of the current study provide evidence that keeping the finger in flexion for many years can lead to a structured deformity and possible ankylosis of the PIP joint. Therefore, ankylosis became a contraindication for conservative treatment in our service.

The dropout rate was high among participants of the present study, but the literature lacks data on dropout during conservative treatment. Participants with type-II camptodactyly presented the highest dropout rate, followed by subjects with type I (44%). Some participants with type-I camptodactyly had their first orthosis made and did not return. The dropout rate among participants with type-III camptodactyly was the lowest. We believe that, because of the severity of type-III camptodactyly, which affects several fingers simultaneously and has been associated with syndromes,[5] these participants have more reasons to remain in treatment and a higher commitment from their caregivers and legal guardians. For type II, which appears in adolescence,[5] participants may present higher rates of dropout because they are old enough to give their opinion, accept the deformity, and decide whether or not to continue with treatment. Another hypothesis for the high number of participants who abandoned treatment would be the fact that they were looking for a quick solution, such as surgery, and when they found another type of longer approach, they gave up. This data was not found in the literature, but was observed in the rehabilitation clinic for this population.

The main outcome, camptodactyly correction with static orthoses, was calculated only for the fingers of participants who adhered to the conservative treatment. Correction of the rigid form of type I was complete, and the flexible form was corrected in 81.2% of the cases. Type-II correction occurred in 33% of the cases, with the flexible form being completely corrected, as described by Goffin et al.[15] These authors reported that flexible type-II camptodactyly is more easily correctable with orthoses. For type III, the flexible form was completely corrected, while the rigid form presented a correction rate of 48%. Overall, rigid camptodactyly was corrected in 59% of the fingers, and flexible camptodactyly, in 86% of the fingers within the cohort observation period. It is worth highlighting that most subjects from our cohorts used orthoses with dorsal support, which have not been described in any study consulted. We believe that this difference facilitates deformity correction, as the dorsal support enables better positioning of the PIP joint in the orthosis.

Conclusion

The use of static orthoses for camptodactyly treatment, especially types I and III, started early and has proven to be a safe, effective, and low-complexity solution. After analyzing the data from our sample, we consider that conservative treatment can and should be indicated as the first alternative for camptodactyly correction. However, it is necessary to make it clear to the patient/legal guardian that discipline in the use of orthoses is a decisive factor in achieving the successful correction of the deformity.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Surgical Rhizarthrosis Treatment: Trapezius Resection Arthroplasty Associated with Tendon Interposition versus the Kuhns Technique

Tratamento cirúrgico da rizartrose: Artroplastia de ressecção do trapézio associada a interposição tendínea versus *técnica de Kuhns*

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Abstract

Objective This study aimed to evaluate and compare the clinical and functional outcomes of two surgical procedures performed in patients with severe grade III and IV rhizarthrosis.

Methods We evaluated 39 patients who underwent two surgical techniques for rhizarthrosis treatment: trapeziectomy using the Kuhns technique or tendon interposition, with a minimum follow-up period of 6 months. The primary outcome assessment used the specific Trapeziometacarpal Arthrosis Symptoms and Disability (TASD) questionnaire, and the secondary outcome evaluation employed the shortened version of the Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire and the Visual Analog Scale (VAS).

Results There was no statistically significant difference between groups in the TASD, QuickDASH, and VAS results, and both techniques demonstrated good functional and pain outcomes. No complication required a new surgical approach. We found a positive correlation between TASD and QuickDASH questionnaire scores, suggesting they are both effective in assessing functionality and disability in subjects with rhizarthrosis.

Conclusion Trapeziectomy using the Kuhns technique and tendon interposition proved effective in the surgical treatment of rhizarthrosis. There was no significant difference between the techniques concerning functional outcomes.

Keywords
- orthopedic procedures
- osteoarthritis
- trapezium bone

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Resumo

Objetivo O objetivo deste estudo é avaliar e comparar os resultados clínicos e funcionais de dois procedimentos cirúrgicos realizados em pacientes com rizartrose grave graus III e IV.

Métodos Avaliamos 39 pacientes submetidos a 2 técnicas cirúrgicas para o tratamento da rizartrose: trapeziectomia pela técnica de Kuhns ou com interposição tendínea, com mínimo de 6 meses de seguimento. O desfecho primário foi avaliado pelo questionário específico Sintomas e Incapacidade da Artrose Trapeziometacarpiana (Trapeziometacarpal Arthrosis Symptoms and Disability, TASD, em inglês), e os desfechos secundários, pela versão abreviada do Questionário de Incapacidades do Braço, Ombro e Mão (Disabilities of the Arm, Shoulder, and Hand, QuickDASH, em inglês) e a Escala Visual Analógica (EVA).

Resultados Não houve diferença estatisticamente significantativa entre os grupos nos resultados do TASD, QuickDASH e EVA e ambas as técnicas demonstraram bons resultados funcionais e da dor. Não houve complicações que necessitassem de nova abordagem cirúrgica. Verificamos uma correlação positiva entre as pontuações no TASD e no QuickDASH, o que sugere que ambos são eficazes na avaliação da funcionalidade e incapacidade da rizartrose

Conclusão A trapeziectomia com técnica de Kuhns e com a interposição tendínea se mostraram efetivas no tratamento cirúrgico da rizartrose. Não houve diferença significativa entre as técnicas em relação aos resultados funcionais.

Palavras-chave

- osso trapézio
- osteoartrite
- procedimentos ortopédicos

Introduction

Rhizarthrosis is a progressive degenerative condition affecting the carpometacarpal joint of the thumb. It is one of the most common forms of osteoarthritis in the hands, and it is more frequent in women oldr than 50 years of age. This condition can be debilitating, limiting the subjects' daily living and work capacity.[1] Several therapeutic options are available to manage symptoms and improve quality of life, including lifestyle changes, motor and analgesic physical therapy, orthoses, pharmacological treatments, infiltrations, and surgery.[2]

Surgical treatment is an option for patients with rhizarthrosis who do not obtain symptom relief through nonsurgical therapies.[2] Trapeziectomy is a resection arthroplasty of the trapezius that was first described is by Gervis, with good outcomes.[3] Some authors described the metacarpal's proximal migration and the compromised functional outcomes as complications of this technique.[4] Thus, to prevent these complications, techniques associated with trapeziectomy were described, including tendon interposition,[5] ligament reconstruction,[6] arthroplasty with implants,[7] the distraction hematoma formation technique (Kuhns technique),[8] ligament reconstruction with tendon interposition,[6] and acellular material interposition.[5] Although these associated techniques can be effective, they may increase the risk of other complications, such as infection, pain, implant loosening, and muscle strength loss.[4] The current literature has no studies with conclusive evidence regarding the most effective technique for the surgical treatment of rhizarthrosis.[4]

Therefore, this study aimed to evaluate two surgical techniques: trapeziectomy with the Kuhns technique and with tendon interposition, in 39 patients, with a minimum follow-up period of 6 months.

These techniques were chosen due to the high number of patients who underwent these procedures to provide a comprehensive and representative analysis, allowing a significant comparison between them and contributing to validating the obtained results.

Materials and Methods

This retrospective cohort study evaluated 39 patients. Inclusion criteria were the following: patients with clinical and imaging diagnosis of Eaton and Littler grade-III and -IV rhizarthrosis,[9] from both sexes, who underwent surgical treatment with trapeziectomy using the Kuhns technique[8] (group 1, n = 18), or trapeziectomy with tendon interposition[5] (group 2, n = 21), from 2018 to 2022, operated by four experienced hand surgeons, with a minimum follow-up period of 6 months.

Data were collected from the electronic records of the study's hospital, searching for patients with the following diagnosis codes of the International Classification of Diseases, Tenth Revision (ICD-10): M18.0, M18.1, and M19.9. Retrieved information included age, sex, operated side, dominant side, degree of osteoarthritis, and type of surgical procedure (►**Table 1**).

Exclusion criteria were the following: patients with rheumatological, traumatic, or neurological diseases affecting hand or wrist joints, those who underwent previous surgery in the thumb region, those lost to postoperative follow-up, and those who did not sign the informed consent form for the study.

Table 1 Demographics of the patients

Data	Group 1	Group 2	Total	*p*-value
Mean age (in years)	62.4	58.0	60.1	0.056
Sex	94.5% F	90.5% F	92.4% F	0.052
	5.5% M	9.5% M	7.6% M	
Dominant side	94.5% R	81% R	87.2% R	0.921
	5.5% L	19% L	12.8% L	
Operated side	44.5% R	42.9% R	43.6% R	0.209
	55.5% L	57.1 L	56.4% L	
Arthrosis grade (Eaton and Littler)	67% III	72% III	70% III	
	33% IV	28% IV	30% IV	0.748
Questionnaire application time (in months)	Mean: 39.8	Mean: 21.6		
	Minimum: 8	Minimum: 6	Mean: 30	0,08
	Maximum: 62	Maximum: 50		

Abbreviations: III, grade III; IV, grade IV; F, female; L, left; M, male; R, right.

After inclusion, we invited patients for an in-person assessment in a single outpatient visit with four residents in hand surgery. We asked the patients to answer questionnaires about their clinical and functional outcomes, including the Trapeziometacarpal Arthrosis Symptoms and Disability (TASD),[10] the shortened version of the Disabilities of the Arm, Shoulder, and Hand (QuickDASH),[11] and the Visual Analog scale (VAS)[12] for pain, as shown in the ►**Annexes 1**, **2**, and **3**. The average time between the surgical procedure and the application of the questionnaires was 30 months.

For statistical analysis, we imported data to the IBM SPSS Statistics for MacOS (IBM Corp., Armonk, NY, USA) software, version 25.0. The descriptive statistics of categorical data included absolute and relative frequency. Continuous data underwent the Shapiro-Wilk normality test, and their description used mean ± standard deviation (SD), median, and 25th and 75th percentiles. Data with parametric distribution underwent the Student *t* test for two independent samples, while those with nonparametric distribution underwent the Mann-Whitney test for two independent samples. A difference was statistically significant when the type-I error, that is, the *p*-value, was lower than 0.05.

Surgical Procedures Performed and Evaluated in the Study

For the first group, we performed the surgical technique described by Kuhns[8] using a longitudinal dorsal approach of approximately 4 cm in the carpometacarpal joint of the thumb between the tendon of the abductor pollicis longus muscle and the tendon of the extensor pollicis brevis muscle. Next, we opened the joint capsule in a T shape to expose and remove the trapezius; fixation was performed under radioscopy with two 1.5-mm Kirschner wires between the first and second metacarpals, maintaining the carpometacarpal joint space (►**Fig. 1**). The procedure ended with suturing the joint capsule and skin. Then, a sterile dressing and an antebracheopalmar plaster splint, including the thumb, were applied and kept for 4 weeks. We removed the Kirschner wires in the outpatient clinic 4 weeks after the surgery.

As for the second group, a trapeziectomy and tenoarthroplasty technique was performed with the palmaris longus muscle,[5] using the same approach described for group 1. Then, we resected the tendon and the palmaris longus muscle using three approaches (►**Fig. 2**), creating a ball, and interposing it between the scaphoid and metacarpal bones (►**Figs. 3**–**4**). We closed the joint capsule (►**Fig. 5**), sutured the incision, and applied a bandage and a plaster splint. The sutures were removed after 2 weeks and immobilization was maintained for 4 weeks.

Clinical Outcomes

Primary Outcome

The primary outcome was the TASD questionnaire,[10] which consists of a specific self-reported assessment of rhizarthrosis-related functional limitations. The TASD was translated and culturally adapted to Brazilian Portuguese in 2021.[13] It contains a series of questions about pain intensity and functional thumb capacity. The answers are scored from 0 to 100, with higher scores indicating higher dysfunction.

Secondary Outcomes

The QuickDASH[11] assesses upper limb functional disability and pain, listing 11 related activities. The answers are scored from 0 to 100, and higher scores indicate greater functional disability and pain reported by the patients.

The VAS[12] assesses the intensity of pain reported by patients. It consists of a horizontal line with a scale from 0

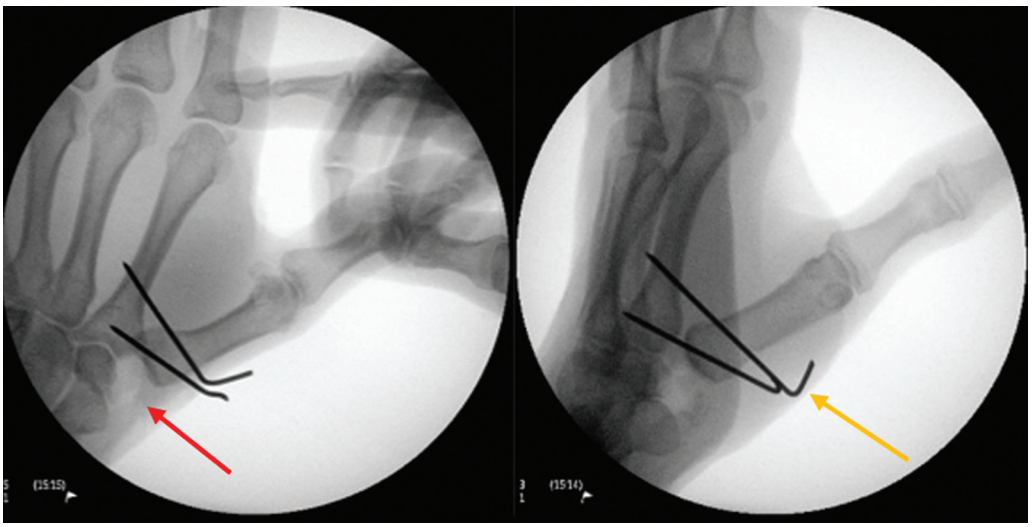


Fig. 1 Completed surgical procedure using the Kuhns technique. Intraoperative images demonstrating the space (red arrow) after trapezium bone resection and the two Kirschner wires (yellow arrow) used to fixate the first to the second metacarpal bones.

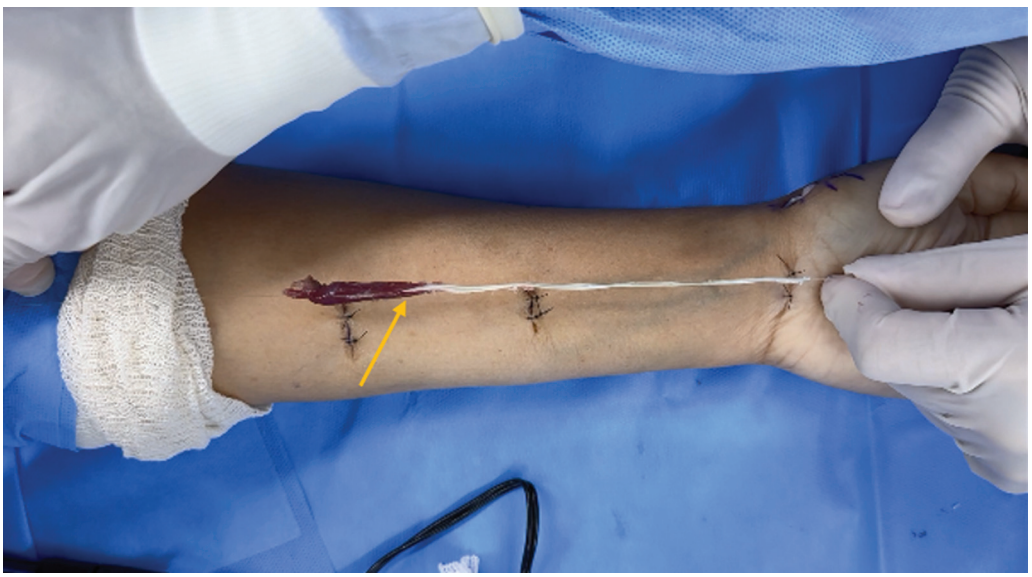


Fig. 2 Image demonstrating the removal of the palmaris longus muscle for use as a graft. Palmaris longus muscle's musculotendinous graft (yellow arrow) removal from the three approaches.

to 10, in which 0 represents no pain, and 10, maximum pain. Patients were asked to mark the degree of pain they were feeling at that moment on the scale.

A single evaluator not linked to the study applied the questionnaires during outpatient visits to ensure the standardization of data collection.

The ethics committee of our institution approved the study under the CAAE number 71550023.1.0000.5487.

Results

The average time to apply the questionnaire to patients was of 30 months postoperatively, with a minimum time of 8 and a maximum of 62 months for group 1, and a minimum time of 6 and a maximum of 50 months for group 2 (►**Table 1**).

In the analysis of the primary outcome, the mean TASD score was of 25.2 ± 27.5% in the Kuhns technique group, and of 24.9 ± 22% in the tendon interposition group (►**Fig. 6**).

In the analysis of the secondary outcomes, the mean QuickDASH score was of 25.5 ± 30.7% in the Kuhns technique group and of 31.6 ± 24.6% in the tendon interposition group (►**Fig. 7**).

As for pain, the mean VAS score was of 3.2 ± 3.2% in the Kuhns technique group, and of 3.0 ± 2.7% in the tendon interposition group (►**Fig. 8**).

We found a positive correlation between the TASD and QuickDASH scores: an increase in the score on one questionnaire corresponded to an increase in the score on the other questionnaire. This suggests that both tools are effective in measuring aspects related to functionality and disability in rhizarthrosis in a consistent manner (►**Fig. 9**).



Fig. 3 Palmaris longus muscle graft before being placed at the trapezius site.



Fig. 5 Joint capsule closure.



Fig. 4 Graft placement at the site of the resected trapezius.

Discussion

The study sample was homogeneous and representative, as described in the literature.[1] This study used the TASD questionnaire as the primary outcome, and the QuickDASH questionnaire and the VAS as secondary outcomes, since these tools assess function and potential limitations in daily living activities and pain in operated patients. The literature reports that these are the most appropriate tools to evaluate the effectiveness of surgical treatment.[10,11]

Our positive functional outcomes with the Kuhns technique[8] were consistent with those reported in the literature.[5,8,14] We observed as advantages of this technique, a shorter surgical time, the lack of need to make new incisions, and the exemption from tendon graft removal. These benefits simplify the procedure and result in a faster postoperative recovery, potentially reducing complications associated with additional incisions and grafting procedures. Its disadvantages are the potential complications inherent to the insertion and maintenance of the Kirschner wire and the need for a second procedure for pin removal, which occurred in the outpatient clinic of the institution in which the present study was conducted.

The technique of trapeziectomy with tenoarthroplasty of the palmaris longus muscle also seeks to avoid proximal migration of the first metacarpal bone by using the tendon graft as a biological spacer. The main advantage is the use of an autologous graft with no synthetic implant requirements. As the main disadvantages of this technique, we noted that, despite its performance on the same operated limb, it is limited for patients who lack the palmaris longus muscle and scarring complications from graft removal. The positive functional outcomes noted with the use of this technique in the present study are consistent with those of the literature, in which several authors[5,15] have reported good and excellent outcomes.

Comparing both surgical techniques, we observed that trapeziectomy with long palmar muscle tendon interposition was not superior to the Kuhns technique. Although we did not find studies specifically comparing both procedures, the outcomes were consistent with the literature addressing similar surgical techniques.[16–19] The findings of this review support the effectiveness of both approaches in rhizarthrosis treatment.

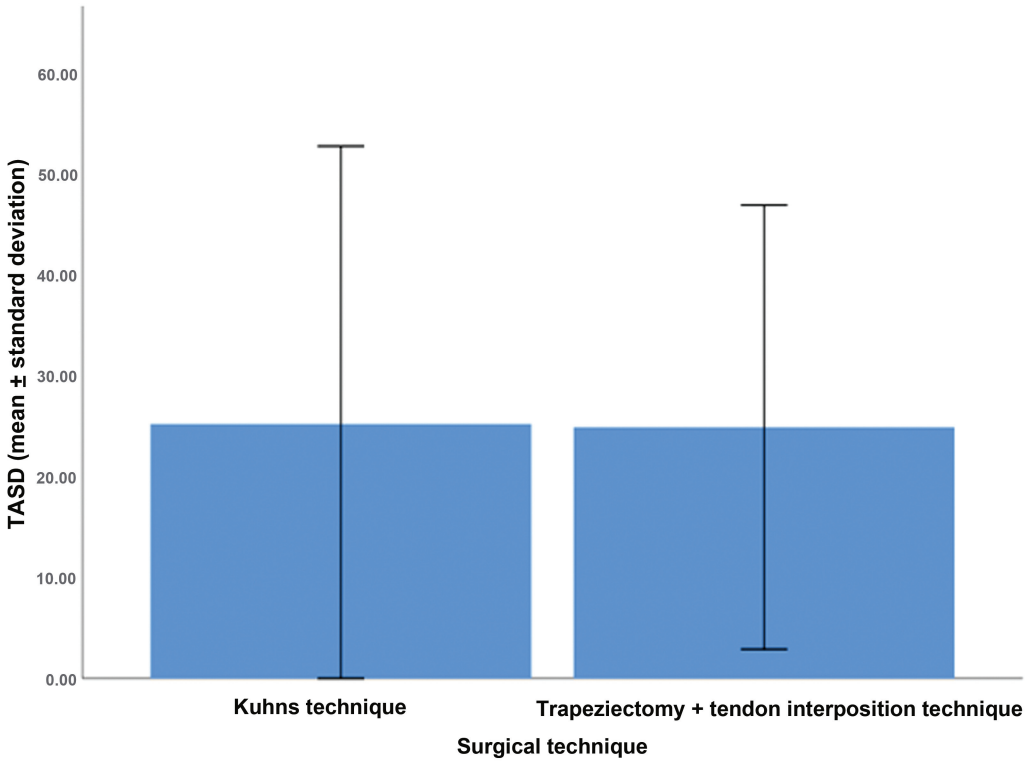


Fig. 6 Analysis of the TASD scores in patients who underwent the Kuhns or tendon interposition techniques.

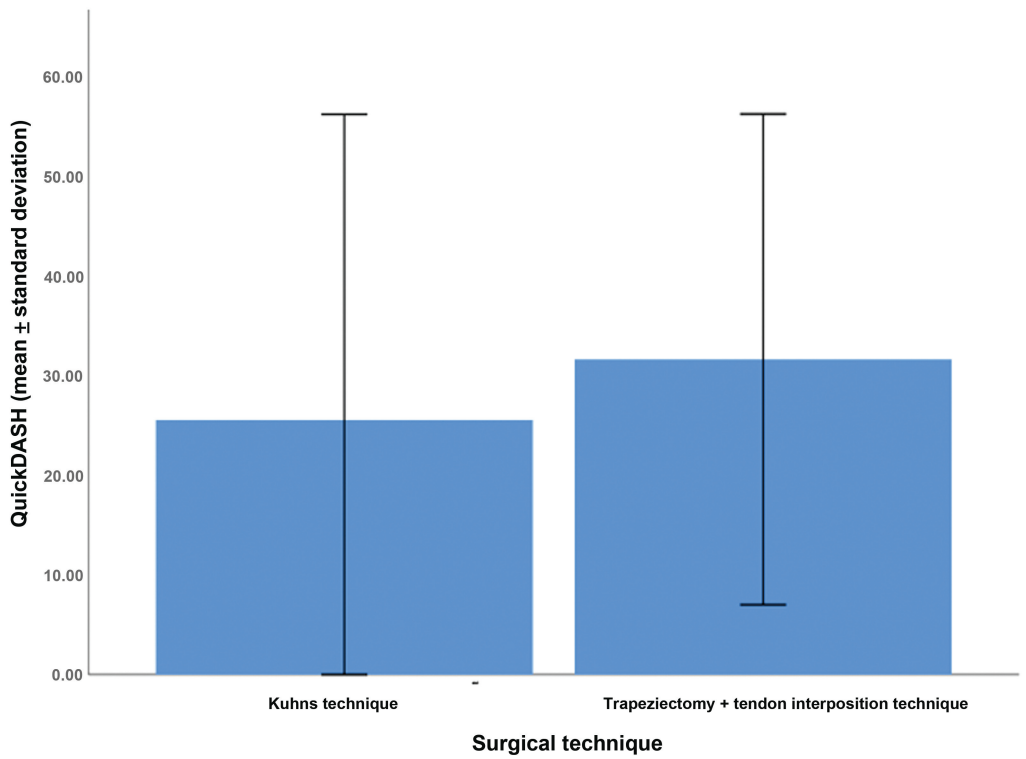


Fig. 7 Analysis of the QuickDASH scores in patients who underwent the Kuhns or tendon interposition techniques.

However, based on the Cochrane Review,[20] we cannot currently make recommendations regarding the superiority of any surgical procedure over another for this condition.

We observed a positive correlation between the TASD a QuickDASH, a result consistent with the findings in the literature.[10,21]

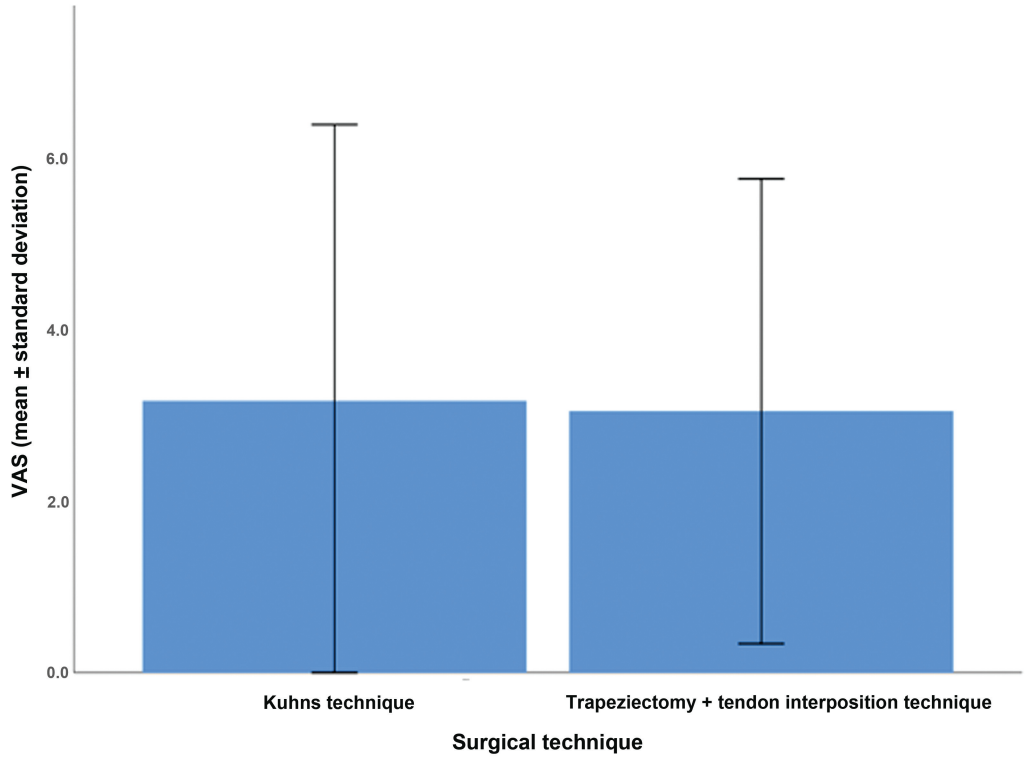


Fig. 8 Analysis of the VAS scores in patients who underwent the Kuhns or trapeziectomy + tendon interposition techniques.

Conclusion

The two techniques evaluated proved effective for treating patients with rhizarthrosis per the TASD, with an average postoperative follow-up of 30 months. There was no superiority in functional outcomes between the groups when comparing trapeziectomy techniques with tendon interposition or distraction. The specific TASD and the generic QuickDASH functional questionnaires proved equivalent to measuring the patients' degree of functional limitation.

