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Hill-Sachs Lesion: Diagnosis, Classification, and Treatment

Lesão de Hill-Sachs: Diagnóstico, classificação e tratamento

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Abstract

A lesão de Hill-Sachs é uma condição frequentemente associada à instabilidade anterior do ombro, que desempenha um papel crucial nos resultados de seu tratamento The Hill-Sachs lesion is a condition frequently associated with anterior shoulder instability, which plays a crucial role in the outcomes of its treatment. It is characterized by a posterior compressive fracture in the humeral head caused by an impingement against the anterior rim of the glenoid cavity during dislocation. A thorough understanding of this lesion is essential to support clinical decisions and choose the most appropriate treatment. Advances in imaging modalities, such as magnetic resonance imaging and computed tomography, enabled lesion identification with greater precision and its classification per depth, location, and volume, resulting in a detailed assessment of its role in shoulder instability. The present article reviews the main classifications, diagnostic methods, and treatment options to provide orthopedists with a comprehensive and updated view of the strategies to promote better functional outcomes and minimize the risk of instability recurrence.

Keywords

- humeral fractures
- joint instability
- orthopedic procedures
- shoulder dislocation

Resumo

A lesão de Hill-Sachs é uma condição frequentemente associada à instabilidade anterior do ombro, que desempenha um papel crucial nos resultados de seu tratamento. É caracterizada por uma fratura compressiva posterior na cabeça do úmero, que resulta do impacto contra a borda anterior da cavidade glenoidal durante um episódio de luxação. A compreensão aprofundada dessa lesão é essencial para embasar decisões clínicas e para a escolha do tratamento mais adequado. Com os avanços nas modalidades de imagem, como a ressonância magnética e a tomografia computadorizada, tornou-se possível identificar a presença da lesão com maior precisão e classificá-la de acordo com sua profundidade, localização e volume, o que possibilita uma avaliação mais detalhada do seu papel na instabilidade do ombro. Este artigo revisa as principais classificações, métodos de diagnóstico e opções de tratamento, com o objetivo de fornecer ao ortopedista uma visão abrangente e atualizada das estratégias que promovem melhores desfechos funcionais e minimizam o risco de recorrência da instabilidade.

Palavras-chave

- fratura do úmero
- instabilidade articular
- luxação do ombro
- procedimentos ortopédicos

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Introduction

Although the Hill-Sachs (HS) lesion is widely known, the literature still debates its contribution to the development of shoulder instability and its implications in the surgical or conservative treatment of patients with this condition.

The first description of shoulder dislocation dates to ancient Egypt, around 3,000 BC, in the Edwin Smith papyrus. Malgaigne was the first author to mention a humeral head lesion in 1855. In 1940, 2 radiologists, Harold Arthur Hill and Maurice David Sachs, described and named the lesion.[1,2] The HS lesion is a depression of the humeral head in the posterolateral region in the presence of an anterior shoulder dislocation. This compression fracture occurs due to the impingement of the humeral head spongy bone against the anterior cortex of the glenoid cavity.[3] The HS lesion is associated with bone or labral involvement on the anterior face of the glenoid cavity and may contribute to shoulder instability.[4]

Current data indicate that shoulder dislocation mainly affects young and active populations, generating concern about its socioeconomic implications.[5]

The incidence of HS lesions ranges from 40% to 90% in anterior shoulder dislocations and reaches up to 100% in recurrent dislocations.[3,4,6] It is worth noting that an HS lesion rarely occurs in isolation, reinforcing the concept of bipolar injury (that is, with scapular glenoid cavity involvement), which is present in 63% of the cases.[7,8]

Arm positioning at the time of dislocation is relevant, since the location and inclination of the resulting HS lesion affect shoulder stability. A dislocation occurring with the shoulder in abduction presents a greater risk of engagement (HS lesion fitting into the anterior glenoid rim).[9] More extensive HS lesions, especially in medial positions,[4] also increase the risk of instability due to reduced contact of the humeral head with the articular surface of the glenoid cavity.

History and Clinical Picture

Patients with HS lesions typically complain of instability. They may present a history of shoulder pain, which worsens in joint abduction or hyperextension,[3] or signs such as crepitation and clicking during movement. The potential for a new dislocation increases with the number of episodes and the bone defect size. A positive apprehension test with lower degrees of abduction (mid-range) presents a higher association with glenoid cavity defects. In contrast, a positive result at the end of abduction and lateral rotation (end range) results from HS lesions.[4]

To date, there is no description of a specific propaedeutic maneuver to evaluate HS lesions. A routine physical examination should assess shoulder instability, including an evaluation of generalized ligamentous laxity (Beighton criteria), and performance of the sulcus, Gagey, apprehension, surprise, and relocation tests.[10]

Other tests include the hyperextension–internal rotation (HERI) test[11] and the bone apprehension test.[12] There is still controversy in the literature about the sensation of instability in lower degrees of abduction (bone apprehension test) in detecting significant bone loss in the glenoid cavity or humerus (HS).[12,13] It is crucial to confirm the finding of dislocation/instability on physical examination under anesthesia.

Imaging Tests

The initial investigation routinely uses shoulder radiographs in classic anteroposterior (AP), true AP, lateral, lateral scapular, and lateral axillary views (►**Fig. 1**).

The specific radiographic investigation of the humeral bone defect from an HS lesion can use the following radiographic views:[3]

- Stryker notch: medial humeral head rotation to highlight the posterolateral defect.
- Garth view: AP view of the shoulder in the scapular plane with a 45° caudal inclination of the radius.
- AP with medial rotation: this view can reveal the HS lesion size, depth, and orientation in the posterolateral region of the humeral head.[14] Often, the AP radiographic view with lateral rotation does not show the lesion, only a bone rarefaction medial to the greater tubercle[1,15] (►**Fig. 2**).

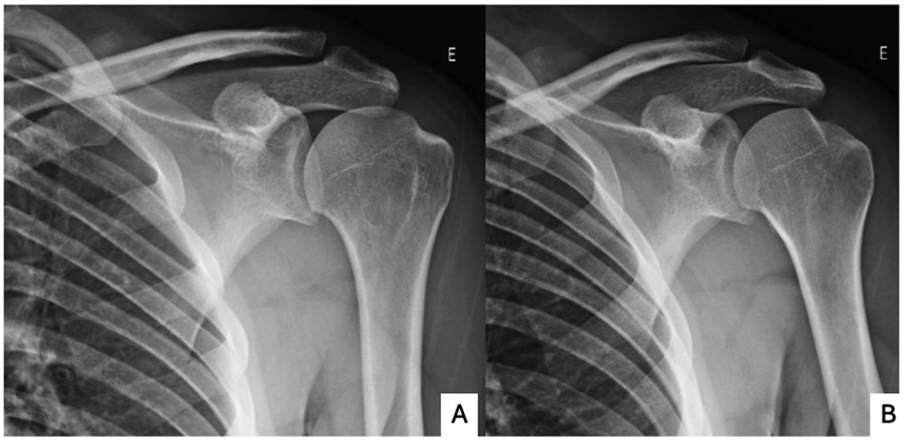


Fig. 1 Radiographs of the shoulder with a Hill-Sachs (HS) lesion in true anteroposterior (AP), AP, axillary lateral, and scapular lateral views.

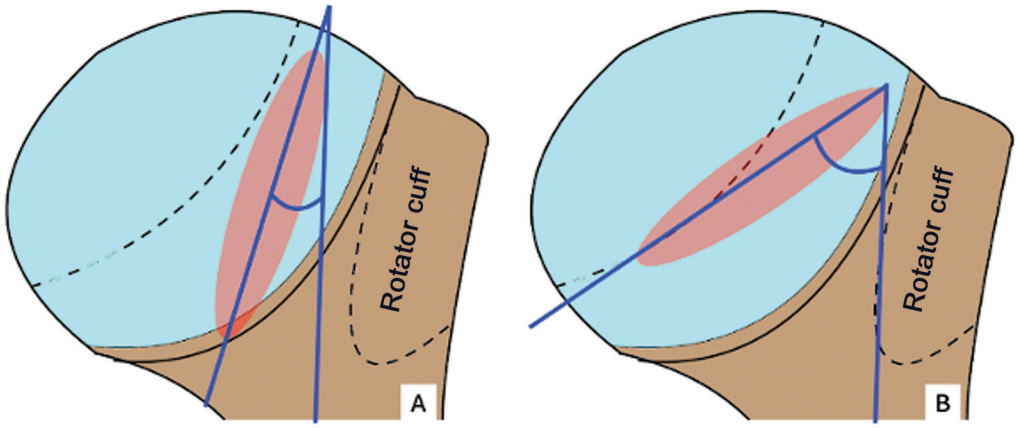


Fig. 2 (A) Anteroposterior radiograph with lateral rotation, not showing the HS lesion; (B) AP radiograph with slight medial rotation, showing the HS lesion.

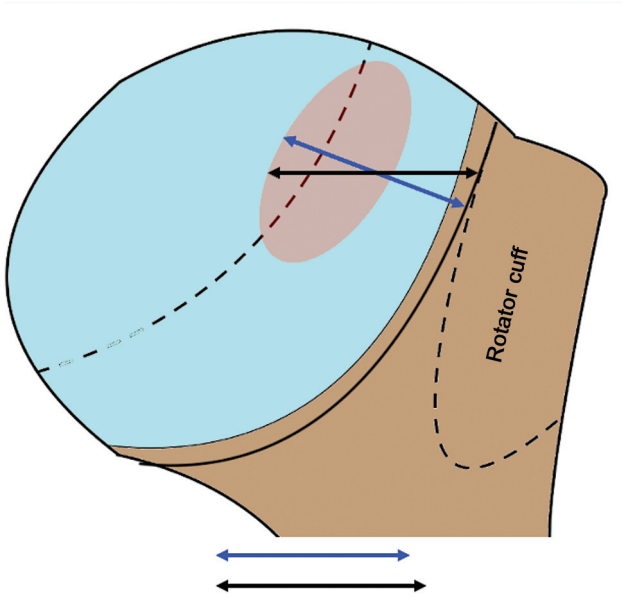


Fig. 3 Computed tomography (CT) scans showing the HS lesion. Two-dimensional images in the axial, sagittal, and coronal sections. Three-dimensional images in the lateral and posterior views.

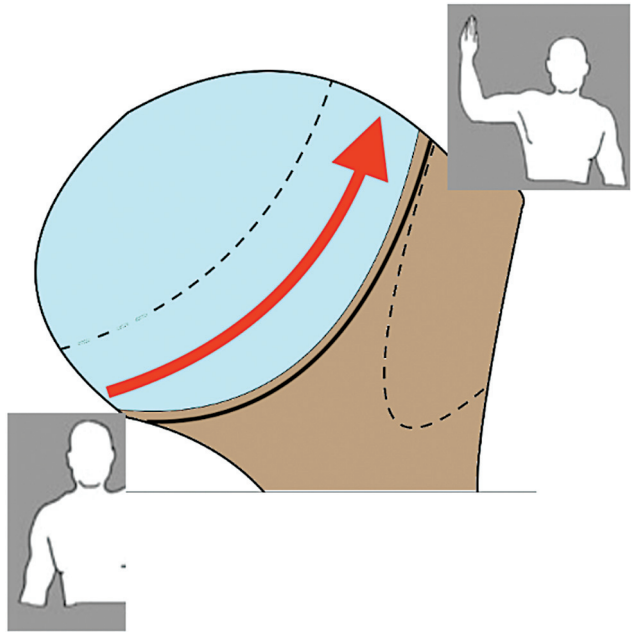


Fig. 4 T2-weighted magnetic resonance imaging (MRI) scans showing the HS lesion the in coronal, sagittal, and axial sections.

- Modified Didier: in this view, the patient is in ventral decubitus with the back of the hand resting on the posterior iliac crest, the elbow in flexion, and the radius at a 45° angle to the ground in the direction of the humeral head.[16]

Radiographs have low interobserver reliability and cannot provide enough data for preoperative planning,[17] since up to 60% of bone defects may be overlooked in cases using this method alone for analysis.

Computed tomography (CT) and magnetic resonance imaging (MRI) are complementary imaging methods (►**Figs. 3**–**4**) that are more sensitive than radiographs in the detection of HS lesions.[14]

It has been proven that there are differences in defect measurements in two- and three-dimensional (3D) images. Computed tomography with t3D reconstruction (3D-CT) is the gold standard to quantify the HS defect.[7,17] The measurements are made in slices perpendicular to the bone defect, but they can vary.[18,19]

Three-dimensional CT defines the HS lesion angulation per the line passing deep to the injury dent and the longitudinal axis of the humeral diaphysis (►**Fig. 5**).[17] The higher the angulation, the greater the risk of engagement.

The use of MRI with 3D reconstruction (3D-MRI) is growing. Studies[20,21] have reported equivalent accuracy in measuring the defect of the HS lesion with 3D-CT and 3D-MRI. Three-dimensional MRI presents the advantage of not using ionizing radiation, and it has better diagnostic potential for soft tissue injuries, such as in the evaluation of rotator cuff attachment. In 3D-CT, this evaluation can result in high variability and low interobserver agreement due to the

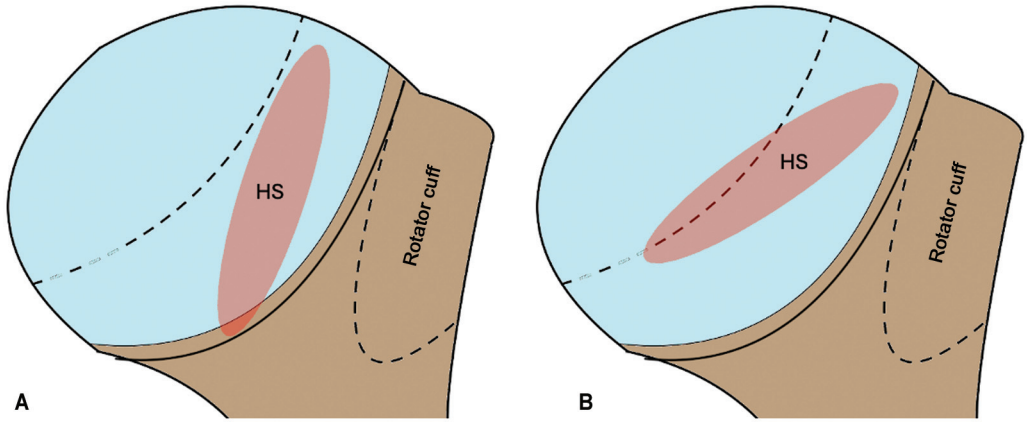


Fig. 5 (A) The smaller angle presents a lower engagement risk. (B) A larger angle presents a higher engagement risk. We considered that the HS lesion was the same size in A and B.

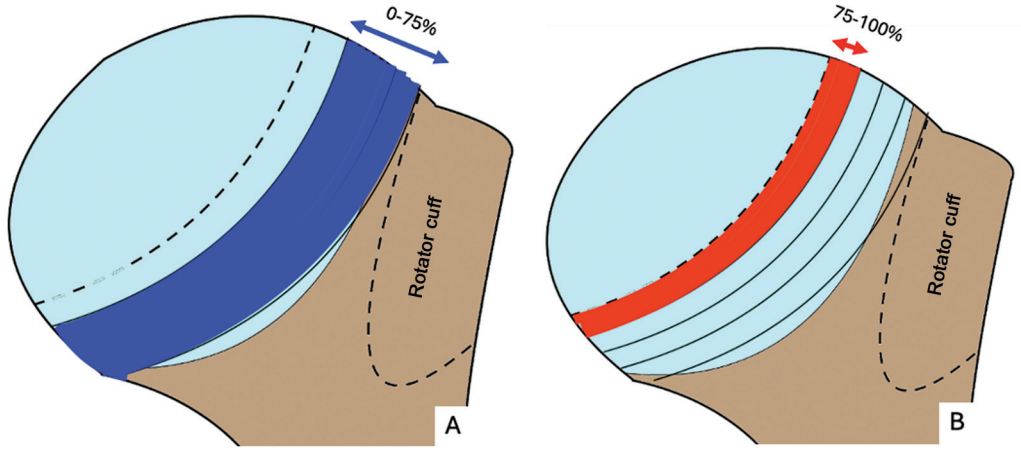


Fig. 6 Magnetic resonance imaging scan evaluated in the axial section (black arrow); three-dimensional CT scan evaluated perpendicularly to the defect (blue arrow). Note that the black arrow is larger than the blue arrow, which may overestimate the defect and change the case management.

difficulty in visualizing this structure. The disadvantages of the reconstruction methods include their high costs and limited accessibility. It is worth highlighting that measuring the size of the HS lesion with two-dimensional CT or MRI increases the likelihood of obtaining an overestimated measurement (diagonally), which increases the chance of classifying the lesion as off-track and may influence the choice of the surgical technique (►**Fig. 6**).

Differential Diagnoses

It is easier to diagnose HS lesions by associating the patient's clinical history with imaging tests. However, it is critical to remember that some conditions can cause bone erosions in the humeral head, simulating HS lesions, such as ankylosing spondylitis, rheumatoid arthritis, septic arthritis, hyperparathyroidism, hydroxyapatite storage disease, malignant tumor, or benign cysts.[14]

Classification

The classification of HS lesions can follow the arthroscopic visualization criteria described by Calandra,[7] which rely on quantifying the defect depth. A grade-1 lesion affects the articular cartilage alone; a grade-2 lesion extends to the subchondral bone; and a grade-3 lesion presents a sizable subchondral defect.[16] However, its clinical applicability is limited.

One of the most crucial concepts in HS lesions is the glenoid track (GT), that is, the area of contact between the glenoid cavity and the humeral head during movement from the neutral position to the abduction and external rotation (ABER) position.[20] In this movement, the area of contact moves from inferomedial to superolateral in the humeral head (►**Fig. 7**). Cadaveric studies have shown that the area covered by the glenoid cavity corresponds to 84%, while clinical studies indicate an 83% of coverage.[19]



Fig. 7 The arrow indicates the change in the contact region of the humerus with the glenoid cavity rim in the resting position to the abduction and external rotation (ABER) position.

We can use the contralateral side of the glenoid cavity to assess the size of the bone defect; however, this assessment must be careful, as 8% of glenoid cavities present a difference $\geq$ 3 mm regarding the contralateral side.

The Di Giacomo et al.[9] method for GT measuring includes four steps:

1. Measurement of the diameter of the inferior glenoid cavity using a perfect circle (D);
2. Measurement of the anterior bone loss of the glenoid cavity (d);
3. Calculation of the GT width = (0.83 × D) – d;
4. Measurement of the width of the HS interval (HSI) = width of the HS + width of the bone bridge (BB).

If HSI > GT, the HS lesion is off-track, that is, with a risk of engagement.

If GT > HSI, the HS lesion is on track, that is, with no risk of engagement[17] (►**Fig. 8**).

Although the use of this method is frequent in the clinical practice, its intra- and interobserver agreements are low, mainly due to the difficulty in defining the medial margin of the HS lesion, the correct rotator cuff attachment on CT, and the overlap of the lateral edge of the HS lesion on the medial edge of the rotator cuff attachment.[18,19] Another criticism to the GT method is that it does not consider joint mobility, especially in subjects with ligamentous laxity, which may result in higher humeral head excursion.[21]

Another imaging classification relies on the location of the HS defect, which was developed from the observation that even some on-track lesions submitted to the Bankart surgery alone evolved with failure. This classification divides the humeral head GT into four zones, and HS lesions reaching the most medial peripheral zone (peripheral track) presented[19] worse results in the Western Ontario Shoulder Instability Index (WOSI) score when compared with other zones (central track) (►**Fig. 9**).

Other measurement methods are under development to reduce failures in on-track lesions treated with labral repair alone. The distance to dislocation (DTD)[22] considers the inferior craniocaudal extension of the HS lesion.[5] Another method is the global track,[21] which uses the dome of the humeral head and its central point as a reference instead of the rotator cuff attachment to measure the HS defect. However, these methods still require validation and testing in the clinical practice.

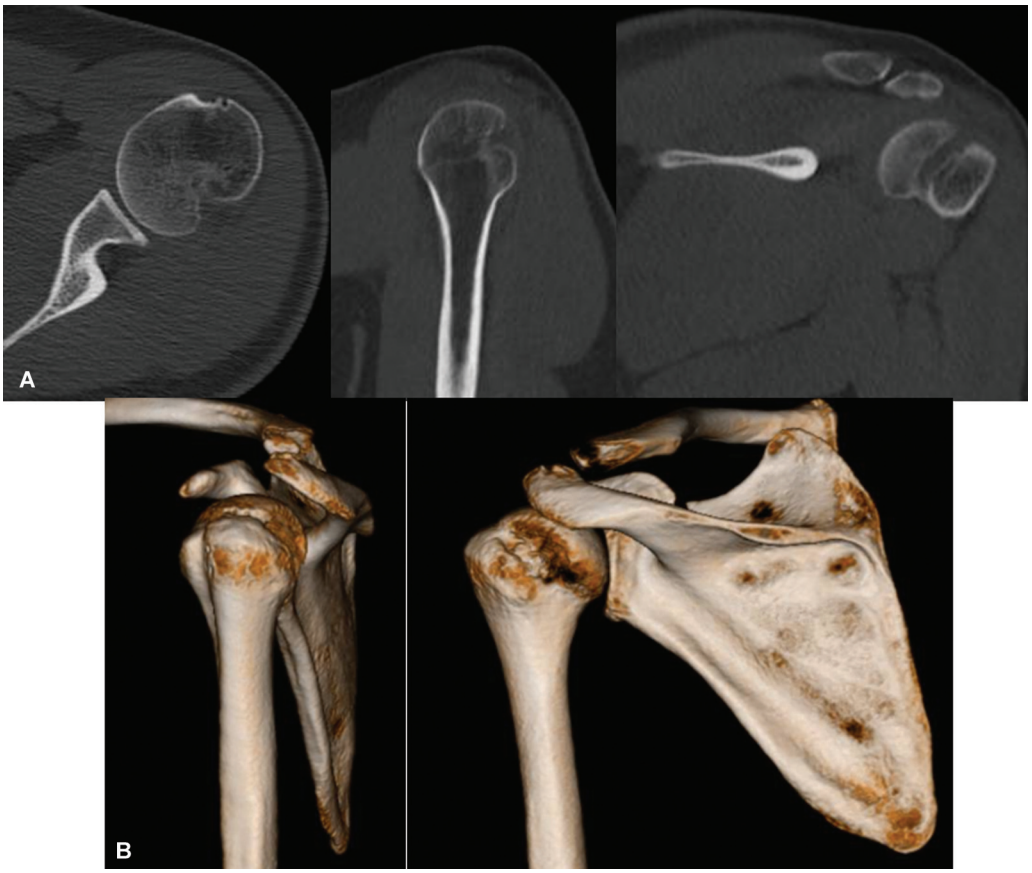


Fig. 8 (**A**) On-track lesion (Hill-Sachs interval [HSI] lesion < glenoid track [GT]); (**B**) off-track lesion (HSI > GT).

Treatment

The treatment of anterior shoulder instability, which is frequently associated with HS lesions, can be conservative in the first dislocation episode in patients with low demand. This treatment strengthens the deltoid, rotator cuff, and scapular stabilizer muscles. It is important to be aware of risk factors for recurrence, such as age (under 20 to 25 years), male sex, epilepsy, fall risk, ligament laxity, and participation in activities requiring ABER or competitive sports.[7,23,24]

In cases with surgical indication, HS lesion treatment is not usually performed in isolation, since the labral or ligament complex lesion is virtually always present, and its association with the bone defect of the glenoid cavity (bipolar lesion) occurs in 63% of the cases.[7]

The presence of the HS lesion is essential for therapeutic decision-making, as its size, location, and inclination influence the treatment. Some authors[7,25] argue that patients with small bone defects (< 20% of the humeral head) or no engagement can undergo isolated labral repair. Cases of larger defects or engagement may require other procedures. As some cases of failure occur even in the absence of engagement, there is a growing tendency to address the HS lesion in patients with anterior instability, even in situations with borderline bone lesions, especially with the remplissage technique.[21,22,26]

Humeral Head Procedures

The remplissage technique was described in 1972 and comes from the French word for "filling". Wolf modified it to perform it arthroscopically, "filling" the HS lesion by capsulodesis and infraspinatus tenodesis with labral repair. The prevalence of off-track lesions is of approximately 7%.[27] The ability to convert the HS lesion from intra-articular to extra-articular, reducing the engagement with the inferior edge of the glenoid cavity and the recurrent subluxation rate, determines the success of this technique. Even though the current recurrence rate ranges from 0% to 10%,[28,29] the size of the bone defect in the glenoid cavity influences these values.

The advantage of this procedure is its minimally-invasive approach, avoiding the need for bone block surgeries in the glenoid cavity and its complications. The theoretical disadvantage of this technique is the alteration of the rotator cuff anatomy and the shoulder biomechanics, potentially reducing lateral rotation and causing pain in the posterosuperior region of the shoulder.[30] However, this is a controversial topic, with some studies demonstrating no difference in

these outcomes compared with the isolated labral repair technique, especially with the technical development and studies on the ideal location for anchor insertion.

Other options for HS lesion treatment include two procedures: humeroplasty (for acute defects) and osteochondral bone grafting.

Humeroplasty (elevation of the impinged fracture and support with a graft) restores the geometry of the humeral head with no internal fixation. It is indicated for acute injuries of up to 3 weeks presenting less than 40% articular surface involvement.[3]

This method consists of elevating the cartilage and filling the defect with calcium phosphate,[31] restoring the local anatomy with a 5° gain in lateral rotation. Another way to elevate the defect uses a percutaneous vertebroplasty balloon with potential videoarthroscopy assistance,[32,33] with report demonstrating a 99.3% reduction in HS lesion bone defect.[7]

Partial arthroplasty using allograft fills the defect with an osteochondral graft via an open or arthroscopic approach. Allografts provide better biomechanics restoration, unlike non-anatomical grafts. The potential disadvantages include disease transmission, procedural difficulty, graft reabsorption or failure, subluxation, and cyst formation.[7] In addition, differences in the size and geometry of the defect and the implant may require humeral cartilage milling.

Glenoid Cavity Procedures

The treatment of glenoid cavity injuries depends on the size of the bone defect. Currently, Bankart repair alone has limited indications. The literature[34] has shown an increasingly guarded prognosis regarding critical bone loss for the performance of the Bankart repair. Adding remplissage to the Bankart repair may reduce the number of surgical treatment failures.[23,35]

Bone procedures increase the surface area of the glenoid cavity and indirectly treat potential failures resulting from the HS lesion. The most widespread techniques are the Latarjet procedure, the Eden-Hybinette technique, and the tibial allograft.

The potential disadvantages of the bone graft techniques in the glenoid cavity are loss of lateral rotation (on average, 11°), infection, hematoma, graft resorption, pseudoarthrosis or fibrous union, and subscapularis injury.[23,30]

Arthroplasties

Partial resurfacing prostheses present the advantages of no donor site morbidity compared with autografts and shorter surgical time. The disadvantages are the difficulty in obtaining proper fixation and the inability to align the prosthesis surface with the humeral articular surface.[36]

Another option is hemiarthroplasty, a procedure indicated for elderly patients with an HS defect $>40\%$ of the articular surface. An increase of 10° to 15° in retroversion may improve stability.[7,25]

Other arthroplasty types are uncommon and intended for more severe instability or complications from previous procedures.

Options with a Historical Interest

Weber's derotation osteotomy is a treatment option still in use as a salvage procedure in young patients. This technique consists of an osteotomy on the surgical neck of the humerus and a retroversion of the humeral head in relation to the diaphysis. This procedure presents variable outcomes and relatively high complication rates, such as pseudarthrosis, iatrogenic fracture, and osteoarthritis.[7]

Final Considerations

The HS lesion plays a fundamental role in shoulder instability, and research on this topic has exponentially increased in recent times.

The search for an algorithm for decision-making on the best treatment for patients with anterior shoulder instability continues. However, despite all attempts and concepts developed to date, there is no ideal option.

Therefore, it is essential to consider HS lesions and their correct treatment to improve outcomes and achieve high success rates, with no dislocation recurrence and excellent function according to patients' expectations. We expect that the evolution we are witnessing will bring long-term better functional outcomes and fewer complications to these patients who, as already discussed, are mostly young, active people, with high expectations.

Authors' Contributions

Each author contributed individually and significantly to the development of this article: MJST: conceptualization, formal analysis, investigation, methodology, and writing – review & editing. AYU and RAZ: writing – original draft, writing – review & editing, validation, and visualization. FTM: formal analysis, investigation, methodology, and writing – review & editing. NAN: conceptualization, formal analysis, and data curation.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Review of Osteoporotic Fractures: Occurrence, Prevention, and Consequences

Revisão sobre fraturas osteoporóticas: Ocorrência, prevenção e consequências

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Abstract

Osteoporosis is a metabolic condition that compromises bone density and architecture, increasing the risk of fractures and impacting morbidity and mortality. The diagnosis involves bone densitometry, in which mineral density in areas prone to fractures is assessed. Primary osteoporosis is age-related and may remain asymptomatic for years, while secondary osteoporosis results from comorbidities or medications. Approximately 80% of postmenopausal Caucasian women have osteoporosis, with an expected increase with aging. Orthopedic treatments are common for fractures, which are often caused by falls in the elderly. Fracture prevention requires public health policies and therapies focused on this goal.

Keywords
- diagnosis
- fractures, stress
- osteoporosis
- risk assessment
- treatment

Resumo

A osteoporose é uma condição metabólica que compromete a densidade e a arquitetura ósseas, o que aumenta o risco de fraturas e tem impacto na morbimortalidade. O diagnóstico envolve a densitometria óssea, em que se avalia a densidade mineral em áreas propensas a fraturas. A osteoporose primária, relacionada à idade, pode permanecer assintomática por anos, ao passo que a secundária resulta de comorbidades ou medicamentos. Cerca de 80% das mulheres brancas na pós-menopausa têm osteoporose, com expectativa de aumento com o envelhecimento. Tratamentos ortopédicos são comuns para fraturas, que são frequentemente causadas por quedas em idosos. A prevenção de fraturas é crucial, e requer políticas de saúde pública e terapias com este objetivo.

Palavras-chave
- avaliação de risco
- diagnóstico
- fraturas por estresse
- osteoporose
- tratamento

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Introduction

Definition

Osteoporosis is a decrease in bone density and quality, which increases the risk of fractures due to bone porosity and fragility. Bone loss is gradual and asymptomatic; as such, osteoporosis is often called a "silent disease". Fractures, usually in the spine, wrist, hip, and shoulder, are the first obvious symptoms.[1,2]

Epidemiology

Osteoporosis is a severe global public health problem, affecting approximately 200 million women worldwide and with an increasing incidence in older age groups.[1–4] Approximately 30% of postmenopausal women in the United States and Europe have osteoporosis, and a significant proportion will suffer fragility fractures throughout their lives.[2] Populational aging will contribute to a substantial increase in osteoporosis incidence, and projections indicate significant increases in hip fracture rates by 2050 compared with 1990.[3]

Healthcare Costs

Osteoporosis impacts more than 10 million adults in the United States. It causes high social costs (22 billion dollars in 2008) and is underdiagnosed and undertreated. Projections indicate an increase in the annual number of fractures from 1.9 million to 3.2 million by 2040, with associated costs exceeding US$95 billion. Osteoporosis-related interventions can reduce fractures and expenses.[4–8] The economic burden exceeds that of conditions such as migraine and resembles that of rheumatoid arthritis. Continued use of osteoporosis medications reduces fracture risks and healthcare costs. Predictions show direct medical costs reaching $25.3 billion by 2025, highlighting the importance of improving medication persistence for payers and patients.[4,5]

Risk Factors

The risk factors for the development of osteoporosis can be permanent (such as age and gender) and modifiable (including smoking, alcohol consumption, and eating habits). These factors increase the likelihood of osteoporosis development, and the presence of multiple factors elevates the risk. Presenting risk factors does not necessarily lead to the development of osteoporosis; however, the greater the number and intensity of risk factors, the higher the probability of developing the conditionis.[2,5–9]

History of Osteoporosis Research

Osteoporosis, a condition affecting the bones, was identified approximately three centuries ago, although the disease has existed for millennia. The discovery of the bone-remodeling process by John Hunter 250 years ago was crucial for the understanding of bone tissue removal and replacement.[10] Surgeon Astley Cooper linked the decline in bone density to an increased risk of fractures. Jean Lobstein introduced the term *osteoporosis* in the 1830s.[11,12]

At the beginning of the twentieth century, Kyes and Potter[13] observed the relationship between estrogen levels and bone density in pigeons. Later, Fuller Albright et al.[14,15] contributed significantly to the understanding of osteoporosis by identifying osteoblast deficiency and associating it with menopause in women. They developed the first effective osteoporosis treatment using estrogen.

In 1955, Alexander Cooke[16] defined osteoporosis as an inadequate bone formation due to a lack of "matrix", suggesting that histological examinations should base the diagnosis. Cooke[16] also mentioned the beneficial and adverse effects of androgens. Subsequent therapeutic trials with fluoride, anabolic steroids, and calcitonin have had limited success and some side effects.[15–18]

Pathogenesis

Osteoporosis can occur due to failure to reach peak bone mass, excessive bone resorption, decreased bone formation during remodeling, or any combination of these factors. They all likely contribute to osteoporosis in varying degrees.[19]

Bone Mass Peak

Peak bone mass occurs when bone mineral density (BMD) reaches its highest point. Bone mass increases during childhood and adolescence, reaching its peak around age 30. After that, BMD gradually decreases with aging. Reducing this loss is crucial to prevent osteoporosis and fractures in adulthood. A 10% increase in peak bone mass can result in a 30% reduction in hip fractures. Genetic factors play a significant role, contributing to about 80% of the variability in peak bone mass, as evidenced by twin studies. Genetic variants, including low-density lipoprotein receptor-related protein 5 (LRP5)[5] and sclerostin, have been identified by genome-wide association studies.[19] Moreover, environmental factors, such as nutrition, exercise, and smoking, play key roles in bone mass peak.[19] Modulation of this peak can occur during intrauterine life, being affected by maternal nutrition, smoking, and exercise levels.[20]

Imbalance in Bone Resorption and Formation

Bone remodeling involves a coordinated action of osteoclasts and osteoblasts and is crucial to maintain bone health in adult life and repair microdamage. Although increased bone resorption appears to influence bone loss and the risk of fracture, compromised bone formation also plays a critical role in osteoporosis.[21] This impairment partly results from a reduced number of osteoprogenitor/preosteoblastic cells, an age-related defect in transforming stromal cells into adipocytes rather than osteoblasts, or both. Age- or menopause-associated bone loss is a significant osteoporosis determinant, and genetic factors account for variations in skeletal integrity among elderly people in the same age group.[22,23]

Osteoporosis-related Conditions

Subjects with certain health conditions resulting in higher bone loss and/or risk of falls present a greater risk of developing osteoporosis.[24,25] Secondary osteoporosis results from several comorbidities, medications, or both (►**Table 1**), e and it is associated with diseases that affect the

Table 1 Causes of secondary osteoporosis in adults[25]

Rheumatoid arthritis and other rheumatological conditions
Malabsorption syndromes
Sex hormone deficiency
Primary hyperparathyroidism
Chronic kidney disease
Chronic liver disease
Diabetes
Chronic obstructive pulmonary disease
Untreated hyperthyroidism
Neurological conditions
Cancer

mechanisms involving the balance of calcium, vitamin D, and sexual hormones.[26] About a third of postmenopausal women, in addition to many men and premenopausal females, present concomitant causes of bone loss,[25] such as renal hypercalciuria, which is treatable with thiazide diuretics.[26] Treatment is specific for each associated disease and requires a multidisciplinary approach.[25]

Metabolism and Bone Regulation in Osteoporosis Patients

Bones undergo constant remodeling through a balance between their formation by osteoblasts and resorption by osteoclasts.[9] Osteoporosis increases the risk of fracture due to reduced bone density.[16,17,21] Metabolic bone disease encompasses abnormalities from genetic disorders or mineral (calcium and phosphorus) and vitamin D deficiencies, including osteoporosis, osteomalacia, rickets, and bone Paget disease.[27]

Osteoporosis may result from inadequate calcium intake and vitamin D deficiency,[28] and proper vitamin D levels help maintain bone strength. Despite this, calcium and vitamin D therapy may not completely prevent bone loss, and although estrogen- and progesterone-based hormone therapy slows osteoporosis progression, it has side effects. Bone metabolism tests may offer therapeutic alternatives.

Blood levels determine the supplementation doses of calcium and vitamin D. certain indicators, such as urinary calcium levels and hormonal tests, help assess intestinal absorption and determine the origin of osteoporosis (primary or secondary).[28]

Calcium and Phosphate in Bone Metabolism

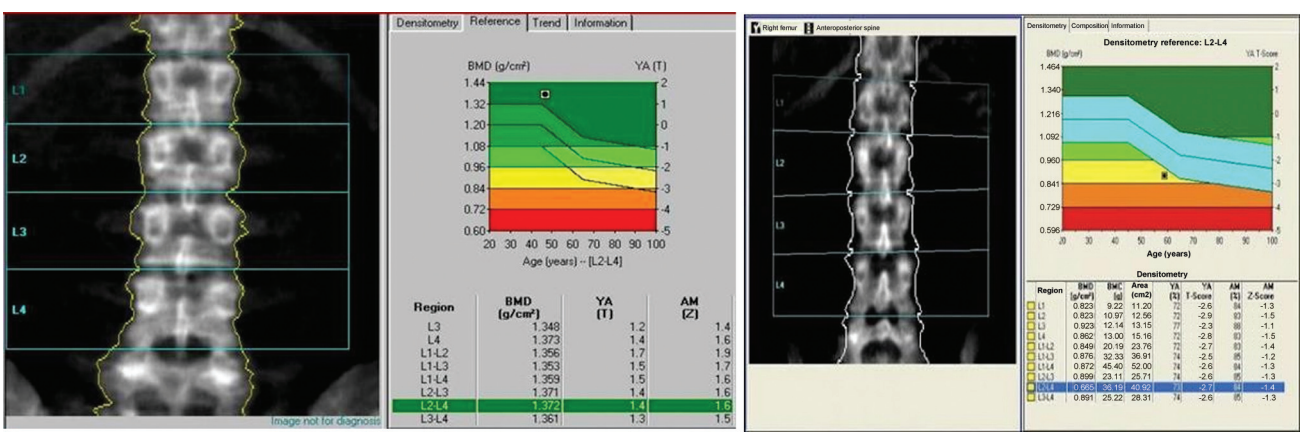
Bone and blood calcium levels are essential for physiological balance. They are dynamic and regulated by hormones, including vitamin D, calcitonin, and the parathyroid hormone (PTH). Vitamin D facilitates intestinal calcium absorption, maintaining adequate levels for bone mineralization and hypocalcemic tetany prevention. Vitamin D deficiency can lead to brittle and deformed bones, while proper vitamin D levels prevent rickets in children, osteomalacia in adults, and osteoporosis in the elderly.[28–31]

Osteoporosis deteriorates bone microarchitecture. Its assessment may use bone turnover markers (BTMs) to complement BMD determination and evaluate the risk of fracture. Sex hormones, especially estrogen, play a crucial role in primary osteoporosis, and estrogen deficiency in menopause is a significant cause of osteoporosis. A lack of estrogen directly affects osteoclasts, leading to bone disorders, including osteoporosis.[32,33]

Assessment of Bone Mineral Density

The Z-score on bone densitometry indicates the number of standard deviations above or below the expected value from a subject with the same age, gender, weight, and ethnic or racial origin as those of the patient under evaluation. A low Z-score suggests abnormal bone loss, and a high score is normal. This score is not age-related and may indicate an underlying, treatable condition to slow or stop bone loss[34–37] (►**Figs. 1,2**).