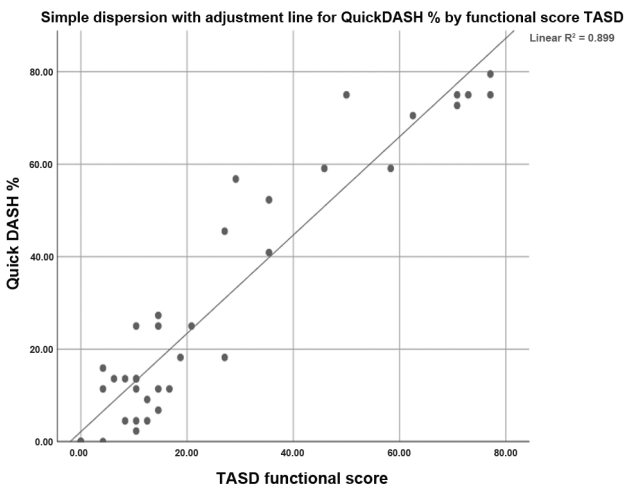


Fig. 9 Correlation of the QuickDASH and TASD scores in postoperative patients who underwent the Kuhns or tendon interposition techniques.

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Conflict of Interests

The authors have no conflicts of interests to declare.

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Percutaneous Surgical Treatment of Trigger Finger

Tratamento cirúrgico percutâneo do dedo em gatilho

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Abstract

Objective To evaluate the efficacy of percutaneous release therapy for patients with trigger finger.

Methods We obtained the hospital records of 120 patients who underwent percutaneous release, and their final status was evaluated by telephone.

Results The sample was composed of 84 (70%) female and 36 (30%) male patients, with a mean age of 55.4 (range: 30–79) years, and a mean follow-up of 28.6 (range: 6–74) months. Successful results were obtained in 118 (98.3%) patients. In the first week after the procedure, release was performed through the open surgical method in two patients who had complaints of re-entanglement in their fingers. No limitation to the joint range of motion was detected in any finger.

Conclusions Percutaneous release has advantages over the open surgery method in the surgical treatment of trigger finger, due to its low cost, ease of application, performance outside operating room conditions, and similar complication rates.

Keywords

- tendons
- trigger finger disorder/pathology
- trigger finger disorder/surgery
- trigger finger disorder/therapy

Resumo

Objetivo Avaliar a eficácia da terapia de liberação percutânea em pacientes com dedo em gatilho.

Métodos Obtivemos os prontuários hospitalares de 120 pacientes submetidos à liberação percutânea, e seu estado final foi avaliado por telefone.

Resultados A amostra foi composta de 84 (70%) pacientes do sexo feminino e 36 (30%) do sexo masculino, com média de idade de 55,4 (variação: 30–79) anos e tempo médio de acompanhamento de 28,6 (variação: 6–74) meses. Bons resultados foram obtidos em 118 (98,3%) pacientes. Na primeira semana após o procedimento, a liberação foi realizada por método cirúrgico aberto em dois pacientes que apresentavam queixa de recidiva do quadro. Nenhuma limitação da amplitude de movimento articular foi detectada em nenhum dedo.

Conclusão A liberação percutânea apresenta vantagens em relação ao método cirúrgico aberto no tratamento cirúrgico do dedo em gatilho, como baixo custo, facilidade de execução, realização fora de centro cirúrgico, e taxas de complicações semelhantes.

Palavras-chave

- dedo em gatilho/cirurgia
- dedo em gatilho/patologia
- dedo em gatilho/terapia
- tendões

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Introduction

Trigger finger is a common disorder that causes symptoms such as pain and snagging during finger movements.[1] Conservative treatment is recommended, especially in patients with mild-to-moderate symptoms. Conservative treatment includes the use of non-steroidal anti-inflammatory drugs, local corticosteroid injection, splint use, and physiotherapy and rehabilitation.[1]

Surgical methods are preferred in cases that do not respond to conservative treatment or recur afterwards. Two techniques have been described: open and percutaneous surgery. It has been reported that the recurrence rates in release with the open surgical method are lower than with the percutaneous method. However, it is known that the percutaneous method is more advantageous in terms of length of hospital stay, cost, and scarring.[2–4]

In the present article, we evaluated the efficacy of percutaneous release therapy for patients with trigger finger.

Materials and Methods

Study Design and Sample

By scanning the hospital automation system, we obtained data from the hospital records of 120 patients who admitted to the Orthopedics and Traumatology Outpatient Clinic due to trigger finger between November 2016 and August 2022 who underwent percutaneous release. The final status of the patients was evaluated by telephone.

Patients over the age of 18, who had entanglement in the fingers and no infection, contracture, or other pathologies in the operated site, and who had been operated on by the same surgeon were included in the study. Patients under the age of 18 who had undergone previous surgery in the operated site were excluded from the study. The Green classification was used in the clinical evaluation of the patients.[5]

As for the percutaneous surgical release procedure, the patients were informed about trigger finger and the treatment methods. Free and informed consent was obtained for the percutaneous release. The anatomical location of the A1 pulley was determined by considering the anatomical landmarks described by Wilhelmi et al.[6] and Sato et al.[7] In addition, the anatomical region was confirmed through the detection of the triggered area by asking the patients to perform active and passive flexion-extension movements of the finger under palpation. Subsequently, 2 mL of 2% prilocaine were injected under the skin over the A1 pulley. After anesthesia was provided, penetration of the A1 pulley and flexor tendon was ensured, with the sharp end of the 21-gauge (with 0.8 in diameter and 38 mm in length) needle parallel to the longitudinal direction of the tendon. Then, it was checked whether the needle was also moving by passively moving the patient's finger, and it was confirmed that the needle was on the tendon. Then, the needle was pulled back and removed from the tendon, the tendon sheath and A1 pulley were passed, and the A1 pulley was cut by moving it parallel to the tendon. While the A1 pulley was being released, it was felt that the needle tip penetrated the band/pulley and released it. At the end of the procedure, it was felt that the needle tip moved freely without friction against any band/fibrous structure. Then, the needle was withdrawn, and the patients were asked to actively flex and extend their fingers and whether there was any snagging. Afterwards, the surgeon made passive flexion-extension movements of the finger to check whether it was stuck or not. If there was no feeling of being stuck after the examination, the procedure was terminated by considering that the loosening was completed. The procedure was repeated in patients with ongoing complaints and persistent trapping of the tendon. After the release, the entry site of the needle was closed with a bandage for 1 day (►**Video 1** and ►**Fig. 1**).

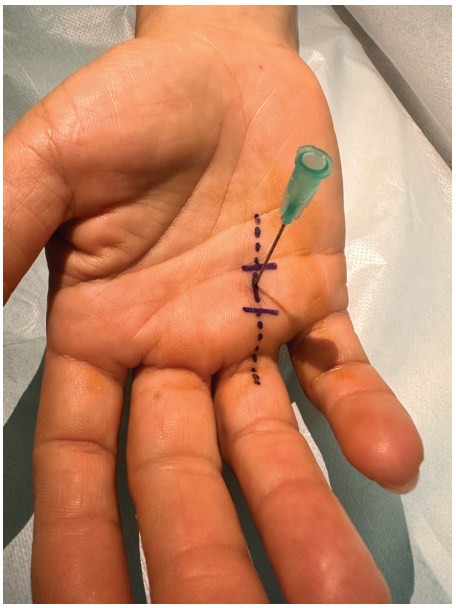


Fig. 1 Topographic entry site of the needle on the A1 pulley.

Video 1

Checking the location of the needle with finger movement in closed trigger finger treatment: We confirm that the needle is on the tendon because it moves with finger movement. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1788670.

After percutaneous release, the patients were shown and asked to perform frequent movements during the day for 10 days, bringing the metacarpophalangeal, proximal and distal interphalangeal joints to full hyperextension and full flexion and holding them for a few seconds. The patients returned to the outpatient clinic for follow-up one week after the procedure. Information about the patients' range of motion of the finger joints, snagging, pain, and swelling was obtained by telephone interviews. To do so, we contacted the patients through the telephone number listed in

their file. After verbal consent was obtained, we thoroughly questioned and recorded their current complaints. To evaluate the range of motion, we instructed patients to take a photograph of their fingers in both fully-flexed and fully-extended positions and send it to us. Patients who could not establish adequate and healthy communication over the phone (such as patients with speech and comprehension disorders) were required to attend the hospital for an outpatient clinic appointment.

This study was approved by the Clinical Research Ethics Committee at the Hamidiye Faculty of Health Sciences, University of Health Sciences, on October 16, 2022, under registration number 22/93. The study was conducted in accordance with the principles of the Declaration of Helsinki. The patients and/or their families were informed that data from the case would be submitted for publication and gave their consent.

Results

The sample was composed of 84 (70%) female and 36 (30%) were male patients, with a mean age of 55.4 (range: 30–79) years and a mean follow-up of 28.6 (range: 6–74) months. The distribution of fingers and their laterality is presented in ►**Table 1**. The dominant hand in 119 patients was the right, and only 1 patient's dominant hand was the left. According to the Green classification, 75 fingers were compatible with type 2, 60 fingers, with type 3, and 5, with type 4. Successful results were obtained in 118 (98.3%) patients. In the first week after the procedure, release was performed though open surgical method in 2 patients who had complaints of re-entanglement in their fingers. During open release, it was observed that the A1 pulley was cut incompletely, and there were small, superficial injuries along the longitudinal axis of the flexor tendon. Complications such as tendon rupture, infection, nerve injury and hematoma were not observed in any of the patients. It was observed that only 5 patients continued to complain of pain in the region of the A1 pulley. The complaints of these patients also regressed within 1 month. No limitation to the joint range of motion was detected in any finger.

Discussion

Trigger finger is more common among women, especially in the fifth and sixth decades of life. The dominant extremity is more frequently involved. Furthermore, trigger finger is most common in the thumb, followed by the ring, middle, index, and little fingers.[1] Our data were also found to be compatible with those of the literature, including the age at disease incidence and gender distribution.

Green classified trigger finger into four types according to the flexion-extension movement.[5] According to the Green classification, conservative treatment methods are preferred in the early stages (types 1 and 2), and surgical methods are preferred in advanced stages (types 3 and 4).[4,8,9] The patients included in the present study were classified as types 2 to 4.

The superiority of the percutaneous surgical treatment over the conservative treatment or steroid injection has been proven in the treatment of trigger finger.[9,10] In the study by Zyluk and Jagielski,[10] in which percutaneous release and steroid injection were compared, the results of steroid injection were better in the 1-month short-term follow-up. However, recurrence was observed in 6 (11%) of the patients who received steroid injection in the 6-month follow-up, while no recurrence was observed among those submitted to percutaneous release, who obtained better results. In the current study, a success rate of 98.3% (118 patients) was obtained, which is in accordance with the data reported by Zyluk and Jagielski.[10]

Although tendon and peripheral nerve injury can be observed with both surgical methods, inadequate release and damage to the flexor tendon are at the forefront in percutaneous surgery.[11,12] Wound issues and scar appearance are at the forefront in open surgery, but some authors[13,14] do not categorize these skin problems as complications. On the other hand, some studies have reported that tenderness on the scar may even lead to flexion limitation.[15] In the present study, open surgical release was only performed in 2 patients with inadequate release. The clinical significance of flexor tendon injury is not clear. We followed up our patients for a mean of 28 months, and no problems related to tendon damage were detected.

Table 1 Distribution of fingers and laterality among the patients

Finger	Right	Left	Total	%
1.	31	29	60	42.86
2.	4	2	6	4.29
3.	16	13	29	20.71
4.	17	18	35	25.00
5.	8	2	10	7.14
Total	76	64	140	100.00
%	54.29	45.71	100.00	

Limitations

The weaknesses of the present study are that it is retrospective and does not have a comparison group. However, the long follow-up period, the sufficient number of patients, and the fact that it was performed by a single physician are the distinguishing features compared to similar studies. Prospective, well-designed studies with a comparison group are needed to reach clearer data on this subject. Another important limitation of the current study is that we did not use a visual pain scale. On the other hand, we chose to prioritize the presence of pain over its degree, as our investigation focused on the results of the percutaneous technique.

Conclusion

In conclusion, percutaneous release has advantages over the open surgery method in the surgical treatment of trigger finger, due to its low cost, ease of application, performance outside operating room conditions, and similar complication rates.

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Conflict of Interests
The author has no conflict of interests to declare.

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The COL5A1 Gene Allelic Combination and ACL Injury Risk in Team Sport: A Preliminary Report

Gene COL5A1 e o risco de lesões do LCA no esporte de equipe: Um relatório preliminar

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Abstract

Objective: The aim of this study was to examine the relationship between BstUI restriction fragment length polymorphisms (RFLP) C/T (rs 12722) and DpnII RFLP B1/B2 (rs 13946) COL5A1 polymorphisms and the anterior cruciate ligament (ACL) rupture in competitive team-sport athletes.

Methods Sixty-eight team-sport players (n = 36 women and n = 32 men) with non-contact ACL rupture (ACLR) occurred during sport practices (ACLR Group) and 42 healthy players (n = 20 women and n = 22 men) (Control Group) participated in the study. Genomic DNA was extracted from buccal swab with salting out method. All samples were genotyped for the polymorphisms rs12722 and rs13946 by polymerase chain reaction (PCR) and restriction enzymes analysis.

Results No significant difference has been found between ACRL and Control groups in age, height, weight body, mass index, sport practice (hours/week) and gender distribution among the different team-sports. Control group had longer sport careers ($p < 0.005$). The frequency distributions of COL5A1 DpnII nucleotide polymorphisms were in Hardy-Weinberg equilibrium (HWE) in both groups (p of the Hardy-Weinberg (HW) -test > 0.005). Genotype frequencies of COL5A1 BstUI RFLP C/C was lower in the ACLR group compared to the Control group (p of the HW-test = 0.001). Combined CC, B1B1 genotypes showed a protective effect against ACL rupture (OR = 83.3 / 16.7 = 5).

Keywords
- anterior cruciate ligament
- athletes
- athletic injuries
- polymorphism, single nucleotide
- rupture

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Conclusions The COL5A1 gene may be one of the genetic factors associated with ACLR in team-sport.

Resumo

Objetivo: O objetivo deste estudo foi examinar a relação entre os polimorfismos do comprimento do fragmento de restrição (RFLP) BstUI C/T (rs 12722) e RFLP DpnII B1/B2 (rs 13946) COL5A1 e a ruptura do ligamento cruzado anterior (LCA) em atletas de esportes coletivos.

Métodos Sessenta e oito atletas de esportes coletivos (n = 36 mulheres e n = 32 homens) com ruptura do LCA (RLCA) sem contato ocorreram durante práticas esportivas (Grupo RLCA) e 42 jogadores saudáveis (n = 20 mulheres e n = 22 homens) (Grupo Controle) participaram do estudo. O DNA genômico foi extraído do swab bucal com o método salting out. Todas as amostras foram genotipadas para os polimorfismos rs12722 e rs13946 por reação em cadeia da polimerase (PCR) e análise de enzimas de restrição.

Resultados Nenhuma diferença significativa foi encontrada entre os grupos RLCA e Controle em idade, altura, peso corporal, índice de massa, prática esportiva (horas/semana) e distribuição de gênero entre os diferentes esportes coletivos. O grupo controle teve carreiras esportivas mais longas (p< 0,005). As distribuições de frequência dos polimorfismos de nucleotídeos COL5A1 DpnII estavam em equilíbrio de Hardy-Weinberg (EHW) em ambos os grupos (p do teste de Hardy-Weinberg (HW) > 0,005). As frequências genotípicas de COL5A1 BstUI RFLP C/C foram menores no grupo RLCA em comparação com o grupo Controle (p do teste HW = 0,001). Os genótipos combinados CC, B1B1 mostraram um efeito protetor contra a ruptura do LCA (OR = 83,3 / 16,7 = 5).

Conclusões O gene COL5A1 pode ser um dos fatores genéticos associados à RLCA em esportes coletivos.

Palavras-chave
- atletas
- ligamento cruzado anterior
- polimorfismo de nucleotídeo único
- ruptura
- traumatismos em atletas

Introduction

Anterior cruciate ligament rupture (ACLR) is a frequent disabling injury among athletes, that causes knee joint instability. In the USA, estimated incidence of ACLR ranges between 100,000 and 200,000 / year.[1] Reconstructive surgery allows sports practice and a better quality of life. In Italy, the incidence of ACL reconstruction surgery is 21-33 rate per year in 100,000 people, with an incidence between 0.16 and 2.04 procedures per 100,000 individuals younger than 15 years.[2,3]

Despite surgical ligament reconstruction, about 79% of these patients develop knee osteoarthritis and 20% suffer a new injury within the next 2 years.[4]

Sport ACLRs can be contact injuries (with a teammate or opponent), more frequent in contact sports such as soccer or basketball,[5] or non-contact injuries. In a 10-year period of observation, Majewski et al.[6] noted that 60% of sport knee injuries treated in their hospital were volleyball-related ACL injuries. Agel et al.[7] found that 14% of injuries in volleyball occur via non-contact.

Over a 16-year period of collegiate injuries registration, Hootman et al.[8] reported an injury rate per 1000 athlete-exposures of 0.07 and 0.09 for male basket and soccer players. They report 0.23, 0.28 and 0.09 for female basket, soccer and volleyball players respectively.

The risk factors for ACL injury are classified as exogenous (e.g. laying surface) and endogenous like genetic factors.[9] In inheritable collagen disorders, genetics influence laxity of tissues[10]: generalized joint laxity and hyperextension were found to significantly increase the risk for ACL injury in female athletes.[11] Mutations within the COL5A1 gene cause the classic form of Ehlers-Danlos syndrome (EDS) characterized by joint hypermobility involved in sprains, dislocation / subluxation, and early osteoarthritis.[12] As reported by Mokone et al.[13], the COL5A1 gene contains RFLP of BstUI (rs 12722) and DpnII (rs13946) within its 3'-untranslated region (UTR). The functional COL5A1 specificity protein 1 (Sp1) binding site polymorphism - BstUI RFLP C / T is positively correlated with tendon and ligament injuries, especially in Caucasian subjects.[14,15] Accordingly, a study on soccer players found that the T/T genotype of the COL5A1 BstUI RFLP showed a trend toward a higher severity of musculoskeletal injuries with respect to the individual carriers of the CC genotype.[15]

The aim of this study was to correlate the COL5A1 gene BstUI RFLP and DpnII RFLP polymorphisms with ACLR in volleyball, basketball and soccer athletes.

Materials and Methods

Subjects

68 Caucasic players (n = 36 women and n = 32 men) with ACLR occurred during sport practices (ACLR Group) and 42 healthy players (n = 20 women and n = 22 men) (Control Group) participated to the study. All of them

practiced team-sports (Volleyball, Basketball, and Soccer) in Italian teams. Subjects gave informed consent to participate. To obtain demographic information and data regarding sport practice; each athlete completed a self-administered questionnaire. The ACLR Group (32 athletes practiced Volleyball, 19 Basketball and 17 Soccer) provided information on the mechanisms and date of anterior cruciate ligament injury.

The study was approved by the Institutional Review Board of the University of Cagliari (Prot. PG/2017/1700) and was carried out in accordance with the ethical and humane principles of the research.

DNA Analysis

Genomic DNA was extracted from buccal swab, performed on the oral mucosa of the cheek, through salting out method, and amplified by standard PCR following the protocol suggested by Galasso et al.[16]

PCR products were subjected to two enzymatic digestions: digestion with BstUI produced two fragments for the T allele (351 and 316 bp) and three fragments for C allele (316, 271, and 80 bp); digestion with DpnII produced a unique fragment for B2 (612 bp) and two fragments (412 and 194 bp) for B1. The fragments obtained were separated through an 8% polyacrylamide gels for BstUI and a 2% agarose gel for DpnII and visualized with Syber Safe staining.

Statistical Analysis

All data were initially entered into an Excel database (Microsoft, Redmond, Washington – United States) and the analysis was performed using the Statistical Package for the Social Sciences Windows, version 15.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics consisted of the mean ± standard deviation (SD) for parameters with gaussian distributions (after confirmation with histograms and the Kolgomorov-Smirnov test).

Comparison among groups was performed with the ANOVA one-way for continuous parametric variables or the Chi-square test or Fisher's exact test (if cells < 5) for frequencies variables.

HWE tests were conducted considering population frequencies ($p2 + 2pq + q2 = 1$) and then reported in SPSS, Chi-square nonparametric test. Similarly, the G-square test (G^2 test) was performed. A p value of < 0.05 was considered statistically significant.

Results

No significant difference has been found between ACRL and Control groups in age, height, weight body mass index, sport practice (hours/week) and gender distribution among the different team-sports). Control Group athletes have longer sport careers ($p < 0.005$) (►**Table 1**).

The genotype and allele frequencies of COL5A1 BstUI RFLPC/T and COL5A1 DpnII RFLP B1/B2 are shown in ►**Table 2**. Genotype frequency distributions of COL5A1 DpnII and COL5A1 BstUI RFLP nucleotide polymorphisms meet the HWE in both groups (p. value > 0.05).

Linkage disequilibrium was tested with LDlink (Machiela and Chanock, 2015)[17] using data from 1000 genomes (1000 Genomes Project Consortium, 2015). The two single nucleotide polymorphisms (SNPs) resulted in a linkage disequilibrium for European populations.

The distribution of the C/C genotype and the C allele of the COL5A1 BstUI RFLP were lower in the ACLR Group compared with the Control Group (pG^2 test= 0.001-►**Table 3**). No significant differences have been found in the distribution of the DpnII RFLP polymorphism between ACLR Group and controls (►**Table 3**). Finally, the combination of CC + B1B1 genotypes was more frequent in the controls than in the ACLR group, and associated with a protective effect (OR = 83.3 / 16.7 = 5). The TT, B2B2 genotypes were absent among participants.

Discussion

Although the biological changes underlying the increased risk of ACL sports injury have not yet been find out, the family predisposition of athletes to ACL ruptures is a consolidated knowledge.[18,19]

The COL5A1 gene, located at 9q34.2-q34.3, contains 66 exons distributed over 150 kb of gDNA, and it encodes the 1 chain of type V collagen.[20]

Table 1 Characteristics of the of the ACL rupture Group (ACLR) and Control Group

	ACLR	Control	*p*
Number	68	42	
Age (years)	27.3 ± 6.4	28.5 ± 8.5	0.406*
Height (cm)	173.0 ± 9.5	174.0 ± 11.4	0.588*
Weight (kg)	70.0 ± 11.8	70.2 ± 12.3	0.945*
Body mass index (kg/cm^2)	23.30 ± 3.30	23.16 ± 2.99	0.782*
Gender (n°males/n°females)	32 / 36	22 / 20	0.200^
Sports (Volleyball; Basketball; Soccer)	32; 19; 17	26; 8; 8	0.312^
SPORT (years)	10.8 ± 4.9	16.8 ± 8.5	0.001*
SPORT (hours/week)	7.7 ± 3.2	7.8 ± 4.0	0.799*

Values are expressed as mean ± standard deviation or a number (n) where applicable.
(*) Anova oneway (^) Chi-Square test.

Table 2 Genotype Frequencies of the ACLR Group and Control Group - Hardy-Weinberg equilibrium verification

BstU	ACLR	Control
CC	58.90	22.22
CT	34.25	44.44
TT	6.85	33.33
MAF (T)	0.2397	0.5556
p	0.3881	0.3274*
DpnII	ACL	Control
B1B1	71.23	75.56
B1B2	26.03	20.00
B2B2	2.74	4.44
MAF (B2)	0.15	0.1444
p	0.556	0.2060*

(*) Hardy-Weinberg equilibrium test.

The COL5A1 gene codes for a protein chain in type V collagen, which is found in ligaments and tendons, and mutations within it are indicated as a cause responsible for the increased risk of ACL rupture.[19,21]

We examined the association between COL5A1 rs12722 C / T (BstUI RFLP) and COL5A1 rs13946 B1/B2 (DpnII) polymorphisms individually and as haplotypes with risk of anterior cruciate ligament rupture in male and female athletes competing in contact / noncontact team sports.

Our results show a lower frequency of the COL5A1 BstUI C/C genotype in the ACLR group compared with the Control Group. No significant differences in genotype distribution or allele frequencies of COL5A1 DpnII was observed.

Posthumus et al.[21] found an underrepresented C/C genotype of COL5A1 BstUI RFLP in Caucasian females but not in males with surgically diagnosed ACL ruptures recruited from sports and recreational clubs.

In male recreational skiers, Stępień-Słodkowska et al.[22] noted no significant differences in genotype distribution or allele frequencies of COL5A1 BstUI RFLP C/T (rs 12722) and COL5A1 DpnII RFLP C/T (rs 13946) polymorphisms between the ACLR group and control group. These authors found an underrepresentation tendency of the C-T haplotype in the ACLR group compared to controls.

Luliska-Kuklik et al.[23] found a significant decrease in frequency in the dominant model of the C/C genotype for the COL5A1 rs13946 gene in male professional soccer players with surgically diagnosed primary ACL rupture.

In our study, athletes within the ACLR and control groups were matched for age, height, body weight, BMI, sport, and length of their sport career. The longer is the sport career the higher is the risk of trauma exposure.

In addition to having a higher frequency of the C/C genotype, the athletes in the Control Group have a longer sports career than those of the ACLR Group: with caution due to the small number of subjects, we hypothesize a protective effect of the C/C genotype, especially if associated with B1B1 (CC, B1B1 OR protective = 83.3 / 16.7 = 5).

Likewise, Posthumus et al.[24] found a significant age dependent increase in the distribution of the COL5A1 BstUI RFLP C/C genotype in a group of physical activity male, asymptomatic for musculoskeletal soft-tissue injuries (without a reported history of tendon injuries). According to these authors, prolonging exposure time to extrinsic risk of injury selects individuals who are genetically low risk of injury, who will be found in greater numbers among older asymptomatic subjects than in the younger asymptomatic subjects.

The COL5A1 BstUI RFLP C/C polymorphism may play a role in increasing the length of the sports career of athletes.

It is unclear which phenotypic expression of COL5A1 gene polymorphisms may be associated with an increased risk of ACL rupture.

In EDS, several COL5A1 gene mutations occur concurrently with specific clinical features.[10] The connective tissue of these patients shows structural changes and ligamentous laxity causing different degrees of joint hypermobility.

Hypermobility has been implicated in ACL injury,[25] and lower limb joint proprioception is reduced in those with benign joint hypermobility syndrome[26]: no correlation has been described between the COL5A1 BstUI RFLP and COL5A1 DpnII polymorphisms with an increase in ligamentous laxity. Future investigations should include the search for an association between changes in joint mobility or ligament tension and the presence of these polymorphisms.

In a retrospective genetic case-control association study, O'Connell et al.[27] found the COL5A1 C/C genotype significantly overrepresented in triathlon and ultra-marathon athlete without a history of exercise-associated muscle cramping (EAMC) compared with athletes with a history of EAMC. The efficiency of the knee flexor muscles, the abductors muscles of the hip and trunk stabilizers muscles efficiency prevent ACL injuries.[28]

According to Collins and Posthumus,[29] the COL5A1 rs12722 TT genotype is associated with a surplus V collagen production with a higher risk of some musculoskeletal injuries due to collagen fibril structural changes in collagen fibrils and changes in the properties of soft tissues.

Laguette et al.[30] demonstrated greater stability of the COL5A1 mRNA (encoding for α1(V)) in C/T genotype and speculated that small changes in COL5A1 mRNA stability,

Table 3 Genotype Frequencies of the ACLR Group and Control Group

ACLR		Control	*p*
COL5A1 BstUI% (CC; CT; TT)	23,8;61,0; 79,2 (0.954)	76,2; 39,0; 20,8 (0.368)	0.001°
COL5A1 DpnII% (B1B1; B1B2; B2B2)	60,8;66,7; 50,0 (0.990)	39,2;33, 3; 50,0 (0.497)	0.952°

(°) Chi-Square test.

even if within the normal physiological range, could result in inter-individual variation in fibrillogenesis; therefore, a different vulnerability to musculoskeletal lesions COL5A1-dependent. We theorize that, in the study group (ACLR Group), the frequent exposure of the ACL to abnormal stresses during team sport practice, reveals the relative susceptibility of the ACL of the athletes with C/T genotype.