Radiography is a non-invasive medical test widely used to diagnose and treat medical conditions. It is the oldest imaging method and can examine the entire body or specific body parts using low doses of ionizing radiation. In some cases,



Figs. 1 and 2 Bone mineral density (BMD) values of a healthy elderly woman (►**Fig. 1**) and an elderly woman with osteoporosis (►**Fig. 2**). ►**Fig. 1** shows a BMD test of a healthy elderly woman. Radiography reveals normal hip bones. The graph shows the BMD value within the green (normal) zone. ►**Fig. 2** shows a BMD test from an elderly woman with osteoporosis. Radiography shows weaker hip bones. The graph shows the BMD value within the red (osteoporotic) zone, significantly increasing the risk of fractures. **Abbreviation:** BMC, bone mineral content.

peripheral radiography or ultrasound devices may evaluate low bone mass. Computed tomography (CT) with special software can also diagnose or monitor low bone mass; however, it is used less frequently than LRP screening through dual-energy X-ray absorptiometry (DXA).[36,37]

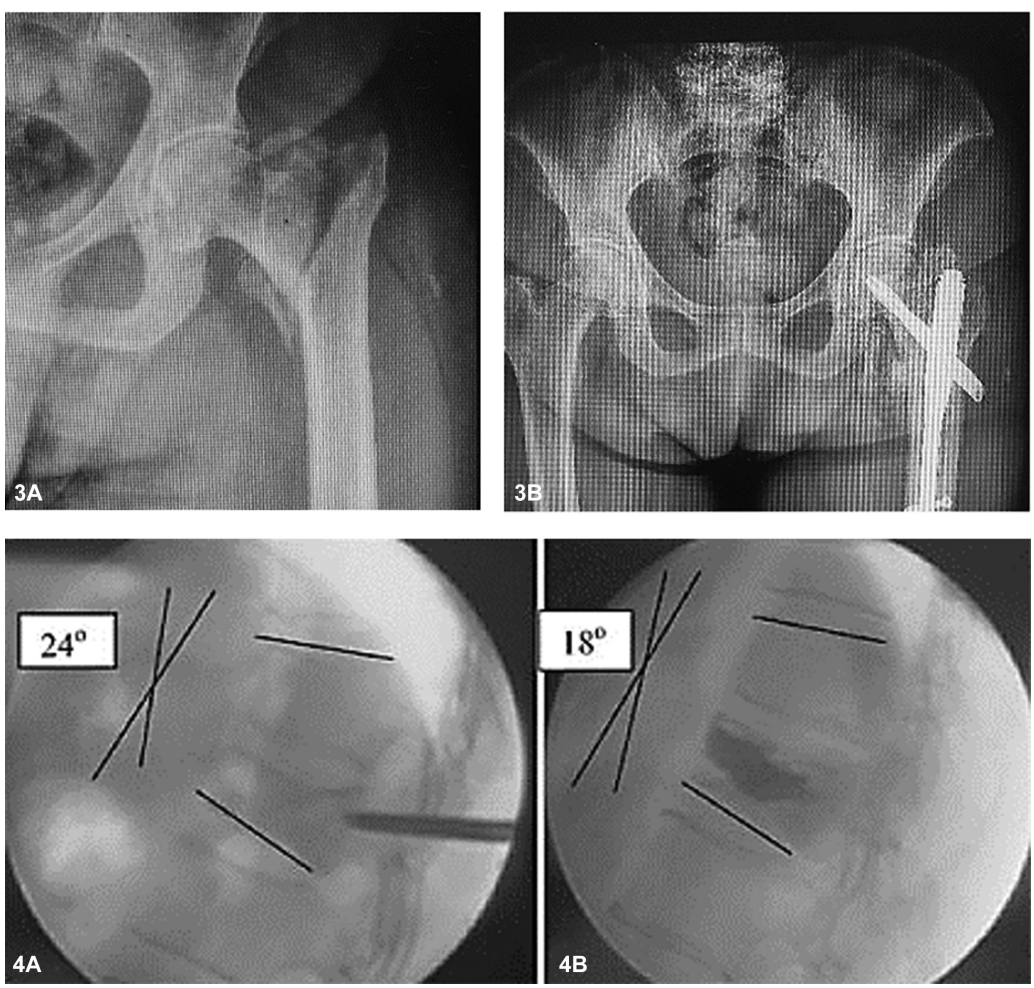
Fracture Types

Osteoporosis is an asymptomatic condition frequently diagnosed after fractures, which are the main manifestation of the disease and evidence bone atrophy. Age-related osteoporosis is underdiagnosed because it remains silent for several years until fractures occur, especially in the elderly, resulting in daily activity limitation. Osteoporotic fractures can result in severe complications, increasing morbidity and mortality rates.[9,10] Adult patients with fractures must undergo osteoporosis screening, since approximately 30% of the cases have secondary causes, notably in premenopausal women, men with osteoporosis, and patients with hip fractures. Appropriate laboratory tests are useful to investigate secondary causes.[3,9–11]

The increasing incidence of fractures in the elderly has become a significant health problem in several countries. Moreover, these issues will probably increase due to populational aging. More than 90% of fractures result from low-energy falls and cause high mortality rates. For instance, the incidence of hip fractures in Australia is expected to increase from 20 thousand to 50 thousand cases in 2050 due to the aging of the population.[8,9,11,12]

Osteoporotic fractures, often resulting from falls, mainly affect the vertebrae, hips, wrists, and shoulders (►**Figs. 3,4**). Osteoporosis affects approximately 80% of postmenopausal Caucasian women and will have an increasing impact as the population ages.[11–13] These fractures, especially of the hip and vertebra, have a 12-month mortality rate of up to 20% due to hospitalization and increased risk of complications. Diagnosis often occurs after the first fracture, usually requiring orthopedic surgical treatment.[4,5,11]

The validated Fracture Risk Assessment Tool (FRAX) calculates the 10-year fracture risk based on individual factors, including BMD. The FRAX is widely integrated into national guidelines, affordable, easy to apply by healthcare professionals, and useful, considering the exponential increase in hip fracture rates with age.[4,11,12,38]



Figs. 3 A,B and 4 A,B Examples of the two most common sites affected by osteoporotic fractures and their orthopedic treatments. (**3A**) Preoperative transtrochanteric fracture. (**3B**) Surgical treatment. (**4A**) Preoperative assessment of vertebral fracture. (**4B**) Surgical treatment after kyphoplasty (intraosseous injection of orthopedic cement). Angular kyphosis was reduced from 24 to 18 degrees.

Identification and Determination of the Risk of Fracture

Osteoporosis increases the risk of fractures due to low BMD, impaired bone microarchitecture/mineralization, reduced bone strength, or any combination of these factors. Often asymptomatic, it is frequently diagnosed following low-trauma fractures of the hip, spine, proximal humerus, pelvis, or wrist, which may require hospitalization, representing a significant economic burden for healthcare systems. The risk factors include permanent features, such as age and gender, and modifiable ones, related to personal lifestyle.[4–9]

Permanent Risks

Permanent risk factors such as age, female gender, family history of osteoporosis, previous fracture, ethnicity, menopause/hysterectomy, long-term glucocorticoid therapy, rheumatoid arthritis, and primary/secondary hypogonadism in men cannot undergo any change. However, subjects need to be aware of these factors to take steps to help reduce bone mineral loss. Additionally, secondary risk factors from disorders and medications weaken bones, increasing the risk of fall-related fractures.[2,5,6]

Modifiable Risks

Modifiable risk factors such as alcohol consumption, smoking, low body mass index, poor nutrition, vitamin D deficiency, eating disorders, lack of exercise, low dietary calcium intake, and frequent falls directly affect BMD and increase the risk of fractures.[7,8] The diagnosis of osteoporosis often relies on BMD measurements, especially in the hip and lumbar spine, using the DXA device. The FRAX, which considers factors such as age, race, alcohol consumption, gender, body mass index, smoking history, fracture history, and BMD, is an effective tool to predict the 10-year risk of osteoporotic fractures.

Treatment

a) Medical drug therapy evidence.
b) Non-pharmacological management and physical activity medical drug therapy evidence.

Osteoporosis treatment depends on its cause. Treatment of secondary osteoporosis is more complex, as it directly relates to the underlying disease. Pharmacological therapy aims to reduce the risk of fractures, and many therapeutic methods also prevent osteoporosis.[1,2]

Primary osteoporosis, often linked to age and sex hormone deficiency, results in continued deterioration of bone trabeculae. In age-related osteoporosis, reduced estrogen production in postmenopausal women leads to significant bone loss. Sex hormone-binding globulin, which inactivates testosterone and estrogen in men during aging, may contribute to the decreased BMD over time.[37–39]

Secondary osteoporosis results from several comorbidities, medications, or both. These comorbidities affect mechanisms leading to calcium, vitamin D, and sexual hormone imbalances. For example, in Cushing syndrome, the excess production of glucocorticoids can accelerate bone loss. Glucocorticoids are the medications most commonly involved in drug-induced osteoporosis, with a rapid bone level reduction within 3 to 6 months of starting the therapy.[39,40]

Secondary osteoporosis has different causes depending on the gender of the subject. In male patients, excessive alcohol intake, the use of glucocorticoids, and hypogonadism are more common. Among female subjects, 32.4% of the cases have secondary causes, especially hypercalciuria, calcium malabsorption, hyperparathyroidism, vitamin D deficiency, hyperthyroidism, Cushing disease, and hypercalcemia, according to Tannenbaum et al.[41] Doctors and patients should talk about the best treatment based on the patient's needs and preferences and address the advantages and disadvantages of treatment alternatives. If patients are unable to understand the information, their caregivers should participate in the discussion, according to the guidelines of the United Kingdom's National Institute for Health and Care Excellence (NICE).[42]

Osteoporosis medications have different mechanisms of action to strengthen bones and reduce the risk of fractures. Bisphosphonates inhibit osteoclasts for BMD preservation. Selective estrogen receptor modulators (SERMs) such as raloxifene act as agonists in some bone tissues. Hormone-replacement therapy (HRT) uses estrogen and progesterone in postmenopausal women. Receptor activator of nuclear factor Kappa-B ligand (RANKL) inhibitors, such as denosumab, reduce bone resorption. Teriparatide is a PTH analog that stimulates bone formation. Medications such as romosozumab stimulate bone formation by inhibiting sclerostin, an osteocyte-produced protein. Additionally, calcium and vitamin D are often recommended to maintain bone health. Treatment selection relies on individual factors under the guidance of a specialized physician.

The first-line treatment for postmenopausal women is bisphosphonates, whether alendronate or risedronate. Intravenous bisphosphonates or denosumab are recommended for patients who cannot tolerate oral bisphosphonates, and HRT with raloxifene or teriparatide may also be considered.[42]

An atypical femoral fracture can occur after minimal trauma, especially in subjects under chronic bisphosphonate therapy (►**Fig. 5**). The recommendation is to stop these medications, consider treatment with teriparatide, and evaluate vitamin D and calcium supplementation. Prolonged bisphosphonate use impairs bone quality by inhibiting cellular bone remodeling. The contralateral side requires examination to determine if the condition is bilateral.[43] Despite the care currently provided, the prognosis for these fractures remains unfavorable, with a consolidation time ranging from 12 to 60 months.[43] Alendronate and risedronate are first-line treatments for men, with zoledronic acid, denosumab, or teriparatide as alternatives. Femoral neck BMD T-scores in men should be based on the United States' National Health and Nutrition Examination Survey (NHANES) female reference database.[44]

Bone protection therapy is recommended for subjects older than 70 years of age under high doses of glucocorticoids, especially prednisolone at does higher than 7.5 mg/day.



Fig. 5 Radiograph showing an atypical right subtrochanteric femoral fracture in an elderly person after minimal trauma.

Postmenopausal women and younger men under high doses of glucocorticoid should also consider this therapy. For those at high risk of fractures, bone protection therapy should start at the beginning of the glucocorticoid regimen, with alendronate and risedronate as first-line treatments.[44]

Selecting Guidelines and Recommendations

The systematic review by Solomon et al.[45] highlights the consistency in osteoporosis guidelines, specifically those from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE).[24] To manage postmenopausal osteoporosis, the first-line treatment options include alendronate, risedronate, zoledronic acid, or denosumab for patients with no previous fragility fractures or at moderate fracture risk. Denosumab, teriparatide, or zoledronic acid are first-line treatments for patients with previous fragility fractures or high fracture risk. Alendronate and risedronate are treatment options. The American College of Physicians (ACP)[37] suggests using alendronate, risedronate, zoledronic acid, or denosumab for 5 years for women with low BMD and osteoporosis.[37] Treatment requires individualization in women aged 65 or older, considering the risks versus the benefits, patient preferences, fracture risk profile, and costs. Menopausal estrogen therapy, combined estrogen and progestin therapy, and raloxifene are not widely recommended, and monitoring BMD for 5 years is controversial.[41,44,45]

The selection of osteoporosis medications is often based on personal preference, convenience, and adherence to the dosing schedule. The ideal duration of the bisphosphonate treatment is controversial due to the uncertainty of atypical femoral fracture. However, most experts suggest a break after 5 years, especially for patients with no fragility fractures and bone density maintenance.[46] Although medications reduce the likelihood of fractures, they do not eliminate all risks, and complementary treatments such as physical exercise and physical therapy are equally important in osteoporosis management.[46]

Non-pharmacological Management and Exercise

The management of non-pharmacological osteoporosis encompasses adequate calcium and vitamin D intake, weight-bearing exercises, smoking cessation, limitation of alcohol/caffeine consumption, and fall prevention techniques. Vitamin D plays a crucial role in calcium absorption and bone health, and lower daily doses are recommended to reduce the risk of falls.[46] Physical therapy is essential to strengthen muscles, improve joint movements, and reduce sarcopenia, promoting a more stable gait. Implementing balanced exercise routines can significantly contribute to fall prevention, a common factor in fractures in osteoporotic patients.

Fall Prevention

Falls in the elderly population result from a complex interaction between intrinsic and extrinsic factors, with environmental risks contributing to around 40% of falls. Factors such as socioeconomic deprivation increase fracture incidence; more than 90% of fractures result from low-energy falls, with significant mortality rates.[47–50] Aging, comorbidities, and premature hospital discharge increase mortality rates. Studies[2–4,17,48] indicate that half of falls occur while walking, often due to trips or slips, while environmental factors, such as uneven surfaces, wet floors, and loose objects, are frequent triggers. The increasing tendency for outdoor falls also relates to extrinsic factors.

Women who walk quickly and trip are more likely to fall forward, which may result in wrist, arm, and elbow fractures. In contrast, falls to the side can cause hip and spinal fractures.[16–19] Preventing fractures involves preserving well-paved streets, placing warning signs in areas with an elderly population, and investing in public health policies. Shoes with high and wide heels play a significant role in such falls, and the recommendation is to limit their use.[37,49–53] Since medications, in addition to vision and hearing issues, can affect balance, balance programs are beneficial to improve stability. Tai Chi Chuan is an excellent exercise to increase stability and prevent falls in the elderly.[5,37,42,43]

Table 2 T-scores and diagnostic criteria of the World Health Organization for osteoporosis[2]

T-score*	
> -1	Normal bone density
From -1 to -2.5	This score is a sign of osteopenia; bone density is lower than normal and can lead to osteoporosis.
< -2.5	This bone density indicates that the person is likely to have osteoporosis.

Note: *Reference values range depending on geographical location.

In the Timed Up and Go test,[54] the patient gets up from a chair, walks 5 meters, returns, and sit downs without using their arms for support. As a prophylactic measure, crutches or walkers are recommended for patients unable to perform the test without support or at risk of falling. Furthermore, domestic violence can cause falls in the elderly, requiring compulsory notification when confirmed.

Final Considerations

Osteoporosis increases the susceptibility to fractures and leads to substantial rates of morbidity and mortality in the elderly. Its diagnosis includes bone densitometry testing to assess BMD in the bones most likely to fracture, such as the lower spine (lumbar vertebrae), femoral neck, and forearm bones. Osteoporosis may be primary or secondary (resulting from several comorbidities, medications, or both).

Osteoporosis is often diagnosed after the patient's first clinical fracture. Most subjects with osteoporotic fractures require orthopedic surgical treatment. Osteoporosis is usually age-related and underdiagnosed because it remains asymptomatic (silent disease) for several years until the occurrence of a fracture. The FRAX calculates the 10-year probability of a severe osteoporotic fracture. It is necessary to develop public health policies focused on preventing secondary frailty and constantly invest in public health policies focused on providing social and economic benefits to the elderly.

Osteoporosis treatment is multidisciplinary and must include periodic assessment of the patient, prescription of new bone medications, and guidance on fall prevention. Bisphosphonates are the most common medications prescribed, but their prolonged use can cause atypical femoral fractures and patients should be informed about this potential risk.

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

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Lowback Pain Management with a Combination of Uridine Triphosphate, Cytidine Monophosphate, and Hydroxocobalamin: A Systematic Review and Meta-Analysis

Tratamento da dor lombar com uma combinação de trifosfato de uridina, monofosfato de citidina e hidroxicobalamina: Uma revisão sistemática e metanálise

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Abstract

Low back pain is a common complaint. This syndrome comprehends different underlying mechanisms, which are difficult to differentiate in a timely manner only through semiotic, laboratory, and imaging resources available in an emergency setting. Such circumstances make practitioners prone to an initial symptomatic approach in the form of medications (non-steroid anti-inflammatory drugs, analgesics, muscle relaxants) or local procedures (local heat, massage). Peripheral neurotrophic substances, such as pyrimidine nucleotides (uridine triphosphate and cytidine monophosphate) combined with vitamin B12 (hydroxocobalamin), have been used as anabolic precursors able to provide spinal nerve roots with triggering elements useful for nerve and glial cells regeneration, once a likely spinal compression mechanism is contained. The authors performed a systematic review and meta-analysis with the above combination with the aim of better determining its role in low back pain management.

Keywords
- cytidine monophosphate
- hydroxocobalamin
- low back pain
- spinal nerve roots
- uridine triphosphate

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Resumo

A dor lombar é uma queixa comum. Essa síndrome tem diferentes mecanismos subjacentes, difíceis de diferenciar em tempo hábil apenas por meio dos recursos semióticos, laboratoriais e de imagem disponíveis no atendimento de emergência. Isso faz com que os profissionais tendam a uma abordagem sintomática inicial composta por medicamentos (anti-inflamatórios não esteroidais, analgésicos, relaxantes musculares) ou procedimentos locais (calor local, massagem). Substâncias neurotróficas periféricas, como nucleotídeos de pirimidina (trifosfato de uridina e monofosfato de citidina) combinados com vitamina B12 (hidroxicobalamina), têm sido usadas como precursores anabólicos capazes de fornecer às raízes nervosas espinhais elementos desencadeadores úteis para a regeneração de neurônios e células da glia, uma vez que um provável mecanismo de compressão espinhal seja contido. Os autores realizaram uma revisão sistemática e meta-análise com a combinação acima com o objetivo de determinar melhor seu papel no tratamento da dor lombar.

Palavras-chave

- dor lombar
- hidroxocobalamina
- monofosfato de citidina
- raízes nervosas espinhais
- uridina trifosfato

Introduction

Low back pain (lumbosacral pain) associated with compression neuropathy syndromes represents one of the most frequent pathological manifestations of the spine. Low back pain is a rather unspecific term that may comprehend distinct entities clinically expressed in an isolated, combined, or overlapping fashion.[1] Its prevalence ranges from 30 to 70% among the 18-to-74 year old population.[2] Sciatica, on its turn, is a general term used to refer to lumbar radicular pain, often radiating unilaterally to the leg according to the corresponding dermatome. It can be accompanied by motor, sensitive, and/or reflex deficits. Pain is worse than "classic" low back pain, and the chronicity risk is higher.[3] Several therapeutic modalities—conservative, pharmacological, and invasive—have been developed and applied over the last 100 years. The uridine triphosphate (UTP), cytidine monophosphate (CMP), and hydroxocobalamin combination has been prescribed in some countries for the symptomatic control of this syndrome in the last 50 years. The objective of the present systematic review and meta-analysis is to measure the effects of the combination in this setting.

Materials and Methods

Primary Studies Search and Selection

The study was performed by two independent researchers who worked in parallel and blindly, both according to the following parameters: (1) epidemiological studies, observational studies, randomized clinical trials (RCTs), non-RCTs, systematic reviews, and meta-analyses as study types; (2) no language or year of publication restrictions; and (3) the names of the authors of the primary studies were not regarded (even though personal consulting was permissible). Supporting literature, such as textbooks, basic scientific papers, and pharmacological compendiums, was consulted when deemed necessary (not accounted for systematic review purposes). The studies search was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[4] Flowchart is depicted in ►**Fig. 1** (details on the scrutinized sources are listed in the ►**Appendix**).

Endpoints and Outcomes Collection

The researchers' results were crossed by a reviewer for validation, who reported no conflicts between the body of findings of the former two. The studies were selected according to their respective titles and abstracts, as per the following parameters of interest: (1) low back pain, (2) UTP, CMP, and hydroxocobalamin combination in its symptomatic control, (3) efficacy and safety comparison with vitamin B12 (hydroxocobalamin and cyanocobalamin), and (4) additive and/or synergistic pharmacological properties of UTP, CMP, and hydroxocobalamin combination. Text search was extended from the title/abstract to the body of the text when searchers felt necessary. No personal contact with the studies' authors was necessary. A comprehensive literature on the general pharmacology of UTP, CMP, and hydroxocobalamin was also retrieved.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform the present study.[4] The Visual Analog Scale (VAS) measurements were chosen as study endpoint. The mean difference between the baseline and final VAS, along with standard deviation were used for the UTP, CMP, and vitamin B12 group, as well as the vitamin B12 monotherapy group, with 95% confidence intervals (CIs). The Cochran Q test and I2 statistics were used to assess heterogeneity. *P*-values < 0.10 and I2 statistics $\geq 50\%$ were considered to determine the significance of heterogeneity, and the use of a random-effect model. One author conducted the statistical analyses using R software (R Foundation for Statistical Computing, Vienna, Austria).[5]

Spinal Nerve Root Injuries and Chronic Low back Pain

Definition

Low back pain can be defined as a midline pain spanning from the lowest rib down to the gluteal fold. This syndrome can be classified as acute ($<$ 6 weeks), subacute (6–12 weeks), or chronic ($>$ 12 weeks duration). It can be

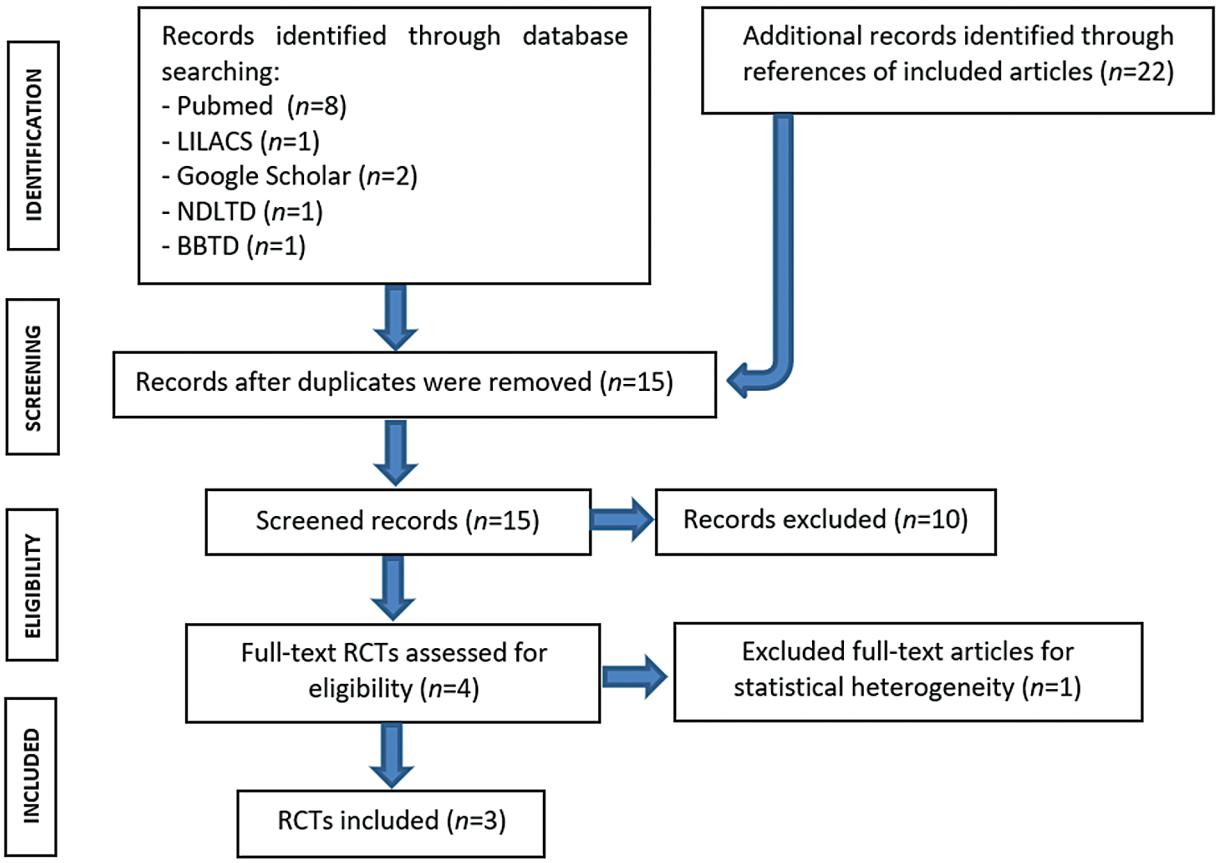


Fig. 1 Diagram for study selection as applied in the current systematic review and meta-analysis.

accompanied by mobility loss, radiation to the legs, groin, and posterior pelvis, mood change, and disturbances in social interactions.[1,2]

Low back Pain Pathophysiology

Low back pain is the outcome of a pathophysiologic complex process involving neural (spinal nerve roots and dorsal root ganglia) as well as somatic (intervertebral facet joints, periosteum, ligaments, tendons, fasciae, paravertebral muscles, and intervertebral discs) structures[6]. In most cases, both mechanisms overlap. Even though a culprit structure cannot be pointed out in 80 to 90% of cases, in 10 to 15% of patients, neural tissue involvement can be demonstrated.[1,2] Herniated discs, chronic spinal degenerative conditions, and spinal stenosis are the most common etiological mechanisms found in clinical practice.[1,6] Acute mechanical compression exerted by a vertebral pedicle on a lumbosacral spinal nerve root and/or dorsal root ganglion can lead to local vascular compromise, microstructural changes, and inflammation, all linked to sensory deficits, pain threshold decrease, as well as loss of somatic strength and autonomic (bladder and bowel) control in the corresponding dermatome.[7] Pain onset is proportional to the degree of extrinsic compression and spinal nerve root irritation, both difficult to determine in the clinical setting.[6,8] During convalescence, local inflammatory cytokines and neurotrophic factors released for neural tissue healing can decrease pain threshold by promoting neuroplasticity and stimulating uninjured neighboring neurons, with paradoxical algic worsening.[8]

Clinical Picture, Diagnosis and Prognosis

If present, neuropathic pain manifests itself as paresthesia, hyperesthesia, allodynia, and hyperalgesia. Pinpointing the pain structural origin can be challenging since pathophysiological mechanisms overlap and evolve dynamically. Similarly, maneuvers such as digital compression and mobility tests are limited due to semiotic inaccessibility of the structures potentially involved as well as poor discriminatory power.[1,2] Differential diagnoses with low back pain are local fracture (trauma, fall from height, preexisting osteoporosis), infections (B symptoms, immune suppression, IV drug abuse), or tumoral disease (B symptoms, pain that increases in supine position, paraproteinemia).[2] Imaging is generally unnecessary in the early stages of low back pain presentation. Nevertheless, if indicated, the assisting physician should take into consideration that segmental and muscle dysfunction, as well as sacroiliac joint syndrome, are not amenable to morphologic demonstration.[2,6] Low back pain resolves within 4 to 6 weeks in 50% of cases and in 12 weeks in 80% of cases. On the other hand, recurrence and inability to work are common features if the etiology is not approached.[2]

Neuroregeneration and Lumbosacral Pain

Dorsal root ganglia have axons that reach laterally and medially towards the spinal nerve roots and spinal cord,

Table 1 Combined Seddon and Sunderland classifications of peripheral nerve injuries[9]

Sunderland	Seddon	Pathophysiology	Recovery
First degree	Neuropraxia	Segmental demyelination	Full
Second degree	Axonotmesis	Axon severed, intact endoneurium	Full
Third degree	–	Axon severed, compromised endoneurium, intact perineurium	Variable
Fourth degree	–	Axon, endoneurium, perineurium discontinuity, intact epineurium	Null
Fifth degree	Neurotmesis	Discontinuity of entire nerve	Null
Sixth degree	–	Mixed	Unpredictable

respectively. Injuries to the former induce a regenerative process, similar to compressive neuropathic lesions while injuries to the latter do not result in regeneration due to the inhibiting environment of the central nervous system (CNS).[6] Presuming that spinal nerve roots' axons present a biology similar to that of peripheral nerves, one can assume that both might share similar regenerative patterns. Therefore, a combined Seddon and Sunderland classification of peripheral nerve injuries could be proposed for classifying spinal nerve root injuries in the context of low back pain (►**Table 1**).

Therapy and Prognosis

Conservative measures include physical therapy (spinal traction, stretching, massage), relaxation techniques, cognitive behavioral therapy, transcutaneous electrical nerve stimulation (TENS), exercising, bedrest, or simply resuming normal daily activities. Preventing muscular contractures is paramount as these can delay function recovery. Medical treatment for the neuralgic component of the syndrome includes antidepressants (gabapentin, oxcarbazepine, and lamotrigine), and pregabalin. Somatic pain component can be treated with paracetamol or non-steroid anti-inflammatory drugs (ibuprofen, diclofenac, naproxen).[1,2,6] Healing from mechanical injury against a spinal nerve root depends on the specific structure involved, the degree of the insult, its mechanism and duration. Even with optimal management, recovery is typically incomplete and dysfunctional, and neuropathic pain can persist. Currently, there are no recognizable prognostic factors for motor recovery or pain resolution associated to these types of lesion.[8–10]

Pyrimidine Nucleotides – UTP and CMP

A nucleotide structural model has been used in the development of several pharmacologically active substances, such as antitumoral metabolites (e.g., mercaptopurine), nucleoside analogs (e.g., lamivudine), and nucleoside antiarrhythmics (e.g., adenosine). In the context of compression neuropathies, pyrimidine nucleotides UTP and CMP are used as metabolic neurotrophic substances involved in the synthesis stimulation of nerve cell membrane, myelin sheath, and axonal proteins (tubulines and enzymes), as demonstrated in ►**Fig. 2**.

Pyrimidine Nucleotides Pharmacodynamics

Increase in nerve cells protein synthesis. Wallerian degeneration is expected to follow the disintegration of axons and Schwann cells after a mechanical trauma on a peripheral nerve or nerve root cell. The velocity of soma and myelinic anabolic pathways is correspondingly accelerated during this phenomenon. Therefore, the quantity of nucleotides consumption is expected to be greater in comparison to nerve cells and glial cells in their steady state, along with other vital metabolites.[11–14]

Increase in myelin sheath synthesis. In the later stages of Wallerian degeneration, the passage of axonal regeneration cones through the Bungner band at the distal neural stump will trigger the wrapping of Schwann cells membrane around the advancing axons, then forming a new myelin sheath. The demand for myelin lipids precursors in Schwann cells, among them nucleotide intermediary metabolites, is expected to be increased under the above-described conditions.[13,15,16]

Increase of nerve cell membrane synthesis. Similarly to the mechanism of myelin sheath increase synthesis, an increase in axolemmal structural elements is supposed to take place, in parallel to regenerative cones' progression. Integration of *de novo* nucleotide metabolic intermediaries in this scenario will be necessary as well.[14,16–23]

Pyrimidine Nucleotides Safety

Uridine triphosphate and CMP are contraindicated in the acute phase of ischemic stroke due to the possibility of nerve-cell membrane phosphatidylcholine degradation into diacylglycerol and free fatty acids, under brain anoxia conditions.[24,25] Individuals with dihydropyrimidine dehydrogenase or ornithine carbamoyl transferase deficiencies may present excessive pyrimidine nucleotides in the CNS. Therefore, UTP and CMP are contraindicated in patients who present the above-described conditions.[16]

Hydroxocobalamin

Hydroxocobalamin is a manufactured injectable form of vitamin B12. It is involved in the so-called one-carbon metabolism reactions (cystein, methionine, and pyrimidine nucleotides synthesis, as well as methylation reactions), mitochondrial metabolism, and myelin basic protein synthesis (myelin sheath structural stabilization). Vitamin B12

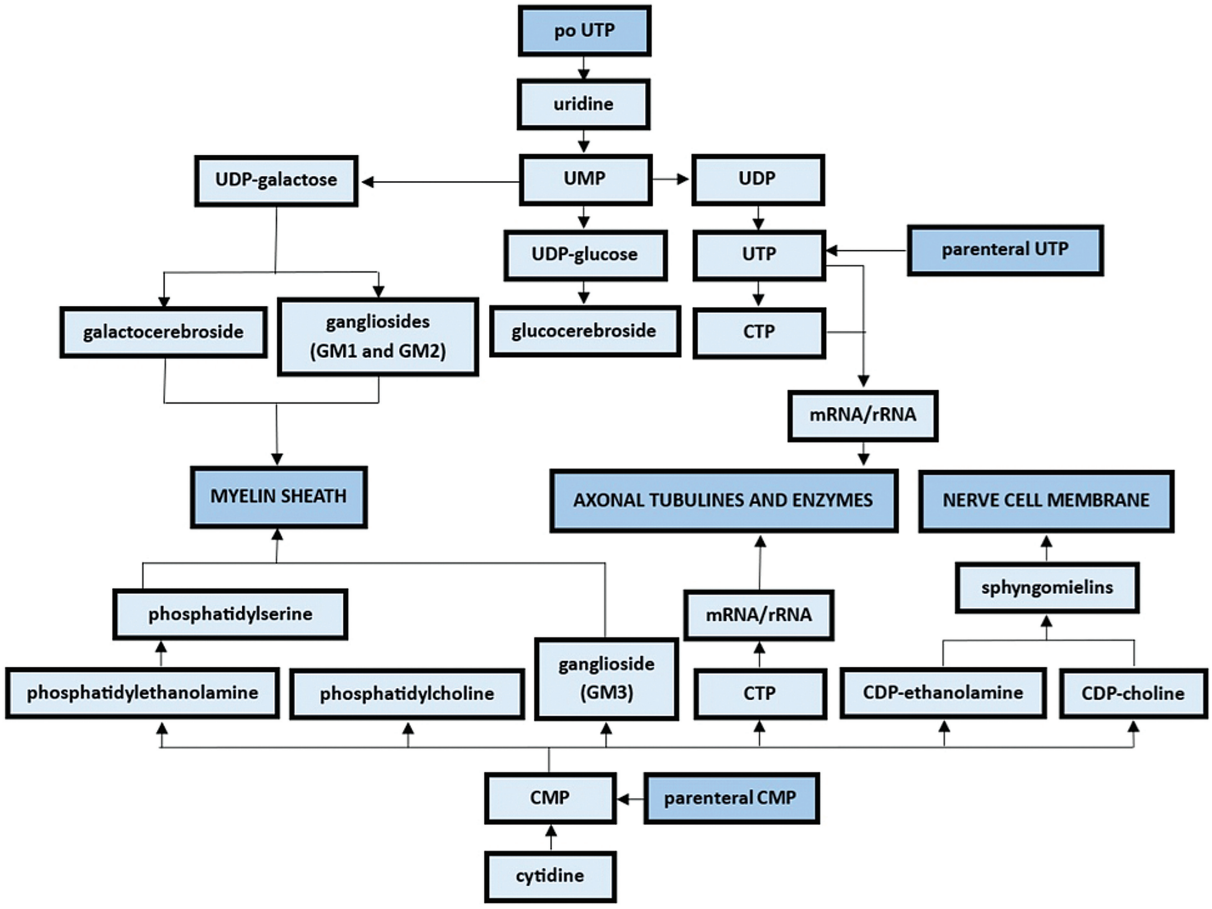


Fig. 2 Nerve cells and Schwann cells biochemical pathways amenable to pharmacological influence from pyrimidine nucleotides.

analgesic properties are still a matter of debate, but, seemingly, it does speed up low back pain improvement due to its participation in myelin sheath recovery.[26] Hydroxocobalamin's adverse reactions are acneiform erythema, fever, exanthematous hot flashes, blood hypertension (intravenous injections), peripheral edema, photosensitivity, pruritus, and hives (case reports).[27–29]

Spinal nerve root compression syndromes present a complex pathophysiology, hinting potential targets for different therapeutic modalities. As shown in ►**Fig. 2**, UTP and CMP share synergistic effects over regenerating peripheral nerve metabolic pathways, whose myelin sheath synthesis arm can be additively influenced by hydroxocobalamin as it promotes MPB synthesis. Assuming that neuropathic low back pain can also be triggered by the disintegration of the microstructures of nerve and Schwann cells of the spinal nerve root, one can presume that their anticipated resynthesis could provide a sooner pain improvement.

Results

We retrieved a total of 30 general studies and 5 clinical trials on UTP, CMP, and hydroxocobalamin (4 RCT and 1 non-RCT) in low back pain management, the latter ones comprehending a total of 1,236 patients (no epidemiological studies, observational studies, systematic reviews, or meta-analyses were found). Reported research endpoints were: (1) Visual Analog Scale (VAS) (selected endpoint for meta-analysis as a 0–100 mm visual scale), (2) Patient Functionality Questionnaire (PFQ), (3) percentage of patients presenting improvement on PFQ, (4) percentage of patients presenting improvement on VAS, (5) patient global evaluation, (6) physician global evaluation, (7) Roland-Morris Questionnaire, and (8) finger-to-floor distance. In 3 RCTs, the combination was found effective in reducing VAS versus a comparative;[30–32] in 1 RCT, it was found to be less effective versus the same combination comprising diclofenac-cholestyramine,[26] and in 1 trial, it was found to be effective in a self-paired design.[32] In all 5 trials, the combination was declared as safe. The findings related to the above-mentioned studies are summarized in ►**Table 2**.

Of the 5 trials on the UTP, CMP, and hydroxocobalamin combination detailed in ►**Table 2**, 3 presented comparable outcomes for meta-analysis (mean differences of VAS scale for the combination versus hydroxocobalamin) (median = 8.77; 95%CI: -3.22–20.76). Pooled analysis of the primary studies and corresponding forest plot representation are presented in ►**Fig. 3**.