As reported by Smith et al.,[19] tree more genetic factors may be associated with an increase in ligament fragility: 1) TT genotype of the COL1A1 Sp1, binding site polymorphism. The COL1A1 gene encodes a protein chain within type I collagen, a major structural component of ligaments; 2) the AA genotype of the COL12A1 AluI polymorphism (only in women). This gene encodes for protein chains in type XII collagen, which is believed to regulate fibril diameter in ligaments; 3) the chromosomal region 11q22, where several matrix metalloproteinase genes of physiologic mediators of collagen cleavage and removal are located.

Multiple genetic dependency of ACL susceptibility to rupture may suggest scanning changes in multiple genes.

The main limitation of the present work is represented by the small number of athletes included in the study, which has precluded the possibility of analyzing any differences between genders. The development of clinical or laboratory tools which identify subjects at great risk to this common musculoskeletal injury, would ease a greater people awareness of their own exposure to an ACL rupture. Besides it would be useful in settle the best therapeutic choice after primary ACL rupture diagnosis.

Conclusions

The COL5A1 gene may be one of the genetic factors associated with ACLR in team-sport. COL5A1 C/C polymorphisms provides a protective effect against the ACLR in both sex. Longer sport career linked to an increased frequency of COL5A1 BstUI RFLP C/C.

Authors' Contributions

Each author contributed individually and significantly to the development of this article: CMC - Design of the study, contributed to data collection;
MM contributed to data collection and review.
AT - Athletes recruitment and technical sports consulting;
GM - Original draft preparation. Review and editing.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Comparison of Manual Two-dimensional and Automated Three-dimensional Methods of Assessing Shoulder Joint Morphology through Computed Tomography Images

Comparação de métodos bidimensionais manuais e tridimensionais automatizados de avaliação da morfologia da articulação do ombro por imagens de tomografia computadorizada

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Abstract

Objective To evaluate the interobserver agreement in the measurement of anatomical parameters of the shoulder using manual methods of two-dimensional (2D) computed tomography (CT) unformatted in the plane of the scapula and to compare them with the automated measurement obtained through the Blueprint (Wright Medical, Memphis, TN, United States) software, which uses reconstructed three-dimensional (3D) images.

Methods The present is a cross-sectional study in which 2D CT images of 38 patients with different diagnoses were used. The anatomical parameters were measured by the manual methods described by Friedman et al., the glenoid vault method, the Maurer et al. method, and shoulder subluxation according to Walch et al., by five independent qualified surgeons and compared with the parameters obtained through the Blueprint automated software.

Results Significant differences were found between the manual measurement version obtained through the Friedman et al. method and the automated version.

Keywords
- artroplasty
- shoulder replacement
- tomography, X-ray computed

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The mean values found for inclination did not show statistically significant differences among the methods. The mean value found for subluxation showed significant differences between the average observed in the analyses performed by the automated method and those performed by the surgeons.

Conclusion The manual measurements of glenoid version and inclination performed by experienced surgeons are effective, and the vault method is superior to the Friedman et al. method in the analysis of severe glenoid deformities.

Resumo

Objetivo Avaliar a concordância interobservador na medida dos parâmetros anatômicos do ombro utilizando métodos manuais de tomografia computadorizada (TC) bidimensional (2D) não formatada no plano da escápula e compará-los à medida automatizada obtida com o programa Blueprint (Wright Medical, Memphis, TN, Estados Unidos), que utiliza imagens tridimensionais (3D) reconstruídas.

Métodos Este é um estudo transversal com a utilização de imagens de TC 2D de 38 pacientes com diferentes diagnósticos. Os parâmetros anatômicos foram medidos pelos métodos manuais descritos por Friedman et al., o método de *vault* glenoidal, o de Maurer et al. e o de subluxação do ombro segundo Walch et al. por cinco cirurgiões qualificados e independentes, e comparados aos parâmetros obtidos pelo programa automatizado Blueprint.

Resultados Foram observadas diferenças significativas entre a versão de medida manual obtida pelo método de Friedman et al. e a versão automatizada. Os valores médios de inclinação não apresentaram diferenças estatisticamente significativas entre os métodos. A média observada de subluxação teve diferenças significativas entre as análises realizadas pelo método automatizado e pelos cirurgiões.

Conclusão As medidas manuais de versão e inclinação da glenoide realizadas por cirurgiões experientes são eficazes, e o método da abóbada é superior ao de Friedman et al. na análise de deformidades glenoidais graves.

Palavras-chave
- artroplastia
- substituição do ombro
- tomografia computadorizada por raios X

Introduction

Correction of joint deformities in the glenoid is essential to perform shoulder arthroplasty, and it can directly impact the functional result and survival of the implant.[1] Therefore, preoperative planning is essential for the successful performance of total shoulder arthroplasty.[1–4]

Traditionally, the assessment of glenoid morphology is performed using angular measurements on two-dimensional (2D) computed tomography (CT) images, which have demonstrated low accuracy and inter- and intraobserver agreements.[5] The use of three-dimensional (3D) CT images has shown limited improvements as the reconstruction of the scapula plane requires reformatting and processing of 2D images.[6,7]

Thus, the emergence of three-dimensional (3D) CT images associated with the development of automated computer software is intended to control the limitations and inaccuracies of manual methods and the reformatting of CT slices in the scapular plane.[8–11]

Therefore, the aim of the present study was to evaluate the interobserver agreement in the measurement of anatomical parameters of the shoulder using manual methods from 2D CT unformatted in the plane of the scapula and to compare them with automated measurement that uses reconstructed 3D images.

Materials and Methods

Selection of Cases

After approval by the institutional Ethics in Research Committee (under no. 35243920.4.0000.5273), a study was carried out to evaluate the CT images of the shoulder joint in patients of both sexes, older than 18 years of age, diagnosed with osteoarthritis.

In total, 38 CT scans were randomly selected from exams performed for patients at the institution from January 2015 to December 2019. All CT exams were performed using the same device (model Brilliance, Philips, Amsterdam, Netherlands), with 64 channels, with the patient in the supine position.

The inclusion criteria were CT scans that had triplanar, coronal, sagittal, and axial sections, with a minimum section thickness of 1 mm, in which the entire scapula was visualized and were processed by the automated surgical planning software selected for the experiment. Images of patients who had undergone previous surgery in the shoulder and who had artifacts on CT images were excluded, such as the presence of a metallic implant or other anatomical changes

that could affect the segmental processing by the automated software.

Manual Measurement

The 2D CT images that were not formatted in the scapula plane were used for the manual measurement of the version, according to the Friedman et al.[12] (►**Fig. 1**) and glenoid vault methods, described by Matsumara et al.[13] (►**Fig. 2**), and of the glenoid inclination using the Maurer et al.[14] (►**Fig. 3**) method in addition to the measurement of the percentage of humeral head subluxation according to Walch et al.[4] (►**Fig. 4**).

These measurements were performed independently by five orthopedists specialized in shoulder surgery using the RadiAnt DICOM Viewer software (Medixant, Poznan, Poland).[15] The observers were uniformly instructed, as described below, to standardize the measurements. All observers were blinded to each other's results.

Automated Measurement

The automated measurement used the CT images in the Digital Imaging and Communications in Medicine (DICOM) format that were processed by the Blueprint[9] (Wright Medical, Memphis, TN, United States) software. The software performs an automatic segmentation process, determines the scapula and glenoid planes, and then performs measurements, providing the version and inclination values, in addition to the percentage of subluxation of the humeral head (►**Fig. 5**).

Statistical Analysis

The interclass correlation coefficient (ICC) was calculated to determine the variability in the manual measurements among surgeons.

For the descriptive statistics, data were presented as mean, standard deviation, maximum, and minimum values. The comparison of the measurements obtained by the different methods of evaluating the version was performed using the Friedman et al.[12] test, followed by the Dunn posttest. The comparison between the measurements of inclination and subluxation by manual and automated methods was performed using the Wilcoxon test. The cases were categorized according to the severity of the version and inclination, using intervals of 0 to 10°, and > 10° when indicated. Those intervals were chosen based on studies that have shown that the normal glenoid version is close to 0°, sometimes with slight anteversion but more often slight retroversion with values typically lower than 10° in either direction,[16] and that the normal intrinsic glenoid inclination angle is generally between 0 and 10°.[17] All analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 21.0.

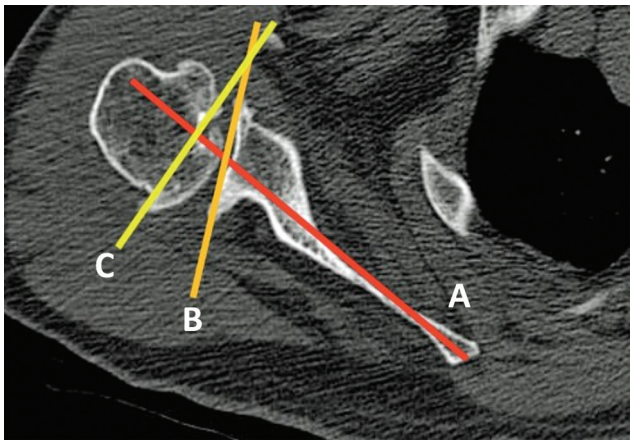


Fig. 1 Friedman et al.[12] method to evaluate the glenoid version. We used the fourth cut distal to the last cut in which the tip of the coracoid process was visualized in the axial plane. The glenoid version was determined by the angle, as shown: (**A**) Friedman et al.[12] line, (**B**) glenoid line, and (**C**) line perpendicular to the scapular axis. A positive value of the glenoid version angle was interpreted as anteversion, while a negative value was interpreted as retroversion.

Results

The present study included 38 cases, 17 of which were diagnosed with cuff tear arthropathy, and 21, with osteoarthritis.

The ICC for the manual measurements is described in ►**Table 1**. The mean version values obtained by the Friedman et al.,[12] vault, and automated methods are presented in ►**Table 2**. The vault method was similar to the automated method ($p > 0.99$), while the Friedman et al.[12] method tended to underestimate this measure, both in relation to the automated and vault methods ($p = 0.003$) (►**Table 2**).

The differences between the version measurements made by Blueprint and the Friedman et al.[12] method were lower than 5° in 23 cases (60.5%), between 5 and 10° in 14 cases (36.8%), and greater than 10° in 1 case (2.6%). Such proportions were similar to those found in the comparison between Blueprint and the vault method: 22 cases (57.8%), 13 cases (34.2%), and 3 cases (7.8%), respectively ($p = 0.57$) (►**Table 3**).

Inclination showed no statistical difference between the automated and manual methods ($11.85° \pm 9.8°$ versus $11.24° \pm 5.44°$; $p = 0.377$) (►**Table 4**). Subluxation measurements resulted in higher values in the automated method in comparison to the manual one ($60.08° \pm 14.72°$ versus $48.47° \pm 7.67°$; $p < 0.0001$) (►**Table 4**).

Cases were categorized considering those presenting a glenoid inclination within the normal range (−10 to +10°) and those with anatomical variation of this parameter. For cases within the normal range, the vault method resulted in significantly higher values than the automated ($p = 0.04$) and the Friedman et al.[12] methods ($p = 0.0004$). Interestingly, for cases with a version higher than 10°, the mean version obtained with the automated method was significantly higher than that obtained with Friedman et al.[12] method ($p = 0{,}001$), but similar to that obtained with vault method ($p = 0.13$). The mean values for subluxation obtained with the automated method were significantly higher than those obtained with the manual method in both subgroups evaluated (►**Table 5**).

The cases were then categorized considering inclination, measured by the automated method. For cases with inclination

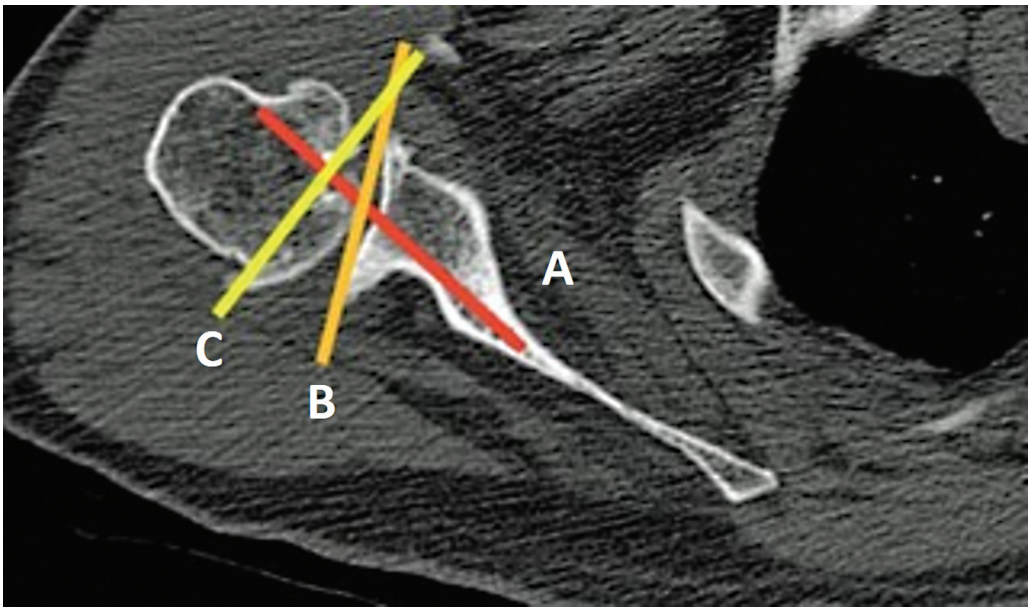


Fig. 2 The vault method for the measurement of the version, which was defined in the axial section as a triangle composed of the anterior and posterior walls of the scapula neck and the glenoid articular surface. The angle is determined by the lines: (**A**) vault axis, (**B**) glenoid line, and (**C**) line perpendicular to the vault axis.

within the normal range, the mean version obtained with the vault method was significantly higher than that obtained with the Friedman et al.[12] method ($p = 0.1$), with no differences between the automated and the manual methods. For cases with inclination higher than 10°, the mean version was significantly underestimated by the Friedman et al.[12] in comparison to the automated ($p = 0.002$) and the vault methods ($p = 0.007$).

In cases within the normal range of inclination, this parameter was overestimated by the manual method in comparison to the automated one ($p = 0.001$). Regarding subluxation, the mean values obtained with automated method were significantly higher than those obtained with the manual method in both subgroups evaluated (►**Table 6**).

Discussion

The success of shoulder arthroplasty depends on the proper positioning of the implant.[1] The surgeon's ability to identify morphological changes in the glenoid, especially regarding the version and inclination, is extremely important, as it

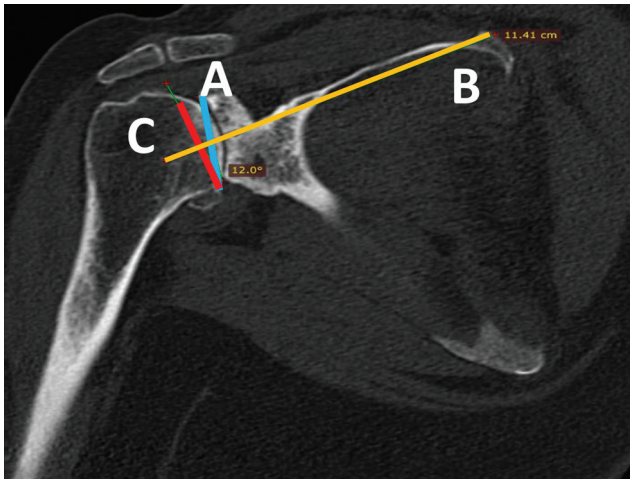


Fig. 3 Maurer et al.[14] method for the measurement of the glenoid inclination, which was performed in the oblique coronal plane of the computed tomography scan, and the slice that best captured the floor of the supraspinatus fossa was selected. (**A**) Line tangent to the anterior and posterior edges of the glenoid, (**B**) supraspinatus fossa line, and (**C**) line perpendicular to line B determining the glenoid inclination.

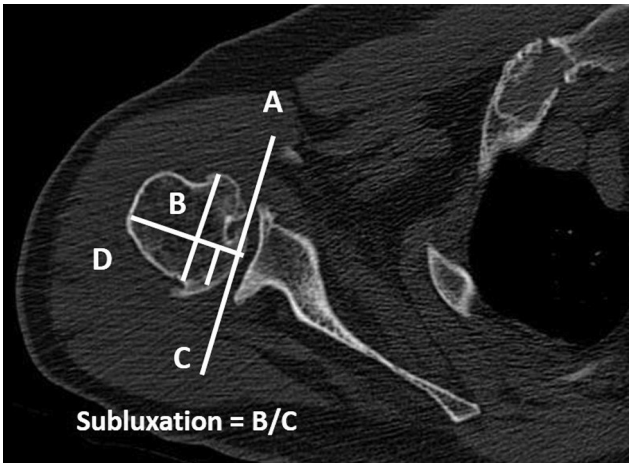


Fig. 4 Walch et al.[4] method to determine humeral head subluxation. (**A**) Line tangent to the anterior and posterior edges of the glenoid, (**B**) line perpendicular to the face of the glenoid at its midpoint, (**C**) line parallel to line A, dividing the middle third of the humeral head, and (**D**) part of the humeral head posterior to the center of the glenoid. Subluxation index = D/C.

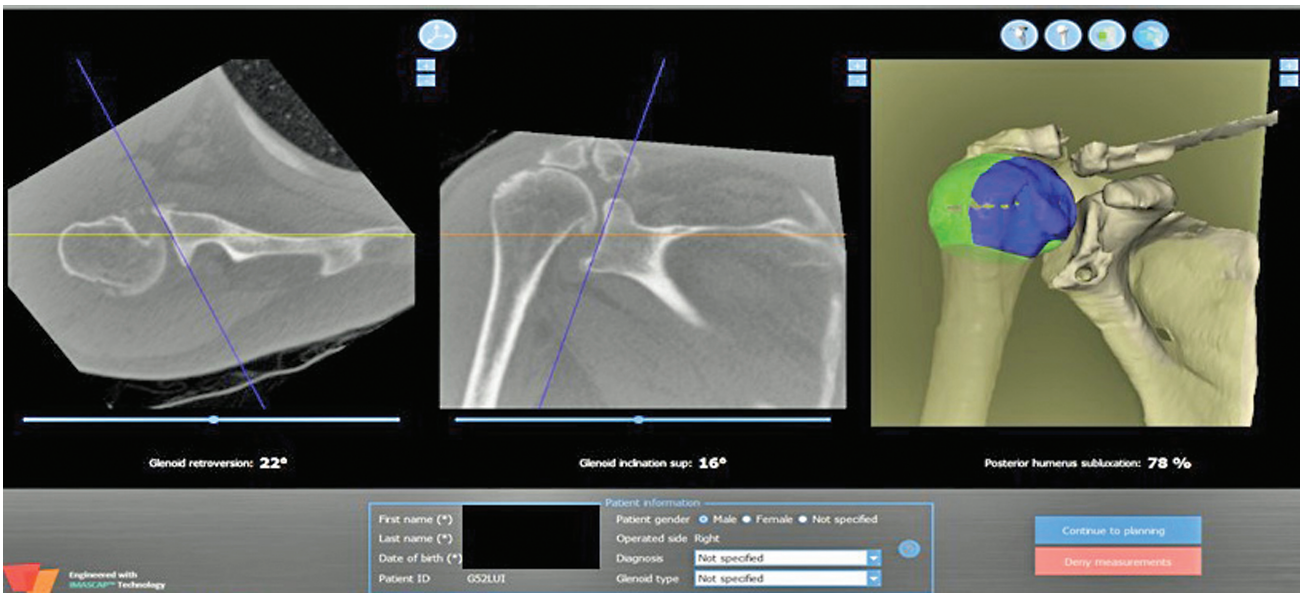


Fig. 5 Initial screen of the Blueprint software showing the values of the glenoid version and inclination, and humeral head subluxation.

Table 1 Interclass correlation coefficients for version, by the Friedman et al.[12] and vault methods, inclination, and subluxation

Variables	ICC	Inferior confidence interval	Superior confidence interval
Version according to the Friedman et al.[12] method	0.847	0.751	0.913
Version according to the vault method	0.845	0.744	0.931
Inclination	0.890	0.821	0.938
Subluxation	0.840	0.712	0.917

Table 2 Version measurement

	Blueprint	Friedman et al.[12]	Vault
Version (mean ± standard deviation)	10.45° ± 7.1°[a]	8.07° ± 6.1°[a, b]	10.42° ± 6.2°[b]
Average difference (95% confidence interval)	–	2.37° (0.79–3.9°)	0.023° (−1.8–1.9°)
Maximum difference		11°	13.64°

Notes: [a]$p = 0.0059$, Friedman et al.[12] test, Dunn posttest; [b]$p = 0.0005$, Friedman et al.[12] test, Dunn posttest.

Table 3 Number of cases in which the mean obtained by measurements using manual methods differed from automated measurements, stratified by degrees of difference

	Friedman et al.[12]	Vault
Difference < 5° in relation to the Blueprint software: n (%)	23 (60.5%)	21 (57.8%)
Difference of 5–10° in relation to the Blueprint software: n (%)	14 (36.8%)	13 (34.2%)
Difference > 10° in relation to the Blueprint software: n (%)	1 (2.6%)	3 (7.8%)

Notes: Chi-squared test; $p = 0.57$.

avoids misplacements that compromise the survival of the procedure.[2,4,7]

However, manual 2D methods to define glenoid morphology present limitations and inaccuracies because of the difficulty in segmenting CT images in the anatomical plane of the scapula. The discrepancies motivated the development of automated programs for preoperative planning, whose use has become increasingly frequent in an effort to improve the

Table 4 Measurement of inclination and subluxation

	Blueprint	Manual	*p*
Inclination (mean ± standard deviation)	11.85° ± 9.8°	11.24° ± 5.44°	0.377
Subluxation (mean ± standard deviation)	60.08° ± 14.72°	48.47° ± 7.67°	< 0.0001

Note: Wilcoxon Test.

Table 5 Comparison regarding the mean version, inclination, and subluxation using the automated and manual methods, categorized by version measured by the automated method

Version (°)		Parameter		*p*-value
Version (°): mean ± standard deviation				
	Blueprint	Friedman et al.[12]	Vault	
0–10 (n = 21)	5.6 ± 2.8[a]	5.4 ± 4.0[b]	7.7 ± 3.9[a, b]	0.01*
> 10 (n = 17)	16.3 ± 6.5[c]	11.3 ± 6.9[c]	13.7 ± 7.0	0.0061*
Inclination (°): mean ± standard deviation				
	Blueprint	Manual		
0–10 (n = 21)	11.5 ± 11.5	10.9 ± 6.0		0.7#
> 10 (n = 17)	10.8 ± 5.0	11.4 ± 4.8		0.5#
Subluxation (°): mean ± standard deviation				
	Blueprint	Manual		
0–10 (n = 21)	51.3 ± 10.4	45.7 ± 7.2		0.005#
> 10 (n = 17)	69.8 ± 12.5	52.0 ± 7.1		< 0.0001#

Notes: *One-way analysis of variance (ANOVA); [a]$p = 0.04$; [b]$p = 0.0004$; [c]$p = 0.001$; Tukey multiple comparisons test; #*t*-test.

Table 6 Comparison regarding the mean of the inclination using the automated and manual methods, categorized by the severity of the inclination measured by the automated method

Inclination (°)		Parameter		*p*-value
Version (°): mean ± standard deviation				
	Blueprint	Friedman et al.[12]	Vault	
0–10 (n = 21)	8.9 ± 6.4	8.3 ± 6.2[a]	10.9 ± 7.3[a]	0.03*
> 10 (n = 17)	12.3 ± 7.8[b]	7.7 ± 6.3[b,c]	9.7 ± 4.8[c]	0.003*
Inclination (°): mean ± standard deviation				
	Blueprint		Manual	
0–10 (n = 21)	5.9 ± 2.9		8.7 ± 3.8	0.001#
> 10 (n = 17)	17.6 ± 9.9		14.0 ± 5.8	0.1#
Subluxation (°): mean ± standard deviation				
	Blueprint		Manual	
0–10 (n = 21)	60.33 ± 15.0		49.9 ± 6.8	0.0001#
>10 (n = 17)	58.7 ± 14.5		46.8 ± 8.6	0.000 #

Notes: *One-way analysis of variance (ANOVA); [a]$p = 0.01$; [b]$p = 0.002$; [c]$p = 0.007$; Tukey multiple comparisons test; #*t*-test.

understanding of the anatomy and the subsequent positioning and fixation of the prosthetic components.[8,9] However, its routine use still does not occur in the practice of most surgeons who perform shoulder arthroplasties.[8,18–20] Moreover, there are controversies regarding the accuracy of these methods and the ideal placement of the implants.[21–25]

In the clinical practice at low- and middle-income countries, 2D CT images unformatted in the plane of the scapula are broadly used, which, despite representing a limitation, is a reality. In the present study, manual measurements of the version, by both the Friedman et al.[12] and vault methods, as well as inclination and subluxation, showed a good ICC. Interestingly, other studies[5,6,9,10] have shown that the version of the glenoid measured on 2D CT images presents significant interobserver variability due to the variation in the coronal and sagittal rotation of the scapula in relation to

the patient's position on the examination table. However, in the present study, we obtained a good ICC, which we attribute to the fact that all evaluators are shoulder surgeons with more than five years of training and with experience in performing shoulder arthroplasties.

In the present study, the mean glenoid version measured through the automated method was similar to that obtained through the vault method. However, the version measured by the Friedman et al.[12] method was lower than that obtained by the automated and vault methods. Still, based on the comparisons of the versions, only 1 case showed a difference greater than 10° when comparing the Friedman et al.[12] method with the automated method. Therefore, it was shown that the Friedman et al.[12] method is less accurate than the vault method when the automated method was used as a standard. In 2014, Matsumara et al.[13] compared the measurement of the version by the Friedman et al.[12] and vault methods and, similarly, stated that both methods present good interobserver agreement, but that the vault method enables an easier measurement, since it does not depend on the anatomical variations of the body of the scapula or its inclusion in the exam.[11,13,15,23]

Remarkably, using the automated method as a standard, in cases in which the version was within the normal range, we did not observe significative differences between the automated and Friedman et al.[12] methods; however, in cases in which the version was out of the normal range ($> 10°$), the mean version obtained by the Friedman et al.[12] method was significantly lower than that obtained by the automated method. Altogether, these results enable us to conclude that the use of version measurement by the automated method is more important in cases in which deformities on the glenoid surface are more severe, possibly influencing the clinical practice, both in the correction of the version and in the correct positioning of the implant. This finding is compatible with that found in the literature, in which Chalmers et al.[26] demonstrated that, in deformities classified as B2 using the morphological classification proposed by Walch et al.,[4] the measurement of the version by CT images is superior.[26,27]

In a recent study, Reid et al.[28] found results similar to ours, showing that the measurement of the version in 2D CT scans, using the Friedman et al.[12] method, presents both high intra- and interclass correlation rates. On the other hand, this study[28] also found significant differences between measurements using manual and automated methods. However, when the cases were categorized according to version severity, the authors[28] did not find differences between the methods in the different subgroups evaluated, suggesting that the version magnitude does not influence the differences between the methods. This result contrasts with the findings of the present study, as we found that the manual method underestimated glenoid inclination, in comparison to automated method, in cases with a version greater than 10°. The different version ranges used to stratify the cases and the different diagnosis included in our series may explain these differences.