Discussion

Low back pain syndromes are frequently presented as chronic conditions that compromise patients' wellbeing, personal productivity, and quality of life. Their complex

Table 2 Selected RCTs, non-RCTs, and self-paired study on the combination of UTP, CMP and hydroxocobalamin* for the management of spinal nerve compression syndromes

Authors	Study objectives	Regimens	Study type	*n*	Results	Safety	Conclusion
Goldberg et al.[29] (2009)	To assess a combination of UTP, CMP, and hydroxocobalamin in the treatment of neuralgia due to degenerative orthopedic spine alterations with neural compression	Group A: 2 capsules of UTP, CMP, and hydroxocobalam. Group B: 2 capsules of hydroxocobalamin 1,000 mcg. Both regimens tid for 30 days	Double-blind and randomized	$n_A = 40$ $n_B = 40$	There was VAS reduction in both groups, though significantly greater in group A ($p < 0.0001$)	Adverse events were considered mild to moderate, with a statistically better overall performance with group B	Group A combination presented a positive effect in the parameter of pain on degenerative orthopedic spine alterations with neural compression
Mibielli et al.[26] (2010)	To evaluate the efficacy and safety of UTP, CMP, and hydroxocobalamin in the treatment of acute, non-traumatic low back, hips, and neck pain	Group A: (1) box A containing 6 capsules of UTP, CMP, and hydroxocobalamin, and (2) box B containing 2 capsules of diclofenac-cholestyramine. Group B: (1) box A containing 6 capsules of UTP, CMP, and hydroxocobalamin, and (2) box B containing 2 capsules of placebo. Box A taken as 2 capsules tid, and box B as one capsule bid, for both groups, for 10 days	Double-blind and randomized	$n_A = 40$ $n_B = 41$	Group A combination resulted in a higher number of subjects with VAS score reduction > 30 mm in comparison with group B ($p < 0.0006$)	The number of subjects presenting adverse events did not vary significantly between groups	Group A combination reduced pain among subjects with non-traumatic low back, hips, and neck pain
Mibielli et al.[32] (2014)	To corroborate analgesic effects of UTP, CMP, and hydroxocobalamin observed in group B of Mibielli et al.[26] (2010) trial	Box A containing 6 capsules of UTP, CMP, and hydroxocobalamin taken as 2 capsules tid. Box B containing 2 capsules of placebo taken as one capsule bid for 10 days	Self-paired	$N = 41$	The difference between V3 (10^{th} therapy day) and pretreatment VAS score was statistically significant ($p < 0.0001$)	The same as for Mibielli et al. (2010)	Group B combination seems to have analgesic properties in medium-term use in acute, non-traumatic low back, hips, and neck pain
Goldberg et al.[30] (2017)	To assess the safety and efficacy of the combination UTP, CMP, and hydroxocobalamin in patients with neuralgia due to degenerative orthopedic alterations and trauma (low back, hip, and carpal tunnel syndrome) associated to neural compression	Group A: 2 capsules of UTP, CMP, and hydroxocobalam. Group B: 2 capsules of hydroxocobalamin 1,000 mcg. Both regimens tid for 30 days	Double-blind and randomized	$n_A = 200$ $n_B = 200$	There was a statistically significant superiority of group A regimen in VAS reduction ($p = 0.0003$)	There were transitory adverse events and no severe adverse event in both Groups	Group A combination was safe and effective in the treatment of neuralgias due to degenerative orthopedic alterations associated with neural compression
Mibielli et al.[31] (2020)	To compare the efficacy and tolerability of the combination of UTP, CMP, and hydroxocobalamin compared to the combination of thiamine, pyridoxine and cyanocobalamin in patients with low back pain	Group A: 2 capsules of UTP, CMP, and hydroxocobalam. Group B: 2 capsules of thiamine, pyridoxine and cyanocobalamin. Both regimens tid for 60 days	Double-blind and randomized	$n_A = 317$ $n_B = 317$	VAS score reduction was statistically significant in both Groups at D30 and D60 ($p < 0.0001$), with a comparative better performance of Group A combination at D30 ($p < 0.001$)	75 (24%) and 105 (33%) of subjects presented adverse effects in groups A and B, respectively	VAS score reduction was documented both groups' combinations at D30 and D60, with a comparative better performance for group A combination at D30

Note: *The capsules of the combination contained 1.5 mg, 2.5 mg, and 1,000 mcg of UTP, CMP, and hydroxocobalamin, respectively.

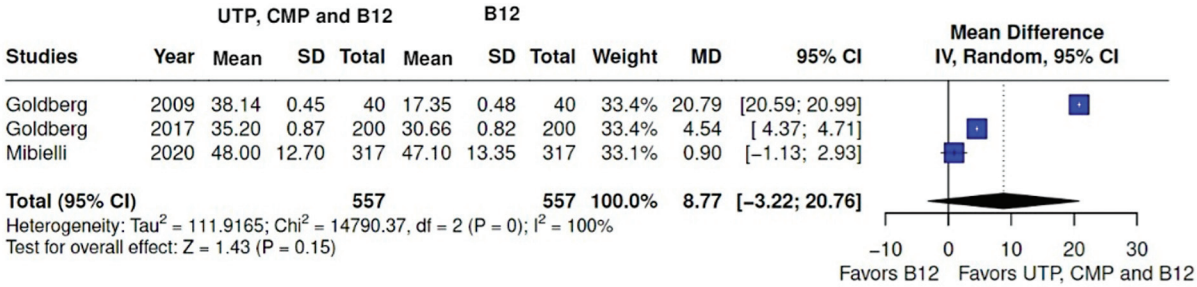


Fig. 3 Meta-analysis on UTP, CMP, and hydroxocobalamin combination on low back pain control. Forest plot graph favors the combination over vitamin B12.

pathophysiology makes a multi-target therapeutic approach feasible, with an association of drug combinations as a plausible modality. The combination of UTP, CMP, and hydroxocobalamin showed evidence of its efficacy and safety on low back pain control, possibly involving spinal nerve root compression, through several RCTs and the current systematic review and meta-analysis. Their combination in this setting is based on a pathophysiological rationale, expressed through additive and synergistic effects. One limitation of our study was the limited number of RCTs amenable to meta-analysis. Notwithstanding, we consider that our findings warrant the UTP, CMP, and hydroxocobalamin combination as a potentially useful resource for the management of low back pain associated with spinal nerve root compression.

Conclusion

Based on the results of the current systematic review and meta-analysis, we consider the combination of UTP, CMP and hydroxocobalamin for the management of low back pain associated with spinal nerve root compression to be safe and effective.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Appendix 1 Sources analyzed and their respective parameters

1. Pubmed: (1) uridine triphosphate, UTP, cytidine monophosphate, CMP, hydroxocobalamin, vitamin B12, spinal nerve root, and pyrimidine nucleotides in the title, and/or (2) low back pain, lumbago, lumbopelvic pain, or sciatica anywhere in the text;
2. LILACS: (1) *uridina trifosfato*, UTP, *citidina monofosfato*, CMP, *hidroxocobalamina*, *vitamina B12*, *raiz dorsal*, *nucleotídeos pirimidínicos* in the title, and (2) *lombalgia*, *dor lombar* or *ciatalgia* anywhere in the text;
3. Google Scholar: (1) uridine triphosphate, UTP, cytidine monophosphate, CMP, hydroxocobalamin, vitamin B12, spinal nerve root, and pyrimidine nucleotides in the title, and or (2) low back pain, lumbago, lumbopelvic pain, or sciatica anywhere in the text, and (3) up to three search pages;
4. NDLTD: uridine triphosphate, UTP, cytidine monophosphate, CMP, hydroxocobalamin, vitamin B12, spinal nerve root, and pyrimidine nucleotides in the title;
5. BBTD: *uridina trifosfato*, UTP, *citidina monofosfato*, CMP, *hidroxocobalamina*, *vitamina B12*, *raiz dorsal*, or *nucleotídeos pirimidínicos* in the title;
6. Bibliographic references from the selected publications.

Analysis of Microbiological Findings on the Surface of External Fixator Pins Comparing Steel Pins with Hydroxyapatite-Coated Pins

Análise dos achados microbiológicos identificados na superfície dos pinos de fixadores externos comparando pinos de aço com pinos revestidos por hidroxiapatita

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Abstract

Objective To compare the microbial retrieval rates and the organism types on the surface of stainless-steel pins (SSPs) and hydroxyapatite-coated pins (HCPs) from external fixators (EFs).

Methods The present prospective, non-randomized, multicenter, comparative interventional cohort study occurred from April 2018 to October 2021. The sample consisted of 44 patients with EFs, including 33 with SSPs and 11 with HCPs. We collected two pins from each patient, the one with the best and the one with the worst clinical appearance according to the Maz-Oxford-Nuffield (MON) classification, in an aseptic manner, and sent them for microbiological analysis.

Results The overall superficial infection (SI) rate was 52.3% (23 of 44 patients), affecting 45.5% (5 of 11) patients with HCPs and 54.5% (18 of 33) patients with SSPs ($p = 0.732$). Of the 88 pins, 43.2% (38 of 88 pins) yielded microbial identification, with 42 pathogens isolated. *Staphylococcus aureus* was the most frequent organism, accounting for 59.5% (25 of 42 pathogens) of the positive samples. In the best-looking pins, the microbial retrieval rate was significantly lower in HCPs than SSPs, with 18.2% (2 pathogens in 11 pins) and 45.5% (15 pathogens in 33 pins), respectively ($p = 0.036$). In the worst-looking pins, the microbial retrieval rate in HCPs and SSPs was 27.3% (3 pathogens in 11 pins) and 54.5% (18 pathogens in 33 pins), respectively ($p = 0.036$).

Keywords
- bone nails
- bone wires
- external fixators
- hydroxyapatite
- infections

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Conclusion Microbial retrieval rates were lower in HCPs than in SSPs. However, these differences did not impact clinical infection rates, which were similar in both groups.

Resumo

Objetivo Comparar as taxas de recuperação microbiana e os tipos de microrganismos identificados na superfície dos pinos de aço inoxidável (PAIs) e nos pinos revestidos com hidroxiapatita (PHAs) de fixadores externos (FEs).

Métodos Este estudo de coorte prospectiva de intervenção, não randomizado, multicêntrico, comparativo foi realizado entre abril de 2018 e outubro de 2021, com 44 pacientes tratados com FE, 33 dos quais receberam PAIs e 11 receberam PHAs. Foram coletados e enviados para análise microbiológica dois pinos de cada paciente, o de melhor e o de pior aspecto clínico conforme a classificação de Maz-Oxford-Nuffield (MON), de forma asséptica.

Resultados A taxa de infecção (TI) superficial global foi de 52,3% (23 de 44 pacientes), sendo 45,5% (5 de 11 pacientes) entre pacientes que receberam PHAs e 54,5% (18 de 33 pacientes) entre pacientes que receberam PAI, respectivamente ($p = 0,732$). Dos 88 pinos, 43,2% (38 de 88 pinos) apresentaram identificação microbiana, sendo isolados 42 patógenos no total. O *Staphylococcus aureus* foi o mais frequente, representando 59,5% (25 dos 42 patógenos). Nas amostras de "melhor aspecto," a taxa de recuperação microbiana foi significativamente menor nos PHAs do que nos PAIs, 18,2% (2 patógenos em 11 pinos) e 45,5% (15 patógenos em 33 pinos), respectivamente ($p = 0,036$). Nas amostras de "pior aspecto," a taxa de recuperação microbiana nos PHAs e nos PAIs foi 27,3% (3 patógenos em 11 pinos) e 54,5% (18 patógenos em 33 pinos), respectivamente ($p = 0,036$).

Conclusão As taxas de recuperação microbiana foram menores nos PHA comparadas às dos PAI. Entretanto, estas diferenças não impactaram nas taxas de infecção clínica, que foram semelhantes nos dois grupos.

Palavras-chave
- fios ortopédicos
- fixadores externos
- hidroxiapatita
- infecções
- pinos ortopédicos

Introduction

The external fixation method is widely used in the orthopedic field to treat fractures, pseudoarthrosis, and correct deformities. An external fixator (EF) is a metal device sustaining the rigidity or stability of the bone structure through transosseous wires or pins applied percutaneously. It usually consists of stainless steel, titanium, or metal alloys due to these materials' mechanical resistance and ability to withstand loads during bone healing. In addition to the base material, surface coating with other compounds, such as hydroxyapatite or silver, can improve the fixator's performance. Despite all potential uses, EFs are subject to complications, including surgical wound infection, pin loosening, and pin tract infection.[1–3]

The most common complication is pin insertion site infection, especially in EFs used for a long time, with an incidence ranging from 11.3 to 100% of cases.[4,5] The current definition of tract infection consists of inflammatory signs around the pins, which require antibiotic administration, wire or pin removal, or surgical debridement.[6] Several hypotheses have been proposed for its pathophysiology. However, it is consensual that progressive inflammation in the presence of organisms alters the tissue microenvironment and reduces the immune system's ability to withstand bacterial proliferation. In addition, bacteria can adhere to the implant and form a biofilm by producing an extracellular matrix.[4,7]

A biofilm is a three-dimensional, multicellular, and metabolically less active structure adhered to dead bone or the implant.[8] Biofilm formation hinders the action of antibiotics by restricting their entry through the extracellular matrix. Moreover, biofilm-associated bacteria present different physiological activity than that of free organisms, have an abnormal gene expression pattern, show slow and stationary growth, and develop in oxygen-deprived areas.[9] Due to these mechanisms, infection treatment may require high doses of antibiotics for a prolonged period and debridement or removal of the orthopedic implant.[8]

In the literature, *Staphylococcus aureus* is the most commonly reported pathogen in pin tract infections, followed by *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli*, and *Corynebacterium* spp., among other organisms.[5,10,11] Therefore, in cases requiring empirical antibiotic treatment, anti-staphylococcal drugs are warranted until culture results are available.[5] However, the presence of biofilms may alter the antimicrobial action profile. In an in vitro study, monotherapy with high daptomycin doses had a bactericidal action against methicillin-resistant *S. aureus* (MRSA) strains, but only combined therapy with linezolid could sustain bactericidal activity against the biofilm of the same strain.[12] In another study in an animal model, systemic amikacin administration and implant impregnation with clarithromycin prevented the formation of *P. aeruginosa* biofilm.[13]

Apparently, there is no correlation between the clinical picture and the infectious agent.[10]

Strategies for infection prevention include coated pins or pins from different materials,[11,14,15] daily care around the pins with crust removal, and cleaning with chlorhexidine, iodine, or saline solutions.[4,7,16,17] Pin coating with hydroxyapatite is one of the most studied systems as it has osteoconductive properties and improves pin-bone fixation. Nevertheless, a recent prospective study showed no impact on superficial and deep infection rates associated with EF pins.[18] A meta-analysis comparing stainless-steel pins (SSPs), hydroxyapatite-coated pins (HCPs), silver, and titanium showed no statistically significant difference in infection rates.[14]

Existing studies usually evaluate and compare infection rates in superficial and deep tissues in contact with EF pins according to the type of pin coating. However, the literature lacks an analysis of the most common microbiota on the surface of these devices. The current study aimed to assess infection rates in tissues in contact with EF pins, describe the organisms colonizing EF pins, and compare microbial retrieval rates in SSPs and HCPs.

Materials and Methods

The present prospective, non-randomized, multicenter, comparative intervention cohort study including patients undergoing surgical treatment with any EF type from April 2018 to October 2021 occurred in 2 tertiary hospitals specialized in orthopedic diseases. These patients underwent an initial study to compare the infection rates in the tracts of pins with hydroxyapatite coating or not.[18] The current study compared microbial retrieval rates and identified the pathogens from EF pins with and without hydroxyapatite coating. The Research Ethics Committee approved this study under number CAAE 84939418.6.0000.5342, and all participants signed the informed consent form (ICF).

We included patients who agreed to participate by signing the ICF concerning data use and who underwent surgical treatment with any EF type to correct deformities or treat fractures, osteomyelitis, and/or pseudoarthrosis with the expectation of maintaining the EF for a minimum of 3 weeks. Patients underwent prospective follow-up every 4 weeks or as needed for treatment. We excluded subjects lost to follow-up in less than 1 year and those remaining with the EF for less than 3 weeks.

Using the Maz-Oxford-Nuffield (MON) classification[19] (►**Table 1**), previously validated for EF pin-associated infections, we collected two pins from each patient at the time of EF removal: the one with the best clinical appearance and the one with the worst clinical appearance in the tissues surrounding it. Thus, we formed two groups: one with the best-looking pins and one with the worst-looking pins from each patient. We used the microbial retrieval rate to assess the

Table 1 Maz-Oxford-Nuffield (MON) classification

Minor grades	Signs and symptoms	Treatment
1. Clinically, it is not seen as an infection, but a reaction	Slightly erythematous, with mild discharge	Improve pin care and observe local changes
2. Clinically seen as skin infection at the pin site	Skin erythema, serous or purulent discharge, soft-tissue pain and tenderness, and able to mobilize with analgesia.	Improve pin care, swab for culture and sensitivity, and start oral anti-Staphylococcus antibiotic regimen.
3	Severe erythema plus pain and purulent discharge with edema. Unable to mobilize with analgesia. Periosteal reaction on X-ray? Pin loosening?	Intensive care at pin site. Intravenous antibiotic administration for 5 to 7 days; limb elevation; x-ray to exclude periosteal reaction and pin loosening, which, if present, leads to grade 4
Major grades		
4	Severe soft-tissue involvement $>$ 1 pin, periosteal reaction present, look for osteolysis	No response to local treatment or antibiotics. Pin removal; intravenous antibiotic administration for 5 to 7 days; plan to place a new pin at a new stage
5	Severe soft-tissue involvement $>$ 1 pin plus osteomyelitis	Pin removal, additional surgery for bone infection control, specimen collection for culture and sensitivity, and prolonged intravenous antibiotic administration.
6	Sequestrum $+/-$ fistula formation during treatment with the device	Potential for fixator removal; debridement of sequestration and collection of samples for culture and sensitivity. Limb salvage treatment and prolonged intravenous antibiotic administration.
Following device removal 6B	Pain/tenderness over the old pin tract $+/-$ fistula formation. Sequestration in the old pin tract on X-ray	Pin tract debridement; collection of samples for culture and sensitivity; intravenous antibiotic administration for 3 weeks after surgery followed by oral administration for 2 weeks

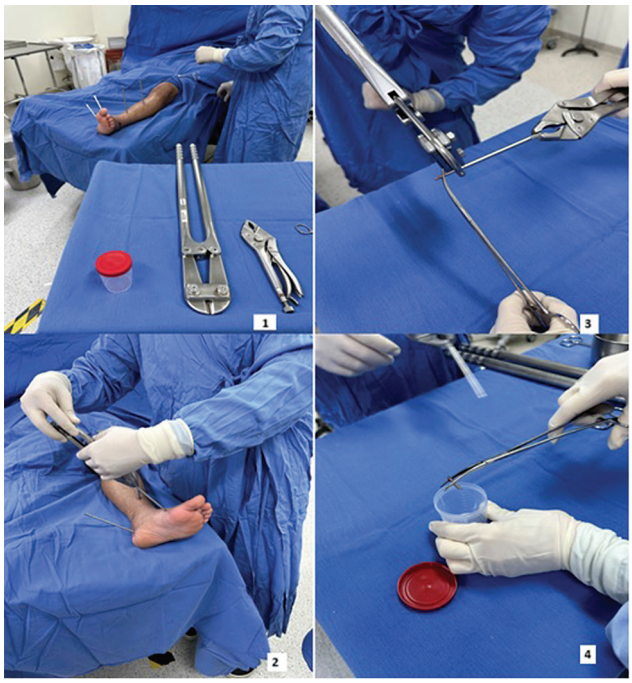


Fig. 1 Method of aseptic collection of the pin intraosseous tip. (**1**) Asepsis and antisepsis with sterile field placement. (**2**) Pin removal. (**3**) Pin intraosseous tip section. (**4**) Sending the tip for culture.

frequency of positive microbiological tests. To calculate the overall infection rate, patients who presented any pin with grade 2 or higher in the MON classification were considered infected.

We removed the pins from the EF aseptically, cut the intraosseous tips, and sent them for microbiological analysis in sterile and identified vials (►**Fig. 1**). We homogenized the samples in 3 mL of brain-heart infusion (BHI) broth and inoculated them in aerobic blood agar, chocolate agar, anaerobic blood agar, and thioglycolate broth. We incubated blood and chocolate agar plates at 35 to 37 C for 5 days (aerobic cultures) and 14 days (anaerobic cultures). We incubated thioglycolate broth for 14 days and, in case of bacterial growth, we placed the fluid on blood agar plates (aerobic and anaerobic cultures). Mass spectrometry identified the isolated bacterial colonies. The determination of the sensitivity profile from all strains occurred according to microbiological techniques standardized by the Clinical and Laboratory Standards Institute.[20]

Statistical analysis was performed in IBM SPSS Statistics for Windows (IBM Corporation) version 27.0. We expressed categorical variables as absolute and relative frequencies. We assessed associations between variables using the Chi-squared test or Fisher's exact test when necessary. Statistical significance was set at $p < 0.05$.

Results

Of all patients ($n = 44$) included in this study, 33 were treated with EFs using SSPs and 11 with HCPs. The study population had 30 (68.2%) male and 14 (31.8%) female subjects. Considering the MON classification, the maximum grade in this sample was 3 (►**Table 2**). The overall infection rate was 52.3% (23 of 44 patients), with 45.5% (5 of 11) patients with HCPs and 54.5% (18 of 33) patients with SSPs ($p = 0.732$).

The total number of pin cultures was 88 (2 pins from each patient: the best-looking and the worst-looking pins according to the MON classification). Bacterial retrieval occurred in 38 (43.2%) of the 88 pins evaluated, with 42 pathogens isolated. *S. aureus* was the most frequent among these 42 pathogens, appearing 25 (59.5%) times.

Of the 11 patients with HCPs, microbial retrieval occurred in 3 (27.3%). Of these 3 patients, 2 (66.6%) had Gram-positive bacteria, 1 (33.3%) had Gram-negative bacteria, and 1 (33.3%) had multidrug-resistant bacteria (►**Tables 3**, **4**). Of the 33 subjects with SSPs, microbial retrieval occurred in 21 (63.6%). Of these 21 patients, 16 (76.2%) had Gram-positive bacteria, 6 (28.6%) had Gram-negative bacteria, and 9 (42.3%) had multidrug-resistant bacteria (►**Tables 3**, **4**). The microbial retrieval rate was significantly higher in SSPs than in

Table 2 Characteristics from the study population ($n = 44$)

	Hydroxyapatite ($n = 11$)	Stainless steel ($n = 33$)	*p*
Male sex	7 (63.6%)	23 (69.7%)	0.722
Smoking	—	5 (15.2%)	0.309
Systemic hypertension	1 (9.1%)	6 (18.2%)	0.659
Diabetes mellitus	—	2 (6.1%)	1.000
Maximum Maz-Oxford-Nuffield grade			
1	6 (54.5%)	15 (45.4%)	0.871
2	2 (18.2%)	7 (21.2%)	
3	3 (27.2%)	11 (33.3%)	
Microbial retrieval rate			
Total number of patients	3 (27.3%)	21 (63.4%)	0.036
Worst-looking pin	3 (27.3%)	18 (54.5%)	0.036
Best-looking pin	2 (18.2%)	15 (45.5%)	0.036

Notes: Values represent absolute and relative frequency; *P*, probability value (Chi-squared test).

Table 3 Proportion of gram-positive, gram-negative, and multidrug-resistant organisms among colonized patients

	Hydroxyapatite		*p*
	Yes	No	
Worst-looking pin	n = 3	n = 21	
Gram-positive	2 (66.7%)	16 (88.9%)	0.489
Gram-negative	1 (33.3%)	5 (27.8%)	1.000
Multidrug-resistant	1 (33.3%)	9 (44.4%)	1.000
Best-looking pin	n = 3	n = 14	
Gram-positive	3 (100%)	12 (80.0%)	1.000
Gram-negative	0	3 (20.0%)	1.000
Multidrug-resistant	0	7 (46.7%)	0.485

Note: Values represent absolute and relative frequency.

Table 4 Proportion of gram-positive, gram-negative, and multidrug-resistant organisms among all patients

	Hydroxyapatite		*p*
	Yes (*n* = 11)	No (*n* = 33)	
Worst-looking pin			
Gram-positive	2 (18.2%)	15 (45.5%)	0.158
Gram-negative	1 (9.1%)	5 (15.2%)	1.000
Multidrug-resistant	1 (9.1%)	8 (24.2%)	0.411
Best-looking pin			
Gram-positive	2 (18.2%)	12 (36.4%)	0.456
Gram-negative	0	3 (9.1%)	0.561
Multidrug-resistant	0	7 (21.2%)	0.165

Note: Values represent absolute and relative frequency.

HCPs (63.4% [21 of 33 patients] versus 27.3% [3 of 11 patients] respectively, $p = 0.036$).

Analyzing the microbial retrieval rate from the 44 pins with the best clinical appearance, specifically 33 SSPs and 11 HCPs, microbial retrieval occurred in 15 SSPs (45.5%) and 2 HCPs (18.2%). In total, microbial retrieval occurred in 17 (38.6%) of the 44 best-looking pins (►**Table 2**). In the 44 worst-looking pins, that is, 33 SSPs and 11 HCPs, microbial retrieval occurred in 18 SSPs (54.5%) and 3 HCPs (27.3%). In total, microbial retrieval occurred in 21 (47.4%) of the 44 worst-looking pins (►**Table 2**). The microbial retrieval rate in uncoated pins was significantly higher than in hydroxyapatite-coated pins, and this was evident both in the sample of "best-looking" pins, respectively 45.5% (15 of 33 SSP) versus 18.2% (2 of 11 HCP), $p = 0.036$, and in the "worst-looking" pins, respectively 54.5% (18 of 33 SSP) versus 27.3% (3 of 11 HCP), with $p = 0.036$ (►**Table 2**). Of the 21 patients with microbial retrieval in the worst-looking pins, 14 (66.7%) also had a positive culture in the best-looking pins. Of the 17 patients with a positive culture in the best-looking pins, 14 (82.4%) also had a positive culture in the worst-looking pins.

Follow-up cultures revealed that *S. aureus* had the highest absolute frequency among pathogens, being found in 14 of the worst-looking pins and 11 of the best-looking pins, followed by *Serratia marcescens*, found in two of the best-looking pins and one of the worst-looking pins, and *Enterococcus faecalis*, found in two of the worst-looking pins and one of the best-looking pins. Next, came *Acinetobacter baumannii*, coagulase-negative *Staphylococcus*, and other bacteria described in ►**Table 5**. Interestingly, two patients with no bacterial growth in the worst-looking pin had *S. epidermidis* and *Staphylococcus hominis* in the best-looking pin.

Table 5 Bacteria identified in culture during follow-up and respective absolute frequencies

	Worst-looking pin	Best-looking pin
Acinetobacter baumannii	1	1
Bacillus sp.	1	—
Enterobacter cloacae	1	—
Enterococcus faecalis	2	1
Pseudomonas aeruginosa	1	—
Staphylococcus aureus	14	11
Staphylococcus epidermidis	—	1
Staphylococcus hominis	—	1
Serratia marcescens	1	2
Sphingomonas paucimobilis	1	—
Coagulase-negative *Staphylococcus*	1	1
Stenotrophomonas maltophilia	1	—

Note: Values express absolute frequency.

The cultures provided clinically relevant information in addition to the MON classification. As described in ►**Table 6**, approximately 1 in 5 patients were MON 1, that is, without clinical infection, had positive cultures. Furthermore, approximately half of the patients classified as MON 2 and 3, that is, with clinical infection, had negative cultures.

Discussion

In the present study, the microbial retrieval rates in HCPs were significantly lower than those in SSPs. However, we found no statistical difference in the clinical infection rates, as reported by Stoffel et al.[14,18] Pizà et al.[11] also found no significant difference in the infection rates when comparing the tracts of HCPs and SSPs but demonstrated that hydroxyapatite-coated pins present higher pin-bone adhesion and better osseointegration, leading to lower pin loosening rates. Pieske et al.[21] concluded that better pin-bone adhesion in HCPs is clinically irrelevant because it does not reduce pin loosening or infection rates.

Regarding the microbial retrieval rate, our results differ from those usually found in the literature. Although in vivo studies are scarce, several of them concluded that

Table 6 Prevalence of organism retrieval per the Maz-Oxford-Nuffield (MON) classification ($n = 44$ patients/88 pins)

	MON grade			*p*
	1 *(n = 21 / 42)*	2 *(n = 9 / 18)*	3 *(n = 14 / 28)*	
Worst-looking pin	5 (23.8%)	7 (77.8%)	9 (64.3%)	0.014
Best-looking pin	4 (19.0%)	3 (33.2%)	10 (71.4%)	0.024

Notes: Values represent absolute and relative frequency. *P*, probability value (Chi-squared test).

hydroxyapatite is more prone to microbial adhesion and biofilm formation due to its rough and porous surface, which presents more binding sites for organisms. McEvoy et al.[22] found a slightly greater propensity for *P. mirabilis* and *S. epidermidis* to form biofilms on Kirschner wires coated with hydroxyapatite than stainless steel. Oga et al.[23] observed a similar result when evaluating discs from different materials (stainless steel, titanium alloy, and hydroxyapatite) using electron microscopy; these authors demonstrated higher adhesion of *S. epidermidis* on discs coated with hydroxyapatite compared with stainless steel. Ravn et al.[24] performed a microcalorimetric analysis of biofilms collected from materials with smooth surfaces (cobalt-chrome, titanium), porous surfaces (hydroxyapatite), and polyethylene; the group with porous surfaces showed the highest biofilm growth compared with the others. However, Arciola et al.[25] found significantly lower bacterial adhesion of *S. epidermidis* to HCPs in an in vitro study exposing the pins to bacterial solutions and incubating them in a culture medium. The authors identified that, in saline solution, hydroxyapatite releases calcium and phosphorus ions progressively over time, and this release coincides with a decrease in bacterial adhesion.

A rare in-vivo study[11] investigated the infection rate between HCPs and SSPs and found no statistical difference in the infection rate or the microbial retrieval rate, except for *P. aeruginosa*, which was more frequently isolated in HCPs, with no explanation for this finding. In our study, only one pin, also an HCP, had *P. aeruginosa*.

The microbiological profile identified in the present study corroborates the findings from other studies involving EFs. The most frequently identified bacteria in cultures were *S. aureus*, representing approximately 60% of the microbial retrieval, followed by *Serratia mercescens*, *E. faecalis*, and *Acinetobacter baumannii*. Pizà et al.[11] identified *S. aureus* as the etiological agent of pin tract infection in more than 50% of cases, followed by Gram-negative germs, such as *P. aeruginosa*, *P. mirabilis*, and *E. coli*. In a Swedish study[26] with 106 patients, at the end of prolonged treatment with EF, cultures from all pin tips revealed a positivity rate of 39%, with *S. aureus* accounting for 63% of these results.

Among the limitations of this study, we highlight the relatively small sample size of pins, the potential interference of antibiotic use in patients with EFs for a prolonged period, the lack of differentiation between patients treating infection, fracture, or deformity, and the lack of a median time analysis. However, it is known that HCPs are not often used in orthopedic damage control.

Conclusion

The lower microbial retrieval rates in HCPs than in SSPs in both groups could suggest higher resistance to microbial adhesion on HCPs. However, confirmation of this hypothesis would require sonication of the extracted implants, which was not feasible. Nevertheless, these differences did not impact the clinical infection rates, which were similar in patients who used EFs with coated or uncoated pins. *S. aureus* accounted for most of the positive cultures.

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

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Long-Term Pulmonary Function after Combined Anteroposterior Spinal Fusion for Scoliosis in Neurofibromatosis Type 1 and Marfan Syndrome at a Mean Follow-Up of 13 Years

Função pulmonar em longo prazo após fusão espinhal anteroposterior combinada para escoliose em neurofibromatose tipo 1 e síndrome de Marfan com acompanhamento médio de 13 anos

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Abstract

Objective To compare the effect of combined spinal fusion (anteroposterior) on pulmonary function in patients with scoliosis secondary to Marfan syndrome versus neurofibromatosis type 1 (NF1) at long-term follow-up (> 10 years).

Methods Retrospective comparative study with nine patients, operated from March 1997 to December 2009, groups: Marfan syndrome versus NF1. Outcome measures were sex; age (at diagnosis and surgery); corrected height by wingspan; body mass index (BMI); duration of surgery (minutes); estimated blood loss (mL); last follow-up (years); pulmonary and implants related complications; pre- and postoperative Cobb angle of main thoracic curve and of thoracic kyphosis (T5 to T12); number of instrumented levels; absolute and percentage predicted values of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). The data was processed in the IBM SPSS Statistics for Windows software (IBM Corp.), version 20.0, and the comparisons of means used the Student's *t*-test and analysis of variance (ANOVA), or the Mann-Whitney and Kruskal-Wallis/Dunn tests, with a *p*-value of 0.05.

Keywords
- Marfan syndrome
- neurofibromatosis type 1
- pulmonary function
- scoliosis
- spinal fusion

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Results There was no difference in the absolute and predicted percentage values of pulmonary function, FVC and FEV1, and Cobb of the main thoracic curve between the groups, pre- and postoperatively ($p > 0.05$). However, there was a significant reduction in the Cobb of the main thoracic curve in the Marfan syndrome group (74→46°, $p < 0.05$).

Conclusion There was no worsening of pulmonary function in patients who underwent the combined approach after a follow-up of more than 10 years, and there were no significant differences in the postoperative values of the pulmonary function test between the groups.

Level of evidence IV; case series.

Resumo

Objetivo Comparar o efeito da fusão espinhal combinada (anteroposterior) na função pulmonar em pacientes com escoliose secundária à síndrome de Marfan ou à neurofibromatose tipo 1 (NF1) no acompanhamento em longo prazo (> 10 anos).

Métodos Estudo retrospectivo comparativo com nove pacientes, operados entre março de 1997 a dezembro de 2009. Os pacientes foram divididos em grupos com síndrome de Marfan ou NF1. As medidas de desfecho incluíram sexo, idade (ao diagnóstico e à cirurgia), altura corrigida pela envergadura, índice de massa corporal (IMC), duração da cirurgia (minutos), perda sanguínea estimada (mL), último acompanhamento (anos), complicações pulmonares e relacionadas aos implantes, ângulo de Cobb pré e pós-operatório da curva torácica principal e da cifose torácica (T5 a T12), número de níveis instrumentados, valores absolutos e percentuais previstos de capacidade vital forçada (*forced vital capacity*, FVC, em inglês) e volume expiratório forçado em um segundo (*forced expiratory volume in 1 second*, FEV1, em inglês). Os dados foram processados no programa IBM SPSS Statistics for Windows (IBM Corp.), versão 20.0, e as comparações de médias empregaram o teste *t* de Student e a análise de variância (*analysis of variance*, ANOVA, em inglês), ou os testes de Mann-Whitney e Kruskal-Wallis/Dunn com valor de *p* de 0,05.

Resultados Não houve diferença nos valores percentuais e absolutos previstos da função pulmonar, ou seja, FVC e FEV1, e no ângulo de Cobb da curva torácica principal entre os grupos nos períodos pré e pós-operatório ($p > 0,05$). Entretanto, houve redução significativa do ângulo de Cobb da curva torácica principal no grupo com síndrome de Marfan (74→46°; $p < 0,05$).

Conclusão Não houve piora da função pulmonar nos pacientes submetidos à abordagem combinada após um acompanhamento de mais de 10 anos. Além disso, não houve diferenças significativas nos valores pós-operatórios dos testes de função pulmonar entre os grupos.

Nível de evidência IV; série de casos.

Palavras-chave

- escoliose
- função pulmonar
- fusão espinal
- neurofibromatose tipo 1
- síndrome de Marfan

Introduction

Scoliosis affects about 62% of patients with Marfan syndrome, and is the most common spinal deformity.[1,2] In patients with moderate or severe deformity of the rib cage, whether due to scoliosis, pectus excavatum, or both, is common to have a restrictive disorder of pulmonary function.[3,4]

Whereas in neurofibromatosis type I (NF1), Von Recklinghausen's disease, the prevalence of scoliosis is 10 to 60%, and it can be nondystrophic or dystrophic. In these cases, there may be a significant impairment of the pulmonary function of these patients if three or more dysplastic features are present—short, sharp, single thoracic curve; rib penciling; wedging of one or more vertebral bodies; masses in paraspinal or intraspinal soft tissues; marked rotation at the apex of the deformity; dysplastic pedicles; widened spinal canal and foramen.[5]

Regarding the surgical treatment of these spinal deformities in scoliosis secondary to NF1, when a combined

arthrodesis (anterior and posterior) is performed with the use of an autologous graft taken from the resected ribs, the deformity can be corrected with stable instrumentation and a larger surgical area, in order to reduce the effects of continuous bone erosion in dystrophic cases.[5,6] In Marfan syndrome, the curves tend to be rigid and rapidly progressing, which indicates the need for surgical intervention.[7,8]

Due to the scarce literature on the evaluation of pulmonary function in long-term follow-up after surgery for syndromic scoliosis, the present study aims to compare the long-term effect ($>$ 10 years) of combined spinal fusion on pulmonary function in patients with scoliosis secondary to Marfan syndrome versus NF1.

Materials and Methods

This was a case series study, conducted at a national referral center for spinal surgery, with the evaluation of the pulmonary function of 168 patients with scoliosis, operated from March 1997 to December 2009. The inclusion criteria were patients of both sexes with scoliosis secondary to Marfan syndrome and NF1 who underwent combined arthrodesis, with hooks and pedicle screws or only pedicle screws implants, without thoracoplasty and/or halo traction.

The exclusion criteria were patients with heart disease, pulmonary illnesses, infection, cognitive changes that influenced the understanding of the tests, and inability to perform the proposed evaluation. Eligible patients underwent an assessment during the last follow-up period with radiography and spirometry tests and were allocated into two groups for comparison: NF1 versus Marfan syndrome.

Data were obtained from medical records and follow-up visits, after approval by the institutional research ethics committee and signing of the consent form by the patients. During the follow-up, pulmonary function tests (PFTs) and radiographs (in anteroposterior and lateral) were performed, which were reviewed by two independent physicians not involved in the study, using the same terminal vertebrae used in the calculation of the preoperative Cobb angle. Data were collected of the following variables: sex; age (at diagnosis, at surgery, and at last follow-up); corrected height by wingspan; body mass index (BMI); duration of surgery (minutes); estimated blood loss (cc); follow-up (years); pulmonary and implant-related complications; pre- and postoperative Cobb angle of the main thoracic curve and thoracic kyphosis (T5 to T12); number of fused levels; predicted absolute and percentages values of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1).

Pulmonary function tests were performed with the patient in the sitting position, performing the forced maximal expiration maneuvers. None of the patients reported being smokers. At least three acceptable curves and two reproducible curves were obtained, and the following parameters were recorded and classified according to the American Thoracic (ATS) and European Respiratory (ERS) societies' 2005 guidelines.[9]

The diagnoses of Marfan syndrome cases followed the Ghent criteria,[10] which were updated in 2010.[11] However, in our study, the criteria in force at the time were used. The diagnosis of NF1 is based on clinical criteria, requiring two or more criteria. Dystrophic scoliosis in these patients presents with a single rigid thoracic curve ($<$ 30% of flexibility), short and sharp; rib penciling; wedging of one or more vertebral bodies; masses in paraspinal or intraspinal tissues; marked rotation at the apex of the deformity; dysplastic pedicles; and widened spinal canal and foramen.[5,12]

The choice of the combined approach was based on radiographic criteria (rigid curves, flexibility $<$ 30%, and/or severe curves $>$ 80°). After interbody anterior fusion the patient remained hospitalized in the intensive care unit and/or ward to undergo posterior fusion. In the posterior approach, posterior column osteotomies (PCOs) were performed at three to four levels. In all surgeries, the wake-up test was performed, because, during this period, the intraoperative neurophysiological evaluation with somatosensory and motor evoked potentials was not available in the institution.

Statistical Analysis

Quantitative data were expressed as mean and standard deviation, submitted to the Kolmogorov-Smirnov normality test and compared between groups using Student's *t* test, Analysis of Variance (ANOVA)/Bonferroni (parametric data), and Mann-Whitney or Kruskal-Wallis/Dunn tests (nonparametric data). The intragroup analysis was performed using the paired t test (parametric data) or Wilcoxon test (nonparametric data). Categorical data were expressed as absolute and percentage frequencies and associated using Fisher's exact or Pearson's chi-square tests. All analyses were performed in the IBM SPSS Statistics for Windows (IBM Corp.), version 20.0, adopting a 95%CI.