Glenoid inclination presented similar values when assessed by the manual or automated methods. Iannotti et al.,[21] regarding inclination measurements on formatted CT scans, observed that there were no differences from those obtained with the automated method. In relation to unformatted images, an expressive difference was found. In 94% of the cases, the difference in inclination between the unformatted and the formatted images was greater than 5°, again a value with significance in the clinical practice.[21] In our series, when the cases were categorized according to severity of the inclination, differences were found in the measurement of mild cases (0–10° of inclination), in which the manual method resulted in a mean that was significantly higher than that obtained by the automated method ($p = 0.001$). In a study published in 2020, Choi et al.[29] compared inclination measured by automated and 2D methods and found that the 3D method resulted in measurements that were significatively lower than those obtained with the 2D method. Although the authors[29] did not perform a subgroup analysis, the data evaluated presented mean values for version and inclination compatible with the cases included in the subgroup of mild cases of the present study.

In relation to subluxation, significant differences were found between the manual and automated methods. Other studies[30] have already reported an error intrinsic to the measurement of subluxation using the Walch et al.[4] method. The subluxation index, described by Walch et al.,[4] is measured on a CT transverse cut. The scapular body has an inclination compared to the body of the patient in whom the CT cross-sections are aligned, which leads to errors in the 2D CT measurements.[5,10,11,26,27,30] Jacxsens et al.[30] concluded that measurements based on shoulders reconstructed in 3D seem to be more appropriate, as they reconstruct the bone anatomy regardless of the patient's orientation at the time of the exam, and could be, therefore, another more reliable measurement than the 2D one, which is underestimated.

An interesting finding of the present study was that the differences between the subluxation measurements obtained by the automated and manual methods tended to increase with the severity of the version, suggesting that the greater the version angle, the more the manual method underestimates the measurement of the subluxation, when the automated method is used as the default. Further studies are needed to assess the clinical impact of such a finding, once it can directly impact on surgical planning.

Chalmers et al.[26] evaluated the glenoid version and inclination and humeral head subluxation values using corrected and uncorrected CT scans, and compared these measurements with the values provided by the Blueprint software. They[26] concluded that the orientation of the slices of CT scans formatted in the plane of the scapula presented a decrease in retroversion measurements compared to unformatted CT scans. On the other hand, the authors[26] verified that there are no differences between unformatted CT scans and the values of automated programs. In 48% of the cases, the difference between the uncorrected and corrected versions was greater than 5°, which is considered significant in the

clinical practice.[21] These findings are similar to the results obtained in our series.

Shukla et al.[23] used the same automated program used in the present study and found similar results between the manual and automated methods for the measurements of version and inclination, but with an important difference in the percentage measurements of subluxation of the humeral head. Thus, like these authors,[23] we believe that measuring the percentage of subluxation is essential in the preoperative planning of shoulder arthroplasty, and that such variability in the values of this parameter between the manual and automated methods should be taken into consideration, since the percentage of posterior head subluxation is a radiographic criterion that influences the surgical technique to be used and the selection of implants and manual measurements of this parameter are underestimated by the manual method.

As a limitation of the present study, we used a single automated preoperative planning program. We understand that these programs present a variability of measurements among them, since they use different anatomical parameters to format the images.

Conclusion

The manual method is effective in measuring the glenoid version and inclination when performed by experienced surgeons, and the vault method is more accurate than the Friedman et al.[12] method in patients with glenoids with greater deformities. However, the measurement of the percentage of posterior subluxation of the humeral head presents a great discrepancy between the manual and automated methods. Such differences underscore the need for further studies that aim to assess the impact of such differences on the outcome of procedures, since several uncertainties exist regarding the accuracy of manual and automated methods and the selection and correct positioning of the implants.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Osteopontin, WNT3A, and ABCB5 Biomarkers Expression in Osteosarcoma Patients

Expressão dos biomarcadores osteopontin, WNT3A e ABCB5 em pacientes com osteossarcoma

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Abstract

Objective This study aimed to correlate the expression, by immunohistochemistry, of the proteins OPN, ABCB5, and WNT3A from anatomopathological materials obtained from paraffin blocks, slides, or both, from patients with osteosarcoma (OS), analyzing the epidemiological characteristics, their presence, and influence on the evolution and progression of the disease.

Methods After the initial case selection, we searched for the respective paraffin blocks and took only those with sufficient tumor mass to allow additional sections to be resected without exhausting the biological material. The identification of sarcoma areas in representative paraffin blocks was performed to create multisample blocks (tissue microarray [TMA]) on a BenchMark ULTRA (Roche Diagnostics Corporation, Indianapolis, IN, USA) instrument. Then, we analyzed the association between the expression of ABCB5, WNT3A, and osteopontin (OPN) markers with the variables age, location, and tissue type (Fisher exact test/Chi-squared test).

Results The average age of the patients was 23 years, and the rate of males and females was the same. We analyzed 40 slides from 28 OS patients seen from 2005 to 2017. Their follow-up time was 80.0 months, and the 5-year survival rate was 46.7%. Most metastases occurred in lung tissue (92.9%). Proteins ABCB5, OPN, and WNT3Adid not present statistical significance when compared with age group, neo-adjuvant and/or adjuvant chemotherapy, location, survival, or death. Osteopontin was negative in all samples. WNT3A expression occurred in patients who died early.

Conclusion In an immunohistochemical study, ABCB5, OPN, and WNT3A did not have statistical significance. In the parameters analyzed, they did not seem to be a predictive or aggressive factor for OS.

Keywords
- tumor biomarkers
- immunohistochemistry
- osteopontin
- osteosarcoma

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Resumo

Objetivo Correlacionar a expressão, por imunoistoquímica, das proteínas OPN, ABCB5 e WNT3A de material anatomopatológico, obtido de blocos de parafina e/ou lâminas, em pacientes com osteossarcoma (OS), analisando as características epidemiológicas, sua presença e influência na evolução e progressão da doença.

Métodos Após a seleção inicial dos casos, ocorreu a busca dos respectivos blocos de parafina, dentre os quais foram selecionados somente aqueles que possuíam massa tumoral suficiente para serem realizados cortes adicionais sem que todo o material biológico fosse utilizado. Foram identificadas áreas do sarcoma nos blocos de parafina representativos para a confecção de blocos multiamostrais (microarranjo de tecidos, ou *tissue microarray* [TMA], em inglês), realizada em instrumento *BenchMark ULTRA* (Roche Diagnostics Corporation, Indianapolis, IN, USA). Foi então analisada a associação entre a expressão dos marcadores ABCB5, WNT3A e OPN com as variáveis idade, localização e tipo de tecido (teste exato de Fisher/Qui-quadrado).

Resultados A média de idade foi de 23 anos, e a incidência de pacientes dos sexos masculino e feminino foi a mesma; foram analisadas 40 lâminas de 28 pacientes com OS, entre 2005 e 2017, com tempo de segmento de 80,0 meses, e o tempo de sobrevida foi de 46,7% em 5 anos. Metástases ocorreram em tecido pulmonar (92,9%). Quanto aos marcadores ABCB5, OPN e WNT3A, não apresentaram significância estatísticas quando comparados com faixa etária, neo-adjuvância e/ou adjuvância quimioterápica, localização, sobrevida ou óbito. O OPN mostrou-se negativo em todas as amostras. E o WNT3A expressou-se nos pacientes com óbitos precoces.

Conclusão As proteínas ABCB5, OPN e WNT3A, em estudo imunoistoquímico, não se mostraram presentes com significância estatística. Nos parâmetros analisados, não surgem como sendo fatores preditivos ou de agressividade para o OS.

Palavras-chave

- biomarcadores tumorais
- imuno-histoquímica
- osteopontina
- osteossarcoma

Introduction

This article addresses the study of osteopontin (OPN), WNT3A, and ABCB5 as biomarkers in osteosarcoma (OS) patients.

When analyzed in other tumors, especially carcinomas, the ABCB5 biomarker has a critical role on the evaluation of resistance to chemotherapy agents commonly used in OS treatment.

The WNT3-signaling pathway is common in several tumors, including carcinomas and sarcomas. This pathway plays a significant role in intracellular process regulation, and its presence in different tumor types highlights its importance in several contexts.

Although OPN is present in many cases of carcinoma, its crucial function in bone tissue relates to the preosteoblast maturation into osteoblast. This transformation is key for osteosarcoma presentation, emphasizing the complex role of osteopontin, especially in bones.

There are no known biomarkers capable of revealing the presence of bone tissue sarcomas, and their aggressiveness and propensity to metastasize. The opportunity to explore and study the biomarkers analyzed in the present article has presented itself, and we are taking this chance to integrate our experience into this investigation. This is a crucial step towards deepening our understanding of the nature of these sarcomas, significantly contributing to advancing the diagnosis and treatment of these complex conditions.

In OS, a highly aggressive form of bone sarcoma, biomarkers play distinct and crucial roles in tumor progression. The ABCB5 gene, recognized as a biomarker associated with therapeutic resistance, modulates the activity of the WNT3-signaling pathway, contributing to supporting the proliferative capacity and cellular resistance in OS. The WNT3-pathway, an intrinsic biomarker, regulates the expression of genes related to uncontrolled bone growth and carcinogenesis.

Simultaneously, OPN, also considered a biomarker, suffers influences from other factors, including the WNT3 pathway, and it is implicated in bone formation, playing a significant role in bone tumorigenesis. The expression and activity of biomarkers such as ABCB5, the WNT3-signaling pathway, and OPN are associated with OS aggressiveness.

Studies observed that high levels of these biomarkers often correlate with more aggressive disease behavior. The presence of ABCB5, for instance, has been associated with resistance to conventional treatments, potentially contributing to OS progression. Abnormal activation of the WNT3 pathway is related to uncontrolled tumor growth and invasiveness, while increased OPN expression has been associated with a greater capacity for metastasis.

Therefore, analyzing these biomarkers can offer prognostic insights, since they are widely studied in lung and breast carcinomas and melanomas.

Identifying and understanding these biomarkers are essential to guide more precise and effective therapeutic

strategies against OS. The biggest difficulty is finding studies with a significant number of cases.

Approximately 8.7 per million children and adolescents under the age of 20 suffer from OS, which originates in the mesenchymal tissue. As such, this is the most common malignant tumor in the age group up to 20 years.

The definitive diagnosis relies on the clinical presentation of pain and swelling, followed by radiological imaging investigation, biopsy confirmation, or both.

The survival rates, in a 5-year time range, are higher in patients with no metastases. This depends on the biological behavior of the condition.

Most metastases occur in lung tissues. The advent of neoadjuvant polychemotherapy followed by surgical treatment and adjuvant chemotherapy improved survival by around 50 to 70% depending on the heterogeneous nature of this disease.

Several prognostic factors with biomarkers have already been researched for OS. However, studies found no biomarker with strong evidence for diagnosing or evaluating prognoses, especially from metastatic diseases, and identifying potential therapeutic targets. Our study highlights WNT3A, OPN, and ABCB5 as biomarkers.

Laboratory experiments revealed that WTN3A is a protein from the canonical WNT family, the most involved in abnormal ß-catenin levels in the cell nucleus.[1] In normal bone tissue, OPN is vital for osteoblast development. Furthermore, ABCB5 is a novel human membrane transporter from the ABC protein group, identified and characterized in human skin.

This study aimed to correlate the expression, by immunohistochemistry, of OPN, ABCB5, and WNT3A from anatomopathological materials obtained from OS patients' paraffin blocks and/or slides, analyzing epidemiological characteristics, their presence, and influence on the evolution and progression of the disease.

Materials and Methods

The institutional ethics committee approved this study under number CAAE 69385417.7.1001.0103.

We obtained clinical and anatomical data from the electronic medical records of the hospital's Philips Tasy Electronic Medical Record (Philips Healthcare, Best, Netherlands) system and reviewed the physical records and pathological anatomical reports from the pathological anatomy service from the 64 patients with OS treated from 2005 to 2017.

The initial search used the International Classification of Diseases (ICD) code C40 and collected the clinical notes from each case in a standardized protocol with the following variables: name, patient age at diagnosis, gender, number of tumors, paraffin block number, histological diagnosis, primary tumor location, date of diagnosis, presence of metastases, metastasis location at diagnosis (if any), survival time in months, death (if any), follow-up time, and disease progression.

The end date for assessing patient survival was December 2017.

Disease Progression and Survival Time

Some patients, even during treatment, experienced tumor recurrence or disease progression with clinical staging worsening, either due to the tumor recurrence at the surgical site or the appearance of local (skip) or distant metastasis in the viscera or lymph nodes. Distant metastasis occurred in the lungs and lymph nodes.

Subsequently, we calculated the disease-free time in months, that is, the period during which the patient remained with no signs or symptoms of the neoplasm.

We calculated the survival time by subtracting the date of OS diagnosis from the date of death or last assessment. The date in which the last OS diagnosis was given was subtracted from the date of death or last follow-up exam.

Sample Selection

After the initial selection of cases, we searched for the respective paraffin blocks and took only those with sufficient tumor mass to allow additional sections with no complete biological material loss.

A second independent pathologist reevaluated the tumor slides to confirm OS diagnosis.

We requested hematoxylin and eosin (HE)-stained slides from blocks, in case of their unavailability. If more than one paraffin block was available, the pathologist chose the one with the larger neoplastic mass.

We sent the duly-checked blocks to OPN, WNT3A, and ABCB5 biomarker immunostaining.

Immunohistochemistry

The immunohistochemistry technique used the Ventana BenchMark ULTRA (Roche Diagnostics Corporation, Indianapolis, IN, USA) instrument with integrated 3-in-1 processing. Preparation occurred in the following order: deparaffinization; rehydration; antigen retrieval with the Cell Conditioning 1 (high pH) and 2 solutions (Roche Diagnostics Corporation) (low pH) buffers; primary antibody incubation for 16 to 20 minutes at room temperature; immunoperoxidase technique; staining amplification using the UltraView Universal DAB Detection Kit (Ventana Medical Systems, Oro Valley, AZ, USA). After immunostaining, we analyzed the tissue microarray (TMA) slides. Internal and external positive controls tested the fidelity of the reactions.

Antibodies Employed

►**Table 1** describes the primary antibodies employed in this study.

Immunostaining Report

Two different pathologists reviewed the slides at distinct times using an Olympus CX31 (Olympus Life Science, Waltham, MA, USA) microscope and classified them per the following parameters:

- **Positive:** Presence of anti-ABCB5 antibody in the cytoplasmic membrane and the cytoplasm; presence of anti-WNT3A antibody in the cytoplasm; c-staining; and presence of anti-OPN antibody in the cytoplasm.

Table 1 Description of primary antibodies, their respective manufacturers, and dilutions

Biomarker	Primary antibody	Manufacturer	Dilution
ABCB5	Anti-ABCB5, clone 5H3C6	*GeneTex*	1:200
OPN	Anti-Osteopontin, policlonal	*Anti-Osteopontin, policlonal*	1:25
WNT3A	Anti-WNT3A, policlonal	*GeneTex*	1:400

Abbreviation: OPN, osteopontin. **Source:** The authors (2019).

- **Negative:** Lack of chromogenic staining expression for antibody targets.
- **Inconclusive:** Impossibility of evaluating antibody expression due to pre-analytical problems (poor fixation, acid decalcification, and inadequate paraffin).

Results

Information regarding the patients included medical record data, patient number, slides, age at diagnosis, gender, and tumor location per the sample studied (►**Table 2**). We analyzed 40 samples from paraffin blocks of the primary and metastatic tumors' biopsy and surgical specimens, taken from a total of 28 OS patients. These samples were from the anatomical pathology service and dated from 2005 to 2017. We correlated survival, presence or absence, metastasis site, and expression of ABCB5, WNT3A, and OPN markers (►**Table 3**).

►**Table 4** presents the analysis performed based on data from 40 slides of 28 OS patients.

►**Table 5** shows patient-related variables, such as age at diagnosis, gender, number of slides throughout the follow-up period, and deaths.

►**Table 6** reports the survival percentages at each time point per the Kaplan-Meier estimative.

Descriptive Data from ABCB5, WNT3A, and OPN Biomarkers

The results (valid n) included tumor location (lower limbs, upper limbs, axial skeleton), slide type (biopsy, postchemotherapy, or with no chemotherapy), and slide tissue type (treatment-free and after therapy). We considered a single slide per patient, obtaining the following results (n = 28): tumor location – lower limbs (n [%], 20 [71.4]), upper limbs (n [%], 7 [25.0]), axial skeleton (n [%], 1 [3.6]); slide type – biopsy (n [%], 16 [57.1]), postchemotherapy (n [%], 10 [35.7]), no chemotherapy (n [%], 2 [7.1]); tissue type at the slide – treatment-free bone tissue (n [%], 18 [64.3]), posttreatment bone tissue (n [%], 10 [35.7]).

Descriptive data regarding ABCB5, WNT3A, and OPN considering a single slide per patient and percentages and after removing inconclusive results, are the following:

ABCB5, valid n = 28
Negative (n [%], 7 [25.0])
Positive (n [%], 14 [50.0])
Inconclusive (n [%], 7 [25.0])

ABCB5, valid n = 21
Negative (n [%], 7 [33.3])
Positive (n [%], 14 [66.7])

WNT3A, valid n = 28
Negative (n [%], 19 [67.9])
Positive (n [%], 2 [7.1])
Inconclusive (n [%], 7 [25.0])

WNT3A, valid n = 21
Negative (n [%], 19 [90.5])
Positive (n [%], 2 [9.5])

OPN, valid n = 28
Negative (n [%], 21 [75.0])
Inconclusive (n [%], 7 [25.0])

Assessment of Factors Associated with Biomarker Results and Between Factors and Survival

For this analysis, the observation unit was the slide. Slides from the same patient were considered independent units.

For each variable, tissue type, tumor location, and biomarker analyzed, we tested the null hypothesis that there is a lack of association between the variable and the marker versus the alternative hypothesis, that is, the presence of an association.

For age at diagnosis and each marker, we tested the null hypothesis that the mean age is the same for all markers versus the alternative hypothesis, that is, that the mean age is different.

Regarding survival, we tested the null hypothesis which was lack of association between each variable and survival, versus the alternative hypothesis, that is, the presence of an association. These are percentages of deaths according to the variable age at diagnosis, gender, metastases, tumor site, ABCB5, WNT3A, and OPN markers, and *p*-values from statistical tests.

Discussion

The selected OS patients were classified as Enneking grade IIB or III.

In the analysis of the epidemiological profile, 17 patients were under 20-years-old (young patients), and 11 were over 20-years-old. The youngest subject was 10-years-old, which is consistent with the literature.[2–5] In this sample, the male and female incidence was the same, at 50%. Studies with larger samples showed a slight male predominance.[6]

Among the study's patients, regarding metastasis location: 14 patients with metastasis, 13 (92.9%) of whom had metastases in the lung tissue and 1 (7.1%) in the lymph nodes.[2] In this study, 50% of the subjects developed lung metastases. According to Evola et al.,[7] approximately 20% of patients had lung metastases at the initial diagnosis, 40% had metastases at a later stage, and 80% of metastases occurred in the lung.

The 5-year (60-month) survival rate was 46.7%, slightly below literature reports, which range from around 50 to 65%.[2,3,8] Death occurs between the first and third years

Table 2 Data: medical record, patient number, slides, age at diagnosis, gender, and location

Medical record	Patient number	Slides	Age at diagnosis	Gender	Location
14001945	4	162818B	20	Male	Inferior limb
	4	167536B / 2-17	20	Male	Inferior limb
14002913	5	143741B	12	Female	Superior limb
1001989	6	143042B	26	Female	Inferior limb
	6	149162B / 3-11	26	Female	Inferior limb
	6	157099B	27	Female	Inferior limb
13000565	7	130884B	13	Female	Inferior limb
	7	135117	13	Female	Inferior limb
	7	140955B / 1-5	14	Female	Inferior limb
	7	143457B	14	Female	Axial skeleton
12006205	8	140430B	62	Male	Superior limb
13005621	10	138466B 1-57	19	Male	Inferior limb
13002093	11	134093B	20	Male	Inferior limb
	11	135736B	20	Male	Inferior limb
7002221	12	073238B / 1-2	16	Female	Superior limb
	12	073801B	16	Female	Superior limb
7002774	13	074648B	16	Male	Inferior limb
	13	077531B	16	Male	Inferior limb
6008700	14	0608869E	61	Female	Inferior limb
7001977	15	074428B	36	Female	Inferior limb
11003053	34	116772B / 1-8	20	Male	Inferior limb
11004802	36	116711B	45	Male	Superior limb
13001519	38	135295B / 1-25	13	Female	Inferior limb
5006762	40	056664B	13	Female	Inferior limb
6002708	43	0602903B	10	Female	Inferior limb
6001225	45	0606133B / 1	13	Female	Inferior limb
6008407	47	070309B / 1-3	27	Male	Inferior limb
5004056	48	0600157B / 1-2	23	Male	Superior limb
15000164	51	150432B / 1-2	21	Female	Inferior limb
14006899	52	154918B / 2-7	18	Male	Inferior limb
14007558	53	150955B / 3-20	14	Female	Inferior limb
15006646	55	167192B / 1-15	26	Female	Axial skeleton
15007598	56	1610793B / 2-6	32	Female	Inferior limb
16002529	58	163780B	20	Male	Superior limb
	58	168657B / 1-14	20	Male	Superior limb
16004018	59	166003B / 1-9	22	Male	Superior limb
16009072	62	1612817B / 1-2	16	Male	Inferior limb
	62	170557B / 1-13	17	Male	Inferior limb
17008495	63	1714419B	11	Male	Inferior limb

postdiagnosis in most patients, indicating that it is a very aggressive condition.[5]

The tumor was in the lower limbs in 20 patients (71.4%), in the upper limbs in 7 (25%), and in the axial skeleton in 1 (3.6%). These rates are consistent with the literature.[2,5,7,9,10]

The epidemiological variables (age at diagnosis, gender, metastases, location, and biomarkers) had no statistical significance when analyzing death as an outcome. The metastasis variable trends towards significance ($p = 0.086$); however, the sample is too small for this conclusion.

Table 3 Data: survival, metastasis, location, ABCB5, WNT3A, and OPN

Medical record	Survival (months)	Metastasis	Location	ABCB5	WNT3A	OPN
14001945	57	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
	52	Yes	Lung	Positive	Negative	Negative
14002913	67	No		Negative	Negative	Negative
1001989	18	Yes	Lung	Positive	Negative	Negative
	12	Yes	Lung	Negative	Negative	Negative
	2	Yes	Lung	Negative	Negative	Negative
13000565	17	Yes	Lung	Positive	Negative	Negative
	12	Yes	Lung	Positive	Negative	Negative
	5	Yes	Lung	Positive	Positive	Negative
	3	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
12006205	72	No		Positive	Negative	Negative
13005621	3	No		Inconclusive	Inconclusive	Inconclusive
13002093	11	Yes	Lung	Positive	Positive	Negative
	12	Yes	Lung	Negative	Negative	Negative
7002221	24	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
	24	Yes	Lung	Positive	Negative	Negative
7002774	29	Yes	Lung	Positive	Positive	Negative
	25	Yes	Lung	Positive	Negative	Negative
6008700	16	No		Negative	Negative	Negative
7001977	124	No		Negative	Negative	Negative
11003053	75	Yes	Lung	Positive	Negative	Negative
11004802	68	No		Positive	Negative	Negative
13001519	8	Yes	Lung	Positive	Negative	Negative
5006762	41	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
6002708	128	No		Positive	Negative	Negative
6001225	16	Yes	Lymph node	Positive	Negative	Negative
6008407	118	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
5004056	133	No		Positive	Negative	Negative
15000164	55	Yes	Lung	Negative	Negative	Negative
14006899	3	No		Negative	Negative	Negative
14007558	34	Yes	Lung	Negative	Negative	Negative
15006646	2	No		Inconclusive	Inconclusive	Inconclusive
15007598	52	No		Positive	Negative	Negative
16002529	18	Yes	Lung	Inconclusive	Inconclusive	Inconclusive
	13	Yes	Lung	Positive	Negative	Negative
16004018	36	No		Inconclusive	Inconclusive	Inconclusive
16009072	12	No		Positive	Negative	Negative
	11	No		Negative	Inconclusive	Inconclusive
17008495	24	No		Negative	Negative	Negative

Abbreviation: OPN, osteopontin.

The ABCB5 marker had positive expression in 14 patients (66.7) and negative expression in 7 subjects (33.3%) after excluding the 7 inconclusive results. The biomarker WNT3A had positive expression in 2 patients (9.5%) and negative expression in 19 (90.5%), after removing the inconclusive ones. The OPN marker was always negative, with no expression either in slides of tissues receiving neoadjuvant chemotherapy or not.

Table 4 Pre and postchemotherapy slides

Patient	Total	Number of slides	
		Treatment-free bone tissue	Posttreatment bone tissue
1	1	1	
2	1	1	
3	1		1
4	1	1	
5	1	1	
6	1	1	
7	1	1	
8	1		1
9	1	1	
10	1	1	
11	1		1
12	1		1
13	1		1
14	1	1	
15	1		1
16	1		1
17	1		1
18	1		1
19	1	1	
20	2	1	1
21	2	2	
22	2	1	1
23	2	2	
24	2	1	1
25	2	1	1
26	2	2	
27	3	1	2
28	4	1	3
Total slides	40	22	18

When evaluating the expression of markers ABCB5 and WNT3A versus OS location in the upper and lower limbs and age groups below or above 20 years, positive or negative staining had no significance. However, the OPN marker was negative in the upper and lower limb slides and in the age groups above and below 20 years.

When evaluating the slides from the 28 eligible patients, 6 had slides from pre and postchemotherapy samples. The pretreatment evaluation had one slide per patient. For postchemotherapy evaluations, slides were analyzed according to disease progression events (relapses and metastases), which resulted in the analysis of new slides referring to these events. Therefore, the number of posttreatment slides (9) was higher than that of pretreatment slides.

For the ABCB5 marker in the pretreatment evaluation, 3 slides (50%) were positive, none was negative (0%), and 3 were inconclusive (50%). After chemotherapy treatment, 6 were positive (66.7%), 2 were negative (22.2%), and only 1 was inconclusive (11.1%). This biomarker assesses resistance to chemotherapy drugs, being a chemoresistance mediator, identified and proven to be critical and specific to the drug doxorubicin. In the present sample, patients under chemotherapy regimens also received doxorubicin. Therefore, this protein expression was detectable in 50% of pretreatment slides and 66.7% of posttreatment slides. This finding highlights the hypothesis that tumor stem cells develop the capacity to resist cytotoxic drugs, hindering the inhibition of tumor progression.[11–13]

Haydon et al.[14] concluded that deregulation of the WNT/ß-catenin pathway is very common in OS. However, in this sample, only two patients showed signs of activation of this pathway. Nevertheless, when this occurred, it was precisely in patients with the worst prognosis. There was no statistical significance when considering the expression of this protein influencing survival.

There was no OPN detection in osteoblastomas and bone remodeling specimens. Its expression did not influence overall patient or disease-free survival. It does not provide predictive information about the outcome of OS patients. The formation and differentiation of osteoblasts are fundamental for bone tissue development. Furthermore, OPN interferes with the differentiation of the primary mesenchymal cell into preosteoblasts, generating mature osteoblasts. Disruption of this process may be the main cause of OS. Luo et al.[15] reported a decrease in OPN levels in OS, as it does not act in the osteoblast differentiation. This protein's expression was negative in 100% of the slides, which is consistent with the findings of these authors.