Results

From an initial population of 168 patients (221 spirometry), after undergoing the inclusion and exclusion criteria, a sample of 9 eligible patients was reached and evaluated with postoperative spirometry.

When analyzing the preoperative values of clinical and radiographic variables, as well as the pulmonary function test of patients with syndromic scoliosis with and without follow-up, found no significant differences between them (►**Table 1**).

Furthermore, it was found that there was no significant difference between the groups in relation to the variables: age at surgery and at last follow-up, sex, preoperative corrected height by wingspan, preoperative BMI, fused levels, estimated blood loss, and follow-up time. This value was higher in patients with Marfan syndrome, approximately 16 years, but it was greater than 10 years in both groups (►**Table 2**).

Regarding the parameters of preoperative pulmonary function between the groups, it was found that half of the patients with Marfan syndrome had severe pulmonary involvement, while all those with neurofibromatosis had severe pulmonary involvement. It is worth noting that there were no differences between the groups in relation to these variables (►**Table 2**).

Table 1 Comparison between preoperative clinical and radiographic variables of patients with versus without follow-up

	Follow-up		
	Yes	No	*p*-value
Mean age at the last PFT before surgery (years)	16.2 ± 3.9	18.6 ± 9.9	0.50[a]
Sex (F/M)	5/4	7/4	1.00[b]
Mean corrected height by wingspan (cm)	142.3 ± 56.3	151.7 ± 17.7	0.60[a]
Neurofibromatosis type 1/Marfan syndrome	5/4	8/3	1.00[b]
Mean Body Mass Index (kg/m^2)	16.0 ± 1.8	16.3 ± 2.5	0.74[a]
Mean FVC (L)	1.5 ± 0.7	1.8 ± 1.2	0.39[a]
%	41.4 ± 12.9	57.1 ± 25.7	0.11[a]
Mean FEV1 (L)	1.2 ± 0.6	1.5 ± 1.0	0.42[a]
%	39.7 ± 14.9	54.0 ± 25.4	0.15[a]
Mean Main thoracic Cobb angle (°)	71.8 ± 13.3	92.2 ± 21.5	0.06[a]

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PFT, pulmonary function test.
Notes: [a]Student's *t*-test; [b]Fisher's exact test; $^*p < 0.05$.

When comparing the preoperative and postoperative radiographic values between the groups, a significant reduction ($p < 0.05$) of the main thoracic curve after surgery in the magnitude of the Cobb angle was observed in patients with Marfan syndrome. However, there was no difference in this variable between the groups, as well as in the preoperative and postoperative values of thoracic kyphosis (►**Table 3**).

Table 2 Comparison between clinical and radiographic parameters according to the etiology of syndromic scoliosis

	Marfan syndrome	NF1	*p*-value
Mean age at surgery (years)	15.2 ± 4.4	17.5 ± 3.4	0.42[a]
Mean age at last follow-up (years)	32.7 ± 8.3	31.4 ± 4.7	0.78[a]
Sex: n (%)			0.52[b]
Male	2 (40.0%)	3 (75.0%)	
Female	3 (60.0%)	1 (25.0%)	
Mean preoperative corrected height by wingspan (cm)	121.3 ± 69.5	168.5 ± 19.3	0.23[a]
Mean preoperative Body Mass Index	16.5 ± 2.0	15.4 ± 1.7	0.43[a]
Mean fused levels	11.8 ± 1.6	11.7 ± 1.7	0.97[a]
Mean estimated blood loss (mL)	2,624.2 ± 2,081.9	2,255.5 ± 723.5	0.75[a]
Mean operative time (minutes)	577.0 ± 178.1	598.7 ± 167.4	0.86[a]
Preoperative FVC: n (%)			
≤ 50%	3 (60.0%)	4 (100,0%)	0.44[b]
50–65%	2 (40.0%)	0 (0,0%)	
65–80%	0 (0.0%)	0 (0,0%)	
80–100%	0 (0.0%)	0 (0,0%)	
Preoperative FEV1: n (%)			
< 35%	1 (20.0%)	2 (50.0%)	0.52[b]
35–49%	2 (40.0%)	2 (50.0%)	
50–59%	1 (20.0%)	0 (0.0%)	
60–69%	1 (20.0%)	0 (0.0%)	
>70%	1 (20.0%)	0 (0.0%)	
Mean follow-up (years)	15.9 ± 4.5	12.4 ± 1.9 PM	0.20[a]

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; NF1, neurofibromatosis type 1.
Notes: [a]Student's *t*-test; [b]Fisher's exact test; $^*p < 0.05$.

Table 3 Involvement of pulmonary and radiographic parameters in patients with scoliosis secondary to Marfan syndrome and dystrophic NF1

	Marfan syndrome	Dystrophic NF1	*p*-value
Mean FVC (L)			
Preoperative	3.2 ± 1.2	3.9 ± 0.9	0.37[a]
Postoperative	2.3 ± 0.7	2.3 ± 1.7	0.96[a]
***p*-value**	0.29[b]	0.09[b]	
Post–Preoperative	-0.9 ± 1.7	-1.6 ± 1.26	0.55[a]
Mean FEV1 (L)			
Preoperative	1.3 ± 0.9	1.2 ± 0.3	0.87[a]
Postoperative	1.9 ± 0.7	1.9 ± 1.4	0.98[a]
***p*-value**	0.23[b]	0.36[b]	
Post–Preoperative	0.7 ± 1.1	0.7 ± 1.4	0.95[a]
Mean FVC (%)			
Preoperative	44.9 ± 16.6	37.0 ± 5.3	0.40[a]
Postoperative	39.6 ± 23.4	35.0 ± 12.2	0.73[a]
***p*-value**	0.67[b]	0.71[b]	
Post–Preoperative	-5.3 ± 25.6	-2.0 ± 9.9	0.82[a]
Mean FEV1 (%)			
Preoperative	43.4 ± 19.4	35.0 ± 6.7	0.44[a]
Postoperative	53.2 ± 14.3	34.7 ± 11.3	0.07[a]
***p*-value**	0.20[b]	0.95[b]	
Post–Preoperative	9.8 ± 14.5	-0.3 ± 8.4	0.26[a]
Mean Cobb angle of main thoracic curve (°)			
Preoperative	74.0 ± 16.3	69.0 ± 10.0	0.61[a]
Postoperative	46.2 ± 18.0	68.2 ± 21.2	0.13[a]
***p*-value**	**0.04[b]**	0.96[b]	
Post–Preoperative	-27.8 ± 20.5	-0.7 ± 26.9	0.13[a]
Mean thoracic kyphosis (T5–T12) (°)			
Preoperative	30.0 ± 14.1	–	–
Postoperative	56.2 ± 28.2	–	–
***p*-value**	0.18[b]	–	–
Post–preoperative	41.0 ± 17.0	–	–

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; NF1, neurofibromatosis type 1.
Notes: [a]Student's *t* test; [b]Paired *t* test; $^{*}p < 0.05$.

When analyzing the absolute and predicted percentages values of preoperative and postoperative FEV1 and FVC, there were no significant differences within the same group, or between them, during the last follow-up (►**Table 3**).

When evaluating the odds ratio (OR) between the etiology of syndromic scoliosis versus pulmonary complications in patients undergoing dual-approach surgery, there was no greater chance of pulmonary complications of one syndrome compared to the other (►**Table 4**).

Table 4 Analysis of the odds ratio between the presence of postoperative pulmonary complications versus the etiology of scoliosis

	Pulmonary complications		*p*-value	Odds ratio (95%CI)
	Yes	No		
Etiology of the scoliosis			0.20	
Marfan syndrome	1 (25.0%)	4 (80.0%)		12.0 (0.5–28.1)
Dystrophic neurofibromatosis type 1	3 (75.0%)	1 (20.0%)		

Notes: Fisher's exact test; $^{*}p < 0.05$.

In the three patients with NF1 who underwent thoracotomy followed by posterior arthrodesis, the complications were: atelectasis, pneumothorax, hemothorax, and pachypleus in one patient; pneumonia and respiratory failure in another; and pneumonia in the last one. In the Marfan syndrome case, the patient underwent a similar surgical approach, and the pulmonary complication was atelectasis.

Discussion

In the present study, patients with a defined syndromic diagnosis were evaluated, who were divided into two groups: Marfan and dystrophic NF1, with a follow-up time of more than 10 years. In the first, the patients had rigid curves (< 30% of flexibility) and in the second, in addition to stiffness, the presence of dystrophic/dysplastic characteristics. This influenced the choice of the combined approach.

Surgical cases for patients with scoliosis due to Marfan syndrome usually involve more fused levels. In these cases, the anterior release, by removing the intervertebral discs around the apex of the deformity, promotes greater flexibility of the curve, reducing the shear forces between the interface of the implants and the fixation bone structures.[2]

In our study, the mean number of fused levels between the two groups (Marfan syndrome and NF1) did not differ, being 11.80 ± 1.6 and 11.75 ± 1.7 respectively, higher than that used in cases of selective arthrodesis, where the maximum level is around 8 to 10 for thoracic curves.

Patients with scoliosis lower than 55° may already have a decline in forced vital capacity. It is worth noting that the more cephalic the apex of the deformity and the lower the patient's kyphosis, the greater the impairment of pulmonary function.[4]

In the present series, the patients had a mean thoracic kyphosis of $30 \pm 14.1°$ and the Cobb angle of the main thoracic curve of $74 \pm 16.3°$ in the preoperative period. Regarding preoperative pulmonary involvement, it was observed that approximately half of the patients had severe impairment with percentages of FEV1 lower than 50% and the majority had a FVC $\leq$ 50%.

A study that evaluated the preoperative parameters of pulmonary function in patients with scoliosis secondary to Marfan syndrome found no correlation between the preoperative values of thoracic kyphosis (Cobb T5–T12) and curve magnitude (Cobb of the thoracic curve in the coronal plane) with FVC and FEV1 values. In this study, the mean percentages of FVC and FEV1 were of 70.12 ± 22.40 and $67.07 \pm 20.213\%$ respectively.[3]

In our series, in the group of patients with Marfan syndrome, there was a significant reduction in the magnitude of the curve (74.0→46.2°) after the surgical procedure. Regarding pulmonary function assessment, there was no significant variation in the predicted percentages of FVC ($-5.28 \pm 25.65\%$) and FEV1 ($9.82 \pm 14.46\%$) between the preoperative period and the last follow-up.

In a cohort of patients with scoliosis secondary to Marfan syndrome who underwent surgery by dual approach, surgical complications were found to be screw loosening in two patients, stem break in one, and chylothorax with hemothorax in the patient who underwent thoracoscopy.[2]

When evaluating the complications in patients with Marfan syndrome, we observed one case of atelectasis that was managed with antibiotics and respiratory physiotherapy, with resolution of the condition. No implant-related complications were observed.

The other group studied refers to patients with scoliosis secondary to NF1 with a dystrophic pattern, characterized by a single rigid, short, and sharp thoracic curve; rib penciling; wedging of one or more vertebral bodies; masses in paraspinal or intraspinal tissues; marked rotation at the apex of the deformity; dysplastic pedicles; and/or widened spinal canal and foramen. According to certain authors, in the presence of three or more of these characteristics, the mean chance of progression of the deformity is 85%, with a risk of impaired pulmonary function in these patients.[5]

In our study, patients diagnosed with NF1 had scoliosis with a rigid and short thoracic curve (preoperative Cobb: $69 \pm 10°$), associated with dysplastic pedicles and changes in the costal arches (rib penciling). This was associated with severe preoperative pulmonary involvement, with FVC and FEV1 lower than 50%.

Certain authors suggest that, in dystrophic cases, surgery should be performed as soon as possible, due to the rapid progression of the curve. The fact that arthrodesis is performed in younger patients would not necessarily result in a loss in their final height, as the number of fused levels would be lower.[6]

In our study, patients were operated, on average, after the growth spurt and near the end of adolescence ($\sim$ 17 years) with a preoperative corrected height of 168.50 ± 19.3 cm, with an average of about 12 levels fused after surgery.

A study that analyzed the results of surgery combined with thoracotomy in patients with early-onset dystrophic scoliosis (< 10-years-old) showed a reduction in the magnitude of the curve (71.2→23.5°) and changes in the preoperative and postoperative values of FVC (1.4→2.3 L) and FVC (75.0→74%).[5]

The present authors did not find a significant improvement in the Cobb angle of the main thoracic curve after surgery, as well as in the variation (postoperative – preoperative) of pulmonary function parameters: FVC (-1.57 ± 1.26L), FEV1 (0.76 ± 1.40L), and percentages (FVC: $-2.00 \pm 9.94\%$; and FEV1: $-0.28 \pm 8.41\%$).

When evaluating the results of different studies on patients with scoliosis secondary to NF1 with a dystrophic pattern, Jia et al. showed that there was a significant reduction in the Cobb angle of the main thoracic curve in patients who underwent combined arthrodesis and posterior arthrodesis alone, with no difference between the two groups. According to them, both approaches have similar efficacy, stability, and safety in the postoperative follow-up of these patients.[13]

Regarding complications, after anterior and posterior approach to these patients, certain authors reported that about 28.5% of them evolved with complications, such as: malpositioning and loosening of the implants, dural fistula, pseudarthrosis, atelectasis, pressure ulcer, superficial infection, transient paraplegia and paraparesis, crankshaft phenomenon, among others. They point out that the proportion of instrumentation failure or pseudarthrosis was 8.3%.[13]

Our study found that three patients with NF1 who underwent thoracotomy followed by posterior arthrodesis were complicated with: atelectasis, pneumothorax, hemothorax, and pachippleuris in one patient treated with chest drainage and pulmonary physiotherapy; pneumonia and respiratory failure in another, who underwent orotracheal intubation and intravenous antibiotic therapy; and pneumonia in the last patient. All of them progressed well clinically. It should be noted that none of the patients developed complications related to the implants.

When comparing the two groups of patients in the present study, it was observed that, although patients with NF1 had lower values (worse involvement) of the preoperative pulmonary function parameters and in the last follow-up compared to the group with Marfan syndrome, this difference was not significant. Additionally, there was no greater chance of pulmonary complications of one etiology than the other, using the same surgical approach.

As strengths of our research, we can mention this is one of the few studies that presents pre- and postoperative pulmonary function parameters in syndromic scoliosis patients with a long follow-up (greater than 10 years). However, caution must be taken when interpreting the results and in their external validation, due to the inherent limitations of this research.

The limitations can be attributed to the study's retrospective, single center nature; having a small sample; and not having evaluated the effect of only posterior spinal fusion, skeletal traction, vertebral osteotomies, and thoracoplasty on pulmonary function.

Conclusion

When evaluating the effect of combined spinal fusion (anterior and posterior) on pulmonary function in patients with syndromic scoliosis (Marfan syndrome and NF1) in long-term follow-up ($>$ 10 years), it was found that there was no difference in the absolute and predicted percentages of FVC and FEV1 between the groups in the last follow-up. In addition, pulmonary function values did not show significant changes in the last postoperative evaluation compared to the preoperative period.

Authors' Contributions

Each author contributed individually and significantly to the development of this article. JAAO, RRV e AGCB: study conception and design, analysis and/or interpretation of data, and writing – review & editing; GBLA, LEC e JRLS: study conception and design, and writing – review & editing.

Ethical Approval

This retrospective chart review study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Human Research Committee at Universidade Federal do Rio de Janeiro and Instituto Nacional de Traumatologia e Ortopedia Jamil Haddad approved this study with the respective protocol numbers: CAAE: 06671719.9.0000.5257 and CAAE: 06671719.9.3001.5273.

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Conflict of Interest

The authors have no conflict of interests to declare.

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Pain Evaluation after Pulsed Radiofrequency in Patients with Osteoarthritis of the Hip

Avaliação da dor após radiofrequência pulsátil nos pacientes com osteoartrite do quadril

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Abstract

Objective To evaluate the role of pulsed radiofrequency (PRF) in the pain management of patients with hip osteoarthritis (OA) and surgical indication.

Methods We selected 30 patients from the waiting list for total hip arthroplasty, with wait time ranging from 1 to 3 years. The OA degree was measured radiographically according to the Tönnis classification. Patients underwent PRF in the surgical center, performed by two senior hip surgeons from the hospital. The procedure was fluoroscopy-guided and occurred under anesthetic sedation. One nurse assessed all patients before and after PRF using the short form-36 questionnaire.

Results From the initial sample of 30 patients, only 13 underwent PRF. Per the Tönnis classification, one subject was type I, four were type II, and eight were type III. The results showed an improvement in pain in 6 patients (46%), general health status in 9 (69%), social aspects in 8 (62%), and mental health in 3 (8%). Furthermore, 2 subjects (15%) reported pain worsening after PRF, and 3 (23%) reported general health status worsening.

Conclusion In more advanced degrees of hip joint degeneration (Tönnis III), the technique was flawed, risky, and unsatisfactory. The data obtained question PRF cost-effectiveness and its indication for patients with hip OA as a safe and effective alternative conservative treatment.

Keywords

- chronic pain
- hip
- osteoarthritis, hip
- pulsed radiofrequency treatment

Resumo

Objetivo Avaliar o papel da radiofrequência pulsátil (RFP) no manejo álgico de pacientes com osteoartrite (OA) do quadril com indicação cirúrgica.

Métodos Foram selecionados 30 pacientes da fila de cirurgia para artroplastia total de quadril com tempo de espera de 1 a 3 anos. O grau de OA foi mensurado radiograficamente de acordo com a classificação de Tönnis. As RFPs foram realizadas no centro

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cirúrgico por dois cirurgiões seniores especialistas em quadril do hospital. O procedimento foi guiado por fluoroscopia e ocorreu sob sedação anestésica. Todos os pacientes foram avaliados no pré- e pós-procedimento através do questionário Short Form-36 por uma única enfermeira.

Resultados Dos 30 pacientes previamente selecionados, apenas 13 realizaram a RFP. Dentre eles, um era classificado como Tönnis tipo I, quatro como II e oito como III. Os resultados evidenciaram a melhora do quadro álgico em apenas 6 pacientes (46%), do estado geral de saúde em 9 (69%), dos aspectos sociais em 8 (62%) e da saúde mental em 3 (8%). Além disso, 2 pacientes (15%) chegaram a relatar piora do quadro álgico após a RFP e 3 (23%) relataram piora do estado de saúde geral.

Conclusão Em graus mais avançados de degeneração articular do quadril (Tönnis III) a técnica se mostrou falha, arriscada e insatisfatória. Os dados obtidos colocam em questão não só o custo-efetividade da técnica, mas sua indicação para os pacientes com OA do quadril como tratamento conservador alternativo seguro e eficaz.

Palavras-chave
- dor crônica
- osteoartrite do quadril
- quadril
- tratamento por radiofrequência pulsada

Introduction

Populational aging and the increased physical demand in sports and work activities result in a considerable increase in hip osteoarthritis (OA) prevalence. This prevalence increases with age and, after 85 years old, one in four subjects has symptomatic hip OA. Populational studies report a range of hip OA incidence probably due to clinical and radiological dissociation. As such, chronic pain, stiffness, limited range of motion, and instability are significant issues.[1]

The estimated prevalence of chronic hip pain in subjects aged over 45 is 7% in men and 10% in women.[2] The quality of life (QoL) of these patients has a direct association with pain duration and the need for prolonged searches for conservative strategies for pain relief, such as physical therapy, nonsteroidal antiinflammatory drugs, opioids, and intraarticular corticosteroid injections. These methods often provide partial and scarce symptomatic relief.[3]

Several intra- and extraarticular pain sources are primary focus for hip pain, hindering their differentiation. As such, radiofrequency (RF) and intraarticular injections help to elucidate the pain source. Although the literature remains controversial, RF use has been increasing as an alternate treatment for joint pain when it is refractory to other available conservative methods, and in cases with surgical contraindication.[4,5]

Anatomical models showed that the sensory anatomy innervating the hip joint consists of capsular branches of the femoral and obturator nerves, which are the major target points for RF neuromodulation guided by fluoroscopic imaging in the anteroposterior (AP) pelvis.[1]

The Tönnis classification is among the best-known and most widely used worldwide for hip OA assessment. The study of a simple AP radiograph of the pelvis is enough for this classification, which initially described three progressive degrees of joint degeneration. In 1999, grade 0 was added, corresponding to subjects without the disease. Type I describes patients with mild OA, minimal joint space narrowing, increased sclerosis, and absent or minimal loss of sphericity of the femoral head. Type II demonstrates moderate OA with small cysts, moderate joint space narrowing, and moderate loss of head sphericity. Type III describes patients with advanced disease, which includes severe OA with large cysts, severe joint space narrowing, severe loss of head sphericity, and avascular necrosis.[6]

The main objective of this study was to evaluate the improvement in the QoL of patients with hip OA who underwent PRF immediately, 2, 4, and 6 months after the procedure using the short form-36 (SF-36) questionnaire. The second objective was to establish a protocol for performing RF in the hospital for pain relief in patients on the waiting list for surgery.

Materials and Methods

This observational, noncontrolled study occurred in our hospital from May to September 2022. We selected two senior hip surgeons from the same hip surgery group to conduct the study. One nurse performed the initial assessment of the QoL of all patients before the procedure, using the SF-36 questionnaire. All patients signed an informed consent form (ICF) and the Ethics Committee, affiliated with Plataforma Brasil, approved the study under opinion number 6.145.444 and CAAE number 69626023.1.0000.5273.

Patients

We initially selected 30 patients, from both genders, with hip OA in the total hip arthroplasty (THA) waiting list. The inclusion criteria were patients over 50-years-old, presenting the primary disease in the hip, and on the waiting list from 1 to 3 years. We excluded patients under 50-years-old, with secondary hip OA, previous surgeries on the affected

hip, who underwent anesthetic infiltration less than 6-months, and on the waiting list for less than 1 and more than 3 years.

Classification

A resident physician in Orthopedics and Traumatology at the same hospital studied all hips to determine their Tönnis classification (►**Table 1**) using the MDICON imaging software.

Pulsed Radiofrequency

Each surgeon would perform 15 RF procedures randomly. However, we only performed 13 procedures, due to the unsatisfactory partial outcomes, as some patients developed worsening pain. Pulsed radiofrequency (PRF) uses a generator with 45 V amplitude and a duration of 2 times per second. The generator modifies parameters in real-time to reach the desired local temperature. In this method, the maximum temperature was 42° Celsius without causing irreversible tissue damage or motor fiber involvement.

Procedure

All patients were taken to the surgical center and underwent light sedation throughout the procedure and local anesthesia with 2% lidocaine in the affected hip. We used two PRF tips from SOLIEVO (Sollievo Medicina Especializada, São Caetano do Sul, SP, Brazil) for each subject. We inserted one tip into the sensory branches of the obturator nerve, immediately inferior to the teardrop, and one tip into the sensory branches of the femoral nerve, inferomedial to the anterior inferior iliac spine (AIIS). These anatomical parameters were obtained through an AP fluoroscopic image of the hip (►**Fig. 1**). After tip I al of methylprednisolone at 20 mg and ropivacaine 1% into each cannula and applied a compressive dressing.

Short Form-36

The SF-36 is a widely used QoL measure developed in the 1980s in the USA. The questionnaire has 11 questions and 36 items, including 8 components (domains or dimensions) representing functional capacity (10 items), physical aspects (4 items), pain (2 items), general health status (5 items), vitality (4 items), social aspects (2 items), emotional aspects (3 items), mental health (5 items), and one question comparing patients' perception of their current health now and 1-year prior.[7,8]

Table 1 Tönnis classification

Classification	Description
0	No hip OA signs.
I	- Mild OA. - Minimal joint space narrowing and mild sclerosis. - Absent or minimal loss of head sphericity.
II	- Moderate OA. - Moderate joint space narrowing with small cysts. - Moderate loss of head sphericity.
III	- Severe OA. - Severe joint space narrowing with big cysts. - Severe head deformity.

Abbreviation: OA, osteoarthritis.
Note: Adapted from Tönnis and Heinecke 1999.[5]

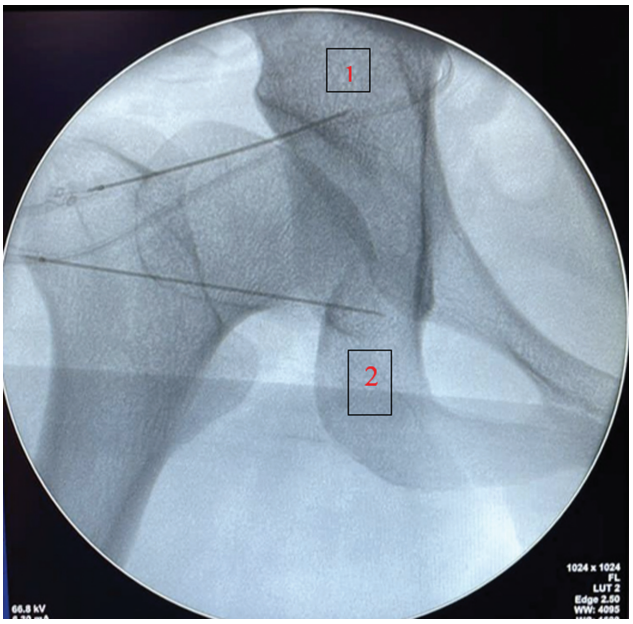


Fig. 1 (1) Femoral nerve (2) Obturator nerve. Source: Fluoroscopic imaging from the hospital.

Statistical Analysis

The values of each SF-36 domain were discrete and ranged from 0 to 100. Additionally, the data presented a nonnormal distribution according to the Shapiro-Wilk test. Thus, values were reported as median (interquartile range [IQR]), and the comparison between pre- and post-PRF values used the Wilcoxon signed-rank test, and the Spearman rank correlation coefficient determined associations between changes in each domain.

Results

Our results include only 13 of the 30 previously selected patients. Per the Tönnis classification, eight subjects were type III, four were II, and one patient was type I. All SF-36 assessments pre-PRF occurred the day of or before the procedure, while for post-PRF the assessments occurred within 49 days, with the shortest and longest intervals being 25 and 96 days, respectively.

►**Table 2** shows the pain, general health status, social aspects, and mental health domain values. We observed pain improvement in only 6 patients (46%), maintenance of the pre-PRF state in 5 (38%), and worsening in 2 (15%). The general health status improved in nine patients (69%), remained the same in 1 (8%), and worsened in 3 patients (23%). Social aspects improved in 8 patients (62%), remained

Table 2 Quality of life domains

	Pre-PRF	Post-PRF	*p*-value
Pain	20 (21)	20 (31)	0.057
General health status	37 (28)	52 (18)	0.168
Social aspects	25 (25)	50 (62)	0.053
Mental health	48 (40)	44 (44)	0.169

Abbreviations: PRF, pulsed radiofrequency; *p*, *p*-value of the Wilcoxon signed-rank test.

the same in 2 (15%), and worsened in three (23%). Mental health improved in only 3 patients (23%), remained stable in 1 (8%), and worsened in 9 (69%). ►**Fig. 2** shows the individual variation in these domains.

We did not observe any correlation between variations in the pain, general health status, and mental health domains (►**Fig. 3**). We detected a borderline value in the statistical correlation test between variations in pain and social aspects domains ($p = 0.056$).

We interrupted the study due to the lack of partial beneficial results for patients after performing 43.3% of PRF procedures.

Discussion

According to Giaccari et al.,[10] OA is the most prevalent joint disorder in the world and one of the main causes of morbidity and functional disability. Hip OA is its second most common form. In 2019, OA prevalence in the last 10 years increased by 113.25%, going from 247.51 million affected people in 1990 to 527.81 million in 2019. Thus, the literature reported that health service costs for this condition represent 1 to 2.5% of the gross national product of developed countries. This value must increase 4-fold by 2030.[11]

In the last 10 years, the waiting time for THA in our hospital from entering the list until surgery is 3.1 years. These patients with chronic pain often overuse analgesic and antiinflammatory medications and receive successive intra-articular steroid injections with limited action. Considering the current reality in our hospital, we envisioned PRF as a potential alternative and effective method for improving pain in these patients and, as a result, their QoL.

Although RF is commonly used for chronic musculoskeletal pain,[10] the literature regarding PRF in patients with hip OA is scarce. In 2017, Short et al.[1] and Bhatia et al.[3] reviewed 14 articles and demonstrated the great potential for reducing secondary pain in up to 3 years, in addition to improving walking, using RF on the sensory innervation of the hip (obturator, accessory obturator, and femoral nerves). Complications of the procedure are rare and involve vascular injury, neuritis, hematoma formation, and inadvertent ablation of motor branches of the obturator and femoral nerves.

The great advantage of PRF is the neuromodulation effects of the local electric field by altering synaptic transmission and, consequently, less damage to local tissues and less pain due to deafferentation.[12] Cooled RF (CFR) is similar to PRF but cooled with water through a probe, reaching 60°C. It can generate a neuronal lesion of a larger area, but its cost can be almost two-fold higher than PRF.[13]

In another study published in 2015, 15 patients with mild-to-moderate hip OA, Tönnis types I and II, underwent PRF and were compared with 14 patients who did not

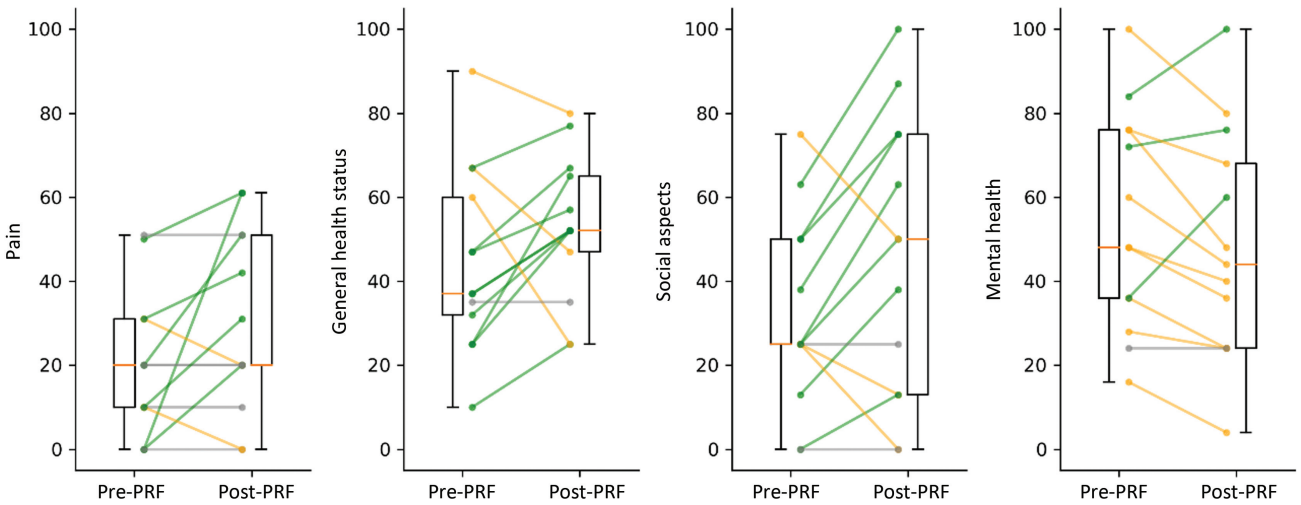


Fig. 2 Variation in the domains assessed before and after pulsed radiofrequency. The group values are presented by boxplots and the individual values by lines. The green lines indicate improvement in the domain, orange indicate worsening, and gray indicate value maintenance.
Abbreviation: PRF, pulsed radiofrequency.

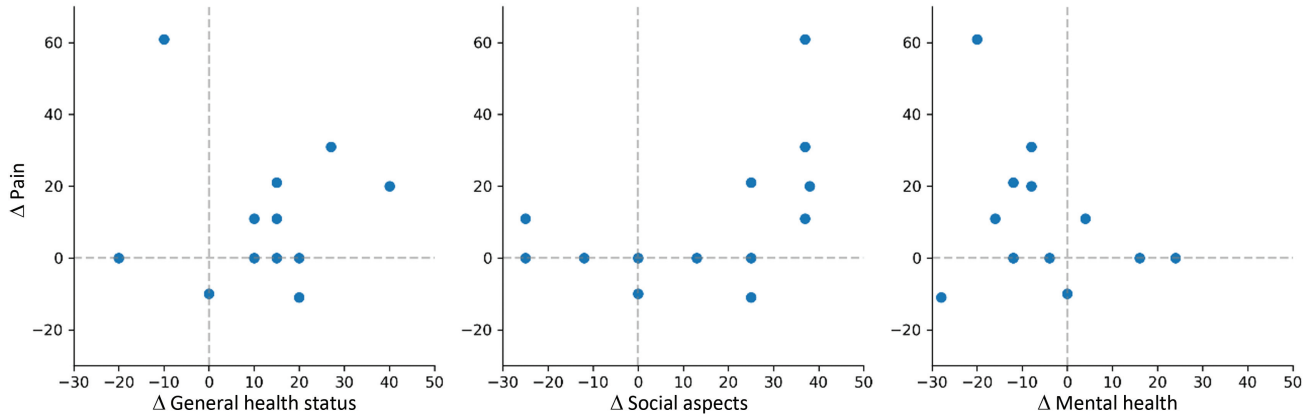


Fig. 3 Scatter diagram of variations in the domains evaluated. Each point indicates a subject and the dotted reference lines indicate the maintenance of values before and after pulsed radiofrequency. Points located in the upper right quadrant indicate subjects with simultaneous improvement in both domains, while points located in the lower left quadrant indicate simultaneous worsening.

undergo the procedure and received conservative treatment with paracetamol, nonsteroidal antiinflammatory drugs (NSAIDs), and opioids. Patient assessment for pain and hip function used the visual analog scale (VAS) and the Oxford hip score (OHS), and the subjects received pain medications before the procedure and at 1, 4, and 12 weeks after. The VAS and OHS scores showed a significant improvement in pain and hip function among PRF patients in all weeks evaluated. These patients also used fewer analgesics after the procedure.[14]

This study had some limitations. It is known that cooled RF tips can achieve neuromodulation diameters greater than PRF tips. However, due to their high cost, they could not be used. Since 61.5% of the hips were Tönnis type III, presenting severe degeneration, we strongly believe that PRF has no function in them. Further studies with less degenerated hips would be of great value for its validation as an alternative treatment for hip OA.

Conclusion

This study had to be interrupted with only 43.3% of the patients scheduled to undergo PRF, due to the discouraging partial outcomes. Therefore, we must question whether the investment in this technique, considered very expensive, is worthwhile and effective in improving QoL of patients with hip OA.

Author's Contribution

Each author contributed individually and significantly to the development of this paper: RRT collected and organized the data; MICC, PVS, and RRT wrote the manuscript; LP and MFA reviewed and edited the text, approving its final version; and CTL performed the statistical analysis of the collected data.

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Conflict of Interests

The authors have no conflict of interest to declare.

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Topical Application of Estrogen Nanocapsules on Skin Incision Improves Fracture Healing in Osteoporotic Rats

A aplicação tópica de nanocápsulas de estrogênio na incisão cutânea melhora a cicatrização de fraturas em ratas osteoporóticas

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Abstract

Objective The challenge of consolidating osteoporotic fractures, particularly exacerbated by postmenopausal estrogen deficiency, underscores the urgent need for effective interventions. This study aims to evaluate the impact of locally administered estrogen via nanocapsules on the consolidation of osteoporotic fractures in ovariectomized rats, while also assessing the systemic effects of this hormone, using the uterus as a sentinel organ.

Methods Forty-five animals underwent standardized femoral fractures and were divided into three groups: G1 (control), G2 (conventional estrogen), and G3 (estrogen nanocapsules). The estrogen was applied topically to the skin incision region (trichotomized area). Fracture healing was assessed at 15- and 30-days postfracture through radiographic and histological analyses, with uterine histology conducted to evaluate systemic effects.

Results In terms of radiographic analysis of callus formation, G3 (8.75 ± 0.77 mm) exhibited significantly higher callus formation than the control group (7.18 ± 0.4 mm) at day 15, with histological analysis revealing increased callus formation in G3 at day 30, indicating an accelerated healing process. Furthermore, uterine histological analysis at day 30 showed a reduction in endometrial thickness in G3 ($510{,}073 \pm 54{,}705.11$ µm) compared with G2 ($623{,}729 \pm 101{,}592$ µm).

Conclusion These findings suggest that topical estrogen nanocapsules may enhance callus formation in the treatment of osteoporotic femoral fractures in rats, potentially with fewer systemic effects.

Keywords
- estrogens
- fracture healing
- nanotechnology
- osteoporosis

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Resumo

Objetivo O desafio de consolidação de fraturas osteoporóticas, particularmente exacerbadas pela deficiência de estrogênio pós-menopausa, ressalta a necessidade urgente de intervenções eficazes. Este estudo tem como objetivo avaliar o impacto do estrogênio administrado localmente via nanocápsulas na consolidação de fraturas osteoporóticas em ratas ovariectomizadas e analisar os efeitos sistêmicos deste hormônio usando o útero como órgão sentinela.

Métodos Quarenta e cinco animais foram submetidos a fraturas femorais padronizadas e divididos em três grupos: G1 (controle), G2 (estrogênio convencional) e G3 (nanocápsulas de estrogênio). O estrogênio foi aplicado topicamente na região da incisão da pele (área tricotomizada). A cicatrização da fratura foi avaliada 15 e 30 dias após a fratura por meio de análises radiográficas e histológicas. A histologia uterina analisou os efeitos sistêmicos.

Resultados Na análise radiográfica dos calos ósseos, G3 ($8{,}75 \pm 0{,}77$ mm) exibiu formação de calo significativamente maior do que o grupo controle ($7{,}18 \pm 0{,}4$ mm) no dia 15 e a análise histológica revelou aumento da formação de calo em G3 no dia 30, indicando um processo de cicatrização acelerado. Além disso, a análise histológica uterina no dia 30 mostrou uma redução na espessura endometrial em G3 ($510.073 \pm 54.705{,}11$ µm) em comparação a G2 (623.729 ± 101.592 µm).

Conclusão Estes achados sugerem que nanocápsulas tópicas de estrogênio podem aumentar a formação de calos no tratamento de fraturas femorais osteoporóticas em ratas, potencialmente com menos efeitos sistêmicos.

Palavras-chave

- consolidação da fratura
- estrogênios
- nanotecnologia
- osteoporose

Introduction

Osteoporotic fractures represent a significant public health issue, with their incidence increasing each year.[1–3] Most treatment strategies focus on preventing these injuries by increasing bone mass, but there is less emphasis on the consolidation process of osteoporotic bone.[4] Additionally, the consolidation of osteoporotic fractures presents a significant challenge for orthopedic surgeons.[5]

Estrogen deficiency, particularly postmenopausal, is a major risk factor for osteoporosis. This hormone has both anabolic and anticatabolic effects, influencing osteoblasts and osteoclasts in the bone remodeling process.[6–8] Moreover, it is crucial for the regulation and formation of cartilaginous tissue, affecting both growth cartilage and joint surfaces.[9]

While the role of estrogen in bone metabolism and its protective effect on bone mineral density are well-known,[10] its impact on fracture consolidation remains unclear. Few studies have specifically evaluated the role of this hormone in the healing process of postmenopausal osteoporotic fractures.[11–13] The reduction of estrogen levels during menopause directly contributes to an imbalance in bone neoformation that can adversely affect the bone consolidation process in osteoporotic patients.[14,15] To mitigate these effects, topical application is advantageous, as it avoids first-pass hepatic metabolism, thereby reducing the necessary concentration and minimizing side effects.[16]

Advances in nanotechnology allow for the manipulation of particles to create drug transport vehicles that safely target specific organs, improving transport effectiveness.[17] Nanomaterials have unique structures with adjustable size, shape, and surface properties that significantly impact cellular absorption.[18] In biological systems, smaller particles can be ideal for the cellular absorption of active compounds.[19,20] Nanosystems can be beneficial in drug delivery by improving the bioavailability of poorly soluble actives, reducing side effects, releasing the drug in a controlled manner, and allowing administration at lower doses.[21]

In this study, we evaluated the role of topical estrogen applied to the skin incision, administered both conventionally and through nanocapsules, radiographically and histologically, in the femoral fracture consolidation process in osteoporotic rats, while also assessing the systemic effects of this hormone, with the uterus as a sentinel organ.