Conclusion

In an immunohistochemical study of OS, the biomarkers ABCB5, OPN, and WNT3A showed no statistical significance regarding epidemiological parameters. They did not prove to be a predictive or aggressive factor for OS. A slight increase in ABCB5 was observed postchemotherapy. Blocking ABCB5-protein expression supports the hypothesis of increased survival free from disease recurrence. The OPN protein was present in the etiology and development of OS. In this study, the canonical WNT/ß-catenin pathway was not convincingly present in the expression of the WNT3A marker. Further prospective studies with frozen, randomized, and controlled tumor bank material are required to consolidate and promote advances in future research.

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Conflict of Interests
The authors have no conflict of interests to declare.

Table 5 Patient-related variables ($n = 28$)

Variable	Valid n	Classification	Result*
Age at diagnosis (years)	28		23 ± 13.4 (10–62)
		Up to 20	17 (60.7)
		Over 20	11 (39.3)
Gender	28	Female	14 (50)
		Male	14 (50)
Number of slides during follow-up period	28	1	19 (67.9)
		2, 3, or 4	9 (32.1)
Death	28	No	14 (50)
		Yes	14 (50)
Follow-up time (no death) (months)	14		80.0 ± 42.0 (27.5–150)
Survival time (death) (months)	14		18.2 ± 12.1 (2.7–42.1)
General follow-up time (months)	28		48.9 ± 43.6 (2.7–150)
Metastasis	28	No	14 (50)
		Yes	14 (50)
Metastasis location (per patient)	14	Lung	13 (92.9)
		Lymph node	1 (7.1)

Note: *Mean ± standard deviation (minimum–maximum) or frequency (percentage).

Table 6 Survival rates at up to 5 years

Time (months)	Survival (%)
0 (diagnosis)	100%
3 months	100%
6 months	96.4%
1 year	92.9%
1.5 years	67.9%
2 years	64.3%
3 years	56.9%
4 years	52.5%
5 years	46.7%

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Radiographic Evaluation of the Surgical Treatment of Pediatric Supracondylar Humeral Fractures

Avaliação radiográfica do tratamento cirúrgico das fraturas supracondilianas do úmero em crianças

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Abstract

Objective To perform a radiographic assessment of the quality of supracondylar fracture fixation by identifying the factors that have contributed to inadequate reduction and increased the chance of reduction loss during outpatient follow-up. The variables analyzed were as follows: fracture line, initial displacement, time of day the surgery was performed, and chosen fixation technique.

Methods Review of electronic medical records and radiographic evaluation of supracondylar fractures operated from January 2017 to December 2022. The radiograph assessment was based on the Baumann angle and the anterior humeral line. Determination of fixation quality was based on the number of cortices, crossing site, and wire divergence.

Results We evaluated 194 cases, and postoperative reduction was poor in 17% of the subjects. Reduction loss occurred in 39 cases (20.10%), and 19 (48.7%) of these patients presented insufficient fixation ($p = 0.002$). Among the cases operated during the day, 12.5% lost the reduction compared with 32% of the patients who underwent surgery at night and early in the morning ($p = 0.001$).

Conclusion Reduction quality and postoperative fixation loss were closely related to technical errors and the time of day the surgery was performed.

Keywords
- child
- elbow
- fracture fixation, internal
- humeral fractures

Resumo

Objetivo Avaliar de forma radiográfica a qualidade da fixação das fraturas supracondilianas, identificando os fatores que contribuíram para uma redução inadequada e que aumentaram a chance de perda de redução no seguimento ambulatorial. As variáveis

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analisadas foram: traço de fratura, deslocamento inicial, período do dia em que a cirurgia foi realizada e técnica de fixação escolhida.

Métodos Revisão de prontuário eletrônico e avaliação radiográfica das fraturas supracondilianas operadas de janeiro de 2017 a dezembro de 2022. A avaliação das radiografias foi baseada no ângulo de Baumann e na linha umeral anterior. Já a qualidade de fixação foi mensurada pelo número de corticais, pelo local de cruzamento e pela divergência dos fios.

Resultados Foram avaliados 194 casos, sendo a redução pós-operatória considerada ruim em 17%. A perda de redução aconteceu em 39 casos (20,10%), sendo que 19 (48,7%) desses pacientes apresentaram fixação insuficiente ($p = 0{,}002$). Dos casos operados durante o dia, 12,5% perderam a redução, comparados a 32% dos realizados nos períodos noturno e da madrugada ($p = 0{,}001$).

Conclusão Dessa forma, a qualidade da redução e a perda da fixação pós-operatória mostraram-se intimamente relacionadas aos erros técnicos e ao período do dia em que a cirurgia foi realizada.

Palavras-chave
- cotovelo
- criança
- fixação interna de fraturas
- fraturas do úmero

Introduction

Supracondylar humerus fractures account for up to 15% of all childhood fractures and for 60% of all pediatric elbow fractures.[1,2] The maximum incidence occurs from 5 to 7 years of age, peaking at age 6.[3,4] Supracondylar humerus fractures are those that most frequently require surgical treatment in the pediatric population.[5]

The most common trauma mechanism is fall with a flat hand and hyperextension of the elbow, resulting in a fracture extending to the distal fragment. The rarer flexion type results from direct trauma to the posterior region of the elbow, leading to an anterior displacement of the distal fragment.[6]

Some variables can influence the quality of surgical reduction and contribute to the loss of postoperative fixation. The fracture line, the initial displacement, the time of day the surgery is performed, and the chosen fixation technique may directly relate to treatment success. The surgeon must understand the role of each variable and develop methods for better management. The present study aimed to map and evaluate the factors potentially impairing the quality of surgical reduction and contributing to postoperative fixation loss.

Materials and Methods

The institutional Human Research Ethics Committee approved the present study under Opinion Certificate number CAAE 69485623.5.0000.5530.

We cross-sectionally and retrospectively evaluated all pediatric patients aged 1 to 14 years with supracondylar humeral fractures undergoing surgical treatment from January 1st, 2017, to December 31, 2022. We excluded patients with no postoperative follow-up, inadequate medical records, and incomplete radiographic study, in addition to those with fractures showing intra-articular extension.

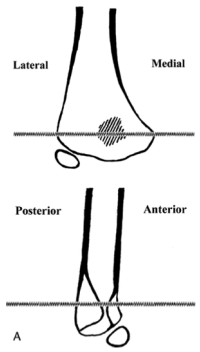
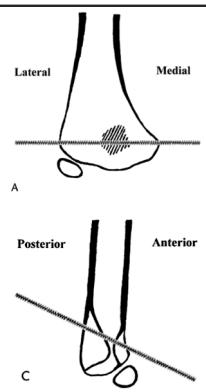
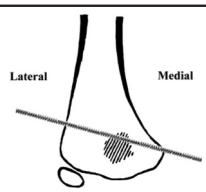
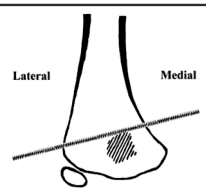
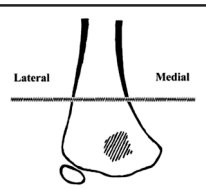
In total, we analyzed 210 cases operated on by different surgeons. After applying the exclusion criteria, we included 194 patients in the study. We reviewed electronic medical records and radiographs, in addition to age, gender, laterality, fracture type (extension or flexion), line morphology, shift during surgery performance, and the presence of neurovascular complications. We classified fracture patterns using preoperative and intraoperative images according to the criteria described by Bakh et al.[7] (►**Table 1**).

We assessed the quality of postoperative reduction in the coronal plane using the Baumann angle (normal range: 9–26°[8]) and in the sagittal plane using the anterior humeral line (which is normal when crossing the central and anterior thirds of the capitellum). The reduction was inadequate when the Baumann angle was outside the normal criteria, the anterior humeral line did not pass through the capitellum, or both (►**Fig. 1**). The reduction loss criteria during follow-up were a 6° change in the Baumann angle[9] or alterations in the thirds of the capitellum's intersection with the anterior humeral line on lateral radiographs.

We also assessed the variables regarding the configuration of the fixation, such as the order of the wires and the stability promoted (number of cortices, crossing site, wire divergence). The fixation technique was inadequate if presenting: 1) a lack of cortical fixation of the distal or proximal fragment by 1 or more wires, totaling less than 4 cortical wires fixed; 2) wire convergence in the proximal cortex; or 3) pins crossing in the fracture focus[10] (►**Fig. 2**). In the present study we considered the fixation good when it included the four cortices, two in the proximal fragment and two in the distal fragment, with adequate separation to fix the two columns. We stratified the time of day for surgery performance into daytime (7 am–7 pm), nighttime (7 pm–midnight), or early morning (midnight–7 am).

Data were collected through a review of the medical records and assessed using specific statistical tests (the Chi-squared test) in the application of the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 25.0, with a significance level of 0.05. Project approval followed Resolution no. 466/2012 of the Brazilian

Table 1 Fracture pattern, radiological representation, and trace stability

Fracture type	Image	Number of cases per fracture pattern	Instability	Definition
Low transversal + low line in the sagittal plane		131	Stable	< 10° obliquity in the coronal plane with transverse fracture close to the epicondyles + < 20° inclination in the sagittal plane
Low transversal + high line in the sagittal plane		42	Unstable	< 10° obliquity in the coronal plane with transverse fracture close to the epicondyles + > 20° inclination in the sagittal plane
Lateral coronal oblique		6	Unstable	≥ 10° obliquity in the coronal plane with fracture line laterally higher
Medial coronal oblique		7	Unstable	≥ 10° obliquity in the coronal plane with fracture line medially higher
High coronal		8	Unstable	Fracture with a line above the olecranon fossa, but within the distal metaphysis of the humerus

Note: Table with changes based on Bahk et al. (2008).[7]

National Health Council (Conselho Nacional de Saúde, CNS, in Portuguese) and current complementary ethical regulations.

Results

We evaluated 194 cases of supracondylar fractures undergoing surgical treatment in the estimated period. These sample included 133 male (68.6%) and 61 female patients (31.4%). The peak incidence ranged from 4 to 7 years of age, with a mean age of 6. The left side was the most affected, accounting for 57.8% of the cases. Regarding fracture displacement, 171 were in extension (87.6%), and 24, in flexion (12.4%).

Neurological injury was observed in 13 (6.7%) cases, with ulnar nerve involvement in 5 patients, median nerve injury in 4 patients, radial nerve injury in 3 patients, and radial nerve injury and impairment in 1 patient. All cases achieved complete recovery from neurological injury within 6 months. The most severe complication was compartment syndrome, which

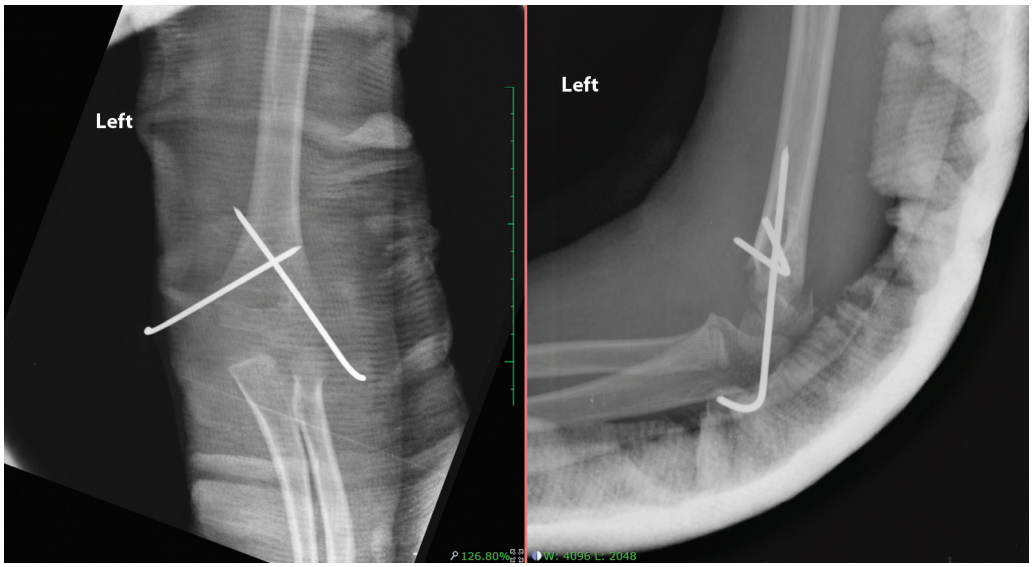


Fig. 1 Anteroposterior (AP) and lateral radiographs of the distal humerus performed immediately after surgery, demonstrating unsatisfactory reduction, as the anterior humeral line does not touch the capitellum. In the AP radiograph, the ulnar spine wire does not appear to fixate the distal fragment.

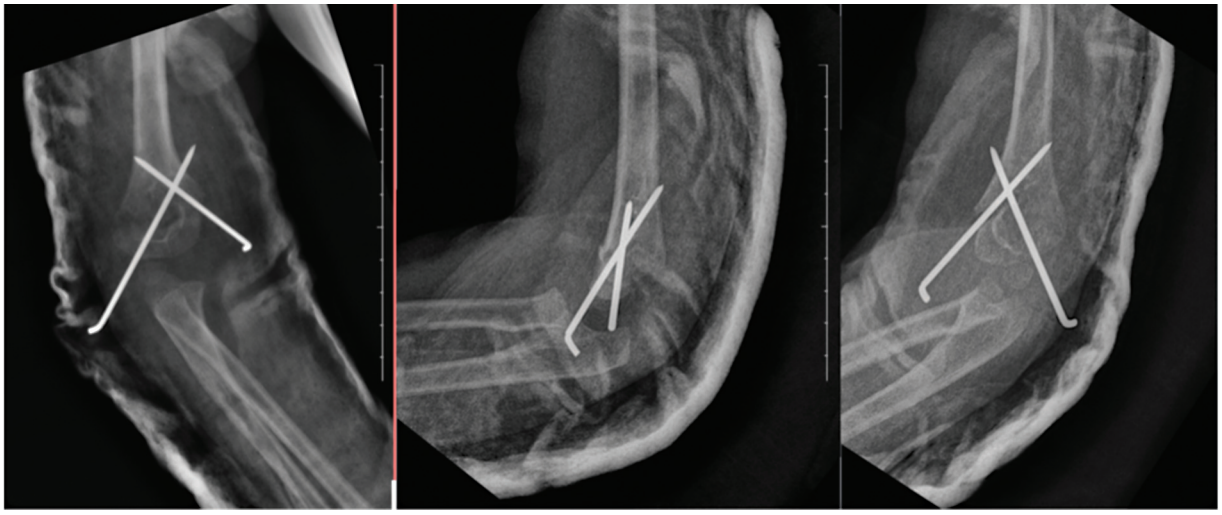


Fig. 2 Anteroposterior and lateral oblique radiographs of the distal humerus performed immediately after surgery, demonstrating an acceptable reduction but inadequate fixation, as one of the wires does not fixate the distal fragment.

occurred in 1 case and required fasciotomy but progressed to Volkmann ischemic contracture. Regarding the approach, 4 cases (2.1%) underwent open reduction, while the others underwent indirect reduction and percutaneous fixation.

We also classified fractures per the fracture line: 173 fractures were low transversal, 7 were medial oblique, 6 were lateral oblique, and 8 were transversal high. Among the low transversal fractures, 42 cases presented a high line in the sagittal plane, leading to instability. We considered 63 fractures (32.47%) unstable due to their morphology.

Crossed wire fixation occurred in 125 cases (64.5%), using 2 lateral wires in 35 cases (18%), 2 lateral wires and 1 medial wire in 27 cases (14%), 3 lateral wires in 6 cases (3%), and atypical configuration with 1 lateral wire and 3 medial wires in 1 subject (0.5%). In total, 55 cases (28.35%) presented insufficient fixation.

Postoperative reduction was acceptable in 161 patients (82.9%). In 33 fractures (17%), the fixation occurred in non-ideal parameters regarding the Baumann angle and the anterior humeral line, and 5 underwent reintervention. The main indication of poor reduction occurred in the sagittal plane when the anterior humeral line did not meet the anterior third of the capitellum. Poorly-reduced fractures included a single case of Gartland type-II, while the remaining were type-III ($p = 0.042$). Regarding fracture line instability, among the 33 unstable fractures, 15 (45.45%) presented inadequate reduction in the immediate postoperative period ($p = 0.105$).

Regarding the time of surgery performance, 19 patients (25.7%) treated during the night or early morning shifts presented unsatisfactory reduction compared with 14 (11.7%) operated on during the day ($p = 0.020$).

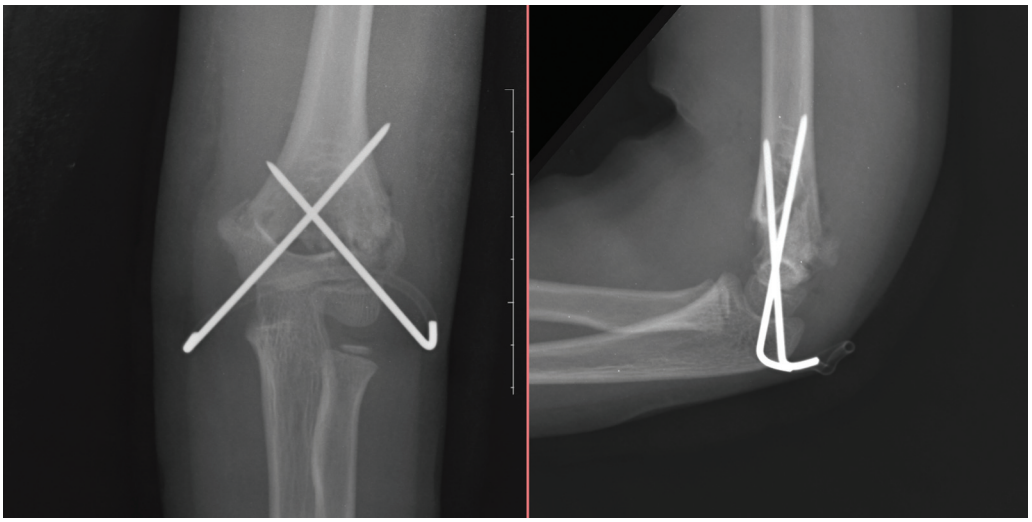


Fig. 3 Anteroposterior and lateral radiographs of the distal humerus immediately after surgery.

Reduction loss occurred in 39 cases (20.10%), including 37 Gartland type-III fractures ($p = 0.032$) and 16 (42%) morphologically-unstable fractures ($p = 0.174$). Reduction losses occurred in the coronal plane (Baumann angle) in 24 patients, in the sagittal plane (anterior humeral line) in 8 subjects, and in both planes in 7 cases (►**Figs. 3** and **4**). Of all patients with reduction loss, 19 (48.7%) presented insufficient fixation ($p = 0.002$). Reduction loss occurred in 15 cases (12.5%) operated on during the day and in 24 (32%) subjects operated on at night or early in the morning ($p = 0.001$).

Discussion

The epidemiology regarding the age of the patients with supracondylar fractures of the humerus is consistent with most references, and these injuries are more frequent in patients aged 4 to 7 years.[3,4] Although fractures in extension prevailed in the sample of the present study, there was a high incidence of deviations in flexion (12.4%) compared with that of the world literature (2%).[8]

Isolated neuropraxia of the anterior interosseous nerve (AIN) is the most common nerve injury in extension deviations,[11] while ulnar nerve compromise occurs in 90% of flexion fractures.[12] It is estimated that iatrogenic ulnar injury occurs in 1 in every 28 patients (4%) undergoing cruciate fixation.[13] Therefore, the higher incidence of 12.4% of ulnar involvement in the sample of the present study may be related to the increased incidence of fractures in flexion and the widespread use of cruciate fixation. The most severe complication was compartment syndrome, which occurred in a single case (0.51%), which is consistent with the study by Omid et al.,[4] who reported an incidence ranging from 0.1 to 0.5%. The low incidence of complications related to the time between injury and fixation corroborates the planned and safe surgical management without the need for an urgent-emergency approach in most cases.

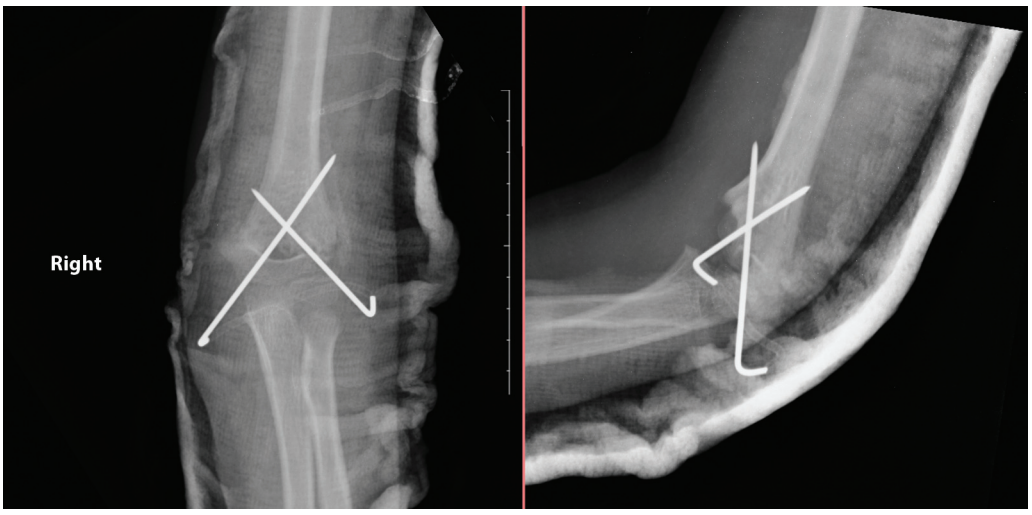


Fig. 4 Anteroposterior and lateral radiographs of the same patient in fig. 3 three weeks after fixation, demonstrating reduction loss.

Most fracture treatments involve indirect reduction and percutaneous fixation. The need for open reduction is rare; it occurs in around 6% of the cases.[8] In the present study, open reduction was used 4 times (2.1%). The main indications for open reduction include irreducible, open fractures, or decreased perfusion after reduction.[14]

The rate of reduction loss after supracondylar fracture fixation ranges from 1.6 to 33.3%.[15] According to Skaggs and Flynn,[14] the main cause for this loss is inadequate fixation attributed to technical errors. The lateral entry pins must be divergent, seeking maximum spacing at the fracture focus.[16] They must not converge or cross at the fracture focus; bicortical fixation is essential.[11] In the present study, insufficient fixation occurred in 48.7% of the cases of reduction loss ($p = 0.002$), being a fundamental causal factor for unsatisfactory outcomes. The high heterogeneity of surgeons on duty and the fact that is the procedures were performed at a training service for new traumatologists are relevant factors in this context.

The time of surgery performance proved to be a critical variable for the radiological outcome: 32% of the cases operated on at night or early in the morning had unsatisfactory radiographs at the end of the follow-up period. The search for a causal justification for this data involves the fact that the surgeons are outside their most comfortable context, that is, on the third shift and with a reduced assistant team. The technical capacity or training of the surgeon should not be a determining factor, since night surgeries are performed by the same group of surgeons as daytime surgeries. This fact cannot be attributed exclusively to the orthopedic surgeon, as approximately 30 on-call staff perform day and night shifts and the same surgery at different times regardless of their subspecialty. Surgical treatment at night was associated with a higher rate of inadequate fixation compared with daytime procedures.[17] Delaying surgery until the following day does not increase the number of complications, as long as warning signs, such as exposure, vascular injury, and secondary complex signs (voluminous edema, ecchymosis, soft tissue pinching), are absent.[18]

Some limitations to this analysis require consideration, including the retrospective nature and data collection according to available medical records. Furthermore, it is essential to further study the clinical correlation of the radiological findings herein described.

Conclusion

The quality of the surgical reduction and its maintenance in the postoperative follow-up were closely related to technical aspects and the time of day of the surgery was performed. Therefore, except for specific situations of greater risk, delaying surgery until the following day results in a better radiological outcome without increasing the incidence of complications.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Congenital Clubfoot: Difficulties in Maintaining the Use of the Dennis-Brown Orthosis by Caregivers

Pé torto congênito: Dificuldades na manutenção do uso da órtese de Dennis-Brown pelos cuidadores

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Abstract

Objective This study aimed to identify the main difficulties faced by the family when a child with congenital clubfoot (CC) uses the Dennis-Brown orthosis.

Method This study interviewed via Google Forms caregivers of children treated from 2015 to 2018 regarding their difficulties in orthosis use.

Results The answers revealed that orthosis-related difficulties are independent of the child's gender, age, or affected side. We noted that 41.7% of the respondents reported some difficulty, especially the child's irritation when using the orthosis (93.3%).

Conclusion The main factor in CC relapses is poor adherence to orthosis use. As a result, studying factors causing or increasing the probability of interrupting orthosis use is significant in creating strategies to facilitate their use, potentially reducing CC recurrence.

Keywords
- clubfoot
- foot deformities
- foot orthoses
- orthopedic devices

Resumo

Objetivo Identificar as principais dificuldades apresentadas pela família durante o uso da órtese de Dennis-Brown.

Método Esse estudo foi realizado com os responsáveis por pacientes tratados no período de 2015–2018, os quais responderam a um formulário com perguntas sobre a criança por google forms quanto às dificuldades no uso da órtese.

Resultado Com as respostas obtidas, identificamos que as dificuldades com a órtese independem do sexo, idade ou lado afetado na criança. Foi possível identificar que 41,7% dos pacientes que fizeram o uso da órtese apresentaram algum tipo de dificuldade, sendo a principal dificuldade a irritação da criança (93,3%).

Conclusão Sabendo que o principal fator de recidivas do PTC é a má aderência ao uso das órteses, o estudo de fatores que causam ou aumentam a probabilidade da interrupção do seu uso se torna um importante aliado para a criação de estratégias para facilitar o uso da órtese, assim possivelmente diminuindo a recidiva da doença.

Palavras-chave
- aparelhos ortopédicos
- deformidades do pé
- órteses do pé
- pé torto equinovaro

Work carried out at the Faculdade Pequeno Príncipe, Curitiba, Brazil.

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Introduction

Congenital clubfoot (CC) is a complex three-dimensional deformity including pes equinus, varus, adductus, and cavus.[1] CC results from ligamentous and myotendinous abnormalities and occurs in 1/1,000 live births.[2]

The Ponseti method is the main form of treatment and consists of joint manipulations of the connective tissue using serial casts. After correction, the patient must use a Dennis-Brown (DB) orthosis for 2 to 4 years.[1]

Many parents of children diagnosed with CC are afraid of the disease and its treatment. CC causes stress, anxiety, and depression in parents.[3] Therefore, it is critical to clarify all doubts regarding the therapeutic process.[4] The Ponseti method requires a lot of commitment from the medical team and the patient's family to be successful.[5,6]

Considering the significance of full adherence to treatment, this study aimed to identify the main difficulties encountered in DB use by caregivers of CC patients.

Method

This descriptive exploratory study relied on a quantitative approach to the difficulties of consistently using DB orthosis by children undergoing conservative CC treatment using the Ponseti method in a reference hospital in Curitiba, PR, Brazil, from 2015 to 2018. The Committee of Research Ethics from our institution approved the study under number CAAE 56086821.0.0000.5580. To collect the required information, we sent a 16-item questionnaire addressing the child, their caregivers, and difficulties in orthosis use to the caregivers. First, we contacted the caregivers (parents, grandparents, or others) by cell phone to inform them that they would receive a questionnaire via Google Forms and its purpose. The questionnaire could be answered by email or cell phone. This study included caregivers of children over 4 years old diagnosed with CC at birth and treated on an outpatient basis at the reference hospital.

Statistical Analysis

We created an Excel spreadsheet with all the answers and inserted it into the Sphinx IQ2 software to analyze profile variables. Next, we proceeded to bivariate analyses to relate the data obtained. We performed three statistical tests (p-value, chi-square, and degree of freedom) concerning the variables looking for any statistical influence on the difficulty of using the orthosis.