Materials and Methods

Development of Pharmaceuticals

The drugs were developed at the Laboratory of Drug Production and Development. Both the nanocapsules and conventional formulation had a concentration of 0.06% of 17-β estradiol.

Obtaining Polymeric Nanocapsules Containing 17-β Estradiol

Nanocapsule suspensions were obtained using PCL (100 mg) dissolved in acetone (30 ml) in the presence of Span 80 (Croda International plc, Snaith, UK) at 0.077 g, 17-β estradiol (50 mg), and medium-chain triglycerides (0.33 g). The solution was stirred for 10 minutes. The aqueous phase was prepared using Tween 80 (Croda International plc) at 0.077 g, and distilled water (53 mL). Then, the organic phase was slowly added to the aqueous phase under constant magnetic stirring at 40°C. The resulting nanoemulsion was stirred for 10 minutes. Next, the organic solvent was removed by evaporation under reduced pressure at 40°C, resulting in a concentrated sample (10 mL).

Field Emission Gun Scanning Electron Microscopy (FEG-SEM)

The morphological and surface evaluation of the nanoparticle and conventional form was performed using a Mira 3 field emission gun scanning electron microscope (TESCAN, Brno, Czech Republic). The samples were metallized with gold using an IC-50 Ion Coater (SHIMADZU, Kyoto, Japan). Electron micrographs were obtained using an acceleration voltage of 15 kV and specific software (Electron Optical Design, Brno, Czech Republic).

Dynamic Light Scattering and Laser Doppler Microelectrophoresis

The particle size and zeta potential of the nanoparticles (E2, PCLN, and ZnON) were determined using a Zetasizer Nano series ZS90 instrument (Malvern Instruments, Worcestershire, UK) after sample preparation (1:500 V/V) in ultrapure water. The analyses were performed in triplicate.

Animal Model

The research was approved by the Ethics Committee on Animal Use (CEUA) under process number 0122368/2019. All applicable institutional and national guidelines for the care and use of animals were followed.

There were 45 female Wistar rats divided into 3 groups. Group 1 (G1) consisted of 15 rats in the control group, group 2 (G2) consisted of 15 rats treated with estrogen conventionally formulated at a concentration of 0.06% of 17 β-estradiol, and group 3 (G3) consisted of 15 rats treated with the same concentration of 17 β-estradiol but formulated through nanocapsules.

Anesthesic Technique

For the ovariectomy and fracture production procedures, the animals were anesthetized with xylazine (10 mg/kg) and ketamine (90 mg/kg). Postsurgery, they received a single dose of fentanyl citrate (0.05 mg/kg) for pain management, followed by dipyrone (200 mg/kg) administered every 6 hours for the first 7 days. Antiinflammatory drugs were not used to avoid potential interference with bone consolidation evaluation. Postoperative pain was monitored by assessing food and water consumption, as well as observing behavioral changes.

Fracture Production

After 40 weeks of ovariectomy, the rats were anesthetized using the same anesthetic technique and underwent a right femur fracture. Trichotomy and antisepsis were performed with topical povidone-iodine (PVPI). A 2 cm incision was made in the lateral thigh in the right hind limb and extended to the knee, dissection was performed by planes, and the patella was retracted to expose the lateral condyles. A 1 mm diameter A Kirschner wire was inserted through the condyles to the greater trochanter and removed on day 15. After intramedullary fixation of the femur, the lateral vastus muscle was retracted, exposing the bone diaphysis. A transverse fracture was made in the femoral diaphysis using a 5 mm osteotome. After the procedure, the muscle fascia was sutured with absorbable polygalactin 2 to 0 suture and the skin with 3 to 0 mononylon. Immediate postoperative radiographs were taken to confirm the fracture.

Estrogen Application

Groups 2 and 3 received daily application of topical estrogen according to their respective groups (paste or nanocapsules at a concentration of 0.06%) for 14 days, around the operative wound (already trichotomized area).

After drug application, each group was subdivided into 15 days postfracture and 30 days postfracture for euthanasia. Afterwards, femurs were removed and cleaned for radiographic and histological analysis.

Radiographic Evaluation

A Lotus 630HF device was used to obtain radiographs of both femurs. The VXvue 1.0.2.6pi (Viewoks Co. Ltd., Anyang, South Korea) software was used to measure the bone callus at its largest diameter and the femoral isthmus of the contralateral femur. Absolute measurement of the bone callus and the ratio between the callus and the contralateral isthmus were evaluated.

Histological Analysis

Bones, cleaned of muscle tissue, were stored in 10% formaldehyde and subsequently decalcified in a solution of 10% ethylenediaminetetraacetic acid (EDTA) changed weekly for 2 months. The fractured segment was embedded in paraffin, longitudinally cut to a thickness of 5 µm, and stained with hematoxylin-eosin (HE). After analysis and selection, histological sections were photographed with an Olympus DP72 (Evident Corp., Shinjuku-ku, Tokyo, Japan) microscope using the cellSens Standard (Evident Corp.) software. Qualitative and quantitative analyses of the samples were performed. The numerical scale proposed by Huo et al.,[22] according to the consolidation stage observed in each slide, was applied.

Uterine Tissue

After euthanasia, all uteri were collected and fixed in 10% formalin. Histological processing was then performed, and the sample was sectioned using a microtome with a thickness of 3 µm and stained with hematoxylin and eosin (HE). Histological sections were photographed using an Olympus AX70 (Evident Corp.) microscope with 20x magnification,

Table 1 Mean and standard deviation of the width of the bone callus and the ratio between the width of the callus and the width of the contralateral isthmus at 15 and 30-days postfracture (in mm)

	Day 15		Day 30	
	Width	Ratio	Width	Ratio
G1	7.18 ± 0.4^{a}	2.04 ± 0.19^{a}	8.3 ± 0.97^{a}	2.4 ± 0.36^{a}
G2	$8.37 \pm 1.4^{a,b}$	$2.43 \pm 0.47^{a,b}$	8.51 ± 0.9^{a}	2.49 ± 0.2^{a}
G3	8.75 ± 0.77^{b}	2.54 ± 0.22^{b}	8.53 ± 1.0^{a}	2.56 ± 0.27^{a}

Abbreviations: G1, group 1; G2, group 2; G3, group 3. **Notes:** Results are displayed in median ± standard deviation. Different letters in the columns denote significant difference $p < 0.05$.

using the T capture program. The thickness of the perimetrium, myometrium, and endometrium layers was measured using the ImageJ software after standardization of the known distance. The mean and standard deviation were calculated for subsequent statistical analysis.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package Social Sciences (SPSS, IBM Corp., Armonk, NY, USA) version 20.0, with analysis of variance (ANOVA) for multiple comparisons, followed by Tukey's test, with a confidence interval (CI) of 95% ($p \leq 0.05$).

Results

Nanocapsule Production Process

The evaluation of the size of estrogen nanoparticles showed a mean value of 191.96 ± 10.37 nm. Scanning electron microscopy (SEM) characterization is a technique that makes possible to evaluate the influence of synthesis conditions on the morphology of nanoparticles. The results obtained for estrogen in conventional form showed large and irregular parts. The SEM of estradiol nanoparticles showed a spherical shape with a homogeneous surface.

Drug Concentration Determination and Encapsulation Efficiency

The determination of the drug concentration incorporated into the nanocapsules, and the encapsulation efficiency was performed in triplicate using the previously validated method. The nanocapsules obtained by the precipitation method of the preformed polymer showed yields greater than 99%.

Radiographic Evaluation

At the 15-day assessment, all animals already showed signs of bone callus formation. After 30 days, all fractures were consolidated in their radiological aspect. The results for the width of the bone callus are substantiated in ►**Table 1**.

In the evaluation conducted at 15 days post-fracture, animals in G3 exhibited a larger bone callus than those in G1 ($p < 0.05$), while animals in G2 showed a statistically equal callus compared with G1 and G3, as shown in ►**Fig. 1**.

The results for the size ratio show the same statistical outcome as the bone callus size, indicating the consistency of

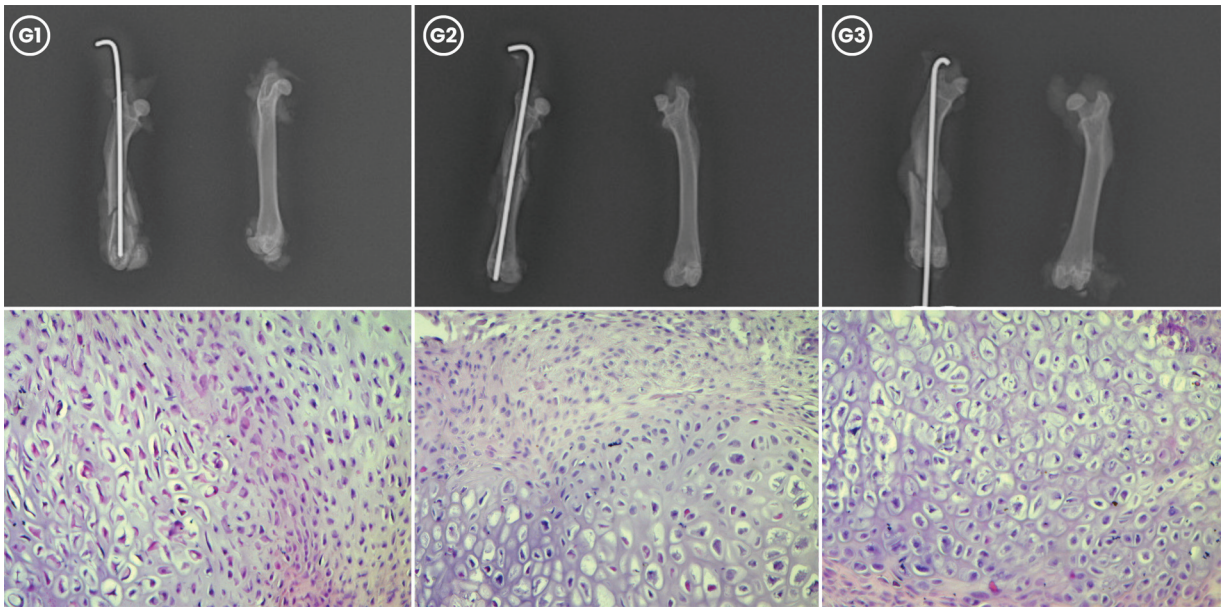


Fig. 1 Radiographic and histological evaluation of femoral fracture healing in G1, G2, and G3 at 15 days postfracture. (Top) Radiographs showing callus formation in G1, G2, and G3. (Bottom) Histological sections of callus formation in each group, stained with hematoxylin and eosin (magnification 20x).

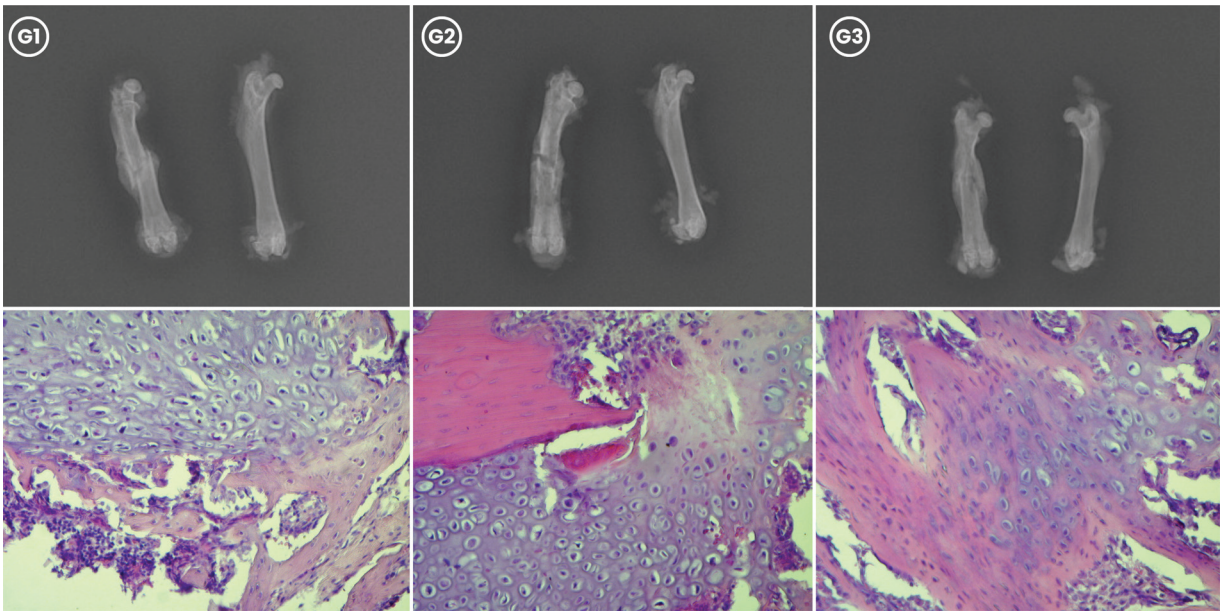


Fig. 2 Radiographic and histological evaluation of femoral fracture healing in G1, G2, and G3 at 30 days postfracture. (Top) Radiographs showing consolidated fractures in G1, G2, and G3. (Bottom) Histological sections stained with hematoxylin and eosin, demonstrating bone tissue formation, with G3 showing more advanced callus maturation compared with G1 and G2 (magnification 20x).

the results (►**Table 1**). At 30 days, no significant difference was observed regarding the size and ratio of bone calluses among the groups, as seen in ►**Fig. 2**.

Histological Evaluation

The analysis of the slides revealed that at 15 days (►**Fig. 1**), all rats presented a predominance of cartilaginous tissue, with no statistical difference between the groups (►**Table 2**). At 30 days (►**Fig. 2**), G3 showed a predominance of bone tissue, while the other groups still had a higher quantity of cartilage ($p < 0.05$).

In the uterine tissue's evaluation, it was observed that there was no difference between G2 and G3 at 15 days, which were significantly larger than G1 in both endometrial and myometrial evaluations. When comparing the groups at 30 days, G3 showed a reduction in endometrial thickness compared with G2. The results of the endometrial and myometrial thickness measurements are shown in ►**Table 3**. Throughout the duration of the experiment, there were no sample losses.

Table 2 Evaluation of the histological score of bone callus maturation as proposed by Huo et al.[22] at 15 and 30-days

	Day 15	Day 30
G1	5.28 ± 0.75^a	7 ± 0.78^a
G2	5.5 ± 1.2^a	6.5 ± 0.79^a
G3	5.8 ± 1.31^a	7.83 ± 0.71^b

Abbreviations: G1, group 1; G2, group 2; G3, group 3. **Notes:** Results are displayed in median ± standard deviation. Different letters in the columns denote significant difference $p < 0.05$.

Discussion

The oophorectomy performed in this experiment was sufficient to produce an osteoporosis model and consequently alter bone callus formation. Lill et al.[4] indicated that this disease decreases bone callus formation in the initial stages of consolidation and callus mineralization in the final stages, with osteoporotic rats exhibiting a 40% smaller callus than the control group.

Estrogen enhances the osteogenic differentiation of mesenchymal stem cells and osteoblast maturation, favoring bone formation. Additionally, this hormone inhibits osteoclast formation and induces osteoclast apoptosis, limiting bone resorption. Estrogen receptors are highly expressed in osteoblasts and osteocytes, generating protective effects on bone.[23]

Estrogen deficiency alters the expression of estrogen target genes, inducing the expression of proinflammatory cytokines such as interleukins (IL)-1, -6, and tumor necrosis factor in the early stages of the consolidation process, reducing osteogenic capacity and delaying callus formation.[24] One of estrogen's actions is to increase TGF-β release, which stimulates collagen and proteoglycan production by mesenchymal cells and osteoblasts, as well as fibronectin production in bone tissue.[25]

Beil et al.[7] analyzed the effect of estrogen on fractures in osteoporotic rats and found increased chondrocyte formation in the early stages of the consolidation process in rats treated with estrogen pearls, demonstrating that this hormone stimulates chondral formation. In the present study, the administration of this hormone in the form of nanocapsules induced greater bone callus production at 15 days,

Table 3 Evaluation of uterine tissue thickness at 15 and 30-days (in μm)

	Myometrium		Endometrium	
	Day 15	Day 30	Day 15	Day 30
G1	382,096 ± 75,017.84[a]	298,256 ± 53,430[a]	427,311 ± 97,735[a]	394,883 ± 79,977[a]
G2	458,528 ± 105,627.8[b]	440,251 ± 58,007[b]	783,537 ± 192,171[b]	623,729 ± 101,592[b]
G3	697,511 ± 98,439.72[b]	390,452 ± 76,422[b]	739,547 ± 131,672[b]	510,073 ± 54,705.11[c]

Abbreviations: G1, group 1; G2, group 2; G3, group. **Notes:** Results are displayed in median ± standard deviation. Different letters in the columns denote significant difference $p < 0.05$.

as observed in the measurements. Estrogen positively regulates chondrocyte function and maturation, influencing the articular surface and growth plate epiphyses.[25] This observation, supported by Richmond et al.,[26] is reinforced by the finding that the bone callus size was significantly larger in the groups treated with it, with G2 and G3 being equal and showing a larger callus than the control group.

It is known that the sooner the inflammatory phase is overcome and the chondral formation process begins, the sooner this tissue will mineralize and the fracture will be repaired.[6] Estrogen's role extends beyond chondrogenesis stimulation in the early stages, as it also influences periosteal consolidation in the final stages of callus formation. Beil et al.[7] found high levels of calcein, a marker of osteoblastic activity, in osteoporotic rats treated with this hormone. Although the present study did not evaluate this marker, we can infer that the macroscopic result found was due to better cellular activity influenced by estrogen.

The greater bone callus formation observed in G2 and G3 showed an acceleration of the process attributed to estrogen, with a statistically better result for the group treated with nanocapsules. The use of nanocapsules improves local action at 15 days, as the group treated with nanocapsules presented a larger bone callus. According to Salimi et al.,[27] the use of estrogen in nanoparticle form may allow control of the release rate of the active ingredient, prolonging the pharmacological effect at the site of injury.

At 30 days, radiographic evaluation showed no significant difference in bone callus size among the groups ($p > 0.05$). Despite G3 having a larger bone callus at 15 days, there were no differences in microscopic callus maturation between groups. Histological evaluation at 30 days revealed better maturation in G3. This improved quality is attributed to the early stimulation of osteochondrogenic cells by estrogen nanocapsules.[28]

There was a better bone callus formation in G3 compared with other groups, with a larger callus at 15 days and better quality at 30 days, attributed to improved drug action and permeation. Kaur et al.[29] found higher permeability with nanocapsule formulations in osteoporotic rats, supporting our findings that they significantly enhance drug diffusion to the fracture site compared with conventional methods.

The evaluation of the uterus as a sentinel organ in this study served to monitor the effect of treatments on endometrial tissue. In both treated groups at 15 days, an increase in endometrial and myometrial tissue was observed compared with the untreated group. However, at 30 days, there was a smaller endometrial size in G3 compared with G2. This observation reinforces the results found in the bone callus formation process. Nanoencapsulated drugs reach the action site better, leaving a smaller amount for systemic effects. Silva et al.[30] in their work did not observe systemic effects of topical estrogen treatment, disagreeing with what was found in this study.

Study Limitations

This study has encountered several limitations. First, we did not assess the minimum effective concentration of estrogen nanocapsules specifically tailored for this application. Furthermore, while our investigation primarily focused on the hormone's local effects on bone healing and its potential systemic implications on uterine tissue, we acknowledge that evaluating other systemic implications beyond uterine tissue could offer a more comprehensive understanding its overall impact. Lastly, we did not explore alternative concentrations in the administration of estrogen, which could reveal dose-dependent effects and provide additional avenues for optimization in future studies.

Conclusion

Considering the results of this study, estrogen accelerated the fracture consolidation process in osteoporotic rats, mainly by accelerating the chondral phase and culminating in better bone matrix at thirty days. The option of estrogen in nanocapsules obtained a better result than conventional administration. Importantly, the systemic effects, evaluated through uterine tissue analysis, revealed a significant reduction in endometrial thickness in the group treated with nanocapsules compared with those treated with conventional estrogen, indicating fewer systemic side effects.

There seems to be room for the use of local estrogen in nanocapsules for the treatment of postmenopausal osteoporotic fractures. The concentration of this hormone at the fracture site stimulates and accelerates the bone callus formation process, thus avoiding complications inherent to

this type of fracture. The administered dose, as well as the reduction of systemic repercussions, should be further analyzed by subsequent studies.

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

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Effects of Intra-articular Bone Marrow Aspirate Infiltration in the Treatment of Knee Osteoarthritis: A Clinical Study Comparing BMA versus Corticosteroid and Genicular Block

Efeitos da infiltração intra-articular de aspirado de medula óssea no tratamento da osteoartrite de joelho: Estudo clínico comparando BMA versus corticosteroide e bloqueio genicular

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Abstract

Objective To assess the efficacy of autologous bone marrow aspirate (BMA) in reducing pain and improving functionality in patients with knee osteoarthritis (OA), in comparison with intraarticular corticosteroid injection and genicular nerve block.

Methods A prospective, randomized, controlled, single-blinded, comparative, and analytical clinical study was conducted. There were 50 patients with knee OA divided into two groups: an intervention group receiving BMA treatment and a control group undergoing standard corticosteroid articular infiltration and genicular block. Outcome measures were evaluated using the Western Ontario and McMaster universities osteoarthritis index (WOMAC).

Results After 6 months, significant pain reduction was noted in the BMA group compared with the control group ($p = 0.030$). No significant differences were found in stiffness and physical activity scores between the groups. The intervention group demonstrated significant improvements in all assessed WOMAC subcategories pre- and posttreatment.

Conclusions Treatment with BMA can significantly reduce pain, potentially leading to an improved functionality, suggesting its potential as a viable therapeutic option for managing knee OA.

Keywords
- bone marrow
- injections, intra-articular
- osteoarthritis, knee
- pain management

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Resumo

Objetivo Avaliar a eficácia do aspirado de medula óssea autólogo (BMA) na redução da dor e melhoria da funcionalidade em pacientes com osteoartrite (OA) de joelho, comparando com a infiltração intra-articular com corticoide e bloqueio genicular.

Métodos Foi conduzido um estudo clínico prospectivo, randomizado, controlado, simples-cego, comparativo e analítico. Foram 50 pacientes com osteoartrite de joelho, divididos em dois grupos: um grupo de intervenção recebendo tratamento com BMA e um grupo controle submetido à infiltração articular padrão com corticoide e bloqueio genicular. Os resultados foram avaliados usando o Índice de Osteoartrite das Universidades de Western Ontario e McMaster (WOMAC).

Resultados Após 6 meses, uma redução significativa da dor foi observada no grupo BMA em comparação ao grupo controle ($p = 0.030$). Não foram encontradas diferenças significativas nos escores de rigidez e atividade física entre os grupos. O grupo de intervenção demonstrou melhorias significativas em todas as subcategorias do WOMAC avaliadas antes e após o tratamento.

Conclusão O tratamento com BMA pode reduzir significativamente a dor, possibilitando uma possível melhora funcional, sugerindo seu potencial como uma opção terapêutica viável no manejo da OA de joelho.

Palavras-chave

- injeções intra-articulares
- manejo da dor
- medula óssea
- osteoartrite de joelho

Introduction

Knee osteoarthritis (OA) is a chronic degenerative condition predominantly affecting females and resulting in the progressive deterioration of the articular cartilage. This disease leads to deformities in the joint, along with possible muscular and ligamentous imbalances, particularly in areas subjected to greater load, as evidenced by typical radiographic features including bone sclerosis, cysts, and osteophytes.[1–3]

The presence of knee OA significantly impacts physical performance and is considered one of the top ten causes of disability globally. Conservative therapeutic approaches commonly employed for the treatment of this condition include weight loss, physical exercises, administration of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, intraarticular injections containing hyaluronic acid (HA) and glucocorticoids, and genicular blocks.[4]

Recently, orthobiologic injections have emerged as a potentially safe and effective option for treating knee OA, including bone marrow aspirate (BMA), mesenchymal stem cells (MSCs), and platelet-rich plasma (PRP).[5] The use of BMA as an innovative cell therapy stands out because its technique is simple, presents low morbidity, and provides MSCs. These cells have the ability to promote the repair of articular tissue and influence the expression of cytokines IL-8 and -1β, and serve as a source of intracellular signaling peptides, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF).[6,7] Thus, orthobiologic injections can be an excellent option in the treatment of gonarthrosis.

Therefore, the aim of this study is to evaluate the efficacy of using autologous BMA to reduce pain and improve functionality in patients with knee OA, in comparison with intra-articular corticosteroid injection and genicular nerve block.

Materials and Methods

Following approval by the Research Ethics Committee (CAAE: 1164923.6.0000.5200), a prospective, randomized, controlled, longitudinal, single-blind (evaluators), comparative, descriptive, and analytical clinical study was conducted. This study involved patients with knee OA who were treated at the orthopedics service of our institution. The patients were organized into two groups through block randomization, with the only specification being an equivalent number of patients in each group. Group 1 (intervention) was assigned to receive treatment with BMA; Group 2 (control) was assigned to receive treatment with articular corticosteroid infiltration and genicular block, standard at the institution. All procedures were performed by the same surgeon.

The number of sample components was stipulated to ensure a 95% confidence interval (CI), a power of approximately 80%, and a between-group difference of 20%; that is, 25 people in the intervention group and 25 in the control group, totaling 50 individuals.[8]

Inclusion criteria were patients between 30 and 90-years-old, with OA grades II to IV according to the Kellgren and Lawrence scale,[9] absence of other inflammatory rheumatic diseases, no prior treatment with corticosteroids, either injectable or oral, in the past 12 months, and who signed the informed consent form.

Exclusion criteria were those with any condition that precluded follow-up, loss of follow-up/contact with the patient, use of oral or IV corticosteroids during the follow-up period, hemoglobin less than 11 g/dl, platelet count less than 150,000/mm^3, or any coagulation disorder.

Group 1 (Intervention): BMA Treatment

Using ultrasound guidance, approximately 15 ml of BMA was drawn from the anterosuperior iliac spine into heparinized

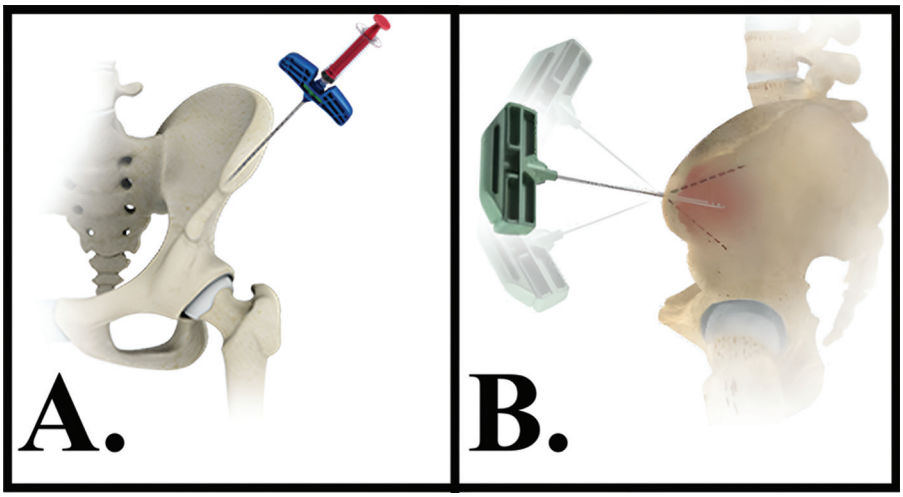


Fig. 1 Bone marrow aspirate (BMA). (**A**) Puncture at the iliac crest near the anterior superior iliac spine, with a 40° inclination from lateral to medial and 40°o from superior to inferior. (**B**) The needle can be withdrawn and reinserted with a slight change in angulation to aspirate bone marrow from another site, which may improve the concentration of MSCs.

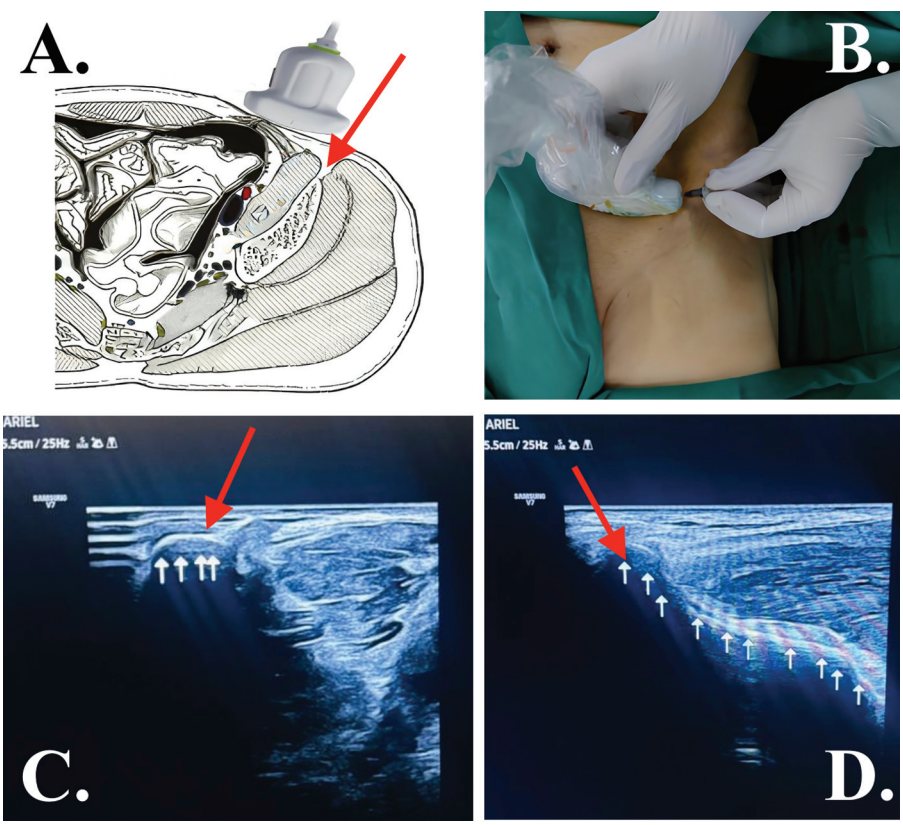


Fig. 2 Bone marrow aspirate (BMA). (**A**) Schematic figure showing the ultrasound probe transversely aligned with the iliac bone. (**B**) Patient image showing the ultrasound probe transversely aligned with the iliac bone. (**C**) Ultrasound image corresponding to the position of the ultrasound probe transversely aligned with the iliac bone. (**D**) By rotating the probe 90°, the ultrasound image corresponding to the position of the ultrasound probe longitudinally aligned with the iliac bone. Red arrow, Iliac puncture site; white arrows, iliac cortical bone.

syringes, using a multi-site low-volume technique,[10] as shown in ►**Figs. 1** and **2**. The patient, under sedation and local anesthesia with 1% lidocaine, BMA was collected using an 11 G biopsy needle/canula.

A 20 ml solution was prepared consisting of 8 ml of ropivacaine (10 mg/ml), 10 ml of 50% dextrose, plus 2 ml of dexamethasone (4 mg/2.5 ml). This solution was used for genicular branch blocks, guided by ultrasound.[11] Then, 5 ml was injected into the medial femoral, 5 ml into the lateral femoral, and 5 ml into the medial tibial genicular branches (►**Figs. 3**, **4** and **5**). The remaining 5 ml were mixed with the 15 ml of BMA and

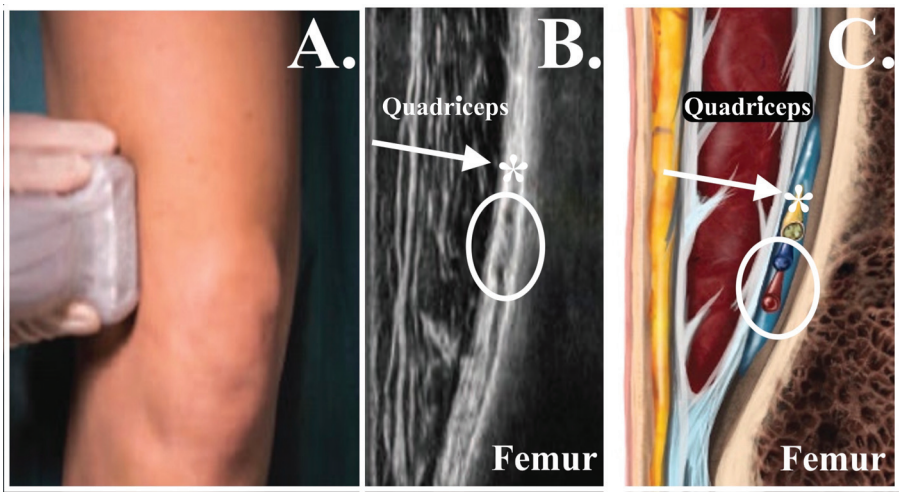


Fig. 3 Anatomical landmarks for the lateral superior genicular nerve (LSGN) block. (**A**) Transducer in the coronal plane at the distal lateral metaphyseal region of the femur. (**B**) Ultrasound image obtained with the transducer in the coronal plane at the distal lateral metaphyseal region of the femur. (**C**) Schematic image in the coronal plane at the distal lateral metaphyseal region of the femur. White arrow and *, lateral superior genicular nerve; white circle, lateral superior genicular vein and artery.

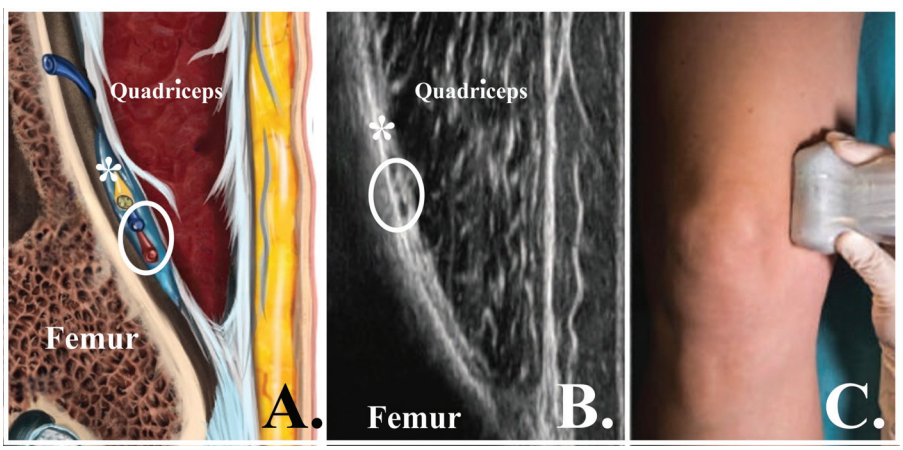


Fig. 4 Anatomical landmarks for the medial superior genicular nerve (MSGN) block. (**A**) Schematic image in the coronal plane at the distal medial metaphyseal region of the femur. (**B**) Ultrasound image obtained with the transducer in the coronal plane at the distal medial metaphyseal region of the femur. (**C**) Transducer in the coronal plane at the distal medial metaphyseal region of the femur. *Medial superior genicular nerve; white circle, medial superior genicular vein and artery.

intraarticularly infiltrated into the knee in question (►**Fig. 6**).

Group 2 (Control): Articular Corticosteroid Infiltration and Genicular Block, Standard of the Institution

A 20 ml solution was produced consisting of 8 ml of ropivacaine (10 mg/ml), 10 ml of 50% dextrose, plus 2 ml of dexamethasone (4 mg/2.5 ml). This solution was used for the genicular branch blocks, guided by ultrasound. Then, 5 ml was injected into the medial femoral, 5 ml into the lateral femoral, 5 ml into the medial tibial genicular branches. The remaining 5 ml were to be intraarticularly infiltrated into the knee in question. This procedure is standard at our institution and the only difference compared with Group 1 is that the control group does not receive BMA infiltration.

Patient Evaluation

All patients were encouraged to discontinue the use of NSAIDs 2 weeks before and several weeks after treatment. If patients experienced postprocedural pain, rescue medication with opioids was prescribed for up to 5 days. Patients were advised to avoid activities that could exacerbate pain throughout their rehabilitation protocol, which would begin with rest and home/community ambulation. The progression of physical activities included swimming or low-impact exercise, followed by walking, resistance training, running, and finally advancing to full functional activity.

The variables analyzed in each group were age, gender, and laterality. To evaluate the therapeutic response, the Western Ontario and McMaster universities osteoarthritis index (WOMAC) was used, validated and standardized

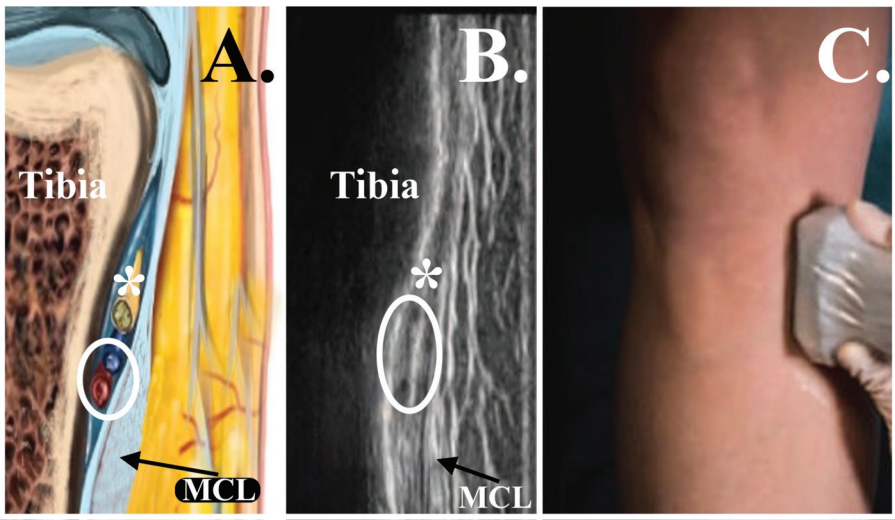


Fig. 5 Anatomical landmarks for the medial inferior genicular nerve (MIGN) block. (**A**) Schematic image in the coronal plane at the proximal medial metaphyseal region of the tibia. (**B**) Ultrasound image obtained with the transducer in the coronal plane at the proximal medial metaphyseal region of the tibia. (**C**) Transducer in the coronal plane at the proximal medial metaphyseal region of the tibia. *Medial inferior genicular nerve; white circle, medial inferior genicular vein and artery. Abbreviation: MCL, medial collateral ligament.