Results

Our sample consisted of 176 patients, and we managed to contact 114 of their caregivers. However, only 36 caregivers answered the form, with a 31.6% response rate. Most (88.9%) patients underwent treatment at the Brazilian Unified Health System (SUS, for its acronym in Portuguese), 8.3% received treatment through an insurance plan, and 2.8% had private treatment. The gender distribution revealed 63.9% of patients were males and 36.1% were female. In 55.6% of subjects, CC was bilateral. CC affected the right foot of 33.3% of patients and the left foot of 11.1% of subjects.

There was no significant correlation between gender and the side affected by CC (►**Fig. 1**), meaning the reported statistical tests revealed no direct relationship between gender and deformity. Most (80.6%) children required a calcaneus tenotomy. Orthosis use after conservative treatment started when the child was less than 12 months old in 66.7% of patients and continued until 48 months old in 38.9% of children. Most (58.3%) caregivers denied any difficulty and 41.7% reported difficulties. There was no association between difficulty in orthosis use and CC side or patient's gender and age, demonstrating that difficulty is independent of these factors.

Of the 41.7% of caregivers reporting some orthosis-related difficulty, the main one was the child's irritation during its use (93.3%). Other issues highlighted included long using time (33.3%), orthosis cost (26.7%), difficulty in putting the

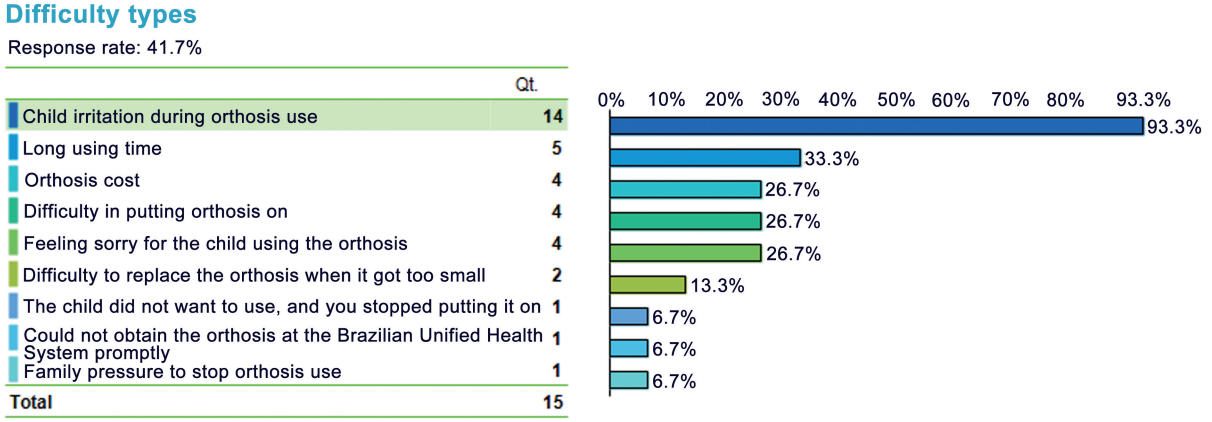


Fig. 1 Types of difficulty faced by the patient. Source: Authors (2022).

orthosis on (26.7%), and feeling sorry for the child (26.7%). Caregivers also cited difficulty in changing the orthosis when it became too small (13.3%), the child not accepting its use (6.7%), failure to obtain orthosis from SUS promptly (6.7%), and pressure from family members to stop using the orthosis (6.7%). Discontinuation in orthosis treatment occurred in 27.8% of patients; of these, none reported CC recurrence but 30% reported the need to resume treatment.

Discussion

The incidence of CC has had a similar pattern over the years: 64.5% in male patients and 35.5% in female patients in 1951,[2] and a predominance of male patients (68%) in 2020.[4] In our study, 63.9% of patients were male. Regarding the affected side, our sample showed a higher CC incidence on the right foot and a difference in frequency, with 75% affecting the right side and 25%, on the left side. In 2011, the incidence of right foot deformities was 56%.[7] In 2020, the same pattern remained, with a 52.1% incidence on the right foot.[4] As for bilateral (55.6%) and unilateral (44.4%) CC, our data are consistent with the literature. Stewart reported an equal distribution between bilaterality and unilaterality.[2]

In our study, 66.7% of patients started CC treatment using the Ponseti method at less than 12 months old, and most (38.9%) completed it by 48 months old. This indicates that most patients underwent 4 years of treatment, consistent with the literature reporting an average follow-up period of 4.6 years.[6] Most (80.6%) of our patients required a percutaneous tenotomy of the calcaneus tendon, consistent with reports from Ponseti[8] and, more recently, Bhaskar and Patni.[9]

In 2004, the lack of commitment to using the abduction orthosis was the main factor associated with CC recurrence, with these patients being 183 times more susceptible to relapses.[10] In 2011, researchers stated that the appropriate orthosis use directly relates to the treatment success.[11] A report from 2022 found that 46% of patients with relapses were incorrectly using the DB orthosis.[12] Of the 36 caregivers participating in our research, 10 (27.8%) reported having stopped using the orthosis before the stipulated treatment period. Among these ten caregivers, three (30%) had to restart treatment and resume orthosis use.

As mentioned before, almost 30% of our patients presented an increased risk of CC recurrence and potential surgical intervention. A report from 2015 identified that this inappropriate use increases the chance of needing a surgical procedure by 7.9-fold.[13] Furthermore, in 2013, researchers highlighted that treatment for recurrent CC is not simple and does not result in the same outcome of improving foot mobility and anatomy compared with conservative treatment.[14]

A study from 2013 described that parents of patients who received greater focus on the need for adherence and clarification during classes about the disease had a lower recurrence and higher therapeutic success when compared with the group that did not receive these instructions[5] Similarly, in 2016, researchers stated the importance of commitment from the doctor and the patient's family from changing casts to orthosis use.[6] A report from 2011 identified some factors specific to parents that influence orthosis use, stating that parents with education levels of up to high school or less had a greater chance of their children developing relapses.[11]

In our study, 41.7% of the sample presented some difficulty using the DB orthosis, consistent with a 2022 study on the Mitchell-Ponseti orthosis stating that 46.7% of families from CC patients reported issues with the orthosis.[15] Therefore, by integrating parents into the treatment, teaching them, and reinforcing the need for orthosis use, it may be possible to reduce orthosis use discontinuation or its irregular use since they would understand the direct relationship between success and proper use.

In 2022, authors identified two main factors for the decrease in compliance with orthosis use: first, after 18 months old, children sleep less, using the orthosis for less time, as they cannot tolerate it when awake.[16] The second point reported by these authors is that when faced with this difficulty, parents do not use the orthosis correctly or even discontinue its use.[16] Our research identified that the most important factor for irregular orthosis use is child irritation, reported by 93% of study participants, consistent with descriptions from previous authors.

Given the above, there is a need to address the reported factors to reduce CC recurrences. Sheta and El-Sayed, in 2020, did not use orthosis, teaching parents stretching exercises for daily performance, and giving them classes three times a week about the disease and its treatment.[4] The authors reported that the children of these parents had above-average results concerning functionality, pain, and other factors. However, the recurrence rate was 21%, consistent with the literature.[4] Therefore, despite removing the concern about inappropriate orthosis use, this method is not more efficient than the traditional one to the point of replacing orthosis completely.

Just as described in a 2022 study, the difficulties encountered by family members in using the orthosis did not influence therapeutic success. In our study, despite 27.8% having discontinued orthosis use, none reported CC relapse.[15] Therefore, although the literature states that inappropriate orthosis use is the main factor in CC recurrence, our study cannot state that orthosis-related difficulties are direct factors for its inappropriate use.

Conclusion

Few studies specifically seek to understand why there are difficulties in using the DB orthosis, even though it is the main orthosis used in SUS. The 41.7% rate of DB orthosis use difficulty is unprecedented, and fundamental to creating strategies to reduce its inappropriate use. Furthermore, our data allows us to understand that despite the issues during orthosis use, they were not factors in CC recurrence. In addition, we noted that the difficulty is independent of the patient's gender, age, and affected side. However, the literature suggests that the socioeconomic condition of the parents impacts recurrence. Finally, the limitation of this study was the low questionnaire response rate.

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Conflict of Interests
The authors declare no conflicts of interests.

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Evaluation of a Blood Reserve Protocol for Hip Fracture Surgery in the Elderly

Avaliação de um protocolo para reserva de sangue para cirurgias de fratura do quadril em idosos

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Abstract

Objective To identify the predictive factors for the need for transfusion during and after surgery to treat hip fractures in the elderly and to evaluate a protocol to guide the request for blood reserves for surgery.

Methods The medical records of 172 elderly patients undergoing surgical treatment for proximal femoral fractures were collected. Data on sex, age, preoperative hemoglobin level, diagnosis, and type of surgery were tested for correlation with blood transfusion. In our sample, we determined the number of units of packed red blood cells reserved, the transfusion rate, and the cross-test:transfusion ratio. We made the same calculations in a hypothetical situation in which the request for blood reserves for our sample followed the criteria of a defined protocol.

Results We found a correlation between the American Society of Anesthesiologists (ASA) classification and the occurrence of transfusions, and an inverse correlation between the hemoglobin level on admission and the number of bags transfused. A reserve of 328 units of packed red blood cells was requested for 167 surgeries. Had the proposed protocol been applied, 72 units would have been requested for 61 surgeries.

Conclusion We found a correlation regarding the variables ASA classification and preoperative hemoglobin level and the occurrence of transfusion. Applying a proposed protocol to decide between requesting a reserve and only typing for elderly individuals undergoing surgical treatment for hip fracture proved suitable to reduce the number of packed red blood cell reserves.

Keywords
- blood transfusion
- blood typing
- hip fractures

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Resumo

Objetivo Identificar os fatores preditivos da necessidade de transfusão durante e após a cirurgia para o tratamento de fratura do quadril em idosos e avaliar um protocolo para orientar a solicitação de reserva de sangue para a cirurgia.

Métodos Foram levantados os prontuários de 172 pacientes idosos submetidos a tratamento cirúrgico de fratura proximal do fêmur. Os dados relativos a sexo, idade, nível pré-operatório de hemoglobina, diagnóstico e tipo de cirurgia foram testados para a verificar a existência de correlação com a transfusão sanguínea. Determinamos o número de unidades reservadas de concentrado de hemácias, o índice de transfusão e a razão prova cruzada:transfusão em nossa casuística, e fizemos os mesmos cálculos em uma situação hipotética em que a solicitação de reserva de sangue para a nossa amostra seguisse os critérios de um protocolo definido.

Resultados Encontramos correlação entre a classificação da American Society of Anesthesiologists (ASA) e a ocorrência de transfusão, e correlação inversa entre o nível de hemoglobina de entrada e o número de bolsas transfundidas. Foi solicitada reserva de 328 unidades de concentrado de hemácias para 167 cirurgias. Caso se tivesse aplicado o protocolo proposto, teriam sido solicitadas 72 unidades para 61 cirurgias.

Conclusão Encontramos correlação entre as variáveis classificação da ASA e nível pré-operatório de hemoglobina e a ocorrência de transfusão. A aplicação de um protocolo proposto para decidir entre a solicitação de reserva e apenas a tipagem para indivíduos idosos que serão submetidos a tratamento cirúrgico de fratura do quadril mostrou-se adequada para diminuir o número de reservas de concentrado de hemácias.

Palavras-chave

- fraturas do quadril
- tipagem sanguínea
- transfusão sanguínea

Introduction

Hip fractures in the elderly are a public health problem worldwide. As well as being associated with high morbidity and mortality rates, they have a significant financial impact on health systems.[1]

Various factors that influence the evolution of these patients are studied, including the importance of multidisciplinary care,[2] the time elapsed between hospitalization and surgery,[3] the problem of previous use of anticoagulants,[4] the types of implants used[5] etc. Among these issues, the management of the use of blood products to treat pre- and postoperative anemia is relevant. Blood transfusion is part of the therapeutic arsenal in the clinical care of elderly individuals with hip fractures. Still, it is a procedure associated with risks such as increased rates of postoperative infection[6] and increases in the cost of treatment.

The criteria to indicate transfusion of packed red blood cells in elderly patients undergoing surgical treatment for hip fractures are still poorly defined. There are liberal protocols that indicate transfusion when hemoglobin levels fall below 10 g/dL, and restrictive protocols that do not indicate transfusion unless the hemoglobin level falls below 8 g/dL or the patient has symptoms related to anemia. There is evidence that liberal protocols do not present advantages in terms of mortality, functional recovery, and complications compared to restrictive protocols, indicating that the restrictive protocol may be considered the better option.[7]

Two other critical questions are in which situations and how many units of packed red blood cells should be requested for patients undergoing surgery. Requesting a reserve of packed red blood cells involves the performance of three procedures by the blood bank: ABO and Rh typing, irregular antibody screening (IAS), and crossmatch tests between donor and recipient samples.[8,9] Therefore, each blood bag reserve requested represents a financial impact and generates a workload for the blood bank.

Not all patients undergoing surgical treatment for hip fractures need to receive blood component transfusions; some studies mention an incidence of around 30% to 40%.[7,10–12] Therefore, knowing the predictive factors regarding the need for transfusion of packed red blood cells can guide the request for blood before surgery. For patients at low risk of transfusion during and after surgery, requesting only the typing without requesting a reserve would represent a significant advance in managing scarce resources such as blood products.

The present study aimed to identify predictors of the need for transfusion during and after surgery to treat hip fractures in the elderly and to evaluate a protocol to guide the request for blood reserves for surgery.

Materials and and Methods

Ethical procedures

The institutional Ethics in Research Committee approved this project under CAAE number 70915423.1.0000.0099.

Design and Study Population

For data collection, this retrospective cohort was developed using the electronic medical records of patients older than 60 years of age who underwent surgical treatment for

Table 1 Blood request protocol for hip fracture surgeries proposed by Khan et al.[14]

Hemoglobin level (g/dL)	Blood requests
≥ 11	Typing
9.0–10.9	Reservation of 1 unit
8.0–8.9	Reservation of 3 units
7.0–7.9	Reservation of 4 units
≤ 6.9	Clinical assessment

proximal femoral fractures at our institution between January 1st and December 31st, 2021. Our institution's Hematology Institute provided the information regarding request and use. Patients with high-energy trauma fractures and those undergoing percutaneous fixation with cannulated screws were excluded.

Data collection

Data on sex, age, preoperative hemoglobin level, diagnosis, and type of surgery were tested for correlation with blood transfusion.

The transfusion index (TI) and the crossmatch test:transfusion ratio (C:T) were calculated.[13,14] The TI measures the average number of blood units used per procedure, and values lower than 0.5 indicate that the routine request for blood reserves is not necessary for the procedure. The C:T is the ratio between the number of blood units requested and the number of units transfused, and it measures the efficiency of blood requests. Values above 2.5 indicate excessive requests.[13]

Based on these criteria, Khan et al.[14] proposed a protocol to request blood for the surgical treatment of hip fractures (►**Table 1**). We included the data obtained in our sample in this protocol to verify its applicability in our casuistry by evaluating the results obtained for the C:T, the number of transfusions carried out without requesting a reserve, and the IT for each hemoglobin level interval in the protocol.

Statistical Analysis

For the statistical analysis, we used the PASW Statistics for Windows (SPSS Inc., Chicago, IL, United States), version 18.0, with a 95% confidence interval and 5% significance level ($p < 0.05$) for the tests applied. The Shapiro-Wilk test was used to verify the normality of the data, and the paired Student *t*-test was used to compare the pre- and postoperative hemoglobin values in the two fracture groups (pertrochanteric and femoral neck).

Results

Data was collected from 172 medical records of patients who met the study requirements (►**Table 1**). Our sample consisted of 118 female and 54 male patients, with a mean age of 80.2 years. The diagnosis was of pertrochanteric fracture in 100 cases and of femoral neck fracture in 72.

The mean preoperative hemoglobin level was of 11.44 g/dL; postoperatively. it was of 9.9 g/dL. The preoperative hemoglobin levels were of 11.0 g/dL and 11.7 g/dL respectively for pertrochanteric and femoral neck fractures. In the classification of the American Society of Anesthesiologists (ASA), 3 patients were classified as ASA 1, 128, as ASA 2, 38, as ASA 3, and 3, as ASA 4. After surgery, the average was of 8.9 for pertrochanteric and 9.2 for femoral neck fractures. Although a reduction in the patients' hemoglobin was observed postoperatively (paired *t*-test; $p = 0.0001$), there were no statistical differences between the fracture groups (unpaired *t*-test; $p = 0.17$, ►**Fig. 1**).

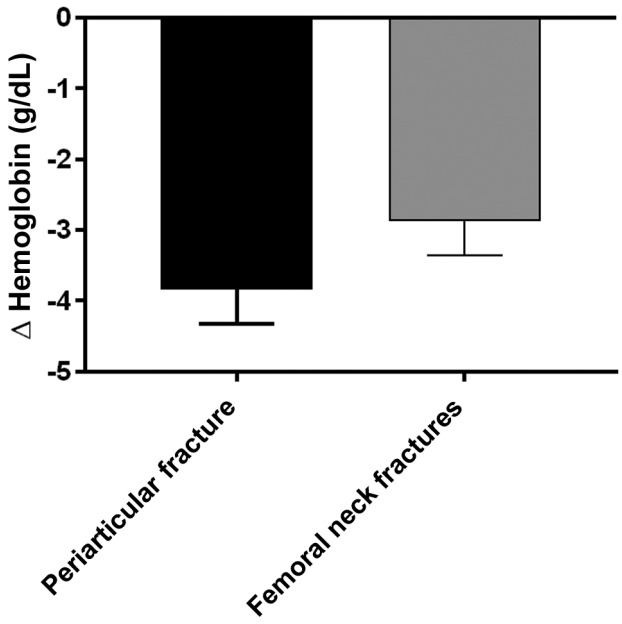


Fig. 1 Hemoglobin variation (g/dL) in the different surgical groups.

Of those diagnosed with a pertrochanteric fracture, 35 (35%) received a transfusion, and of those diagnosed with a femoral neck fracture, 29 (27.8%) received a transfusion of one or more units of packed red blood cells. This difference was not statistically significant (Chi-squared test; $p = 0.32$; ►**Table 2**).

A reserve of 328 units of packed red blood cells was requested for 167 surgeries, representing 97% of the cases, and 112 units were transfused in 55 patients, or 31.9% of the cases. The IT was calculated at 0.65. The C:T was of 2.9 (►**Table 3**).

There was a correlation between the anesthetic risk classification (ASA) and the number of transfused bags, according to the Pearson correlation ($r = 0.23$; $p = 0.003$; ►**Fig. 2**). There was also an inverse correlation between the preoperative hemoglobin level and the number of bags transfused (Pearson correlation: $r = -0.43$; $p = 0.001$; ►**Fig. 3**).

Discussion

In line with other studies, the ASA classification and the preoperative hemoglobin level were predictive factors of blood transfusion, since the groups were matched regarding anthropometric characteristics.

The average hemoglobin level on admission was of 11.44 g/dL, and 61 patients (32.4%) had less than 11 g/dL on admission, which characterized a large proportion of

Table 2 Comparison of transfusion requirement data in the different surgical groups

Surgical groups	Transfusion		
	No	Yes	
Pertrochanteric fracture	65	35	100
	65.0%	35.0%	100.0%
Femoral neck fracture	52	20	72
	72.2%	27.8%	100.0%
Total	117	55	172
	68.0%	32.0%	100.0%

Notes: Chi-squared test = 1.00; $p = 0.32$.

Table 3 Comparison of the units of packed red blood cells reserved and the units that would be reserved using the proposed protocol

Hemoglobin level (g/dL)	n	Number of units transfused	Number of units reserved	Number of units reserved according to the protocol
≥11	111	34	219	0
9–10.9	49	55	88	49
8–8.9	7	12	12	14
7– 7.9	3	7	5	9
≤6.9	2	4	4	0
Total	172	112	328	72

patients who had already been admitted with anemia. We must consider the possibility that this is related to the fact that most of the patients are elderly individuals living in low-income families, and that factors related to the food security of these patients may be present. The average drop in hemoglobin after surgery was of 1.54 g/dL; there was no difference in hemoglobin results between patients with a pertrochanteric fracture and those with a femoral neck fracture.

The observed TI of 0.65 indicates that the surgical treatment of these fractures requires requesting a reserve of packed red blood cells. Still, the C:T of 2.9 indicates that the practice of routinely requesting blood reserves for all patients who will undergo hip fracture surgery has proved inefficient, and that it is necessary to adopt some criteria for the best use of these resources.

Khan et al.[14] proposed a protocol to request blood for the surgical treatment of hip fractures (►**Table 1**). In a simulation in which we used these criteria for our sample (►**Table 2**), we obtained a C:T of 0.64, which would indicate efficiency in the reserve request. We also observed that if this protocol had been used, analyzing only individuals with a hemoglobin level greater than or equal to 11, we would have obtained a TI of 0.30. According to these same authors,[14] surgeries with a TI lower than 0.5 do not require a request for a packed red blood cell reserve, thus reducing the fear of not requesting a blood reserve for this group of patients.

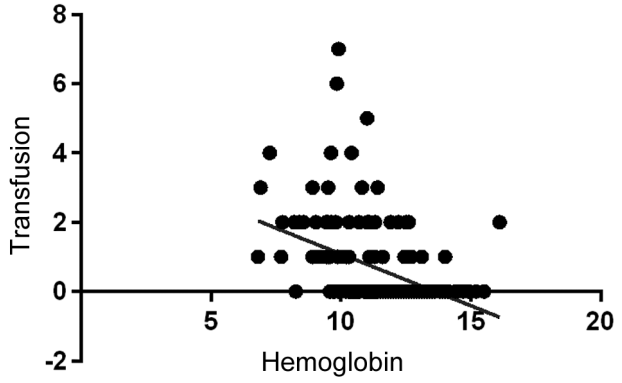


Fig. 2 Correlation between preoperative hemoglobin levels (g/dL) and the number of bags transfused.

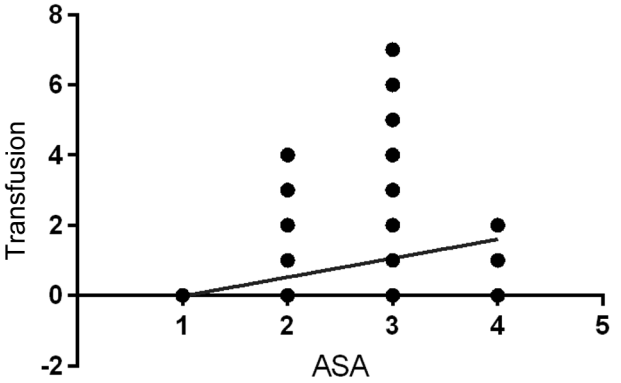


Fig. 3 Correlation between anesthetic risk classification (ASA) and the number of bags transfused.

The limitation of the present study is that it is a retrospective cohort study from a single hospital. Its primary clinical implication is to demonstrate that requesting packed red blood cells indiscriminately for all patients with hip fractures is unjustified, and that adopting the proposed protocol can safely save resources.

In addition to the financial impact, the request for blood reserves without criteria creates an operational burden. The crossmatch test and IAS take up around 40 minutes of the blood bank's time.

Conclusion

We found a correlation between the ASA classification and transfusion. Applying a proposed protocol to decide between requesting a reserve and just typing for these patients proved suitable for our casuistry.

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Conflict of interest
The authors have no conflicts of interest to declare.

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Free Osteoarticular Metatarsal Autograft in the Reconstruction of Giant Cell Tumor of Metacarpal: Report of Two Cases and Description of a Technique

Enxerto osteoarticular livre de metatarso em reconstrução de tumor de células gigantes de metacarpo: Relato de dois casos e descrição de técnica

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Abstract

Giant cell tumors are benign but locally aggressive bone neoplasms containing many multinucleated giant cells similar to osteoclasts. The author reports the case of two patients with giant cell tumor in the metacarpals, one of whom was multicentric. Giant cell tumor in the hand is a rare condition, and, at this location, it commonly presents at an advanced stage, with extensive bone destruction.

Thus, its safe resection, associated with a large resulting bone failure, represents a great challenge to the orthopedist. The various treatment options described in the literature cause severe cosmetic and/or functional impairment to the hand. Thinking about it, the author describes the treatment technique through the transfer of metatarsus-free osteoarticular graft to the metacarpal with good functional and cosmetic results.

Keywords

- bone transplantation
- giant cell tumor of bone
- metacarpal bones
- metacarpus

Resumo

Os tumores de células gigantes são neoplasias ósseas benignas, mas localmente agressivas, que contêm muitas células gigantes multinucleadas semelhantes aos osteoclastos. O autor relata o caso de dois pacientes com tumor de células gigantes nos metacarpos, dos quais um era multicêntrico. O tumor de células gigantes na mão é uma condição rara e, nesta localização, comumente apresenta-se em um estágio avançado, com extensa destruição óssea.

Dessa maneira, sua ressecção de forma segura, associada a uma grande falha óssea resultante, representa um grande desafio ao ortopedista. As várias opções de tratamento descritas na literatura ocasionam severa perda estética e/ou funcional

Palavras-chave

- metacarpo
- ossos metacarpais
- transplante ósseo
- tumor de células gigantes do osso

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da mão. Pensando nisso, o autor descreve a técnica de tratamento por meio da transferência de enxerto osteoarticular livre de metatarso para o metacarpo, com bons resultados funcionais e estéticos.

Introduction

Giant cell tumors (GCTs) are benign but locally aggressive bone neoplasms characterized by a richly vascularized tissue containing many multinucleated giant cells similar to osteoclasts, and two types of proliferative mononuclear stromal cells, round and fusiform.[1] Round mononuclear cells, together with osteoclast-like giant cells, are reactive specialized benign cells derived from monocytes, and are recruited into the tumor by fusiform mononuclear cells, which are believed to be the only true neoplastic cells in GCTs.[2,3] These tumors are relatively uncommon, representing about 5% of all primary bone tumors[3,4] and about 22% of benign bone tumors.[5] They occur predominantly after skeletal maturity, exhibit a slight predominance in females, and have their peak incidence between 20 and 45 years of age.[4,6] About half of the cases occur around the knee,[7] being rare in the bones of the hand,[4] especially in skeletally-immature individuals, with few cases described in the literature.[8] Only 10.9% of the cases occur in patients older than 50 years of age.[5] Tumors of the metacarpals (MCs), metatarsus and phalanges are usually purely lytic and extend to the end of the bones,[9] and, when they reach the bones of the hands, they commonly present at an advanced stage, with extensive bone destruction, thus complicating their treatment.[10] Therefore, the reconstruction of voluminous lesions in the hand represents a great challenge, with a great risk of sequelae, amputation of rays, or deformities.

The aim of the present article is to describe the MC reconstruction technique after GCT resection using a free osteoarticular metatarsus autograft through the report of two cases. Case 1 is that of a 14-year-old female patient with a rapidly-growing GCT in the second left MC. Case 2 is that of a 62-year-old male patient with slower-growing multicentric CGT, with gradual worsening of right-hand pain and function over the course of the last 5 years, located in the fifth MC and fifth ipsilateral metatarsus.

Surgical Technique

To describe the surgical technique, we will use as an example the patient in Case 1 (►**Fig. 1**).