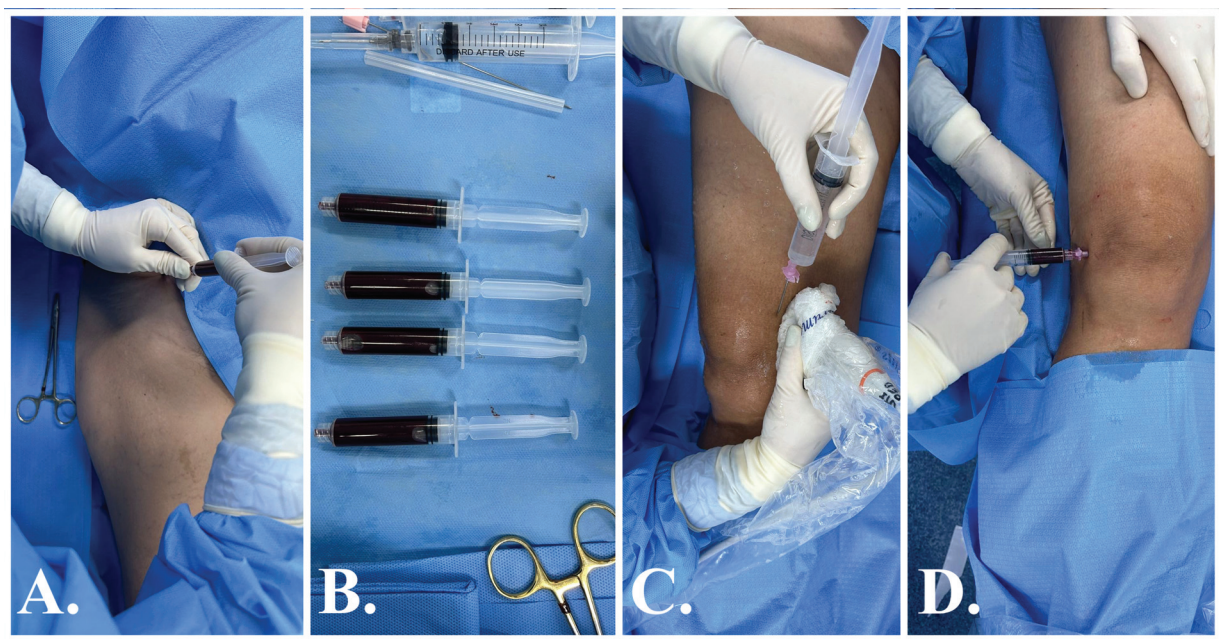


Fig. 6 Group 1 (Intervention), BMA treatment. (**A**) BMA from the anterosuperior iliac spine using heparinized syringes. (**B**) Approximately 15 ml of bone marrow. (**C**) A 20 ml solution was prepared consisting of 8 ml of ropivacaine (10 mg/ml), 10 ml of 50% dextrose, and 2 ml of dexamethasone (4 mg/2.5 ml). This solution was used for genicular branch blocks, guided by ultrasound. From it, 5 ml each were applied to the medial femoral, lateral femoral, and medial tibial genicular branches. (**D**) The remaining 5 ml of the previous solution (ropivacaine + dextrose + dexamethasone) were mixed with the 15 ml of BMA and intraarticularly infiltrated into the knee in question.

for the patients' native language.[12,13] This questionnaire contains 17 questions regarding the level of difficulty in performing daily life activities, pain, and stiffness, to assess patient functionality. The higher the score, the worse the function.[14] In this questionnaire, a clinically relevant difference criterion is used, a possible reduction of 16% of the total score acquired before the intervention.[15] Patients were evaluated before the procedure, after 1, 3, and 6 months of the infiltrative act. The Kellgren and Lawrence (KL) classification was used in the pre-infiltration evaluation.[9]

Data Analysis Methodology

Categorical and numerical variables were tabulated and analyzed using the R (R Foundation for Statistical Computing, Vienna, Austria) software for Mac OS X, which provided

measures of central tendency, percentile values, and dispersion.

To evaluate the efficacy of comparative treatments between the use of BMA and the standard treatment with articular corticosteroid infiltration and genicular block, nonparametric statistical tests were used, given the distribution of the data. The Mann-Whitney U test was applied to compare the WOMAC scores (pain, stiffness, and physical activity) between the two groups at each of the four evaluation times (pre-intervention, and at 1, 3, and 6 months posttreatment). This test was chosen because it does not assume a normal distribution of data and is suitable for independent samples.

To compare the WOMAC scores (pain, stiffness, and physical activity) for each patient before the procedure and after 6 months, the Wilcoxon signed-rank test was used, suitable for paired nonparametric samples.

To investigate the relationship between age and WOMAC scores, Spearman's correlation was used. The chi-squared test was applied to examine the relationships between gender and laterality with the scores categorized into high and low pain, stiffness, and physical activity.

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

Results

After 6 months of follow-up, we concluded with 35 patients, 17 in Group 1 (intervention with autologous BMA) and 18 in Group 2 (control with articular corticosteroid infiltration and genicular block). The average age of participants was approximately 58 years, with 58.06 in Group 1 and 57.78 in Group 2. Regarding age, laterality, and gender, no statistically significant differences were observed between groups 1 and 2. In terms of gender distribution, Group 1 consisted of 12 women and 5 men, while Group 2 had 13 women and 5 men.

Regarding WOMAC – Pain, comparing groups 1 and 2 at the preblock stage, there was no statistically significant difference between the groups ($p = 0.052$). At the 1 and 3-month follow-ups, the differences were also not significant ($p = 0.276$ and 0.960, respectively). At 6 months, there was a significant difference, with the BMA group showing a lower pain score compared with the control group ($p = 0.030$), as shown in ►**Fig. 7**.

Regarding WOMAC – Stiffness, comparing groups 1 and 2, no statistically significant differences were observed at any of the evaluated periods ($p = 0.627$, 0.789, and 0.097 at 1, 3, and 6 months, respectively).

Regarding WOMAC – Physical Activity, comparing groups 1 and 2, no statistically significant differences were observed at any of the evaluated periods ($p = 0.894$, 0.960, and 0.114, at 1, 3, and 6 months, respectively).

However, comparing the total score over 6 months, Group 1 (BMA) showed better results. Nevertheless, although there is a trend toward a difference, it is not statistically significant at the 5% significance level ($p > 0.05$), as shown in ►**Fig. 8**.

The correlation between age and stiffness at 6 months was moderately positive and statistically significant ($\rho = 0.366$, $p = 0.031$), suggesting that older patients may experience

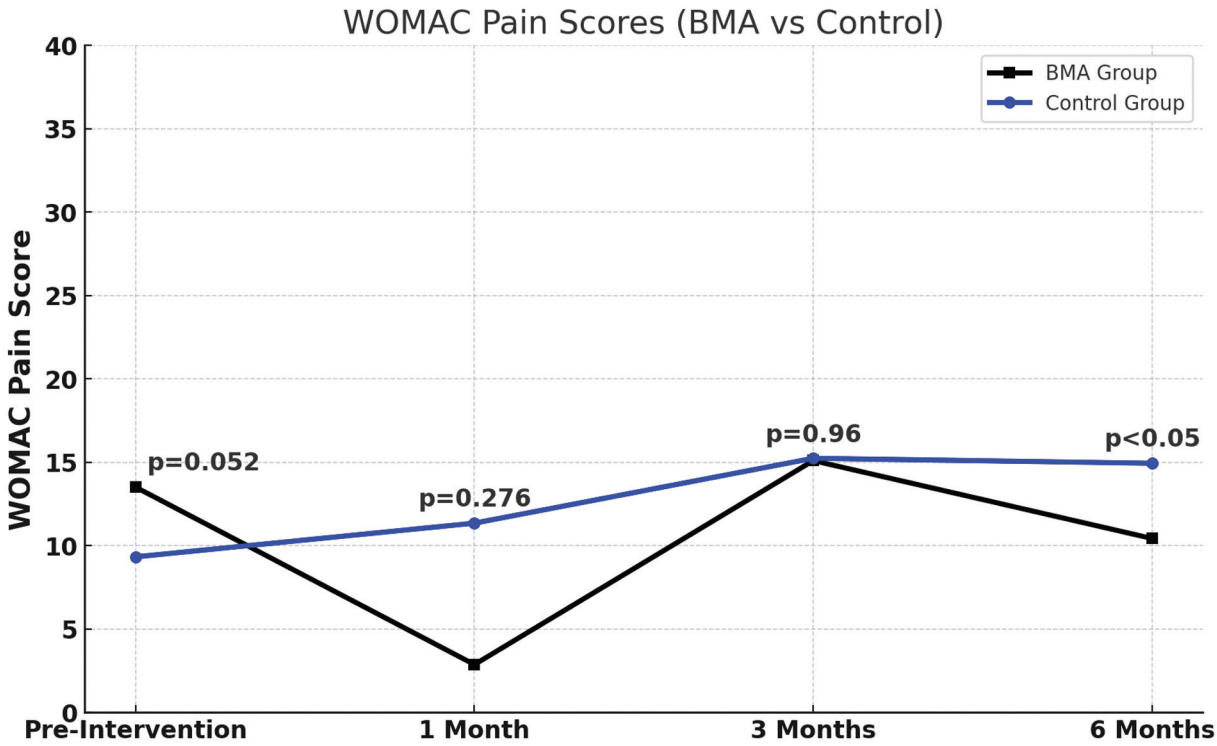


Fig. 7 WOMAC – Pain (BMA vs. Control). Scores between the two groups at each of the four evaluation times (preintervention, and at 1, 3, and 6-months posttreatment). This subsection assesses the intensity of pain during various activities, such as walking, climbing stairs, lying down, and standing. The higher the score, the greater the severity of symptoms and patients' functional limitation. The *p*-value corresponds to the independent *t*-test between the two groups at each of the four evaluation times.

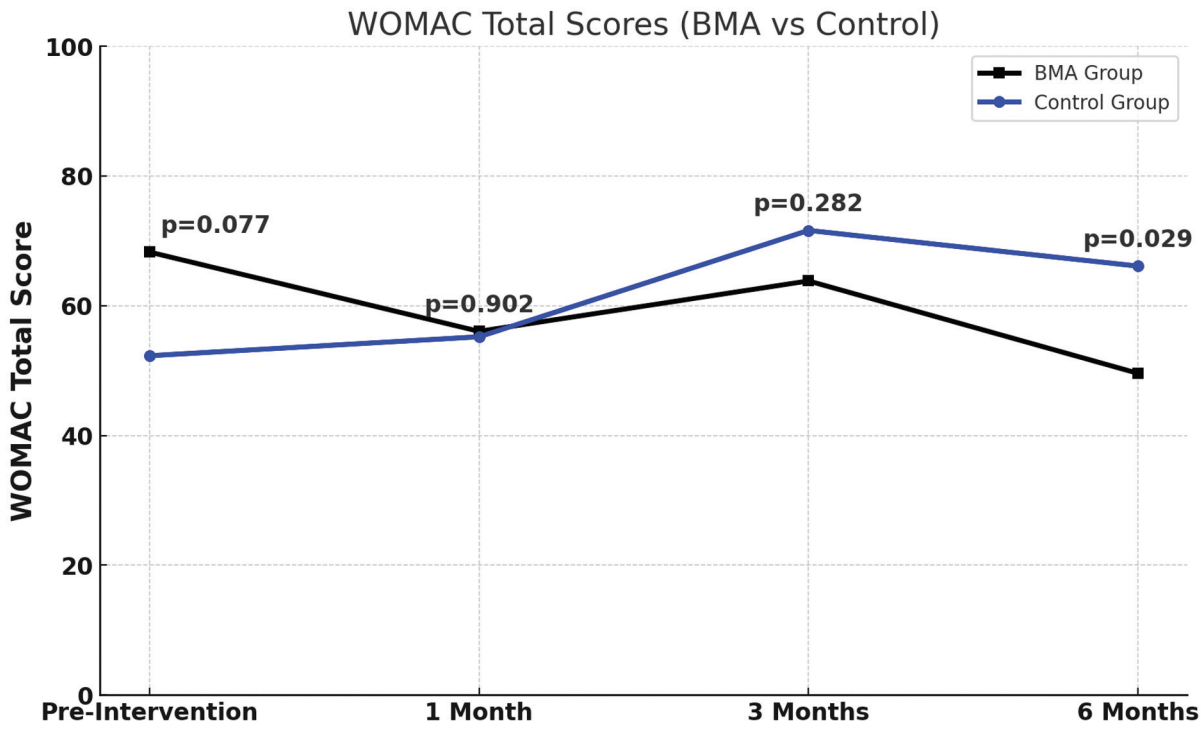


Fig. 8 WOMAC – Total Scores (BMA vs. Control). The total scores between the two groups at each of the four evaluation times (preintervention, and at 1, 3, and 6 months posttreatment). The total score is the sum of the scores from the three subscales (Pain, Stiffness, and Physical Function). The higher the score, the greater the severity of symptoms and patients' functional limitation. The *p*-value corresponds to the independent *t*-test between the two groups at each of the four evaluation times.

greater stiffness over time, regardless of which technique was used. No significant associations were found between gender or laterality and WOMAC scores in any of the evaluated periods.

These results indicate that BMA treatment may offer significant benefits in reducing pain in patients with knee OA, compared with the standard treatment of articular corticosteroid infiltration and genicular block. However, despite both treatments showing improvement in physical activity and stiffness scores over time, there were no significant differences between the groups in these scores (►**Table 1**).

Table 1 The WOMAC scores in groups 1 (BMA) and 2 (control)

Group 1 (BMA)	Preintervention			1-month postintervention		
Patient	Pain	Stiffness	Physical functional	Pain	Stiffness	Physical functional
1	5.2	2.08	16.6	4.1	1.04	51.04
2	11.4	8.03	35	11.4	5.2	45.8
3	17.7	3.12	70.8	3.1	1.04	8.3
4	10.4	2.08	15.6	1.04	0	52.08
5	10.4	2.8	44.7	3.1	0	8.3
6	11.4	8.3	52.2	13.5	3.1	68.7
7	17.2	6.25	36.4	10.4	2.08	51.04
8	9.3	7.2	50	11.4	5.2	45.8
9	14.5	3.1	55.2	11.4	6.2	50
10	9.3	2.08	40.6	2.08	0	30.2
11	17.7	6.2	66.6	13.5	5.2	52.08
12	20.8	8.3	93.7	4.1	6.2	8.3
13	20.8	8.3	68.75	3.1	1.04	51.04

(*Continued*)

Table 1 (*Continued*)

14	17.2	8.08	40.6	4.1	0	12.5
15	11.4	6.25	44.7	13.5	0	8.3
16	10.4	8.3	66.6	27	6.25	58.3
17	14.5	6.25	36.4	13.5	6.2	45.8
Group 1 (BMA)	**3-months postintervention**			**6-months postintervention**		
Patient	**Pain**	**Stiffness**	**Physical functional**	**Pain**	**Stiffness**	**Physical functional**
1	9.3	6.2	15.6	3.1	1.04	8.3
2	17.2	2.08	36.4	11.4	1.04	30.2
3	20.8	8.08	40.6	13.5	3.1	45.8
4	17.2	8.08	66.6	3.1	0	68.7
5	17.7	2.8	44.7	11.4	5.2	58.3
6	11.4	8.3	52.2	4.1	1.04	30.2
7	17.2	6.25	36.4	13.5	5.2	45.8
8	9.3	7.2	50	27	5.2	51.4
9	14.5	3.1	55.2	13.5	1.04	52.05
10	9.3	2.08	40.6	3.1	0	8.3
11	17.7	6.2	66.6	27	3.1	45.8
12	20.8	8.3	93.7	11.4	6.2	8.3
13	20.8	8.3	68.75	3.1	6.2	51.04
14	17.2	8.08	40.6	4.1	0	12.5
15	11.4	6.25	44.7	13.5	1.4	8.3
16	10.4	8.3	66.6	11.4	6.25	58.3
17	14.5	6.25	36.4	3.1	6.2	30.2
Group 2 (control)	**Preintervention**			**1-month postintervention**		
Patient	**Pain**	**Stiffness**	**Physical functional**	**Pain**	**Stiffness**	**Physical functional**
1	4.1	1.04	51.04	9.3	0	52.08
2	11.4	5.2	45.8	10.4	3.1	51.04
3	3.1	1.04	8.3	11.4	2.08	30.2
4	1.04	0	52.08	3.1	5.2	45.8
5	3.1	0	8.3	4.1	1.04	30.8
6	13.5	3.1	68.7	13.5	6.2	68.7
7	10.4	2.08	51.04	10.4	2.08	52.08
8	11.4	5.2	45.8	13.5	2.08	45.8
9	11.4	6.2	50	11.4	6.2	30.2
10	2.08	0	30.2	27	1.04	45.8
11	13.5	5.2	52.08	13.5	5.2	52.08
12	4.1	6.2	8.3	4.1	6.2	8.3
13	3.1	1.04	51.04	3.1	1.04	51.04
14	4.1	0	12.5	4.1	0	12.5
15	13.5	0	8.3	13.5	0	30.2
16	27	6.25	58.3	27	6.25	51.04
17	13.5	6.2	45.8	13.5	6.2	30.2
18	17.7	8.3	68.75	11.4	2.08	45.8

Table 1 (*Continued*)

Group 2 (control)	3-months postintervention			6-months postintervention		
Patient	Pain	Stiffness	Physical functional	Pain	Stiffness	Physical functional
1	13.5	6.2	15.6	20.8	6.25	45.8
2	17.2	2.08	36.4	4.1	3.1	30.2
3	20.8	8.08	40.6	13.5	3.1	52.05
4	17.2	8.08	66.6	20.8	5.2	68.7
5	17.7	2.8	44.7	11.4	5.2	58.3
6	11.4	8.3	52.2	4.1	6.25	51.4
7	17.2	6.25	36.4	13.5	5.2	45.8
8	9.3	7.2	50	27	5.2	51.4
9	14.5	3.1	55.2	13.5	1.04	52.05
10	9.3	2.08	40.6	13.5	3.1	30.2
11	17.7	6.2	66.6	27	5.2	45.8
12	20.8	8.3	93.7	11.4	6.2	68.75
13	20.8	8.3	68.75	17.7	6.2	51.04
14	17.2	8.08	40.6	13.5	1.4	12.5
15	11.4	6.25	44.7	13.5	3.1	30.2
16	10.4	8.3	66.6	11.4	5.2	58.3
17	14.5	6.25	36.4	20.8	6.2	30.2
18	13.5	1.04	52.2	11.4	3.1	58.3

Abbreviation: BMA, bone marrow aspirate; WOMAC, Western Ontario and McMaster universities osteoarthritis index.

Discussion

This study evaluated the efficacy of treating knee OA using autologous BMA compared with joint corticosteroid infiltration and genicular block. Regardless of the group, all patients showed clinical improvement. However, results after 6 months of follow-up indicate a significant reduction in pain for the group treated with BMA, suggesting an improvement in the quality of life for these patients.

The BMA technique has been highlighted in various orthopedic conditions due to its regenerative potential and associated low risk. Specifically, BMA provides a rich supply of regenerative cells capable of differentiating into various tissue types, representing a promising approach for treating OA. With the current understanding of the inflammatory mechanisms in OA, BMA is considered a relevant therapeutic alternative.[5,7] This treatment is based on MSCs, which are pluripotent, meaning they have the ability to differentiate into a variety of tissues, including osteocytes, chondrocytes, adipocytes, mast cells, fibroblasts, and hematopoietic precursor cells.[16] Moreover, these cells have immunomodulatory properties and can suppress chondrocyte apoptosis.[17]

One of the advantages of BMA as a source of MSCs is that its technique is relatively simple. It is a percutaneous procedure with low morbidity because it is an autologous source and does not require processing, unlike bone marrow aspirate concentrate (BMAC) and adipose sources, which need several processing steps.[5,18] Regarding standardization, there is no universally standardized protocol for processing. Different clinics and researchers may use slightly different parameters. The efficacy of BMAC may depend on the quality and purity of the preparation. As for regulations and guidelines, depending on the country or region, there may be specific regulations governing its processing and use. In some countries, the use of processed bone marrow is only allowed through research protocols.

The preferred site for obtaining the aspirate is usually the posterior iliac crest, a safe location that presents fewer complications and has a higher quantity of MSCs compared with the anterior iliac crest.[19] However, there is still no consensus on some aspects of the technique, such as patient positioning, anesthesia, and the choice of collection needles.[20,21] The main factor of the technique is to maintain constant and low aspiration pressure, choosing syringes of 5 or 10 ml.[22] This is because MSCs are diluted in blood when aspirated, causing 85% of the available cells to be collected in the first 2 ml of aspirate. Therefore, every 2 ml collected, the needle should advance 0.5 to 1 cm to optimize collection.[5]

Bastos et al.[23] studied the efficacy and safety of intraarticular injections of expanded autologous stromal MSCs obtained from bone marrow aspiration ($\pm$80–100 ml) from both posterior iliac crests in patients with knee OA. These authors concluded that intraarticular injections of expanded MSCs alone or in combination with PRP are safe and have a beneficial effect on symptoms in patients with symptomatic knee OA. These patients were evaluated with a functionality and quality of life questionnaire called the knee and osteoarthritis outcome score (KOOS) at intervals of 1, 2, 3, 6, 9, and

12 months. Similar to the other study, an initial improvement peak was observed in the first 2 months, stabilizing until the 9th month and then experiencing a slight improvement in the 12th month.

Garay-Mendoza et al.[24] conducted a prospective, open-label, phase I/II clinical trial to assess the safety and efficacy of a single intraarticular injection of autologously stimulated bone marrow stem cells (BM-SC) in patients with knee OA. The BM-SC were obtained by aspiration and administered in a single intraarticular injection. The control group received only oral paracetamol. The visual analog scale (VAS) and WOMAC scores were obtained at 1-week, 1-month, and 6-months in both groups. Patients showed significant improvement, especially in VAS, which was superior to the control group. This study demonstrated the viability and efficacy of a procedure that can be performed on an outpatient basis for treating knee OA.

Despite promising results, the long-term efficacy and optimization of BMA treatment protocols still require validation through additional research. The regenerative potential of MSCs, although promising, is not yet fully understood. Larger and more rigorous studies are needed to consolidate BMA as a viable and effective treatment option for knee OA.[7] In our study, the absence of significant differences between groups in terms of age and gender suggests that it may be applicable to a wide range of patients without the need for selection based on these demographic criteria. This is encouraging, as it indicates that the benefits of the treatment can be generalized across both genders and a wide age range.

In this context, as regenerative medicine advances, the use of BMA for knee OA remains in an exciting phase of development. Enhanced understanding of how these therapies can be integrated into existing treatment plans could significantly alter the approach to managing OA, offering new hopes for reducing pain and improving the quality of life for patients.

Regarding the limitations of this study, we highlight the sample size and duration of follow-up. Unfortunately, we experienced a loss of follow-up with patients. We started the study with 50 patients, 25 in each group, and ended with only 35. Future studies should address these limitations, ideally with larger samples and longer follow-up periods, to confirm and expand the reported findings. Another limitation of the study was that we did not include important demographic data, such as body mass index and the degree of OA in each individual.

Conclusion

Treatment with BMA can significantly reduce pain, potentially leading to improved knee functionality, suggesting its potential as a viable therapeutic option for managing knee OA.

Authors' Contributions

Each author contributed individually and significantly to the development of this article. RC: study conceptualization, methodology, and writing – original draft. DMP: study validation, visualization, and writing – original draft. MVAK: writing – review & editing. TLVR: study conceptualization and validation. RLO: study conceptualization and validation. DAL: data curation, formal analysis, writing – review & editing.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Pathological Threshold of Patellar Tendon-Trochlear Groove Distance Using Magnetic Resonance Image in Patients with Patellar Instability

Limite patológico da distância tendão patelar-sulco da tróclea utilizando imagens de ressonância magnética em pacientes com instabilidade patelar

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Abstract

Objective To evaluate and compare the values of the patellar tendon-trochlear groove (PT-TG) distance in individuals with and without patellar instability. Additionally, we aimed to define a cut-off value for the pathological limit of the PT-TG through nuclear magnetic resonance imaging (MRI) in patients with patellar instability.

Methods The PT-TG distance of 52 knees was measured in 48 individuals with objective patellar instability (instability group) by MRI. These measurements were compared with those made in 50 knees of 44 individuals without a history of patellar instability (control group).

Results The PT-TG distance in the instability group (20.6 ± 5.0 mm) was greater than in the control group (11.8 ± 3.4 mm; $p < 0.001$). A value of 15.5 mm was determined as the pathological limit, with an accuracy of 81.4%, in MRI exams.

Conclusion Individuals with patellar instability have statistically higher measurements of PT-TG when compared with patients without it. Therefore, values higher than 15.5 mm for PT-TG seen in MRI exams represent a pathological lateralization force of the extensor mechanism related to patellar instability.

Keywords
- joint instability
- knee
- magnetic resonance imaging
- patellar ligament
- patellofemoral joint

Resumo

Objetivo Avaliar e comparar a distância tendão patelar–sulco troclear (TP-ST) em indivíduos com e sem instabilidade patelar. Um segundo objetivo foi definir um limiar

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patológico de TP-ST por meio de ressonância magnética (RM) nuclear em pacientes com instabilidade patelar.

Métodos A distância TP-ST de 52 joelhos foi medida em 48 indivíduos com instabilidade patelar objetiva (grupo instabilidade) por RM. Essas medidas foram comparadas àquelas feitas em 50 joelhos de 44 indivíduos sem histórico de instabilidade patelar (grupo controle).

Resultados A distância TP-ST no grupo instabilidade ($20,6 \pm 5,0$ mm) foi maior do que no grupo controle ($11,8 \pm 3,4$ mm; $p < 0,001$). O valor de 15,5 mm foi determinado como limiar patológico, com acurácia de 81,4%, em exames de RM.

Conclusão Indivíduos com instabilidade patelar apresentam medidas estatisticamente maiores de TP-ST em comparação a pacientes sem instabilidade. Portanto, valores de TP-ST superiores a 15,5 mm à RM representam uma força de lateralização patológica do mecanismo extensor relacionada à instabilidade patelar.

Palavras-chave
- articulação patelofemoral
- imagem por ressonância magnética
- instabilidade articular
- joelho
- ligamento patelar

Introduction

Lateral patellar instability is a pathology with an incidence ranging between 7 and 43 cases per 100 thousand inhabitants.[1,2] Anatomical risk factors are described as the main causes for this condition: trochlear dysplasia, increased tibial tuberosity-trochlear groove (TT-TG) distance, patellar tilt, and patella alta.[3,4]

The TT-TG distance is the distance between the deepest bone point of the femoral trochlea (trochlear groove, TG) and the most anterior point of the anterior tibial tuberosity (ATT). It is measured in a computed tomography (CT) scan of the knee, and patients with values equal to or greater than 20 mm, in cases of recurrent objective lateral patellar dislocations, are referred for ATT osteotomy for realignment.[4,5]

Complementary imaging exams are important for identifying risks factors to patellar instability and, thus, for choosing which procedures should be performed. A CT scan of the knee is important to evaluate the TT-TG distance according to the Lyon Protocol.[4]

Usually, nuclear magnetic resonance imaging (MRI) of the knee is useful in the evaluation of articular cartilage, ligaments, and the meniscus.[6] Although a CT scan is considered the exam of choice for the measurement of the TT-TG distance, authors have demonstrated that MRI can also be used to measure it with excellent inter and intraobserver agreement.[6–8] Despite this, it is important to note that the values measured by both methods are not interchangeable. Magnetic resonance imaging measurements tend to be lower than those of a CT scan.[7] The values obtained by MRI are more anatomical compared with the ones by CT and would represent, in a more reliable way, the biomechanical vector that act on patellar instability.[8] The CT scan request would also be dispensable, reducing costs and patient exposure to radiation.

The present study aimed to evaluate the distance measurement between the center of the patellar tendon and the cartilage of the femoral trochlear groove (PT-TG) in MRI exams of the knees in patients with objective patellar instability and to compare them with the values of subjects with no patellar instability, as well as to define the pathological cut-off point of this distance measurement.

Materials and Methods

In a case-control study, we have analyzed 102 knee MRI scans in 92 individuals, selected through simple random sampling from electronic medical records and subsequent analysis in an image bank.

The PT-TG distance of 52 knees was measured in 48 individuals with a documented history of objective patellar instability (instability group). These measurements were compared with those of 50 knees of 44 individuals who underwent a knee MRI without having a clinical history of patellar instability (control group).

The inclusion criteria for the instability group were patients with objective lateral patellar instability[9] documented by history and physical examination in the medical records of our database, in addition to indirect sights on the MRI.[10–13] These indirect sights could be contusion or osteochondral lesion of the lateral femoral condyle or medial facet of the patella, injury to the medial patellofemoral ligament, injury to the medial retinaculum in its patellar insertions or middle substance, laceration of the distal belly of the vastus medialis oblique muscle, and patellar subluxation and tilt.

From the instability group, we excluded patients with previous knee operations, who had a history of trauma (except for patellar dislocation) and presented moderate-to-severe degenerative pathologies of the joint. In the control group, we placed patients who underwent knee MRI for suspected intra-articular ligament injuries, meniscal injuries, and pain, resulting from no history of dislocation or previous patellofemoral symptoms.

Magnetic resonance imaging was performed with the patient lying supine, the limb in neutral rotation and full extension without quadriceps contraction. To obtain the measurement of the PT-TG distance, the axial T2-weighted MRI cut was used, and the following parameters, as described by Schoettle et al.,[8] were observed. The first craniocaudal image

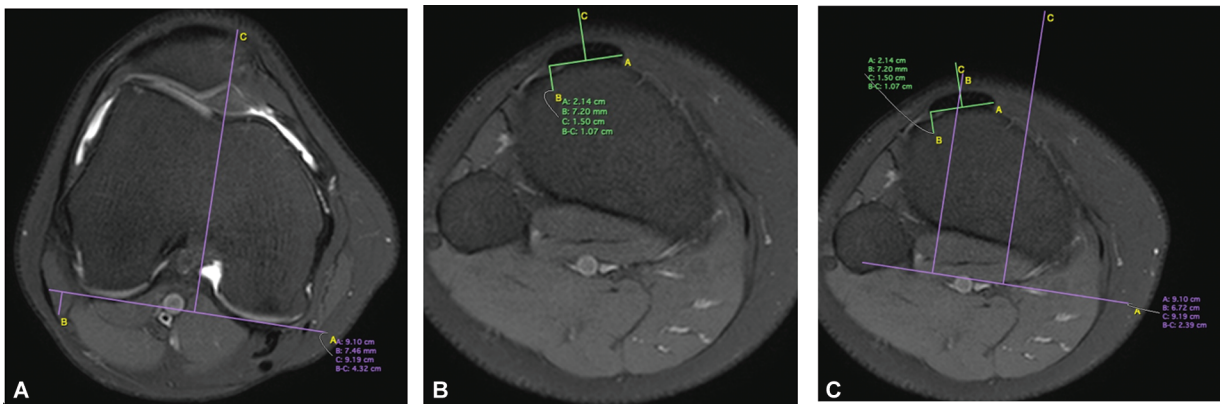


Fig. 1 Measurement of the patellar tendon-trochlear groove (PT-TG) distance. (**A**) The deepest trochlea point, TG; (**B**) the center of the patellar tendon, PT; and (**C**) the distance between these two overlapping points, PT-TG.

that completely demonstrates the entire trochlear cartilage was used to determine the TG, using the cartilaginous edges of the posterior femoral condyles as a reference. The PT is defined in the distally subsequent images in its insertion on anterior tibial tubercle (ATT). The previous TG images were then transferred to the current image, which corresponds to the overlap between the center of the PT and the deepest point of the TG. Thus, the PT-TG is measured in millimeters (►**Fig. 1**).

The measurements were performed by two orthopedists and a radiologist specialized in musculoskeletal MRI using the OsiriX DICOM Viewer (Pixmeo SARL, Geneva, Switzerland) software. Each MRI was evaluated by the three evaluators who repeated their evaluations with a minimum interval of two weeks between measurements. At no time did the evaluators have access to which group the individuals belonged to, the values found by their peers, and their previous measurement.

The exams were performed between April 2014 and September 2019, and the study was approved by our institution's Ethics Committee under number CAAE: 36188820.3.0000.5342.

Statistical Analysis

Quantitative variables were described by the mean and standard deviation, and categorical variables by absolute and relative frequencies. To compare means between the groups, the Student's t-test was applied. When comparing proportions, the Pearsons Chi-squared test was used. To assess the intra- and inter-examiner agreement, the Student's *t*-test for paired samples and the intraclass correlation coefficient (ICC) were applied. The receiver operating characteristic (ROC) curve was used to determine the best cut-off point for the PT-TG measurement in detecting knee instability. The level of significance adopted was 5% ($p < 0.05$), and the analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) software, version 21.0.

Results

Mean age was similar in both groups, with 23.3 ± 8.3 years in the instability group and 25.4 ± 6.4 years in the control group. Regarding the side, 53% and 48% of the measurements were taken on the right knee of the instability and control groups, respectively. As for gender, there was a statistically significant difference between the groups. Female patients accounted for 65.4% of the instability group and 22% of the control group.

Considering the intra-examiner agreement, a good relationship is observed between the two measurements made by the three examiners. The ICC was 0.99 in the instability group and 0.98 in the control group. ►**Fig. 2** shows the analyzed data.

There was no significant difference in the values found by the examiners in the Instability group. In the control group, examiner 3 had slightly lower averages than examiner 2. Nevertheless, the ICC was 0.98 in both groups, showing good inter-examiner agreement (►**Fig. 3**).

Objectively, in terms of the value of PT-TG, a higher average was observed in the instability group when compared with the control group. In the first one, the average was 20.6 ± 5.0 mm, while the average for the second group was $11.8\,\text{mm} \pm 3.4\,\text{mm}$ ($p < 0.001$). The comparison is illustrated in ►**Fig. 4**.

Finally, the pathological limit defined as a new cut-off point for measuring PT-TG in MRI scans is 15.5 mm. This was determined by the ROC, reaching a sensitivity of 82.7%, specificity of 80.0%, positive predictive value of 81.1%, negative predictive value of 81.6%, and accuracy of 81.4%. This cutt-off point is consistent as a tracking variable, as shown in ►**Fig. 5**.

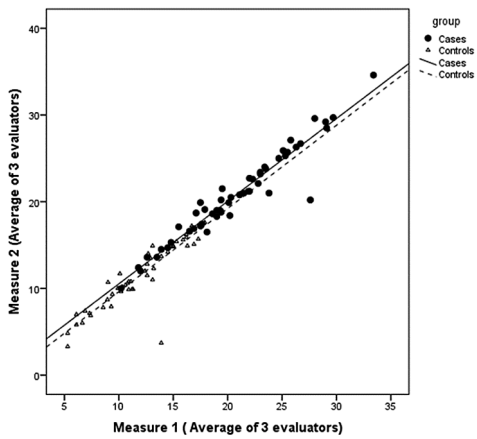


Fig. 2 Evaluation of the intra-examiner agreement.

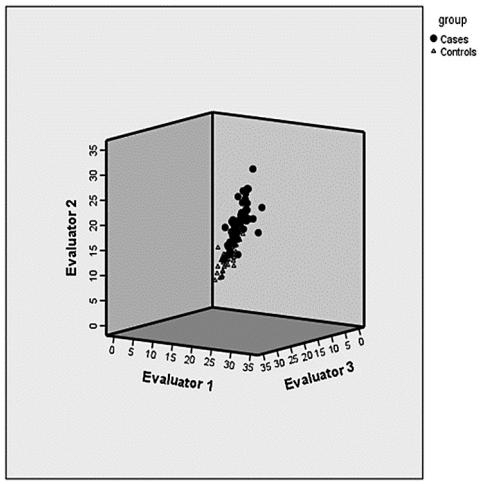


Fig. 3 Evaluation of the inter-examiner agreement.

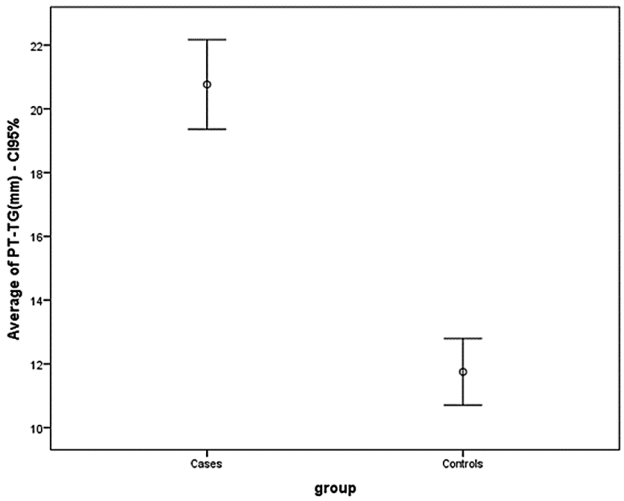


Fig. 4 Comparison of the TT-TG distance measurement between groups.

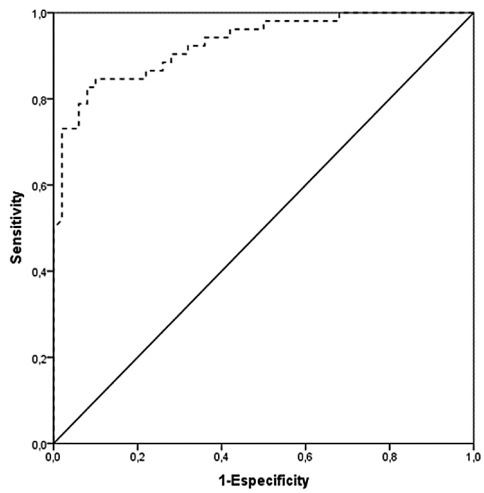


Fig. 5 Receiver operating characteristic curve to determine the best cut-off point for measuring the PT-TG distance in patellar instability screening.

Discussion

The main findings of the present study are that the individuals with lateral patellar instability have a greater measure of PT-TG when compared with patients without it. Besides, the value of 15.5 mm for PT-TG in MRI exams represents a pathological threshold related to lateral patellar instability.

The lateralized force vector of the knee extensor mechanism is recognized as one of the main factors for patellar instability, and CT scans may still be considered the gold standard to assess it. However, it has become debatable since more specific and sensitive exams have become widely accessible. In the current context, MRI has enormous importance and should be used for diagnoses and surgical planning. It allows the evaluation of the femoral and patellar articular cartilage, the precise identification of the insertion of the patellar tendon, and the integrity of the patellofemoral ligaments. In addition, radiation exposure and the additional cost of CT may be avoided.

The definition of a pathological limit of 15.5 mm in the measurement of PT-TG in MRI scans is an important factor for considering the necessity of ATT osteotomy. Thus, MRI should be considered the only necessary complementary examination, in addition to knee radiography for diagnosis and surgical planning of patellofemoral instability.

With greater availability of detailed imaging examination, as in using MRI, quality was added to preoperative diagnosis. When considering soft parts and joint surfaces, MRI enables for a superior definition than the one provided by a CT scan. Even though the tomographic measure is the gold standard for defining the TT-TG distance, studies showed an interobserver confidence lower than 60% in the measurements made by this method. The greatest difficulty faced was determining the deepest point of the TG, especially in excessively dysplastic knee trochlea.[14]

Thus, corroborating with previous studies,[8,15] it is possible to find excellent rates of inter- and intra-observer reliability for PT-TG measurement in knees with previous dislocation or without instability with ICCs as high as 0.98 and 0.99, respectively. This measurement is believed to be more physiological in relation to the bone reference points of a CT, since it truly represents the reference site where the forces responsible for aligning the knee extensor mechanism act.[8,16]

According to Camp et al.,[7] when analyzing the TT-TG and PT-TG distances in knees with patellofemoral instability using CT and MRI scans, both methods have excellent interobserver reliability. The values of PT-TG distance in MRI were constantly lower, with a bigger difference in cases in which the TT–TG distance measurement in CT was greater than 20 mm in dysplastic knees. Therefore, these results suggest that the measurement of PT-TG distance with MRI is valid, but the values of the two imaging methods are not interchangeable in patients with instability.

Pandit et al.,[6] in a study with clinically and arthroscopically normal knee joints, found mean values of 10 ± 1 mm with MRI, and these were lower than what was proposed by Dejour[4] for asymptomatic knees when measured by CT.

Similarly, Thakkar et al.[17] observed lower mean values in MRI when compared with CT for knees without instability.

In relation to knees with patellofemoral instability, Skelley et al.[15] found values of 18.2 mm in MRI, again lower than those found in the measurements by CT in previous studies. This pattern followed in later studies,[18–20] that is, the measurement of both unstable and unaffected knees of PT-TG distance by MRI showed lower values when compared with the TT-TG distance measured by CT.

Few studies have compared knees with and without instability regarding PT-TG distance measured with MRI; thus, it is necessary to validate a new pathological limit for this variable in this type of exam. The present study found a cut-off point of 15.5 mm, and with high sensitivity and specificity, this value has proved to be a consistent tool for a tracking variable.

In the present study, the groups differed in their gender representation. However, it is important to note that the authors did not consider gender at the time of sample selection and randomization because there is no difference between genders in the mean values for the TT-TG and PT-TG distance measurements described in the literature.[6,21]

It is noteworthy that this is a case-control study that used exams that had already been performed. The protocol followed for positioning the patient for knee MRI was the one used in most institutions: the limb in neutral rotation and full extension without quadriceps contraction. Moreover, even though there was a randomization of controls, there were patients who had undergone image examination due to some previous complaints unrelated to the patellofemoral joint; hence, they are not images of completely asymptomatic knee joints.

Individuals with lateral patellar instability have statistically greater measurement of the PT-TG distance than patients without it. Moreover, values greater than 15.5 mm for PT-TG distance in MRI exams represent a pathological lateralization force of the extensor mechanism, which is related to patellar instability.

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

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Treatment of Focal Chondral Lesions in the Patellofemoral Joint with Collagen Membrane: Clinical and Functional Outcomes in a Two-Year Follow-Up

Tratamento de lesões condrais focais na articulação patelofemoral com membrana de colágeno: Resultados clínicos e funcionais em seguimento de dois anos

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Abstract

Objective To evaluate the clinical and functional outcomes of patients undergoing surgical treatment to repair focal chondral lesions in the patella and trochlea using the autologous matrix-induced chondrogenesis (AMIC) technique after a minimum follow-up of 2 years.

Methods A total of 24 patients (25 knees) with a mean age of 39.6 ± 4.7 years underwent the patellofemoral AMIC technique and evaluation over a mean follow-up of 3.64 ± 0.65 years. We collected data on patient factors, lesion morphology, and patient-reported outcome measures, including the International Knee Documentation Committee (IKDC), Tegner, Kujala, Fulkerson, and Lysholm scores, as well as the Visual Analog Scale (VAS).

Results Male subjects accounted for 76% of the sample. The mean defect size of the chondral lesions was of $1.99 \pm 0.36\,cm^2$. All defects were of grade IV according to the Outerbridge classification. At the last follow-up, patients showed the following mean increases in the scores: Kujala – from 61.9 to 87.9; IKDC –from 51.3 to 83.6; Lysholm –from

Keywords
- cartilage, articular
- chondrogenesis
- knee injuries

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64.0 to 88.4; Tegner –from 4.04 to 5.12; Fulkerson –from 60.2 to 89.3; and VAS – from 5.6 to 1.24. All results were statistically significant ($p < 0.05$).

Conclusion The AMIC technique is a safe, effective, and feasible method to treat symptomatic full-thickness chondral defects of the patellofemoral cartilage in properly-selected cases, and it resulted in clinical and functional improvement in all criteria under analysis.

Resumo

Objetivo Avaliar os desfechos clínicos e funcionais de pacientes submetidos a tratamento cirúrgico para reparo de lesão condral focal na patela e na tróclea, pela técnica de condrogênese induzida por matriz autóloga (*autologous matrix-induced chondrogenesis*, AMIC, em inglês), após um mínimo de 2 anos de tratamento.

Métodos Ao todo, 24 pacientes (25 joelhos) com idade média de $39,6 \pm 4,7$ anos foram submetidos à técnica AMIC patelofemoral e foram avaliados em um seguimento médio de $3,64 \pm 0,65$ anos. Os fatores dos pacientes, a morfologia da lesão e as medidas de resultado relatadas pelos pacientes, incluindo os escores do International Knee Documentation Committee (IKDC), de Tegner, de Kujala, de Fulkerson, de Lysholm, e a Escala Visual Analógica (EVA), foram coletados.

Resultados O sexo masculino representou 76% da amostra. O tamanho médio do defeito das lesões condrais foi de $1,99 \pm 0,36\,cm^2$. Todos os defeitos foram classificados como de grau IV, de acordo com a classificação de Outerbridge. No seguimento final, os pacientes apresentaram os seguintes aumentos na pontuação média nos escores: Kujala – de 61,9 para 87,9; IKDC – de 51,3 para 83,6; Lysholm – de 64,0 para 88,4; Tegner – de 4,04 para 5,12; Fulkerson – de 60,2 para 89,3; e EVA – de 5,6 para 1,24. Todos os resultados apresentaram significância estatística ($p < 0,05$).

Conclusão A AMIC é um método seguro, eficaz e viável para o tratamento de defeitos condrais sintomáticos, de espessura total da cartilagem femoropatelar, em casos adequadamente selecionados, e resultou em melhora clínica e funcional em todos os critérios analisados.

Palavras-chave
- cartilagem articular
- condrogênese
- traumatismos do joelho

Introduction

Articular cartilage is a highly specialized tissue whose main function is to enable multiplanar movement of the joint under several conditions of applied load.[1] Another significant role of hyaline cartilage is its ability to transmit load to the adjacent subchondral bone without damaging it. In addition, it provides a smooth, lubricated, low-friction surface that enables the maintenance of joint homeostasis.[2]

Lesions affecting the patellofemoral region occur in up to one-third of the cases, and they can result in severely-limiting symptoms.[3,4] The most common causes include trauma, patellar dislocation, misalignment, and instability.[3,5] These lesions remain a significant challenge for orthopedic surgeons.[6–8] Several treatments have been proposed, with the recommendation of surgical therapy in cases in which conservative modalities have not been successful. The options available include microperforations, autologous chondrocyte implantation, and autologous osteochondral graft, but the ideal treatment remains controversial.[3,9]

Autologous matrix-induced chondrogenesis (AMIC) is part of this technical arsenal to repair focal full-thickness cartilage lesions. This technique stimulates the bone marrow through microfractures and lesion covering with type-I and -III collagen membrane to contain the formed clot and promote adhesion, proliferation, and cell differentiation.[7–13] Notably effective in treating condylar chondral lesions, reports of outcomes from this technique on isolated patellofemoral compartment lesions are lacking.[9,14] However, since its introduction, AMIC has demonstrated good short- and medium-term outcomes.[7,8,10,15–17]

Therefore, the present study aimed to analyze the clinical outcomes of patients undergoing surgical treatment to repair focal chondral lesions in the patella and trochlea using the AMIC technique with a follow-up of 2 years.

Materials and Methods

The current is a descriptive and observational case series study. We obtained data by analyzing medical records of patients who underwent surgical treatment to repair focal chondral lesions in the patella or trochlea using the AMIC

technique from 2015 to 2020. The institutional Ethics in Research Committee approved the study under number CAAE 65062522.9.0000.5505.

A single surgeon operated on 24 patients (25 knees), 19 men and 5 women, who were followed up for at least 2 years after the surgical procedure. All received detailed guidance on the proposed surgical technique and other available treatment options, with their respective advantages and disadvantages, and agreed with the procedure chosen.

The inclusion criteria were age from 15 to 60 years, diagnosis of focal chondral lesion in the patella or trochlea with an area ranging from 0.5 cm^2 to 4.0 cm^2, International Cartilage Repair Society (ICRS) classification grade III or IV, regular physical activity, and lack of response to conservative treatment with physical therapy and functional rehabilitation for up to 6 weeks. The exclusion criteria were patellar malalignment, subchondral bone (osteochondral) lesions, advanced osteoarthritis (grade $\geq$ 2 on the Ahlbäck radiographic classification), and a history of cartilage repairs or concomitant procedures, such as meniscal repair or ligament reconstruction.

All patients with suspected patellar or trochlear chondral lesions underwent a preoperative evaluation, including radiographs and magnetic resonance imaging (MRI) scans to characterize and measure the chondral injury and identify potential ligament injuries or malalignments in the lower limbs. This approach enabled a careful selection of participants meeting the inclusion criteria.

Surgical Technique

The procedure begins with arthroscopy for a detailed evaluation of the chondral lesion and diagnostic confirmation, followed by medial or lateral parapatellar arthrotomy depending on the location of the lesion. After patellar eversion, the edges of the lesion are molded to create stable vertical walls of healthy adjacent cartilage (►**Fig. 1**). The defect is marked and curetted down to its calcified layer, followed by nanoperforation of the subchondral bone. Then, the porcine collagen type-I and -III membrane (Chondro-Gide, Geistlich Pharma AG) is applied over the lesion and fixed with 5–0 monofilament suture (PDS, Ethicon, Inc.), reinforced with fibrin glue (Tisseel, Baxter Medical Pharmaceutical Ltd.) at the edges (►**Fig. 1**).

Rehabilitation

Postoperative rehabilitation includes initial immobilization with a hip brace for 10 days, with full weight bearing on the operated limb. The progressive gain in the range of motion starts according to pain tolerance, with ambulation without orthosis encouraged until gait normalization in 6 to 8 weeks. The patients are allowed to practice contact sports 6 to 8 months after surgery.

Data Collection

We collected demographic data, such as sex, age, laterality, lesion location, size, follow-up, and associated procedures. The preoperative clinical evaluation used internationally-standardized clinical scores, including the Lysholm, Fulkerson, Kujala, Tegner, International Knee Document Committee (IKDC) scores, and the Visual Analogue Scale (VAS). These scores were applied again after 2 years of outpatient follow-up.

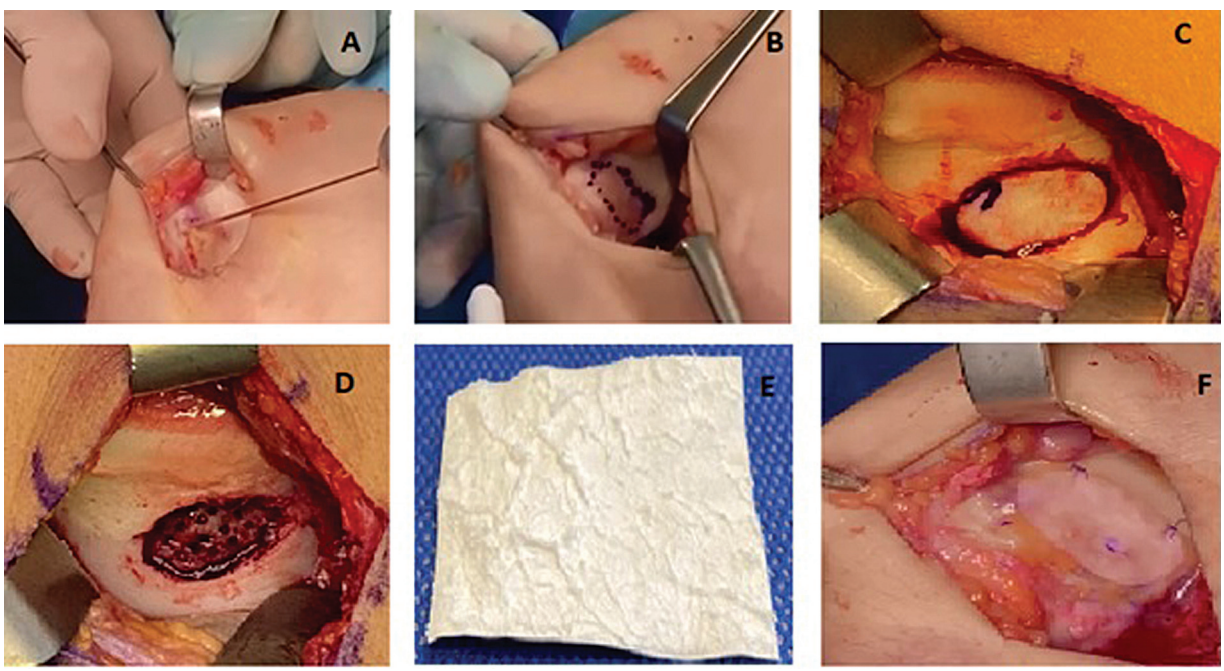


Fig. 1 Clinical image of autologous matrix-induced chondrogenesis (AMIC) in a cartilage lesion. **A**, extensive cartilage defect. **B**, regularization of the lesion edges. **C**, marking of the lesion size after curettage. **D**, subchondral bone nanoperforation. **E**, porcine type I/III collagen membrane. **F**, final appearance of the membrane implant with 5-0 monofilamentous suture reinforced with fibrin glue.

Table 1 Comparison between groups regarding the distribution of qualitative factors

		Patella		Trochlea		Total	
		N	%	N	%	N	%
Side	Right	7	58.3%	5	38.5%	12	48.0%
	Left	5	41.7%	8	61.5%	13	52.0%
Sex	Female	5	41.7%	1	7.7%	6	24.0%
	Male	7	58.3%	12	92.3%	19	76.0%
Site	Lateral	5	41.7%	5	38.5%	10	40.0%
	Medial	4	33.3%	3	23.1%	7	28.0%
	Medial and lateral	3	25.0%	5	38.5%	8	32.0%

Statistical Analysis

Data analysis used the following software: IBM SPSS Statistics for Windows, version 20.0 (IBM Corp.), Minitab 16 (Minitab, LLC), and Excel 2010 (Microsoft Corp.). The analysis of the quantitative variables was performed by calculating means, standard deviations (SDs), and quartiles. For the qualitative variables, absolute and relative frequencies were calculated. Result comparison between groups employed the Wilcoxon, Mann-Whitney, and equality of two proportions tests. Data was shown in tables and boxplots. The level of statistical significance was of 95%, and the *p*-value was set at 0.05.

Table 2 Score comparison per group

			Mean	Median	Standard deviation	N	*p*-value
Lysholm	Patella	Pre	60.1	62.5	± 13.6	12	0.003
		Post	88.3	90.5	± 10.7	12	
	Trochlea	Pre	67.5	63.0	± 13.2	13	0.007
		Post	88.5	89.0	± 13.4	13	
IKDC	Patella	Pre	48.7	46.6	± 14.9	12	0.002
		Post	82.6	89.1	± 13.9	12	
	Trochlea	Pre	53.6	52.9	± 11.5	13	0.003
		Post	84.6	92.0	± 14.5	13	
Tegner	Patella	Pre	3.58	3.00	± 1.62	12	0.017
		Post	4.92	5.50	± 1.31	12	
	Trochlea	Pre	4.46	5.00	± 1.76	13	0.305
		Post	5.31	5.00	± 1.93	13	
Fulkerson	Patella	Pre	56.9	60.5	± 15.0	12	0.002
		Post	88.2	90.0	± 11.6	12	
	Trochlea	Pre	63.3	64.0	± 15.1	13	0.005
		Post	90.3	94.0	± 14.4	13	
VAS	Patella	Pre	5.83	6.50	± 2.48	12	0.005
		Post	1.42	0.50	± 1.93	12	
	Trochlea	Pre	5.38	6.00	± 2.06	13	0.003
		Post	1.08	0.00	± 1.71	13	
Kujala	Patella	Pre	58.3	58.5	± 14.5	12	0.002
		Post	86.4	89.0	± 12.9	12	
	Trochlea	Pre	65.2	70.0	± 14.1	13	0.006
		Post	89.2	91.0	± 12.8	13	

Abbreviations: IKDC, International Knee Documentation Committee; Post, postoperative period; Pre, preoperative period; VAS, Visual Analog Scale.

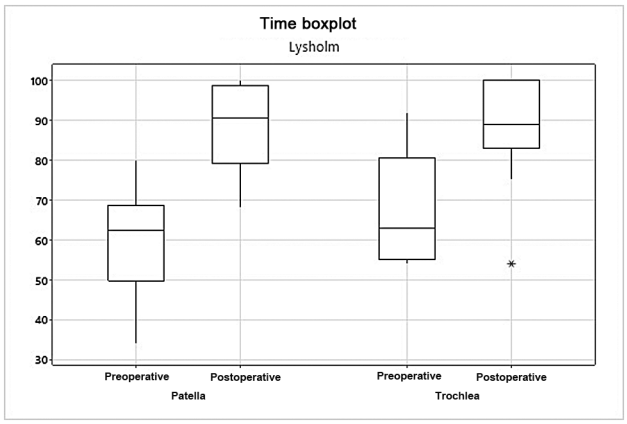


Fig. 2 Analysis of the patella and trochlea groups per the Lysholm score.

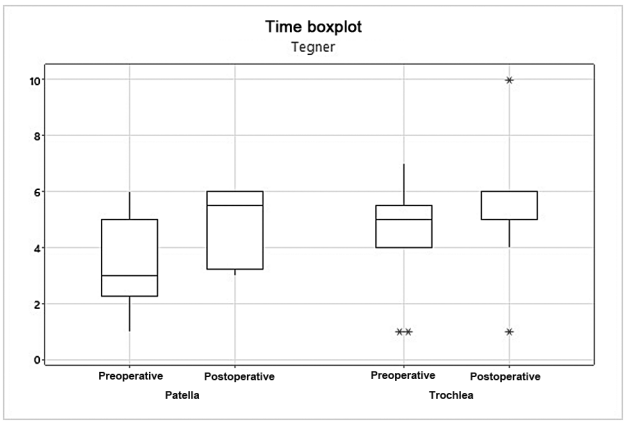


Fig. 4 Analysis of the patella and trochlea groups per the Tegner score.

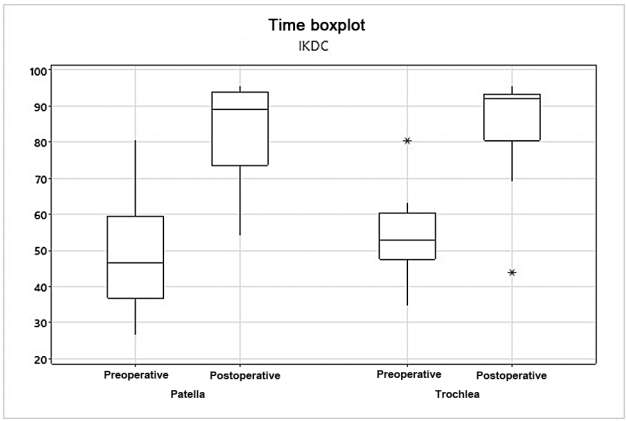


Fig. 3 Analysis of the patella and trochlea groups per the International Knee Documentation Committee (IKDC) score.

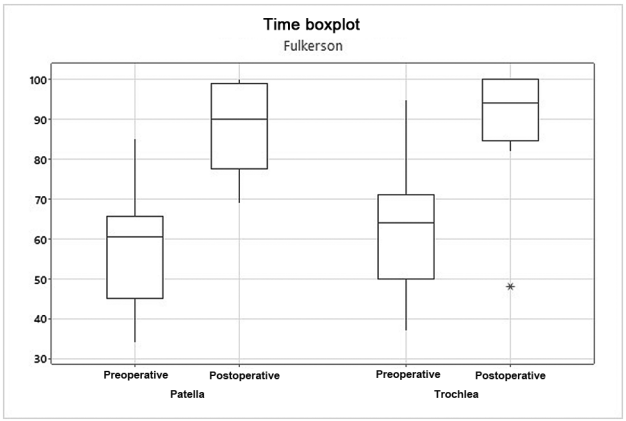


Fig. 5 Analysis of the patella and trochlea groups at per Fulkerson score.

Results

We analyzed 24 patients (25 knees) aged 15 to 60 (mean: 39.6 ± 4.7) years, 5 women and 19 men. The lesions affected the patella in 12 cases and the femoral trochlea in 13 cases, and their sizes ranged from 1.0 cm^2 to 3.99 cm^2 in the patella and from 0.9 cm^2 to 2.94 cm^2 in the trochlea. The mean follow-up was of 3.54 ± 0.65 years. ►**Table 1** shows the frequencies of the lesion site, laterality, and sex.

The evaluation of the Lysholm, Fulkerson, Kujala, Tegner, VAS, and IKDC scores was performed before and after surgery, with a minimum follow-up of 24 months. There was a statistically significant increase in virtually all comparisons, except for the Tegner score for the trochlea group, which presented no statistical significance, even though the mean value increased from 4.46 to 5.31 ($p = 0.305$). ►**Table 2** compares the mean values for the patella and trochlea groups.

The mean Lysholm score increased from 60.1 to 88.3 ($p = 0.003$) in the patella group, and from 67.5 to 88.5 ($p = 0.007$) in the trochlea group (►**Fig. 2**). The mean IKDC score increased from 48.7 to 82.6 ($p = 0.002$) in the patella group, and from 53.6 to 84.6 ($p = 0.003$) in the trochlea group (►**Fig. 3**). The mean Tegner score increased from 3.58 to 4.92 ($p = 0.017$) in the patella group (►**Fig. 4**).

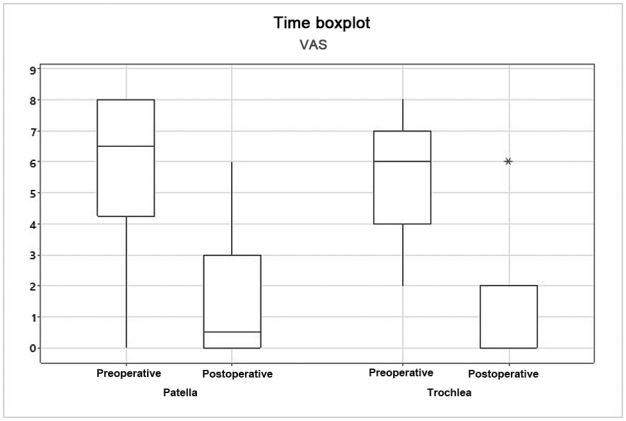


Fig. 6 Analysis of the patella and trochlea groups per the score on the Visual Analog Scale (VAS).

The mean Fulkerson score increased from 56.9 to 88.2 ($p = 0.002$) in the patella group, and from 63.3 to 90.3

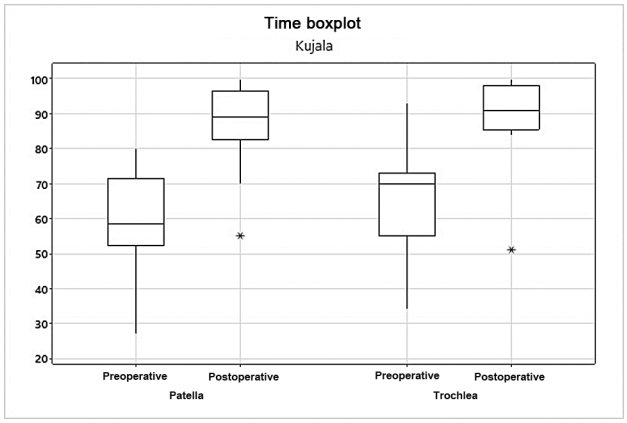


Fig. 7 Analysis of the patella and trochlea groups per the Kujala score.

($p = 0.005$) in the trochlea group (►**Fig. 5**). The mean VAS score decreased from 5.83 to 1.42 ($p = 0.005$) in the patella group, and from 5.38 to 1.08 ($p = 0.003$) in the trochlea group (►**Fig. 6**). Lastly, the mean Kujala score increased from 58.3 to 86.4 ($p = 0.002$) in the patella group, and from 65.2 to 89.2 ($p = 0.006$) in the trochlea group (►**Fig. 7**).

Discussion

The most relevant data from the current study was the efficacy of the AMIC technique to treat full-thickness chondral lesions in the patella and trochlea with a minimum follow-up of 2 years. All scores presented statistically significant clinical and functional improvements, resulting in symptom reduction and sports return at preinjury levels.

Consistent with these findings, Gille et al.[18] conducted a study with a sample of patients with patellofemoral lesions smaller than ours ($n = 11$ versus $n = 25$), but a similar mean age. However, in their study, the patella was predominantly affected (nine versus two), while trochlear lesions were more frequent here (13 versus 12). Likewise, they[18] found improvements in Lysholm scores, which increased from 36 ± 21 preoperatively to 76 ± 24 at the 24-month follow-up. The Tegner and IKDC scores also showed a significant increase in patellar defects during the same analysis period, with these data published in a previous article.[10] Waltenspül et al.[3] observed an elevation in the Kujala score from 63.5 ± 11.6 preoperatively to 72.2 ± 17.4 after a minimum follow-up of 24 months ($p = 0.029$).

Regarding patient satisfaction after AMIC, Panni et al.,[19] after a mean follow-up of 7 years, reported that 76.2% of the patients considered the treatment good or excellent. Gille et al.,[18] when evaluating 27 patients treated with AMIC, found that 87% of them were satisfied with the treatment outcomes. The current analysis confirms these data, revealing positive outcomes, with 84% of patients classifying their satisfaction as good or excellent, a rate consistent with those of the aforementioned literature.

In a 12-month follow-up, Tradati et al.[20] reported significant outcomes in patients undergoing AMIC. The Kujala score increased from 49.6 preoperatively to 87.8 after 12 months ($p < 0.01$). The IKDC score increased from 36.1 to 79.8 ($p < 0.01$). In addition, there was a significant reduction in pain, and the VAS score decreased from 7.5 to 1.5 ($p < 0.01$).[20] The present study reveals that the benefits of the treatment proposed by Tradati et al.[20] are sustained for at least 24 months, since the variations in the scores measured here are symmetrical to those observed by those authors.

The patellofemoral compartment is the most challenging knee region to treat chondral lesions. Hinckel et al.[21] conducted a systematic review to establish which technique is most appropriate in this scenario. They observed that the outcomes of the combination of collagen membrane and autologous chondrocyte implant (ACI) were superior to those of the other techniques. Nevertheless, the AMIC technique was not included in their analysis[21] due to the lack of controlled studies at the time. The use of AMIC is well-established for the condylar region; Astur et al.,[6] for instance, analyzed outcomes similar to those reported here in 15 patients for 12 months, noting a 4-point difference in VAS score at the end of the 12-month follow-up, consistent with our findings after 24 months, even though we dealt with the anterior knee compartment.

A current trend associates the classic AMIC technique herein described with orthobiological agents, preserving the subchondral bone or not. For instance, the AMIC plus technique associates bone marrow aspirate concentrate (BMAC) with the collagen membrane. This combination has shown evidence of postoperative pain relief, functional improvement, and outcome maintenance for up to 3 years.[22] Sciarretta et al.[23] reported promising results using the LIPO-AMIC technique, which combines AMIC with autologous adipose tissue grafting. These authors[23] observed early and progressive improvement, in addition to long-lasting symptom relief; moreover, they noted significant recovery and maintenance of daily functional and sports activities at 2-year and, especially, 5-year follow-ups. Another technique that deserves attention is minced cartilage implantation, which can be applied to small-diameter cartilage defects. This technique can be an alternative to bone marrow stimulation procedures, as minced cartilage implantation can be performed in a single-stage procedure, even using arthroscopic techniques. This minimally-invasive approach is easy to apply and an attractive option to treat focal chondral lesions.[24]

The current study is not free from limitations, many of which are inherent to its design, as it is an observational case series study. First, the number of participants ($n = 25$) may limit statistical robustness, despite being relevant compared with the international literature. Furthermore, the fact that it is a single-arm study and that does not include a control group prevents direct comparison and assessment of the relative efficacy of the interventions. Another limitation is the impossibility of comparing different techniques, such as nanofracture, since control groups are critical for data analysis. The heterogeneity of the lesions among the patients constitutes a significant limitation of the current study, since we included injuries in the trochlea and the patella.

Moreover, we did not consider subtle variations in the anatomical and biomechanical patterns of the patellofemoral region. Another significant limitation is the lack of outcome assessment through imaging. Additionally, a longer follow-up could provide more robust data and enrich the conclusions.

Conclusion

The repair of chondral lesions using collagen membrane is a safe, effective, and viable technique for the treatment of symptomatic full-thickness chondral defects of the patellofemoral cartilage in properly-selected cases, resulting in clinical and functional improvements in all criteria analyzed after 2 years of follow-up.

Informed Consent Form

Consent was waived due to the study design.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Buffalo Horn Sign – A New Finding on MRI for Meniscal Bucket-Handle Tears

Sinal do chifre de búfalo – Um novo achado em RM para rupturas em alça de balde do menisco

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Abstract

Objective To describe a new sign on magnetic resonance imaging (MRI) axial images of patients with bucket-handle meniscal tears.

Methods Of 610 consecutive patients with a surgical diagnosis of meniscal tear, those with a bucket-handle pattern were chosen, and 28 met the inclusion criteria. The most frequent mechanism was a twisting injury with or without a coronal stress (16 patients), and the injury was sports-related in 12 cases. All patients were symptomatic and had X-rays showing a preserved joint line. Next, their MRI examinations were analyzed.

Results The buffalo horn pattern was found in 13 patients (46.4%), occurring in either the medial or the lateral meniscus. It was the 3rd most prevalent sign, after the fragment within the intercondylar notch ($n = 21$; 75.0%) and the absent bow tie sign ($n = 17$; 60.7%). We observed that it had a significant association with other signs of displaced meniscal handle. The sign was neither found on the healthy menisci, nor was affected by the occurrence of an anterior cruciate ligament tear.

Conclusion The buffalo horn is a new finding for displaced meniscal bucket-handle tears; it is easy to identify and relevant in the interpretation of axial MRI images. Its recognition is very important to determine the type of treatment and the surgical plan.

Keywords
- diagnostic imaging
- knee
- magnetic resonance imaging
- tibial meniscus injuries

Resumo

Objetivo Descrever um novo sinal em imagens axiais de ressonância magnética (RM) de pacientes com rupturas em alça de balde do menisco.

Work carried out at the Orthopedics Department, Santa Maria Local Health Unit, Lisbon, Portugal.

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Métodos De 610 pacientes consecutivos com diagnóstico cirúrgico de ruptura do menisco, aqueles com padrão em alça de balde foram escolhidos, e 28 atenderam aos critérios de inclusão. O mecanismo de lesão mais frequente foi a torção com ou sem estresse coronal (16 pacientes). Além disso, a lesão foi relacionada ao esporte em 12 casos. Todos os pacientes eram sintomáticos e tinham radiografias que mostravam a preservação da linha articular. Em seguida, seus exames de RM foram analisados.

Resultados O padrão de chifre de búfalo foi encontrado em 13 pacientes (46,4%) no menisco medial ou lateral. Foi o 3º sinal mais prevalente, depois do fragmento no interior da incisura intercondilar ($n = 21$; 75,0%) e da ausência do sinal da gravata borboleta ($n = 17$; 60,7%). Observamos uma associação significativa a outros sinais de deslocamento da alça do menisco. O sinal não foi encontrado em meniscos saudáveis, nem foi afetado pela ocorrência de ruptura do ligamento cruzado anterior.

Conclusão O chifre de búfalo é um novo achado para rupturas em alça de balde do menisco com deslocamento; é fácil de identificar e relevante na interpretação de imagens de RM de corte axial. Seu reconhecimento é muito importante para determinar o tipo de tratamento e o plano cirúrgico.

Palavras-chave
- diagnóstico por imagem
- imagem por ressonância magnética
- joelho
- lesões do menisco tibial

Introduction

Menisci are crescent-shaped intracapsular fibrocartilagineous laminae with a role in load transmission, shock absorption, stability, lubrication, nutrient diffusion, sensory perception, and proprioception.[1] Meniscal tears are a common problem, with a reported incidence of ~ 60 per 100 thousand inhabitants in the United States.[2] There are several patterns. Bucket-handle tears consist in a full-thickness longitudinal tear that propagates anteriorly and posteriorly, creating an inner fragment – the "handle" – that can displace into the intercondylar notch.[3] These lesions represent ~ 10% of all tears;[3,4] they occur mainly in the medial meniscus,[4,5] but they can also affect the lateral meniscus.[6–8] Since surgical treatment is often required, the correct preoperative diagnosis is important to optimize treatment and save meniscal tissue.[9] Magnetic resonance imaging (MRI) is the gold-standard imaging method with an overall reported sensitivity of up to 90.0% and specificity of up to 89.0%.[10–13] On MRI, meniscal bucket-handle tears usually display some well-known signs, mainly in the coronal and sagittal sections: absent bow tie sign,[14] double posterior cruciate ligament (PCL) sign,[15,16] double anterior horn sign,[17] flipped meniscus sign,[18] disproportional posterior horn sign,[19] double anterior cruciate ligament (ACL) sign,[20] triple PCL sign,[7] triple cruciate sign,[8] quadruple cruciate sign,[6] and the presence of a fragment within the intercondylar notch[4] (►**Appendix A**). The reported sensitivity and specificity for the diagnosis of meniscal bucket-handle tears varies in a wide range, from 64.0 to 93.0%[4,5,21] and from 64.0 to 100%[10,22] respectively – but it improves if more signs are known.[5,22]

To the best of our knowledge, there was only one sign previously described in MRI axial view: the V sign.[23] The present paper aims to report a new sign to be identified in that view, which is perceived as a buffalo horn and appears in patients with meniscal bucket-handle tears. The sensitivity of this finding will be determined and compared with the presence of the other already-known signs.

Materials and Methods

Compliance with Ethical Standards

The current study follows the ethical standards of the institutional Research Committee and of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. It received approval n. 215/22 from the Ethics Board of Centro Acadêmico Médico de Lisboa. Informed consent was exempted as long as personal data protection standards were met, but additional written informed consent was obtained from all patients for whom MRI scans are included in the present article.

This is a retrospective study based on MRI scans of patients diagnosed during surgery with meniscal bucket-handle tears, disregarding age, sex, mechanism, the time between trauma and MRI and between trauma and surgery, treatment, surgeon, ACL injury, and affected knee or meniscus.

A consecutive sample of 1,767 patients operated at the Orthopedics Service of a university hospital for any knee pathology between 2012 and 2021 was obtained (►**Fig. 1**). This period was chosen because contains the highest number of patients available at our institution due to the limited computerization of medical files in the previous years. Only 610 patients had surgically proven meniscal tears, and 49 showed a bucket-handle pattern. Next, the patients with the following criteria were excluded: history of knee surgery, other patterns of meniscal tears, absent meniscal tear, unknown MRI protocol, absent axial sequences or menisci not acquired, and refusal to participate in the research. The collected sample was of 28 patients, 22 men and 6 women, with a mean age of 34.2 (± 14.0; range: 9–63) years. The most frequent mechanism of injury reported by patients was torsion with or without coronal load (16 patients). Four patients experienced the injury after a knee flexion or a squat. Two cases suffered a fall from their height, and one described a complex trauma during surf practice. Five patients could not identify any trauma.

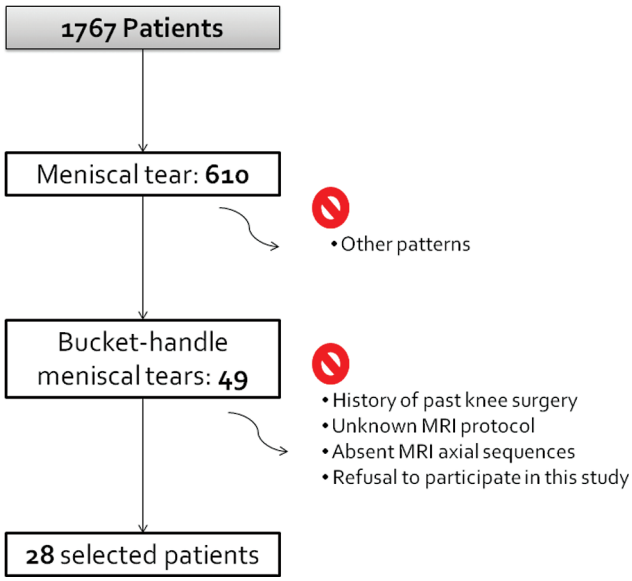


Fig. 1 Flowchart illustrating the search strategy and selection criteria.

Twelve of these injuries were sports-related. Every patient showed, at some degree, knee pain, joint effusion, a sensation of locking or looseness, or loss of extension. All the X-rays showed a preserved joint line.

In total, 24 MRI scans were performed at the hospital where this research was conducted, and 4 were performed elsewhere, but with a similar protocol. Seventeen were performed with Philips Intera 1.5 T scanner, and 11 were performed with the Philips Achieva 3.0 T scanner. The receive-only specific knee coil provided by the manufacturer for each scanner was used. The standard acquisitions are summarized in ►**Table 1**, and they include: a coronal T1, T2 fast field echo (FFE) and short tau inversion recovery (STIR); a sagittal proton density (PD) with and without fat suppression; and an axial T2 FFE. Some exams had an additional coronal T2 spectral attenuated inversion recovery (SPAIR) and an axial SPAIR. A slightly different protocol for the Intera scanner was used to assess the pediatric patient, using a slice of 3 mm and a gap of 0.3 mm.

Table 1 Magnetic resonance imaging acquisition protocols

Philips Intera (1.5 T)							
	Matrix	RT/ET (ms)	Slice (mm)	Gap (mm)	Average	FOV (mm)	FA (°)
Coronal							
T1	400 × 300	500/22	3.5	0.35	2	180	90
T2 FFE	300 × 250	500/14	3.5	0.35	2	180	25
STIR	250 × 200	5,000/80	3.5	0.35	3	180	–
T2 SPAIR	300 × 250	3,000/60	3.5	0.35	2	180	90
Sagittal							
PD	300 × 250	2,500/8	3.5	0.35	2	180	90
PD SPAIR	250 × 250	3,000/30	3.5	0.35	3	180	90
T2	300 × 250	2,500/120	3.5	0.35	2	180	90
Axial							
T2 FFE	250 × 200	600/14	3.5	0.35	2	180	25
SPAIR	250 × 200	3,000/30	3.5	0.35	4	180	90
Philips Achieva (3 T)							
Coronal							
T1	400 × 350	600/20	3	0.3	2	180	90
T2 FFE	400 × 300	450/12	3	0.3	2	180	20
STIR	250 × 200	4,000/80	3.5	0.35	2	180	–
T2 SPAIR	300 × 250	4,000/65	3	0.3	2	180	90
Sagittal							
PD	400 × 300	7,000/9	3	0.3	1	180	90
PD SPAIR	300 × 300	5,000/30	3	0.3	2	180	90
T2	400 × 300	7,000/140	3	0.3	1	180	90
Axial							
T2 FFE	300 × 250	500/12	3	0.3	2	180	20
SPAIR	300 × 250	3,800/65	3	0.3	2	180	90

Abbreviations: ET, echo time; FA, flip angle; FFE, fast field echo; FOV, field of view; PD, proton density; RT, repetition time; SPAIR, spectral attenuated inversion recovery; STIR, short tau inversion recovery.