The objective criteria to choose the ideal metatarsus are the shape and diameter of the distal epiphysis and the width of the diasphysis more similar to the MC to be resected. Initially, a contralateral hand radiograph was performed to establish the relationships of the normal anatomy of the MCs, verifying the length of the second MC and the size relative to the third MC, in addition to radiographs of the ipsilateral foot to determine which metatarsus most resembled the second MC (►**Fig. 2**). Then, after osteotomy of the base of the second MC, the tumor was resected en bloc together with the biopsy scar, taking care to preserve as much as possible the metacarpophalangeal joint capsule. After tumor resection, the third ipsilateral metatarsus was collected through osteotomy at the base, taking care to completely remove the soft tissues around it, but preserving as much as possible the ligaments of the metatarsal-fallageal joint capsule. Osteosynthesis was performed with a plate of minifragments and suture of the remaining ligaments of the joint capsule of the second MC and the third metatarsus (►**Fig. 3**). After the procedure, the patient was immobilized with antebrachio-digital plaster, with the wrist at 20° to 30° of extension, the metacarpophalangeal joints at 70° to 90° of flexion, and the interphaplastic joints in total extension for 4 weeks. Then, physiotherapy of the hand was maintained, on average 3 times a week, and functional orthosis was performed by an occupational therapist, immobilizing the wrist and the metacarpophalangeal joint of the second finger in the 6 subsequent months, until signs of consolidation and radiological signs of increased graft porosity were observed, which are suggestive of graft revascularization. ►**Fig. 4** and ►**Fig. 5** show respectively the pre- and postoperative images of the patient in Case 2, in whom tumor resection and transfer of the third contralateral metatarsus were performed.



Fig. 1 Case 1: frontal and oblique radiographs of the left hand two months after incisional biopsy by an oncologic surgeon. Notice that the exaggerated opening of the pseudocapsule enabled the rapid expansion of the tumor to the soft tissues.



Fig. 2 Case 1: radiographs of the right hand (normal) and left foot (ipsilateral to the lesion) to determine the length of the second metacarpal (MC) and its relationship with the third MC, in addition to verifying which metatarsus presented greater anatomical similarity to the second MC.

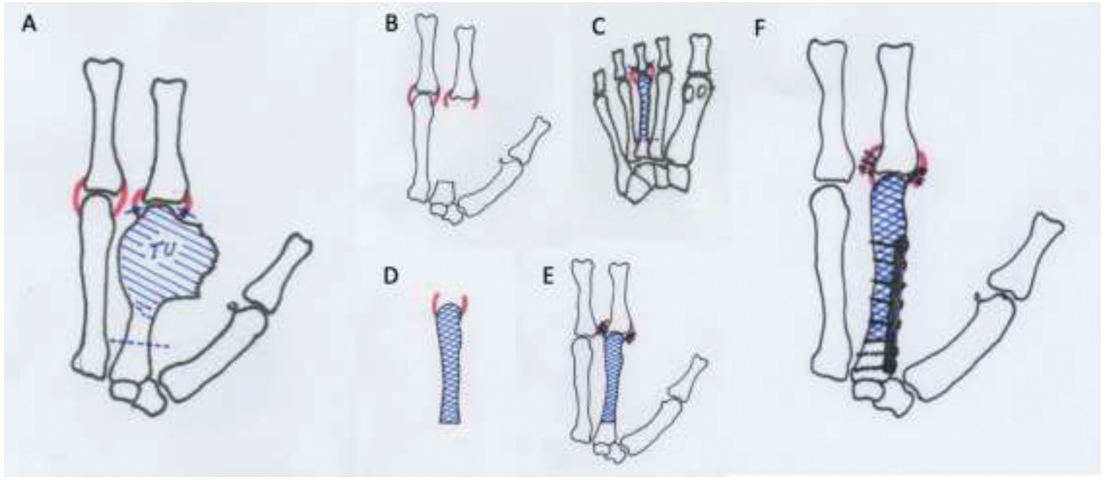


Fig. 3 Scheme of the tumor resection and reconstruction technique with metatarsus-free osteoarticular graft. (**A**) The dashed line demarcates the location of the osteotomy, the full lines demarcate the joint capsule section (TU = tumor mass). (**B**) Hand after tumor resection, in which the base of the MC and the remaining capsular ligaments can be seen. (**C**) Choice of a metatarsus more similar in anatomy to the MC; the dashed line demarcates the location of the proximal osteotomy, and the full lines, the site of resection of the capsular ligaments. (**D**) Free metatarsus with its capsular insertions. (**E**) Suture of capsular ligaments. (**F**) Osteosynthesis with plate of minifragments.



Fig. 4 Case 2: right frontal and oblique radiographs of the right hand and foot, evidencing an expansive osteolytic lesion compromising the entire fifth right MC and the distal metaepiphyseal region of the fifth right metatarsus.

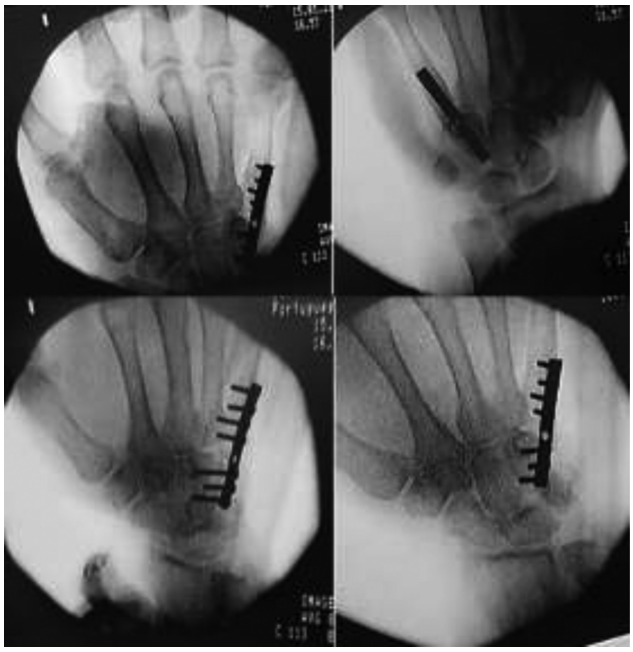


Fig. 5 Case 2: anteroposterior, posteroanterior, and oblique radiographs in the immediate postoperative period of tumor resection and reconstruction with Free osteoarticular metatarsus autograft.



Fig. 6 Patient in case 1 with 8.5 months after tumor resection and reconstruction with free osteoarticular metatarsus autograft. Radiograph 75 days after the iliac graft, showing complete consolidation and integration.

Final comments

After six months of evolution, the osteotomy line showed no signs of consolidation between the graft and the host MC, which is why autologous iliac grafting was performed, evolving with complete bone consolidation in the eighth month (►**Fig. 6**). Currently, 5.5 years after the resection, the patient shows no signs of local recurrence, with function considered excellent according to the MSTS (Musculoskeletal Tumor Society). The male patient presented excellent evolution from the immediate postoperative period until the last revision two months postoperatively, when he returned to his hometown and was lost to follow-up.

None of the patients presented any complaint of foot pain or gait alteration after metatarsus removal. Thus, we conclude that the transfer of the metatarsal osteoarticular ligament complex for the reconstruction of MC defects after resection of giant cell tumors is a safe and efficient procedure, with good functional and cosmetic results in a medium-term follow-up.

Note

The present study was conducted in accordance with the Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research involving Human Beings, and was reviewed by the Institutional Review Committee of Universidade Católica de Pelotas.

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Conflict of Interests

The author has no conflict of interests to declare.

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Systematization of Steps for Printing 3D Models of Orthopedic Deformities

Sistematização das etapas para impressão de modelos 3D de deformidades ortopédicas

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Abstract

As in many areas of knowledge, rapid prototyping technology or additive manufacturing, popularly known as three-dimensional (3D) printing, has been gaining ground in medicine in recent years, with different applications. Numerous are the benefits of this science in orthopedic surgery, by allowing the conversion of imaging tests into 3D models. Therefore, the aim of the present study is to describe a practical step-by-step for the printing of parts from patient imaging. This is a methodological study, considering preoperative computed tomography (CT) scans of patients with orthopedic deformities. Initially, the digital imaging and communications in medicine (DICOM) examination should be imported into the 3D reconstruction software of anatomical structures for the segmentation and conversion process to the stereolithography (STL) format. The next step is to import the STL file into the 3D modeling software, which allows you to work freely by manipulating the 3D mesh. The 3D models were printed additively on the GTMax3D Core A3v2 fused deposition modeling (FDM) technology printer.

Keywords
- orthopedics
- preoperative care
- three-dimensional printing

Resumo

Assim como em diversas áreas do conhecimento, a tecnologia de prototipagem rápida ou manufatura aditiva, conhecida popularmente como impressão tridimensional (3D), vem ganhando espaço na medicina nos últimos anos, com diferentes aplicações. Inúmeros são os benefícios desta ciência na cirurgia ortopédica, ao permitir a conversão de exames de imagem em modelos tridimensionais. Diante disso, o objetivo do presente estudo é descrever um passo a passo prático para a impressão de peças a partir de exames de imagem de pacientes. Trata-se de um estudo metodológico,

Palavras-chave
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- impressão tridimensional
- ortopedia

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considerando exames de tomografia computadorizada (TC) pré-operatórios de pacientes portadores de deformidades ortopédicas. Inicialmente, o exame em formato digital imaging and communications in medicine (DICOM, na sigla em inglês) deve ser importado para o software de reconstrução tridimensional de estruturas anatômicas para o processo de segmentação e de conversão para o formato stereolithography (STL, na sigla em inglês). A próxima etapa é a importação do arquivo STL para o software de modelagem 3D, o qual permite trabalhar de forma livre manipulando a malha 3D. Finalizado o processo de edição, deve-se transferir o arquivo para o software fatiador para realizar as configurações de impressão e para salvar o arquivo em formato G-code para a materialização do objeto na impressora. Os modelos 3D foram impressos de forma aditiva, na impressora de tecnologia fused deposition modeling (FDM, na sigla em inglês) GTMax3D Core A3v2.

Introduction

As in many areas of knowledge, rapid prototyping technology or additive manufacturing, popularly known as three-dimensional (3D) printing, has been gaining ground in medicine in recent years, with different applications.[1] The benefits of this science in orthopedic surgery are abundant, by allowing the conversion of imaging tests into 3D models (►**Table 1**).[1–4] Among them, we mention the printing of anatomical models for a better understanding of deformities and complex fractures, the performance of safer and individualized preoperative planning, patient education, and professional training.[3,4] More recently, much has been studied regarding the printing of custom implants, bone substitutes, and biological materials.[5] It is believed that rapid prototyping can revolutionize the treatment of several orthopedic disorders.[6]

Studies on additive manufacturing in orthopedics, despite exposing results that favor the treatment of patients in various ways, do not explain in detail how to print the models from the imaging exams. Therefore, considering the multiple possibilities of performing protocols for 3D printing of anatomical models, the aim of the present study is to describe a practical step-by-step for the printing of parts from patient imaging.

Table 1 Applicability of Rapid Prototyping Technology in Orthopedics

Printing of anatomical models
Better understanding of diseases
Individualized preoperative planning
Custom implants
Bone substitutes
Education
Patient-specific guides
Custom orthotics

Sources: Wong[3]; Ejnisman et al.[4]; Larsen et al.[5]

Description of Materials and Technique

The research project was approved by the research ethics committee of the institution, as well as the waiver of the free and informed consent form (CAAE: 48296321.8.0000.0097).

This is a methodological study, considering preoperative computed tomography (CT) scans of patients with bone deformities in the upper or the lower limbs, performed in the multislice computed tomography device of the hospital, GE Healthcare Revolution, 64 channels (GE Healthcare, Chicago, IL, USA).

Exam Download and Segmentation

Initially, the digital imaging and communications in medicine (DICOM) CT scan is downloaded directly from the imaging visualization system. Then, DICOM files are imported into the InVesalius (Centro de Tecnologia da Informação Renato Archer, Brazil) version 3.1.1, a free software for reconstruction of images from CT or magnetic resonance imaging (MRI) equipment, so that the segmentation process is performed, that is, the selection of the area of interest for printing.

To perform segmentation, you must follow the following steps: (1) upload the data; (2) select the region of interest; (3) set up the 3D surface; and (4) export the data.

To import the exam, you must click on "import medical images" and select the DICOM images from the exam. Among all the sequences imported into the software, choose preferably the one with the largest number of cuts available so that the reconstruction has the best possible resolution. The smaller the thickness of the tomographic sections and the distance between them, the better the quality of the reconstruction. Once the images have been selected, you must click "import" in the lower left corner of the screen.

The second step in targeting is selecting the region of interest. The program automatically selects an exam area in multiplanar view. This selection can be customized with the brush tool or with the custom adjustment of the selection threshold. Once that is done, click "create surface." The 3D surface will appear in the lower right square of the screen (►**Fig. 1**).

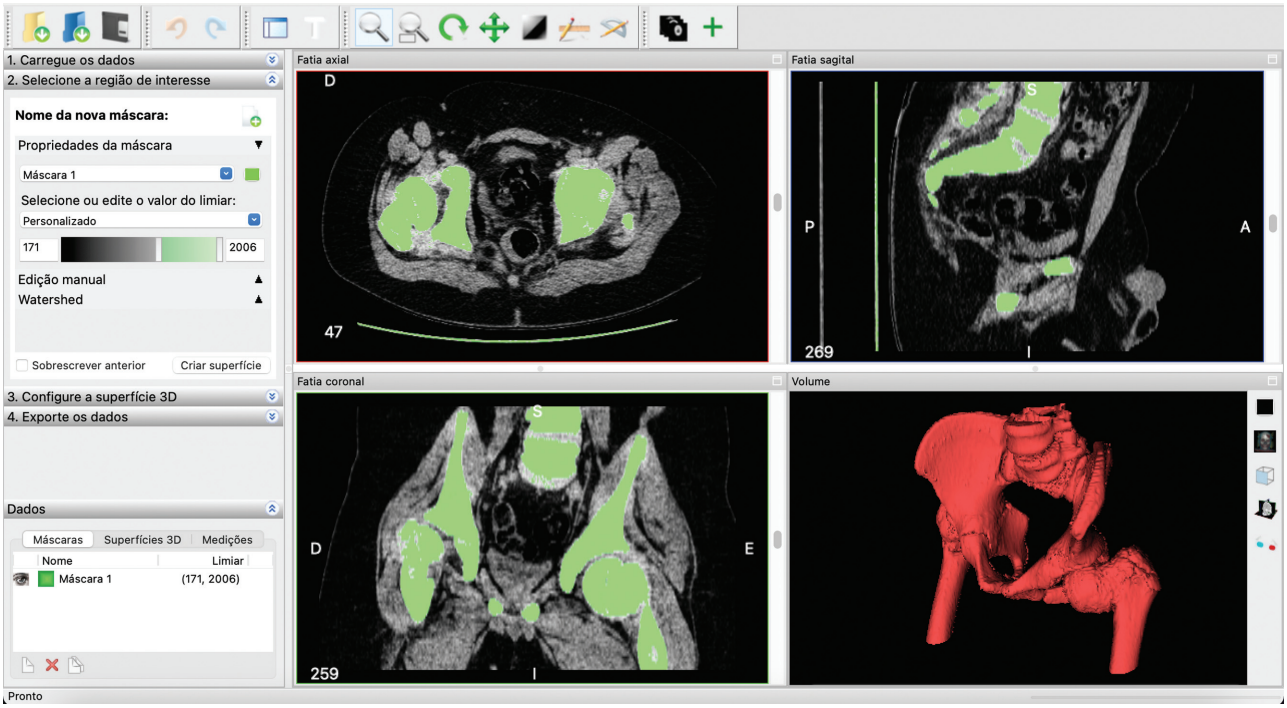


Fig. 1 Segmentation or selection of the area of interest in multiplanar images. The bone part of the pelvis and the hips was selected and adjusted in a personalized way varying the selection threshold (in green). After that, the 3D surface was created (in red). Image obtained by the authors in the InVesalius software (Centro de Tecnologia da Informação Renato Archer, Brazil).

Then, the created 3D surface can be configured, if necessary, in "advanced options". The fourth and final step of segmentation is data exporting. You must click "export 3D surface" and save the file in stereolithography (STL) format.

3D Mesh Edition

Once the segmentation is complete, the next step is to import the STL file into Meshmixer software (Autodesk Inc., San Rafael, CA, United States) version 3.5.474, which allows you to work freely by manipulating the 3D mesh to later materialize the project on the printer.

This program has a multitude of functions for 3D modeling. Among the main functions, we mention selecting, sculpting, mesh surface analysis (►**Fig. 2**), and transforming the object into a solid (►**Fig. 3**).

Slicer and Printing

Once the 3D mesh editing process is complete, you must save the file in STL format and transfer it to the slicer software Cura (Ultimaker, Utrecht, Netherlands) version 4.3 to perform the model print settings. The 3D models were printed additively on the GTMax3D Core A3v2 fused deposition

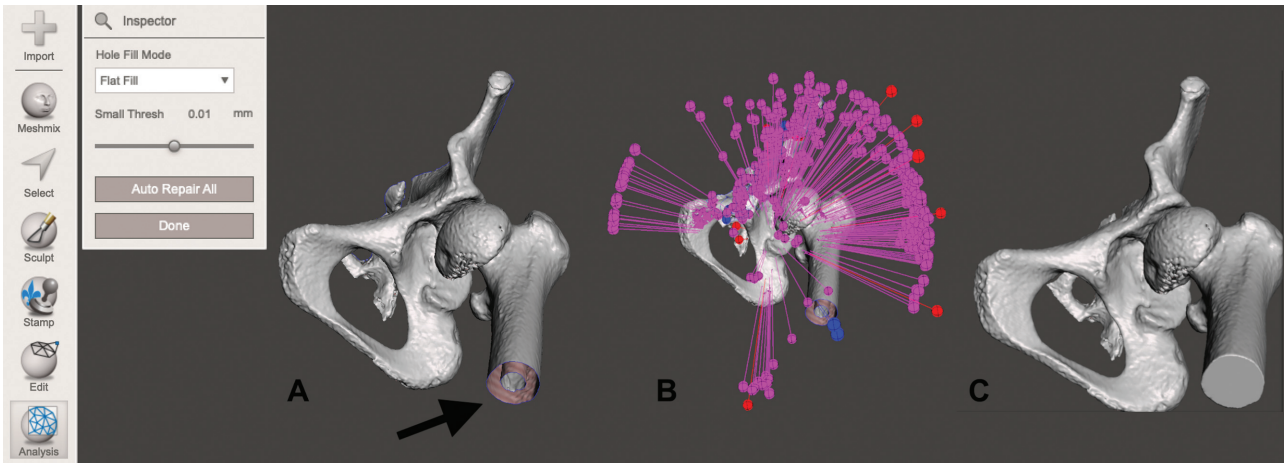


Fig. 2 Analysis of the 3D mesh surface for zones that cannot be printed due to insufficient surface. In (**A**), the cross-section of the femoral dayphysis with insufficient surface (arrow) is observed. In (**B**), the analysis was done automatically by the inspector tool, and, in (**C**), the previously insufficient surface is already filled. Image obtained by the authors in Meshmixer software (Autodesk, San Rafael, CA, USA).

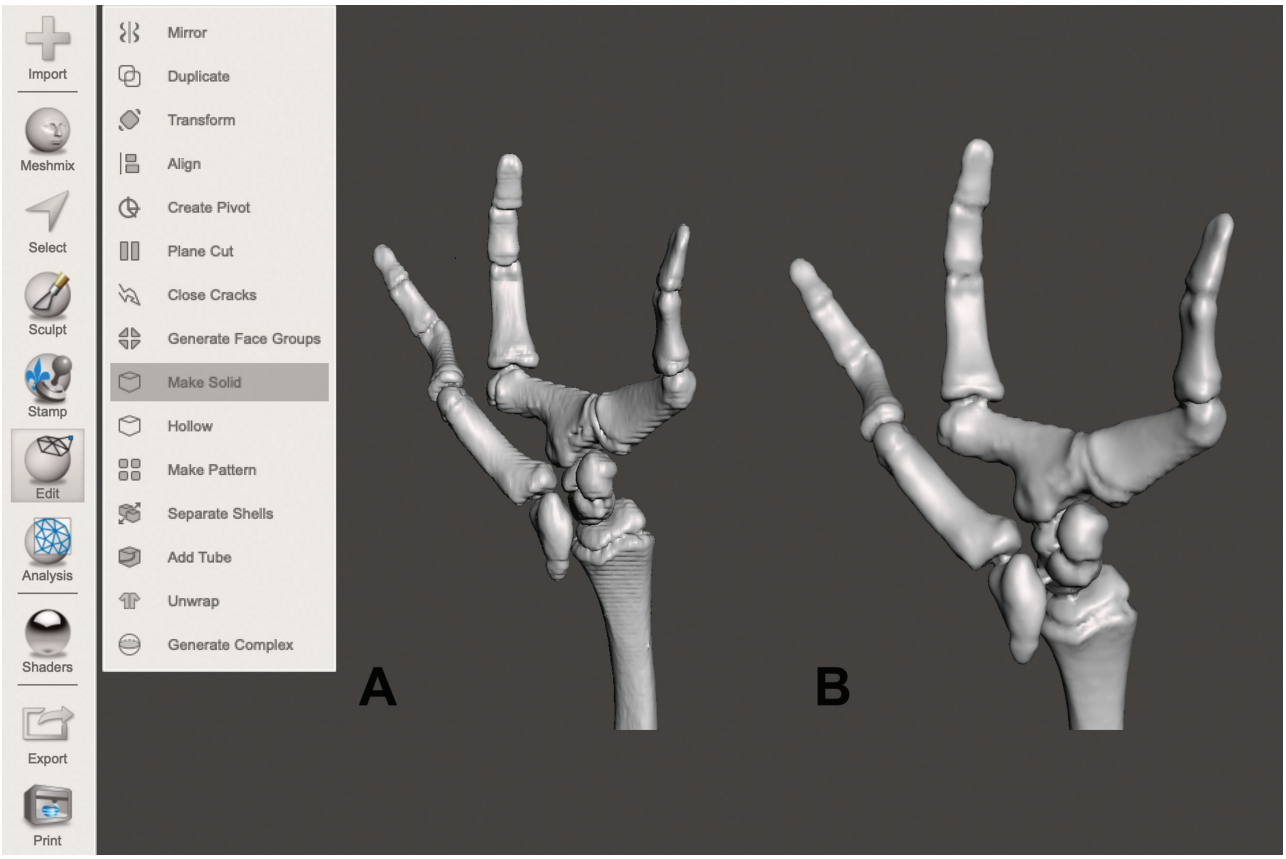


Fig. 3 Transform the object into a solid. In (**A**), the selected area is observed in the segmentation step. Observe the appearance of the connectors joining the carpal bones in (**B**), important for the printing of a single object. Image obtained by the authors in Meshmixer software (Autodesk, San Rafael, CA, USA).

modeling (FDM) technology printer. The material used for printing was styrene butadiene acrylonitrile (SBA), available in filament form with a diameter of 1.75mm.

The first step is to add a printer to the software. Once this is done, the program makes the print desk available with the dimensions of the selected printer. Click "File" > "Open file" and select the edited STL file.

In this software, you must configure the print parameters. The settings depend on the printer model and on the material used. In the case of the printer and the material available in the laboratory of our institution, the following general settings are used: printing speed of 100 mm/s; 0.15 mm layer thickness; 250°C printing temperature; 10% fill density.

It is also important to be aware of some main functions of the Cura software, such as the scale function (►**Fig. 4**), to define the dimensions of the part, and the supports' function, so that the filament has support for printing larger structures that do not have support in the lower layers.

After defining all described settings, click "slice" at the bottom right of the screen. The software performs the slicing of the object, so that it can then be revised layer by layer. The expected time for the completion of the print according to the characteristics of the part and the defined settings is also informed. For object materialization, the G-code format is saved on a memory card to transfer it directly to the 3D printer (►**Fig. 5**).

Final Comments

The use of full-size and haptic models is particularly interesting for education as well as for a better understanding of the disease.[7] In the study by Weidert et al., even experienced surgeons show improved classification and treatment planning with the help of 3D printed models when compared with simple CT data.[8]

There are several softwares available for printing and modeling 3D parts. The authors usually use the programs described in this article because they are free and have a relatively fast learning curve. There is no conflict of interest. In this section of the article, some considerations are made to facilitate the practical understanding of readers.

In the segmentation stage, the automatic selection of the area of interest is performed by tissue density. This way, it becomes relatively easy to segment the bone, because its density is very different from those of other soft tissue structures. The skeleton segmentation process is facilitated by selecting the images in the soft tissue window and not in the bone window.

In the 3D mesh editing phase, the "sculpt" tool allows the bone surface to be smoothed for better quality printing. Although it is very useful, it is extremely important to be very careful during the smoothing of the surface of the piece, so as not to distort the anatomical particularities; therefore, the authors recommend reducing the "strength of the brush" when it is necessary to use this function.

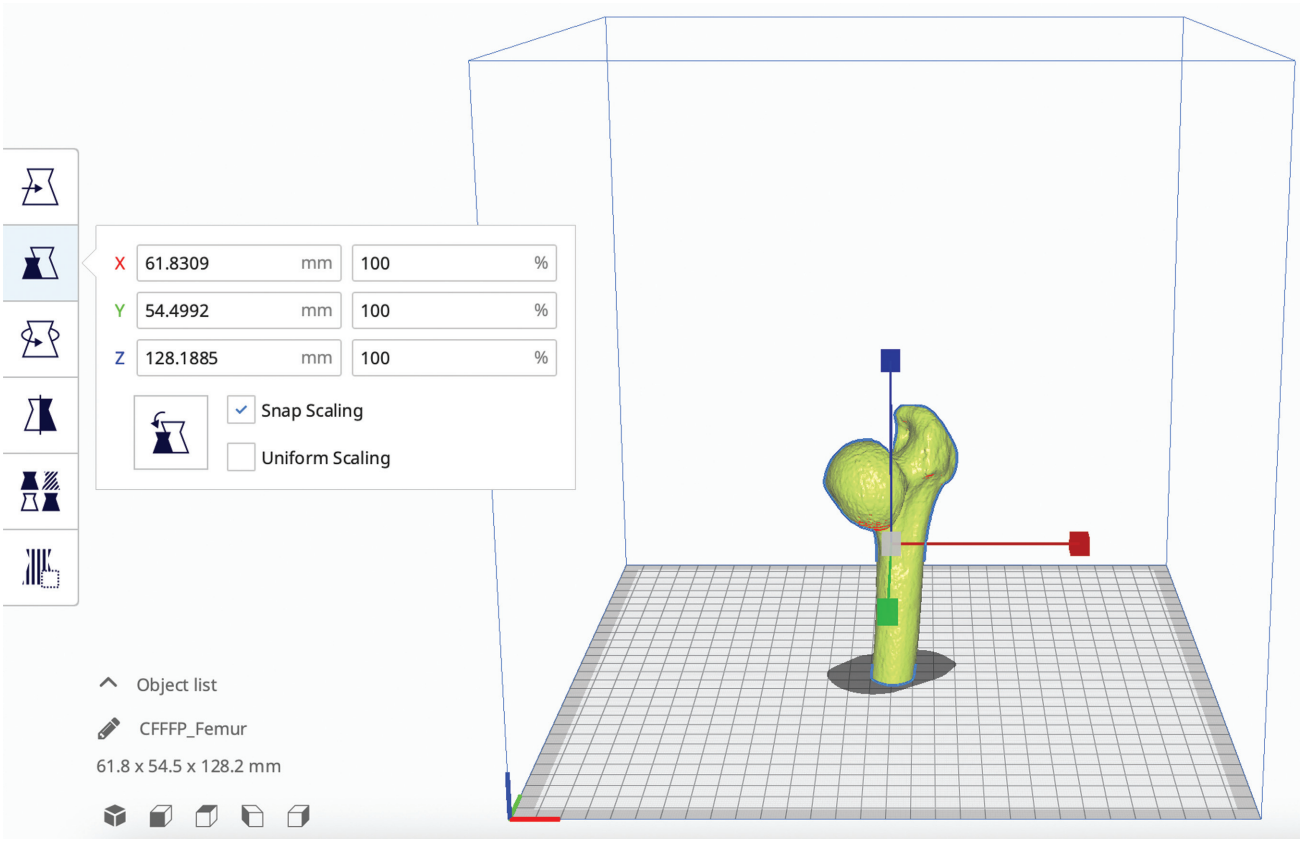


Fig. 4 The "scale" function allows you to configure the dimensions of the object. Image obtained by the authors in Cura software (Ultimaker, Utrecht, Netherlands)

Regarding the scale function of the slicing software (►**Fig. 4**), it offers the option to scale the model to be printed. When it is necessary to make custom implants, the printing of the model in actual size (100%) is necessary. Not all 3D printers support printing large models. In these cases, you can print in parts, as shown in ►**Fig. 5**, where the femurs were printed separately from the pelvis.

When it comes to print settings, one should bear in mind that the better the object resolution, the more print layers are required and, consequently, the longer the printing.

The choice of the printing material should also consider its own characteristics. SBA is an oil-derived thermoplastic that has excellent mechanical resistance and good resistance at high temperatures. In general, printing models using SBA



Fig. 5 Pelvis and proximal regions of the femurs of a male patient, 11 years old, with complex bone deformities, printed by additive manufacturing technology from the preoperative computed tomography examination. Image obtained by the authors.

requires closed printers, such as the one used in our service. Other materials are widely available and are also easy to handle, such as lactic polyacid (LPA), a thermoplastic polymer made with lactic acid from raw materials from renewable sources. Bear in mind that print settings must also be made according to the material chosen.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Transfer of Second Toe for the Treatment of Traumatic Thumb Amputation in a Four-year-old Child: A Case Report

Transferência do segundo dedo do pé para tratamento de amputação traumática do polegar em uma criança de quatro anos: Relato de caso

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Abstract

Microsurgical toe transfer for thumb reconstruction is a challenging procedure, considering the technical skills necessary to perform it, as well as the difficult postoperative evaluation of esthetical and functional aspects. The present is the report of the case of a 3-year-old child who suffered a traumatic thumb amputation. Thumb reconstruction was performed through microsurgical toe transfer months after replantation failure. Subjective and objective outcome assessments were performed five years after the procedure. The functional outcome was evaluated through the Childhood Health Assessment Questionnaire (CHAQ) and the Jebsen-Taylor Hand Function Test (JTHFT). The Jamar dynamometer (Sammons Preston, Bolingbrook, IL, US) and the Jamar Pinch Gauge (Sammons Preston) devices were used to assess the handgrip and pinch strength respectively. The Semmes-Weinstein monofilament and two-point discrimination tests were performed. The patient presented an excellent functional outcome, partial recovery of strength, complete sensory recovery, and minimal donor site morbidity. A radiographic evaluation was also performed, and it demonstrated the preservation of the epiphyseal plate and the growth potential of the transplanted toe. In all aspects, the data observed reinforce the benefits and indications of toe transfer for thumb reconstruction in children.

Keywords

- amputation, traumatic/surgery
- child
- thumb
- toes/transplantation

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Resumo

A transferência microcirúrgica do dedo do pé para a reconstrução do polegar é um procedimento desafiador, considerando-se a habilidade técnica necessária para realizá-la e a difícil avaliação pós-operatória dos aspectos estéticos e funcionais. Este é um relato do caso de uma criança de 3 anos que sofreu uma amputação traumática do polegar. A reconstrução do polegar foi realizada por meio de transferência microcirúrgica do dedo do pé, meses após a falha do reimplante. Uma avaliação subjetiva e outra objetiva dos resultados foram realizadas cinco anos após o procedimento. O resultado funcional foi avaliado por meio do Questionário de Avaliação da Saúde na Infância (Childhood Health Assessment Questionnaire, CHAQ, em inglês) e o Teste Funcional da Mão de Jebsen-Taylor (Jebsen-Taylor Hand Function Test, JTHFT, em inglês). Foram usados o dinamômetro Jamar (Sammons Preston, Bolingbrook, IL, EUA) e os instrumentos de medição Jamar Pinch Gauge (Sammons Preston) para avaliar as forças de preensão palmar e de pinças, respectivamente. Foram realizados os testes de monofilamento e de discriminação de dois pontos de Semmes-Weinstein. O paciente apresentou excelente resultado funcional, recuperação parcial da força, recuperação sensitiva completa, e mínima morbidade do sítio doador. Foi realizada também uma avaliação radiográfica, que demonstrou a preservação da placa epifisária e do potencial de crescimento no dedo do pé transplantado. Em todos os aspectos, os dados observados reforçam os benefícios e as indicações da transferência do dedo do pé para a reconstrução do polegar em crianças.

Palavras-chave

- amputação traumática/cirurgia
- criança
- dedos do pé/transplante
- polegar

Introduction

Traumatic amputations of the upper limb are responsible for significant economic and social impacts. There are few epidemiological studies on finger amputations, but it is known that they are more frequent in young male adults.[1]

Traumatic thumb amputation is rare and dramatic, and replantation should always be attempted. But, in case of failure, the procedure for thumb reconstruction, which includes distraction of the remaining part, pollicization, osteoplastic reconstruction, and toe transfer, should be considered.[2]

Among all available procedures, toe transfer is the most challenging. However, it has great potential to provide a good final outcome.[3]

Considering the many aspects involved in toe transfer, especially in children, we present a case highlighting the long clinical follow-up and the preservation of the growth potential.

Case Report

The patient's parents signed the free and informed consent form. The present study was approved by the Ethics Committee of the hospital under number 4.075.812.

In 2013, a 3-year-old male child suffered a traumatic amputation of his right thumb by a circular saw. Replantation was performed; however, due to failure, the thumb had to be removed on the following week. In 2014, transfer of the second left toe to the right thumb was performed when the child was 4 years old.

Two surgical teams performed the procedure. During the dissection of the second toe, we identified the first dorsal intermetatarsal artery, which was the dominant artery, as well as two veins, two digital nerves, and the flexor and extensor tendons. Simultaneously, the hand dissection included identifying the radial artery, the recipient veins, the proper digital nerves, and the extensor and flexor pollicis longus tendons.

Bone fixation was performed with two Kirschner wires. An end-to-end arterial anastomosis was performed using a vein graft from the foot's dorsum to connect the first dorsal intermetatarsal artery and the radial artery at the level of the anatomical snuffbox. The end-to-end venous anastomosis was performed in a comitant vein. The nerves were coapted primarily with 10-0 nylon. Flexor and extensor tenorrhaphies were performed with 4-0 polypropylene. Full thickness skin grafting was necessary to close the surgical site without tension (►**Figs. 1** to **4**).

Postoperative Assessment

Five years after the procedure, the patient underwent a postoperative assessment performed by an occupational therapist and a hand surgeon. The now 9-year-old patient was completely adapted to his daily activities. The child regularly attends sports classes, has no pain in the operated foot, no running problems, can jump on one foot, and there is no complaint of frequent falls.

The Childhood Health Assessment Questionnaire (CHAQ)[4] was applied to evaluate how much the toe transfer impacted the daily activities. This questionnaire is answered by one of the patient's relatives, and contains eight domains (dressing,

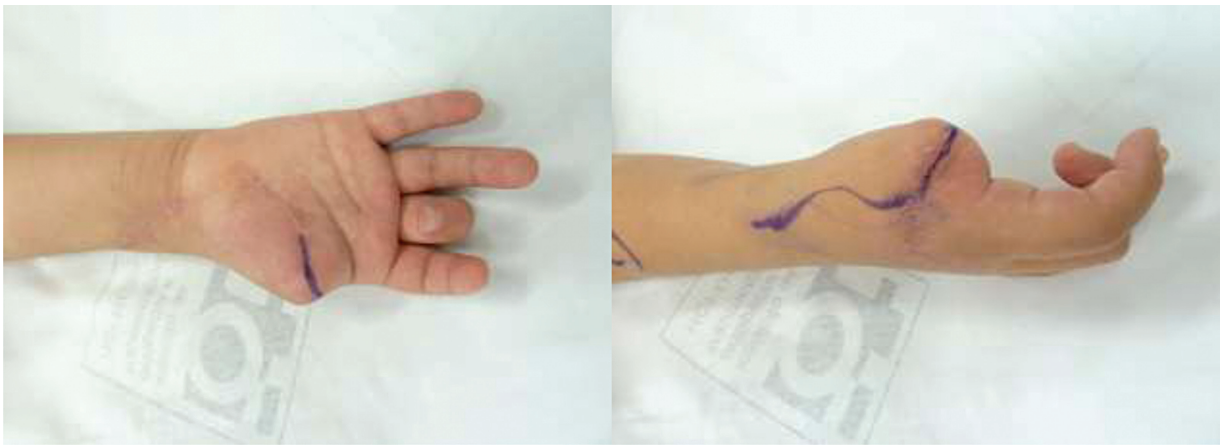


Fig. 1 Planning of the hand incision.



Fig. 2 Planning of the foot incision.



Fig. 3 Immediate postoperative outcome.

arising, eating, walking, hygiene, reach, grip, and activities) and a disability index that ranges from 0 to 3. The CHAQ also has a visual analog scale (VAS) for pain and another scale to assess the child's overall well-being, which ranges from 0 to 100. The result was 0 on the 8 domains of the CHAQ, the disability index, and both the VAS and the overall well-being scale. Furthermore, the patient's mother reported no difficulties in the daily activities, no disability, no pain, and an excellent overall well-being on the part of the child.

The Semmes-Weinstein monofilament and two-point discrimination tests (using the Touch-Test, North Coast Medical, Inc., Morgan Hill, CA, US) were performed. The patient felt the green Semmes-Weinstein monofilament (0.05 g) in the finger pulp (which is considered normal sensibility) and had a two-point discrimination value in the finger pulp of 2 mm.

The Jamar dynamometer (Sammons Preston, Bolingbrook, IL, US), calibrated in the second ring, and the Jamar Pinch



Fig. 4 Esthetic and functional late postoperative outcome.

Table 1 Strength assessment

	Right side	Left side
Tip pinch (kgf)	2.0	2.1
Tripod pinch (kgf)	2.3	4.0
Lateral pinch (kgf)	2.3	4.6
Handgrip strength (kgf)	5.6	18

Abbreviation: kgf, kilogram-force.

Table 2 Time in seconds required to perform the Jebsen-Taylor Hand Function Test

	Dominant hand (left)	Non-dominant hand (right)
Writing	43.4	72.4
Turning over cards	6.8	5.1
Small objects	8.9	11.2
Simulated feeding	15.0	18.9
Stacking checker pieces	3.7	3.6
Large and light objects	4.2	3.9
Large and heavy objects	3.6	4.5

Gauge (Sammons Preston) were used to assess the handgrip and pinch strength respectively (►**Table 1**).

The Jebsen-Taylor Hand Function Test (JTHFT)[5] was applied (►**Table 2**), and it is used to assess hand function and quantify the time required to perform different tasks that mimic those performed in daily life.

For purposes of comparison, we used the results presented by Rufino et al.[6] In the present study, the JTHFT was standardized for children aged between 6 and 10 years (►**Table 3**).

Table 3 Mean time in seconds and standard deviation of the Jebsen-Taylor Hand Function Test in normal children aged 6 to 10 years

	Dominant hand	Non-dominant hand
Writing	39.3 ± 15.4	79.4 ± 29.0
Turning over cards	5.3 ± 1.8	5.8 ± 1.7
Small objects	6.8 ± 1.2	7.6 ± 1.9
Simulated feeding	15.1 ± 5.1	21.2 ± 7.0
Stacking checker pieces	4.5 ± 1.0	5.0 ± 1.1
Large and light objects	3.9 ± 1.0	4.1 ± 0.9
Large and heavy objects	4.2 ± 1.1	5.4 ± 1.6

Comparing the data from (►**Tables 2** and **3**), it is possible to observe that the patient needs more time (11.2 seconds) to pick up small objects and less than the normal time to stack checker pieces (3.6 seconds) when using the operated hand. The other subtests were performed at normal times.

An X-ray was performed (►**Fig. 5**), which showed the proximal phalanx of the transplanted second toe with 20.7 mm and the proximal phalanx of the contralateral toe with 21.2 mm in length. It was also possible to observe the maintenance of the open physis.

Discussion

J. R. Cobbett[7] performed the first reported successful microsurgical toe transfer in 1968. Since then, numerous reports and publications have been made demonstrating the effectiveness, safety, and satisfactory results of the procedure.[8]

When compared to adults, the smaller size of the anatomical structures and the greater spasticity of the vessels in children are the main challenges of this procedure.[9]



Fig. 5 Radiograph of the right hand and foot, under the same magnification, with a comparative measure of the length of the proximal phalanx.

Although challenging, reconstructive surgeries in children, such as toe-to-hand transfer, are incredibly successful regarding the functional outcome. In the present case report, the patient showed excellent ability to develop daily activities, as demonstrated by the CHAQ and the JTHFT. The middle finger's flexion contracture, which was a consequence of the initial trauma extension to the palm, did not significantly impact the overall function (►**Figs. 1** and **4**).

In ►**Fig. 4**, it is possible to see that the final esthetic outcome was not ideal. Transfer of a great toe would probably have resulted in a better esthetic outcome, with a less bulky finger pulp without a claw deformity. However, considering the significant morbidity of the donor site for the great toe transfer, the second toe is usually the best choice for children.[10]

The children's ability to understand and comply with the tests is critical to obtain a reliable result. There is some scientific evidence that children older than 6 years of age are able to complete the standard tests of motor and sensory function, which are applied in cases of peripheral-nerve injuries.[11] Sensory recovery in children is usually better than in adults due to their greater ability to regenerate peripheral nerves and neuroplasticity.[8] In the present case, the recovery of a normal sensibility in the transplanted finger was achieved.

Few studies approach the growth potential of the toe transplanted to the hand.[12] In the case herein presented, the length of the proximal phalanx of the transplanted second toe is very similar to that of the contralateral toe, five years after the surgery. This radiographic analysis provided substantial evidence of the preservation of the epiphyseal plate and growth potential in pediatric toe-to-hand transfers.

Despite this procedure's technical difficulties, especially in children, our analysis of functional aspects, pain, sensibility, donor-site morbidity, and growth potential showed good results. These results provide supportive data for toe transfer in children with traumatic thumb loss.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Retroperitoneal, Liver, and Lymph Node Metastasis from Proximal Tibial Osteosarcoma: A Case Report

Metástase retroperitoneal, hepática e de linfonodo de osteossarcoma tibial proximal: Relato de caso

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Abstract

The present study describes the case of a male adult with an osteosarcoma in the proximal tibia, treated with limb salvage with endoprosthesis and chemotherapy. The patient developed an unusual metastatic pattern compromising the liver, bone, and inguinal lymph nodes, without local recurrence in the tibia or pulmonary metastases. Osteosarcoma (OS) is the second most frequent primary bone tumor after multiple myeloma in adults. Frequent sites of metastases in case of disease progression are the lungs and bone. Extrapulmonary metastases are rare. The development of new schemes of chemotherapy have improved life expectancy in osteosarcoma patients but have also altered the usual patterns of metastases, resulting in unusual metastatic locations.

Keywords

- lymphatic metastasis
- metástasis
- osteosarcoma
- tibia

Resumo

Homem adulto com osteossarcoma na tíbia proximal, tratado com cirurgia de salvamento de membro com endoprótese e quimioterapia. Ele desenvolveu um padrão metastático incomum, comprometendo fígado, ossos e linfonodos inguinais, sem recorrência local na tíbia nem metástases pulmonares. O osteossarcoma (OS) é o segundo tumor ósseo primário mais frequente, depois do mieloma múltiplo em adultos. Os locais frequentes das metástases, em caso de progressão da doença são os pulmões e os ossos. As metástases extrapulmonares são raras. O desenvolvimento de novos esquemas de quimioterapia melhorou a expectativa de vida dos pacientes com osteossarcoma, porém, alterou também os padrões usuais de metástases, resultando em localizações metastáticas incomuns.

Palavras-chave

- metástase
- metástase linfática
- osteossarcoma
- tíbia

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Introduction

Advances in the development of new chemotherapy and radiotherapy schemes, as well as in orthopedic oncologic surgery and prognosis of patients with osteosarcoma (OS) have improved survival from 15 to more than 60%.[1,2] However, approximately 40% of patients relapse and present disease progression with frequent metastases to the lungs and bone.[2] Other sites of secondary compromise, such as abdominal organs, lymph nodes, or retroperitoneum, are rare. Despite the advances in treatment options, the prognosis of patients with unusual metastases remains grim, with high mortality rates. The use of new chemotherapy regimens may be associated with the induction of atypical patterns of spread and disease progression, possibly by favoring the selection of different phenotypes in tumor cells.[2] We present the case of an adult male with unusual metastatic involvement of osteosarcoma, caused by a large retroperitoneal mass, an inguinal lymph node conglomerate, with liver and bone metastases without local or pulmonary recurrence.

Case Report

A 46-year-old male presented with pain in the left knee radiating distally to the leg. X-ray and magnetic resonance studies exhibited a lytic lesion of the proximal tibia that required an open biopsy, which confirmed osteosarcoma (►**Fig. 1A**). Computed tomography scans of the thorax, abdomen and pelvis were negative for metastatic lesions. Neoadjuvant treatment began with 3 cycles of doxorubicin and cisplatin, and, 6 months later, limb salvage surgery was held with complete resection of the tumor and reconstruction with a proximal tibial endoprosthesis. Histopathology confirmed a proximal tibial OS, with tumor-free margins, and a 30% viable tumor, indicating a grade II A response to neoadjuvant management.

Subsequently, the patient completed three cycles of adjuvant chemotherapy with the previous scheme, with adequate tolerance to treatment and without toxicity. One year after the surgical procedure, he presented episodes of limb lymphedema and pain. Doppler ultrasound ruled out deep vein thrombosis, and an abdominal CAT scan disclosed inguinal and iliac lymphadenopathies. Chest CAT scan revealed a non-specific pulmonary nodule smaller than 1 cm. At the time, thoracic surgery service did not consider it as a metastatic lesion. Later, an inguinal node biopsy was performed, and the histopathological analysis confirmed a malignant tumor and OS metastases (►**Fig. 1B**).

Considering that the patient presented with a relapse in the lymph nodes and inguinal soft tissues, without local recurrence at the initial tumor site, resection of the metastasis was decided upon. During the intervention, a solid mass of approximately 10 cm in diameter was evidenced in the left inguinal region adhered to the lateral aspect of the bladder, the external iliac vessels, the spermatic chord, and the inguinal ligament. It presented with an extensive involvement of the inguinal nodes, so a left inguinoiliac lymph node dissection was performed, achieving an R2 resection of the mass (given the compromise of the vascular structures and extensive soft-tissue fibrosis). The histopathological study identified multiple conglomerate nodal structures of 5 to 6 cm in diameter, considered to be metastases with massive angioinvasion and extension to soft tissues. After this intervention, palliative chemotherapy was held using gemcitabine and docetaxel, of which the patient received 1 cycle of treatment.

One month later, the patient presented with severe pain in the lower left limb as well as monoplegia, acute renal failure, and hematuria. A magnetic resonance imaging (MRI) of the lumbosacral spine revealed an irregular left anterolateral paravertebral mass in the lower lumbar segment that infiltrated the psoas muscle and the anterior cortex of the L5 vertebral body (►**Fig. 2**).

In addition, the contrasted thoracoabdominal CAT scan identified multiple hypodense lesions compatible with metastases in the liver parenchyma, pelvic bones, and a mass of approximately 140×78 mm on the left iliac psoas muscle that extended from L3 to the inguinal region and surrounded the internal and external iliac vessels. Additionally,

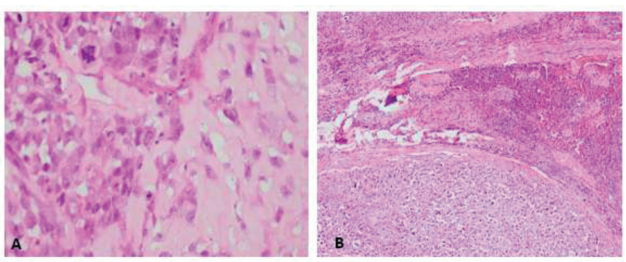


Fig. 1 (**A**) H/E 40x. Malignant tumor with osteoid production corresponding to an osteosarcoma. (**B**) H/E 40x. Lymph node metastases of osteosarcoma. Sheets of pleomorphic cells with extensive necrosis, abundant mitoses and osteoid.

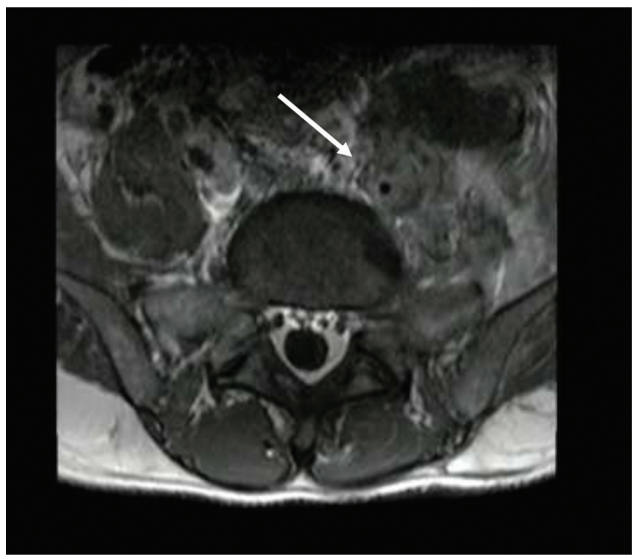


Fig. 2 Magnetic resonance of the lumbosacral spine showing a mass in the paravertebral soft tissues, infiltrating the body of the L5 vertebra (arrow).



Fig. 3 Thoracoabdominal CT in a coronal view, with a soft tissue mass infiltrating the left psoas muscle extending to the inguinal region (arrow).

para-aortic, inter aorto-cava, and right external iliac lymph nodes were found (►**Figs. 3** and **4**).

A CAT-guided biopsy of this mass was performed, showing metastatic involvement due to a high-grade osteosarcoma (►**Fig. 5**).

The patient persisted with clinical deterioration, developed deep vein thrombosis in the lower left limb and acute pulmonary thromboembolism, persistent hematuria, and

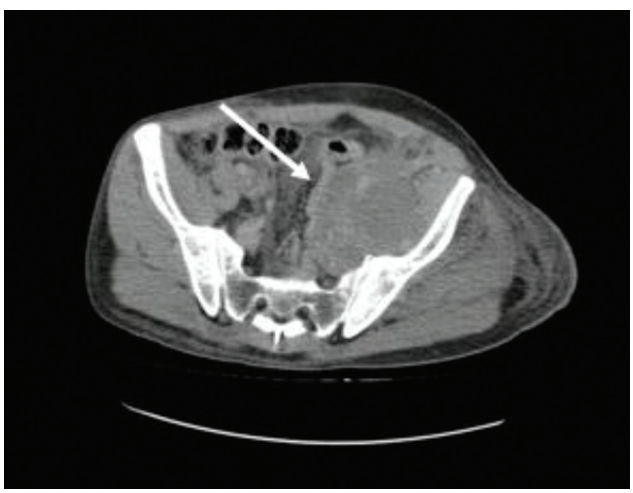


Fig. 4 Axial view of an abdominal CT, with a soft tissue mass infiltrating the left psoas muscle (arrow).

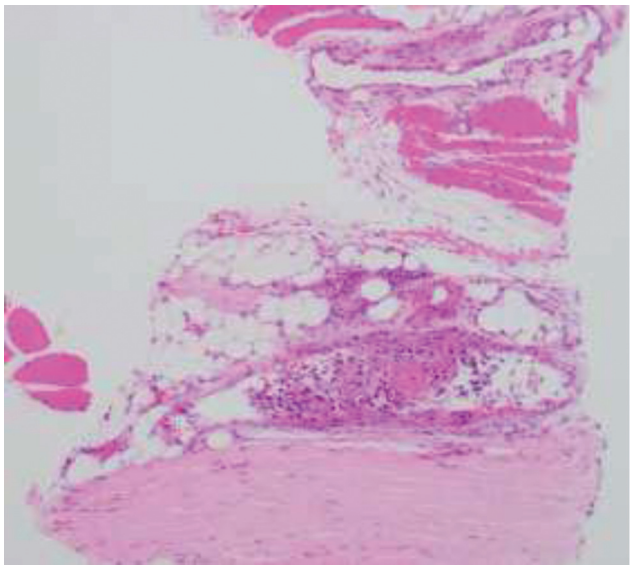


Fig. 5 H8/e 10x. Neoplasic thrombi with osteoid matrix amongst malignant cells compatible with metastatic osteosarcoma.

dehydration, after which he died, 2 years after the initial diagnosis of OS.

Discussion

The occurrence of metastasis is part of the natural course of osteosarcoma (OS), with pulmonary metastasis being the most frequent.[1,3–7] Using chemotherapy as part of the integral management, a change in the usual patterns of metastasis has been described, with respect to what was reported in 1975 by Jeffree et al.[8] Although this may be the result of better identification and reporting of new cases of OS, the improvement in survival of patients with OS has revealed new patterns of extra-pulmonary metastasis, particularly in the peritoneum and lymph nodes.[1–3,6,7,9] The literature is not clear regarding the epidemiology of lymphatic metastases in OS, and most of the available information comes from case reports and case series, with an incidence between 4 and 11%.[1,6,7,9,10] The presence of micrometastases that can achieve a dissemination of OS has also been described, which could impact the survival rates.[4]

One of the most important aspects that impact survival in patients with OS is the development of metastases.[1,8–10] It seems that the presence of certain metastases could be associated with more aggressive OS variants.[1,6–10] It has been hypothesized that this change in the usual pattern of extrapulmonary metastasis is the result of the use of more efficient chemotherapies that target certain tumor cells, leaving room for more aggressive variants with greater metastatic potential.[2–5,9,10] This could explain the outcome of lymph node and abdominal metastases (especially retroperitoneal) that are associated with difficult-to-manage relapse and high mortality at the time of diagnosis.[2,3,9,10]

The present case describes an aggressive and difficult-to-treat type of bone tumor, with a poor response to chemotherapy, with distant recurrence, and, eventually, a fatal outcome. Although the presence of lymph node metastases

is exotic, the occurrence of extrapulmonary metastases is increasing, and, therefore, it is essential to understand the scope of a tumor that science may not have fully understood yet.

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Conflict of Interests
The authors have no conflict interests to declare.

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CONTENTS

Peer Reviewing Process 3
MANUSCRIPT FORMAT **3-6**
Article Types 3
General Guidelines 3
Files/Information Checklist 3
Language 4
Title Page 4
Abstract and Keywords 4
Main Document 4
Acknowledgments 5
Formatting of Funding Sources 5
Conflict of Interest Statement 5
Informed Consent 5
Conflicts arising from papers authored by Editorial Board Members 6
References 6
Figure Captions 6
Tables 6
Videos 6
Supplementary Material 6

DIGITAL ARTWORK PREPARATION **6-7**
General Guidelines 6
Black and White Art 7
Color Art 7
Art Labels 7

SUBMISSION PROCEDURE **7**
Article Processing Charge (APC) and Open Access 7
Submission Procedure 7
Revision Procedure 7

PRODUCTION PROCEDURE **7**
Page Proofs 7

POLICY STATEMENTS **8-9**
Privacy Statement 8
Preprint Server Statement 8
Ethics standards 8
Authorization Letter 8
Conflict of Interest Statement (if any): 8
Informed Consent 8
Copyright Statement 8
Definition of Authorship 8
Contributors 9
Changes to authorship 9

EDITORIAL CONTACTS **9**

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Letters to the Editor (Up to 500 words	N/A	N/A	N/A	2 Figures	Up to 4 References
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