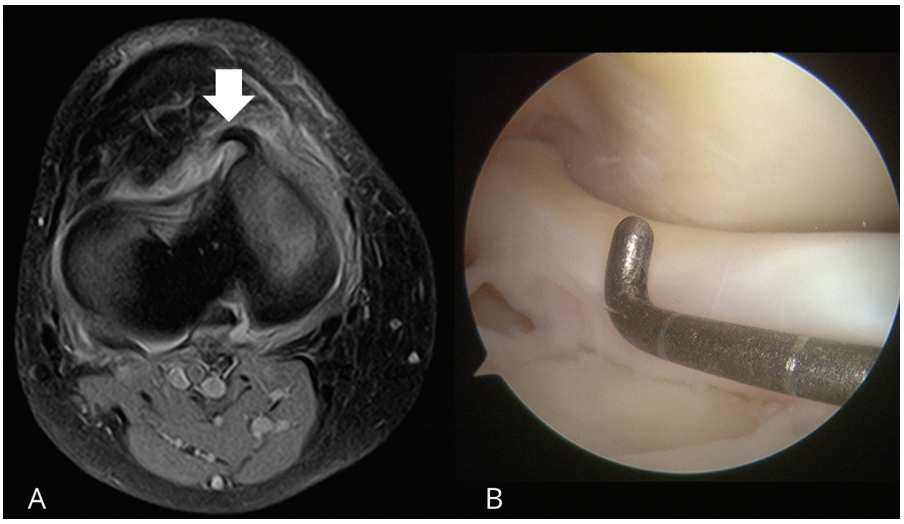


Fig. 2 (**A**) Preoperative MRI scan of a 54 year-old male patient with a surgically-reported bucket-handle tear of the medial meniscus of the right knee showing the buffalo horn sign (arrow) in the axial cross-section. This finding is a low signal intensity area projecting from the anterior border of the medial tibial plateau, resembling a horn. (**B**) Right knee arthroscopy using an anterolateral portal, showing the meniscal fragment of the same patient displaced anteriorly to the femoral condyle. Axial spectral attenuated inversion recovery (SPAIR) sequence: matrix, 250 × 200; repetition time/echo time (RT/ET), 3,000/30 milliseconds; slice, 3,5 mm; gap, 0,35; average, 4; field of view (FOV), 180 mm; flip angle (FA), 90°.

All surgeries were performed by senior knee surgeons, with fellowship training. Meniscal bucket-handle tear was defined as "a longitudinal tear with central migration of the 'inner' handle fragment."[3]

A senior knee surgeon and an orthopedics resident were instructed on MRI interpretation of bucket-handle tears and then prospectively and blindly assessed the images. Consensus was established by the senior musculoskeletal radiologist. Each MRI scan was assessed for the presence of an absent bow tie sign,[14] double PCL sign,[15,16] double anterior horn sign,[17] flipped meniscus sign,[18] disproportional posterior horn sign,[19] double ACL sign,[20] triple PCL sign,[7] triple cruciate sign,[8] quadruple cruciate sign,[6] and the presence of a fragment within the intercondylar notch.[4] When in cross-section, the V sign[23] and the new sign were recorded. The buffalo horn sign is the presence of a low signal intensity area projecting from the anterior border of the medial tibial plateau, resembling a horn which can be appreciated in the MRI axial view, as demonstrated in ►**Fig. 2**. If the lateral meniscus is affected, the sign appears like a low-intensity horn-shaped band lying parallel to the anterior border of the lateral tibial plateau in two consecutive axial images (►**Fig. 3**). The other definitions used are reviewed in ►**Appendix A**. The presence of joint effusion,[24] parameniscal cyst,[25] meniscal extrusion,[26] bone marrow edema and its location[27,28] were also recorded. The cases with MRI suspicion of hemibucket-handle tear of the meniscus were counted.[29] Surgical evidence of rupture of the ACL was reported.

A literature search for the terms and expressions *menisci*, *bucket handle* and *MRI scan* was conducted on the PubMed search engine. Only studies written in English and involving

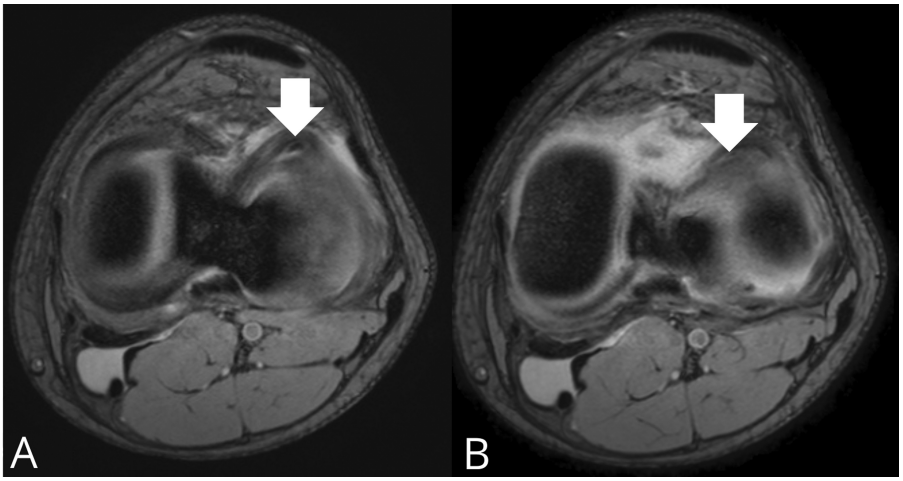


Fig. 3 Preoperative MRI scan of a 17 year-old male subject with a surgically-reported bucket-handle tear of the lateral meniscus of the left knee. (**A**,**B**) Axial cross-section in T2 fast field echo (FFE) showing the buffalo horn sign (arrow) in lateral meniscus appearing as a low signal intensity horn-shaped band lying parallel to the anterior border of lateral tibial plateau in two consecutive axial images. Axial T2 FFE: matrix, 300 × 250; RT/ET, 500/12 milliseconds; slice, 3 mm; FOV, 180 mm; FA, 20°.

human subjects were considered. No reports regarding a buffalo horn sign could be found.

Statistical Analysis

For the statistical analysis, version 18.0 of the software PASW Statistics for Windows was used. Values of *p lower* than 0.05 were considered significant. The nominal variables were analyzed with the Chi-squared (χ^2) test or the Fisher's Exact test when > 20% of the cells had an expected count lower than 5.

Results

The buffalo horn sign was found in 13 out of 28 cases (46.4%), which made it the third most prevalent sign, after the fragment within the intercondylar notch ($n = 21$; 75.0%) and the absent bow tie sign ($n = 17$; 60.7%). It occurred in 7/19 medial menisci (36.8%) (►**Fig. 2**) and 6/9 lateral menisci (66.7%) (►**Fig. 3**). If findings suggesting an anteriorly displaced handle were present ($n = 9$), the new sign appeared in 7 cases (77.8%), 3 medial menisci (33.3%), and 4 lateral menisci (66.7%). If findings suggesting a posteriorly displaced fragment were present ($n = 4$), the buffalo sign was observed in 2 patients (50.0%), 1 medial and 1 lateral meniscus. None of the aforementioned findings were statistically significant.

A significant association was observed between the new sign and a fragment within the intercondylar notch ($p = 0.01$) and a double anterior horn sign ($p = 0.01$) (►**Table 2**). There

Table 2 Frequency of the buffalo horn sign

Buffalo horn sign						
Sign	**Present ($n = 13$): *n* (%)**	**Absent ($n = 15$): *n* (%)**	**Total ($n = 28$): *n* (%)**	**OR (CI)**	**Statistical test**	***p***
Intercondylar fragment	13 (100%)	8 (53%)	21 (75%)	**0.53 (0.33–0.86)**	**FE**	**0.01**
Absent bow tie	10 (77%)	7 (47%)	17 (60%)	3.81 (0.74–19.67)	$\chi^2 = 2.67$	0.10
V sign	6 (46%)	3 (20%)	9 (32%)	3.43 (0.65–18.22)	FE	0.23
Double PCL	6 (46%)	2 (13%)	8 (28%)	5.57 (0.88–35.27)	FE	0.10
Flipped meniscus	6 (46%)	2 (13%)	8 (29%)	5.57 (0.88–35.27)	FE	0.10
Double anterior horn	5 (39%)	0 (0%)	5 (18%)	**1.63 (1.06–2.50)**	FE	**0.01**
Disproportional posterior horn	5 (39%)	2 (13%)	7 (25%)	4.06 (0.63–26.13)	FE	0.20
Double ACL	2 (15%)	0 (0%)	2 (7%)	1.18 (0.94–1.49)	FE	0.21
Indirect signs						
Joint effusion	10 (77%)	7 (47%)	17 (60%)	3.81 (0.74–19.66)	$\chi^2 = 2.67$	0.10
Subchondral marrow edema	5 (39%)	4 (27%)	9 (32%)	1.72 (0.35–8.51)	FE	0.69
Linear subchondral marrow edema	3 (23%)	5 (33%)	8 (29%)	0.60 (0.11–3.21)	FE	0.69
MTP tibial plateau subchondral edema	3 (23%)	6 (40%)	9 (32%)	0.45 (0.09–2.35)	FE	0.44
Meniscal extrusion	2 (15%)	5 (33%)	7 (25%)	0.36 (0.06–2.31)	FE	0.40
Parameniscal cyst	0 (0%)	2 (13%)	2 (8%)	0.88 (0.71–1.06)	FE	0.48
Other conditions						
ACL rupture	5 (39%)	6 (40%)	11 (39%)	0.94 (0.21–4.29)	$\chi^2 = 0.01$	0.93
Hemibucket handle	0 (0%)	3 (20%)	3 (11%)	0.80 (0.62–1.03)	FE	0.23

Abbreviations: χ^2, Chi-squared test; ACL, anterior cruciate ligament; FE, Fisher's exact test; MTP, medial tibial plateau; OR, odds ratio; PCL, posterior cruciate ligament.
Notes: An association was observed between fragment within intercondylar notch and double anterior horn with the new reported sign. The χ^2 and FE tests were performed. Statistically significant *p*-values are in bold.

were no other statistically significant findings. The buffalo horn sign was observed regardless of an ACL tear (►**Table 3**).

Looking at the findings of the axial sections, the V sign was identified in 9 cases, a sensitivity of 32.1%. Of these nine patients, three presented only the V sign, and six also presented the buffalo horn sign. Of 13 patients with the latter, 7 had only the buffalo horn sign, but not the V sign. None of those signs appeared as the only sign for the tear, and all cases had the fragment within the intercondylar notch and the sign of absence of the bowtie.

The medial meniscus was torn in 19 cases (67.8%) and the lateral, in 9 (32.2%) cases. Three cases exhibit the hemi-bucket-handle pattern,[27] which could not be confirmed through the surgical records, and none of these patients presented the buffalo horn sign. Six MRI scans missed the diagnosis of bucket-handle tear, but all presented at least one indirect sign. The new sign was never found on an unaffected meniscus.

Discussion

The most relevant finding of the present study was that the buffalo horn could be a new sign to diagnose meniscal bucket-handle tears. It is useful for both menisci in fragments

Table 3 Anterior cruciate ligament tear and the frequency of signs of bucket-handle tear

ACL tear						
Sign	**Present ($n = 11$): *n* (%)**	**Absent ($n = 17$): *n* (%)**	**Total ($n = 28$): *n* (%)**	**OR (CI)**	**Statistical test**	***p***
Intercondylar fragment	7 (64%)	14 (82%)	21 (75%)	0.38 (0.07–2.16)	FE	0.38
Absent bow tie	8 (73%)	9 (53%)	17 (60%)	2.37 (0.46–12.14)	FE	0.44
Buffalo horn	5 (46%)	8 (47%)	13 (46%)	0.94 (0.21–4.29)	$\chi^2 = 0.01$	0.93
V sign	4 (36%)	5 (29%)	9 (32%)	1.37 (0.27–6.87)	FE	1.00
Double PCL	3 (27%)	5 (29%)	8 (28%)	0.90 (0.17–4.87)	FE	1.00
Flipped meniscus	2 (18%)	6 (35%)	8 (29%)	0.41 (0.07–2.53)	FE	0.42
Disproportional posterior horn	4 (36%)	3 (18%)	7 (25%)	2.67 (0.46–15.35)	FE	0.38
Double anterior horn	4 (36%)	1 (6%)	5 (18%)	9.14 (0.86–97.27)	FE	0.06
Double ACL	0 (0%)	2 (12%)	2 (8%)	0.88 (0.74–1.05)	FE	0.51
Indirect signs						
Joint effusion	7 (64%)	10 (59%)	17 (60%)	1.22 (0.26–5.85)	FE	1.00
Subchondral marrow edema	6 (65%)	3 (18%)	9 (32%)	5.60 (1.01–31.32)	FE	0.38
PTM subchondral edema	6 (65%)	3 (18%)	9 (32%)	5.6 (1.00–31.32)	FE	0.10
Linear subchondral marrow edema	2 (18%)	6 (25%)	8 (29%)	0.41 (0.07–2.53)	FE	0.42
Meniscal extrusion	3 (27%)	4 (23%)	7 (25%)	1.22 (0.22–6.92)	FE	1.00
Parameniscal cyst	0 (0%)	2 (12%)	2 (8%)	0.8 (0.74–1.05)	FE	0.51
Other conditions						
Hemibucket handle	0 (0%)	3 (18%)	3 (11%)	0.8 (0.66–1.03)	FE	0.26

Abbreviations: χ^2, Chi-squared test; ACL, anterior cruciate ligament; FE, Fisher's exact test; MTP, medial tibial plateau; OR, odds ratio; PCL, posterior cruciate ligament.
Notas: There were no differences in terms of the prevalence of the findings between the groups with or without ACL tear. The χ^2 and FE tests were performed.

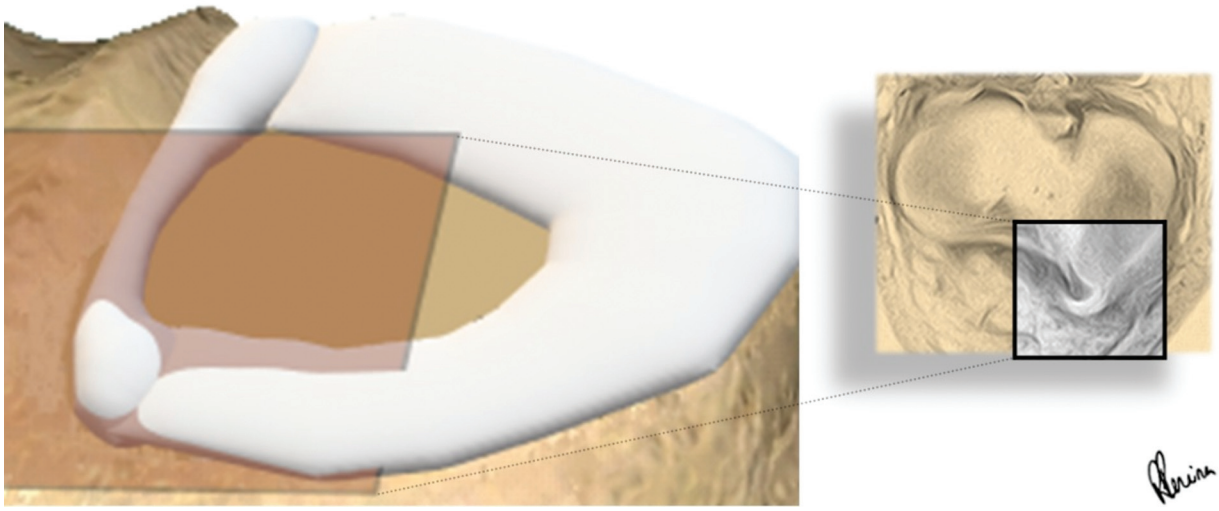


Fig. 4 The dislocated bucket-handle fragment of the medial meniscus of a right knee is sliced in axial section (orange box), appearing as a horn.

displaced anterior[18,20] or posterior[19] dislocated fragments. It was found in 7/19 medial menisci (36.8%) and 6/9 lateral menisci (66.7%), without statistically significant differences. All cases with a double anterior horn presented the buffalo horn sign ($p = 0.01$). In 8/28 (28.6%) cases with a flipped meniscus, the proposed sign appeared in 6 (75.0%). Both patients with double ACL presented it (100%). The studied finding also appeared in 2/4 disproportional posterior horn cases. Additionally, all patients with the new finding presented a fragment within the intercondylar notch ($p = 0.01$), and the new sign never appeared alone, but always in the presence of other signs for a displaced fragment. Thus, one can conclude that the buffalo horn sign means a displaced handle of a meniscal tear, and the horn appears when the axial section bisects it (►**Fig. 4**).

This new finding was observed because the assessment of cross-sectional images is gaining importance in clinical practice, and there was only one sign previously described for this condition in these images: the V sign.[23] Despite being close to each other, these two findings are not the same. The buffalo horn uses a sequence of images, appears anterior, and does not need to have the handle and the meniscus in the same section. Seven patients had the buffalo horn sign but not the V sign, and 3 had the latter but not the former. Six out of nine patients had both findings simultaneously (►**Fig. 5**). In this sample, the V sign had 32.1% of sensitivity, which is lower than the rate previously reported by Rao et al.,[23] of 72.0%, and it is also lower than the sensitivity of the buffalo horn sign in the sample of the present study (46.4%).

The overall sensitivity of MRI in the current study was low, corresponding to the lower half of the previously-reported range of 64 to 93%.[4,5,12,13,21,22] In total, 6 out of 28 MRI scans missed any sign of a meniscal bucket-handle tear, which translates to an overall sensitivity of only 78.6%. This fact may explain the low sensitivity of the buffalo horn sign (46.4%), even though it was the third most relevant sign, with higher

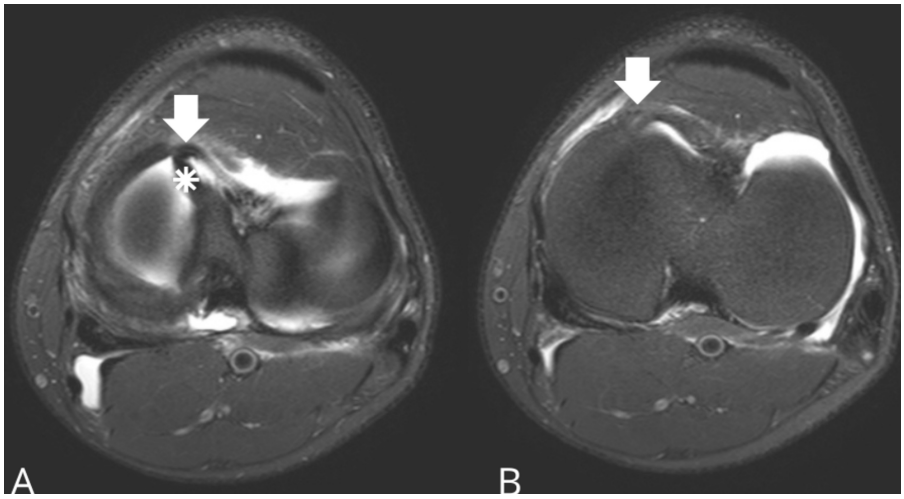


Fig. 5 Cross-sections of a preoperative MRI scan of a 27 year-old male patient with a bucket-handle tear of the medial meniscus of the left knee. (**A**) The V sign (*) and the buffalo horn sign (arrow) are visible. (**B**) In the following section, only the buffalo horn sign (arrow) is found. Axial T2 SPAIR: matrix, 300 × 250; RT/ET, 3800/65 milliseconds; slice, 3 mm; gap, 0.3; average, 2; FOV, 180 mm; FA, 90°.

sensitivity than the other 6 widely-spread findings. Its sensitivity was surpassed by the fragment within the intercondylar notch (21/28; 75.0%) and the absent bow tie sign (17/28; 60.7%). That is consistent with the reported sensitivity by Dorsay and Helms for the fragment within the intercondylar notch of 76.7%,[22] but is lower than the 88.4% described for the absence of the bowtie sign in the same study. In the present research, we do not intend to calculate either the specificity or reproducibility of the sign, but we never found the buffalo horn on an unaffected meniscus; moreover, the observation of the sign requires a displaced fragment to show up. Therefore, we believe that it is specific. Additionally, the proposed definition and the appearance of the buffalo horn sign are easy to spot, maybe more than the fragment within the intercondylar notch or the absence of the bow tie, whose definitions are vague.

The present study has several limitations. The sample is small due to the obstacles faced, such as the limited computerization of medical files before 2012 and a low volume of treated patients. This prevented us from obtaining a larger sample, but we believe that it does not threaten the aim of the current paper. The unaffected menisci were used as controls, and the time elapsed from the trauma to the MRI scan and surgery may be a source of bias. The patients were chosen based on a surgical diagnosis, which did not enable the performance of a test for the specificity. The reliability of the sign was not calculated. The sample gathers different magnetic field intensities, but Van Dyck et al.[30] showed, in a controlled prospective study, that diagnostic accuracy of 3.0 T for meniscal and ACL tears is not significantly higher than 1.5 T, so it seems reasonable to believe that this issue does not compromise the identification of a new sign. Knees with ACL deficiency (acute or chronic; 11/28; 39.3%) were studied aside from ACL-competent knees, but there are controversies regarding their effect on the accuracy of MRI.[10,12] Although all the surgeries were performed by experienced knee surgeons working in the same department, the surgical reports had not been standardized, and some missed the subtype classification of the bucket-handle tear.

Conclusion

In conclusion, the buffalo horn sign could be present in the medial and lateral torn menisci, with and without ACL tear. A dislocated fragment is the cause of the sign, so it is statistically associated with the fragment within the intercondylar notch or the double anterior horn sign. Recognizing this situation is very important to determine the type of treatment and to be able to plan the surgery. Moreover, we believe that this finding is easy to identify, and it is specific for bucket-handle tears, because it was not found on unaffected menisci.

Herein, the buffalo horn sign appears as a new finding that can be relevant to diagnose meniscal bucket-handle tears using axial MR imaging.

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

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Appendix A Definition of the characteristic findings on magnetic resonance imaging of meniscal bucket-handle tears

Authors	Sign	Definition
Weiss et al., 1991[15] Singson et al., 1991[16]	Double PCL	A low signal band anterior and parallel to the posterior cruciate ligament in sagittal images.
Haramati et al., 1993[18]	Flipped meniscus	An abnormally-enlarged anterior meniscal horn ($>$ 6 mm).
Wright et al., 1995[4]	Intercondylar fragment	A band-like area of low signal intensity within the notch but not appearing on the same slice as the PCL.
Helms et al., 1998[14]	Sign of absence of bow tie	The occurrence of only one or no meniscal body segment in consecutive MRI sagittal images.
Ruff et al., 1998[17]	Double anterior horn	The presence of two triangles not vertically juxtaposed but located next to another in the same horizontal plane in a sagittal section appearing like two anterior horns of the meniscus.
Chen et al., 2001[19]	Disproportional posterior horn	Posterior horn in the central section larger than that in the peripheral section on sagittal MRI images.
Bugnone et al., 2005[6]	Quadruple cruciate sign	Four structures in intercondylar notch observed in consecutive coronal sections: both displaced fragments of torn menisci, the stump of torn ACL and the intact PCLç.
Bui-Mansfield et al., 2006[20]	Double ACL	The presence of the fragment immediately posterior to the ACL.
Kakel et al., 2010[7]	Triple PCL	The presence of an intact PCL and two displaced fragments in the intercondylar notch from the two bucket-handle tears on sagittal view in an ACL-deficient knee.
Rao et al., 2012[23]	V sign	The “V” is seen at the junction of the displaced fragment (handle), as it forms a right angle with the meniscus, which is in place.
Sales et al., 2021[8]	Triple cruciate sign	Three structures in intercondylar notch observed in coronal sections: both displaced fragments of torn menisci and the intact PCL.
Barrie, 1979[25]	Parameniscal cyst	A fluid collection in intimate relation with the meniscus either by a direct contact or a fluid track.
Gale et al., 1999[26]	Meniscal extrusion	Quantified in the coronal image at its greatest value and was considered when the peripheral margin of the meniscus extends 3 mm or more beyond the edge of the tibial plateau.
Kaplan et al., 1999[27]	Subchondral marrow edema	Nonlinear edema with no clearly-defined margin.
Kolman et al., 2004[24]	Joint effusion	An anteroposterior measurement of 10 mm or more in the lateral suprapatelar pouch was considered abnormal.
Bergin et al., 2008[28]	Linear subchondral marrow edema	Well-demarcated edema parallel to the articular surface and fewer than 5 mm deep.

Abbreviations: ACL, anterior cruciate ligament; MRI, magnetic resonance imaging; PCL, posterior cruciate ligament.

Lymphocyte Count, Serum Albumin and Transferrin Levels in Patients Undergoing Total Knee Arthroplasty

Contagem de linfócitos e concentrações séricas de albumina e transferrina em pacientes submetidos à artroplastia total de joelho

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Abstract

Objective Describe the prevalence of preoperative malnutrition in individuals undergoing primary TKA and to assess its association with age, sex, body mass index (BMI), and comorbidities, as well as the risk of prolonged postsurgical hospitalization, early prosthetic joint infection (PJI), or readmission.

Methods We conducted a cohort study of TKAs performed between 2014 and 2016. Preoperative malnutrition was defined as a total lymphocyte count $< 1{,}500$ cells/mm^3, a serum albumin concentration < 3.5 g/dL, or a transferrin concentration < 200 mg/dL within the six months before surgery.

Results Out of the 2080 TKAs performed, 1099 had valid lymphometry, albumin, and transferrin data and were included in the analysis. The prevalence of malnutrition was 17.7%. Independent factors associated with a higher prevalence of malnutrition were age (OR = 1.03; 95% CI = (1.01–1.05)), anemia (1.55 (1.05–2.28)), low weight (3.13 (1.50–6.50)), and normal weight (1.85 (1.21–2.82)). Diabetes mellitus was inversely associated with malnutrition (0.60 (0.38–0.96)). Early PJI was diagnosed in 18 (1.6%)

Keywords
- knee
- osteoarthritis
- arthroplasty, replacement, knee
- malnutrition
- periprosthetic joint infection

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participants. There was no statistically significant and independent association between malnutrition and postsurgical complications.
Conclusion Altered lymphocyte count, serum albumin, and transferrin levels is common among individuals undergoing TKA, particularly in older patients, those with anemia, and individuals with normal or low weight. Future studies with larger sample sizes are needed to better assess the relationship between malnutrition and adverse outcomes following TKA.

Resumo

Objetivo Descrever a prevalência de desnutrição pré-operatória em indivíduos submetidos à ATJ primária e avaliar sua associação à idade, sexo, índice de massa corporal (IMC) e comorbidades, bem como o risco de hospitalização pós-operatória prolongada, infecção articular periprotética (IAP) precoce ou readmissão.
Métodos Este é um estudo de coorte de ATJs realizadas entre 2014 e 2016. A desnutrição pré-operatória foi definida pelo número total de linfócitos < 1.500 células/mm^3, concentração sérica de albumina $< 3,5$ g/dL ou concentração de transferrina < 200 mg/dL nos 6 meses anteriores à cirurgia.
Resultados Das 2.080 ATJ realizadas, 1.099 casos tinham dados válidos de linfometria, albumina e transferrina e foram incluídas na análise. A prevalência de desnutrição foi de 17,7%. Os fatores independentes associados à maior prevalência de desnutrição foram idade (razão de chances [OR] = 1,03; intervalo de confiança [IC] de 95% = 1,01-1,05), anemia (1,55 [1,05-2,28]), baixo peso (3,13 [1,50-6,50]) e peso normal (1,85 [1,21-2,82]). O diabetes mellitus foi inversamente associado à desnutrição (0,60 [0,38-0,96]). A IAP precoce foi diagnosticada em 18 (1,6%) participantes. Não houve associação estatisticamente significativa e independente entre desnutrição e complicações pós-cirúrgicas.
Conclusão As alterações em números de linfócitos e concentrações séricas de albumina e transferrina são comuns em indivíduos submetidos à ATJ, em especial em pacientes mais velhos, anêmicos e com peso normal ou baixo. Estudos futuros com amostras maiores são necessários para avaliar melhor a relação entre desnutrição e desfechos adversos após ATJ.

Palavras-chave
- joelho
- osteoartrite
- artroplastia do joelho
- desnutrição
- infecção articular periprotética

Introduction

Malnutrition is an imbalance in caloric, protein, or vitamin intake that leads to acute or chronic nutritional depletion and associated metabolic or functional impairments.[1] This condition may arise from reduced food intake, absorptive disorders, hypercatabolic states, or consumptive conditions.[2] Various diagnostic criteria, including anthropometric indices (e.g., body mass index and body composition analysis), nutritional questionnaires, and serum markers, are used to define malnutrition, each with its own limitations and advantages.

Despite the availability of various methods for screening and assessing malnutrition—such as anthropometric measurements, body composition analysis, nutritional questionnaires, and laboratory markers—its diagnosis remains imprecise. The World Health Organization (WHO) defines malnutrition as a BMI below 18.5 kg/m^2. In contrast, the American Society for Parenteral and Enteral Nutrition (ASPEN) defines it based on the presence of two or more criteria, including inadequate caloric intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may mask weight loss, and decreased functional capacity.[2] The European Society for Clinical Nutrition and Metabolism (ESPEN) has proposed a consensus for diagnosing malnutrition, which combines the use of nutritional risk questionnaires with criteria such as BMI, relative weight loss, or lean mass index.[3] This consensus has been criticized for its impracticality, lack of clear guidance on which nutritional risk questionnaire to use, and its neglect of inflammatory biochemical changes involved in the malnutrition process.[4,5] Serum markers are widely used for nutritional assessment due to their affordability, reproducibility, and ability to detect acute changes in nutritional status. Common parameters for identifying malnutrition include a total lymphocyte count below 1,500 cells/mm^3, serum albumin levels under 3.5 g/dL, and transferrin levels below 200 mg/dL.[6] Other nutritional markers, such as prealbumin, interleukins, C-reactive protein, and leptin, are less frequently utilized.[7]

The link between malnutrition and postoperative complications was first noted in abdominal surgeries.[8] In orthopedics, malnutrition has been associated with poorer outcomes in patients treated for proximal femur fractures, leading to longer hospital stays, increased infectious and noninfectious complications, and higher readmission rates.[9,10]

Total knee arthroplasty (TKA) is a complex surgery aimed at treating advanced knee osteoarthritis to restore function and relieve symptoms. Projections indicate a rising demand for arthroplasties, significantly impacting public and private healthcare costs.[11] Prosthetic joint infection (PJI) is the leading cause of early failure and short-term revision surgery.[12] Research on the link between malnutrition and PJI, as well as noninfectious complications in arthroplasties, is gaining attraction in the literature.[13,14] However, Brazilian data are scarce, highlighting the need to evaluate nutritional status to understand its impact and develop strategies for risk mitigation.

This study aimed to assess the prevalence of preoperative malnutrition and its association with demographic and clinical characteristics, as well as the risk of PJI and noninfectious complications post-TKA in a reference orthopedic surgery center.

Materials and Methods

This cohort study involved a retrospective analysis of prospectively collected data, approved by the Institutional Review Board (CAAE 63639216.3.0000.5273). It included all patients who underwent primary TKA from January 2014 to December 2016. Patients who had simultaneous bilateral arthroplasties or resided outside Rio de Janeiro State were excluded.

All surgeries were performed by specialist knee surgeons. Patients received antimicrobial prophylaxis 30 to 60 minutes before the incision and were transferred to the intensive care unit on the first postoperative day. Hospital discharge occurred from the third day post-admission, based on adequate clinical conditions and pain control. Thromboembolic event prevention was performed with a daily single subcutaneous dose of 40 mg of low-molecular-weight heparin (Clexane®, Sanofi Aventis), starting 12 to 24 hours after surgery and continuing for 14 days. Postoperative patient follow-up was conducted through regular outpatient consultations.

Deep PJI diagnosis followed the Musculoskeletal Infection Society (MSIS) guidelines.[15] PJI was classified temporally based on the interval from the index procedure to symptom onset: early (<3 months), intermediate (3 months to 2 years), or late (>2 years).[16] Only early infections were analyzed due to their direct association with perioperative risk factors.

Malnutrition was defined by at least one of the following laboratory parameters: total lymphocyte count <1,500 cells/mm^3, serum albumin <3.5 g/dL, or transferrin <200 mg/dL.[6] For patients over 60, BMI was categorized per Pan American Health Organization (PAHO) recommendations: underweight (<23 kg/m^2), normal (23 to 27.9 kg/m^2), overweight (28 to 29.9 kg/m^2), and obese (>30 kg/m^2).[17] For those under 60, BMI was categorized using modified WHO classifications: underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), or obese (>30 kg/m^2). Anemia was defined per WHO criteria based on sex: hemoglobin <12 g/dL for females and <13 g/dL for males.[18]

The hospital database was searched for information on all patients who underwent primary TKA between 2014 and 2016. Data collected included age, sex at birth, medical records, weight, height, comorbidities (such as hypertension, diabetes, asthma, heart disease, dyslipidemia, and rheumatoid arthritis), ASA classification, surgery date, admission and discharge dates, reason for discharge, perioperative blood transfusion, and preoperative laboratory results (hemoglobin, hematocrit, albumin, transferrin, and lymphocytes). Valid laboratory tests were those performed within 180 days before surgery; if multiple results existed, the closest to the surgery date was used for analysis. New admissions within 90 days post-procedure were reviewed through physical medical records. Additionally, epidemiological surveillance records from the Hospital Infection Control Committee were utilized to identify patients with early PJI. Data from both sources were entered into a Microsoft Excel 2016® spreadsheet.

Quantitative variables are presented as medians with interquartile ranges (IQRs), minimums, and maximums, while categorical variables are expressed as frequency (n) and percentage (%). The Shapiro—Wilk test assessed sample normality. For normally distributed data, the parametric Student's *t*-test was used, with adjustments for unequal variances as needed. For non-normal data, the Mann—Whitney or Kruskal—Wallis tests were employed. Categorical variables were analyzed using the chi-square or Fisher's exact tests, as appropriate. Odds ratios assessed the association between malnutrition and explanatory variables. Proportional hazard regression analyzed postoperative hospitalization time, treating time as a discrete variable due to its non-normal distribution (*pgmhaz* command). Logistic regression identified independent factors associated with malnutrition. The McNemar test compared malnutrition prevalence based on different criteria. Statistical significance was set at 5% ($p < 0.05$), and data were analyzed using Stata® version 17.0 (StataCorp LLC, College Station, Texas, USA).

Results

Between January 1, 2014, and December 31, 2016, a total of 2,112 primary TKAs were performed. After applying exclusion criteria (14 simultaneous bilateral TKAs and 28 patients from outside Rio de Janeiro State), 2,080 TKAs were analyzed (►**Fig. 1**). Of these, 73.6% were female, with a median age of 68 years (IQR 63–74). Complete patient data are provided in ►**Supplementary Table S1**.

Valid results for serum albumin, total transferrin, and total lymphocyte counts were obtained for 1,433, 1,149, and 1,988 participants, respectively. The median serum albumin was 4.0 mg/dL (IQR 3.8–4.2), with 30 patients (2.1%) exhibiting hypoalbuminemia (<3.5 g/dL). The median transferrin

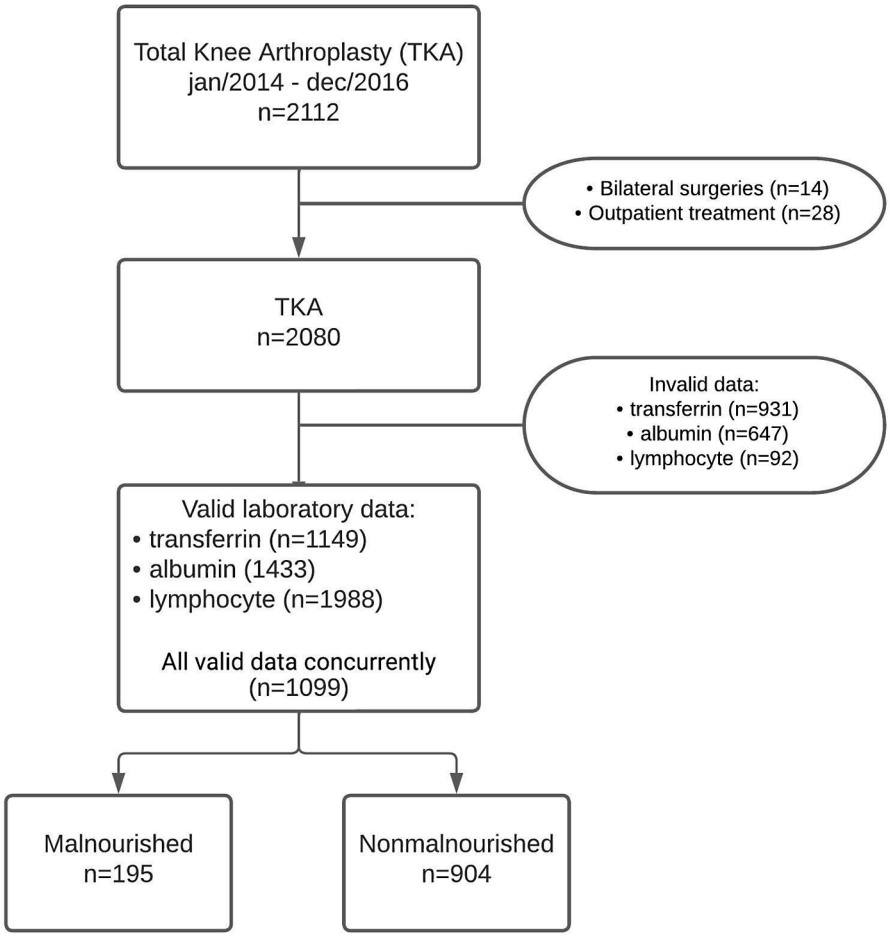


Fig. 1 Flowchart of inclusion of participants in the study.

concentration was 250 mg/dL (IQR 226–279 mg/dL), and 84 patients (7.3%) had transferrin levels <200 mg/dL. The median total lymphocyte count was 2,288 cells/mm^3 (IQR 1,870–2,834), with 205 patients (10.3%) below 1,500 cells/mm^3 (►**Fig. 2** and ►**Supplementary Table S2**).

Out of 2,080 participants, 1,099 had valid data for albumin, transferrin, and lymphocytes, with 195 categorized as malnourished (17.7%) and 904 as nonmalnourished (82.3%). Among the malnourished, 17 individuals (8.7%) showed concurrent abnormalities in two or more serum markers. Pairwise concordance analysis revealed a statistically significant difference ($p < 0.05$), indicating low overlap among these markers (►**Fig. 3**).

Malnourished individuals were older, had lower hematocrit and leukocyte counts, and lower BMI than their nonmalnourished counterparts. The prevalence of males was higher among the malnourished ($p > 0.05$). Malnourished individuals also had higher rates of underweight and normal weight classifications, greater prevalence of anemia, and more frequent blood transfusions compared with the nonmalnourished. Hypertension and diabetes were more common among individuals without laboratory-defined malnutrition (►**Table 1**).

Age, underweight status, normal weight, and anemia were independent factors linked to a higher prevalence of malnutrition, while diabetes mellitus showed an inverse association (►**Table 2**). This analysis included 901 participants with complete data for all variables.

In assessing unfavorable outcomes after primary TKA, malnutrition ($p = 0.025$) and transferrin levels ($p = 0.021$) were associated with postoperative hospitalization time in bivariate analysis. However, other outcomes—early PJI, readmission for any cause, and readmission due to operative wound complications—did not correlate with nutritional status or serum markers (►**Table 3**). In the multivariate analysis, only anemia was independently associated with postoperative hospitalization duration (►**Table 4**). The bivariate analysis of factors related to hospitalization length is presented in ►**Supplementary Table S3**.

Discussion

In this study, we found a laboratory-defined malnutrition prevalence of 17.7% among 1,099 patients undergoing primary TKA. Malnutrition was linked to advanced age, low and normal weight, and anemia, but inversely related to diabetes. No independent association was observed between malnutrition and PJI or noninfectious complications post-TKA.

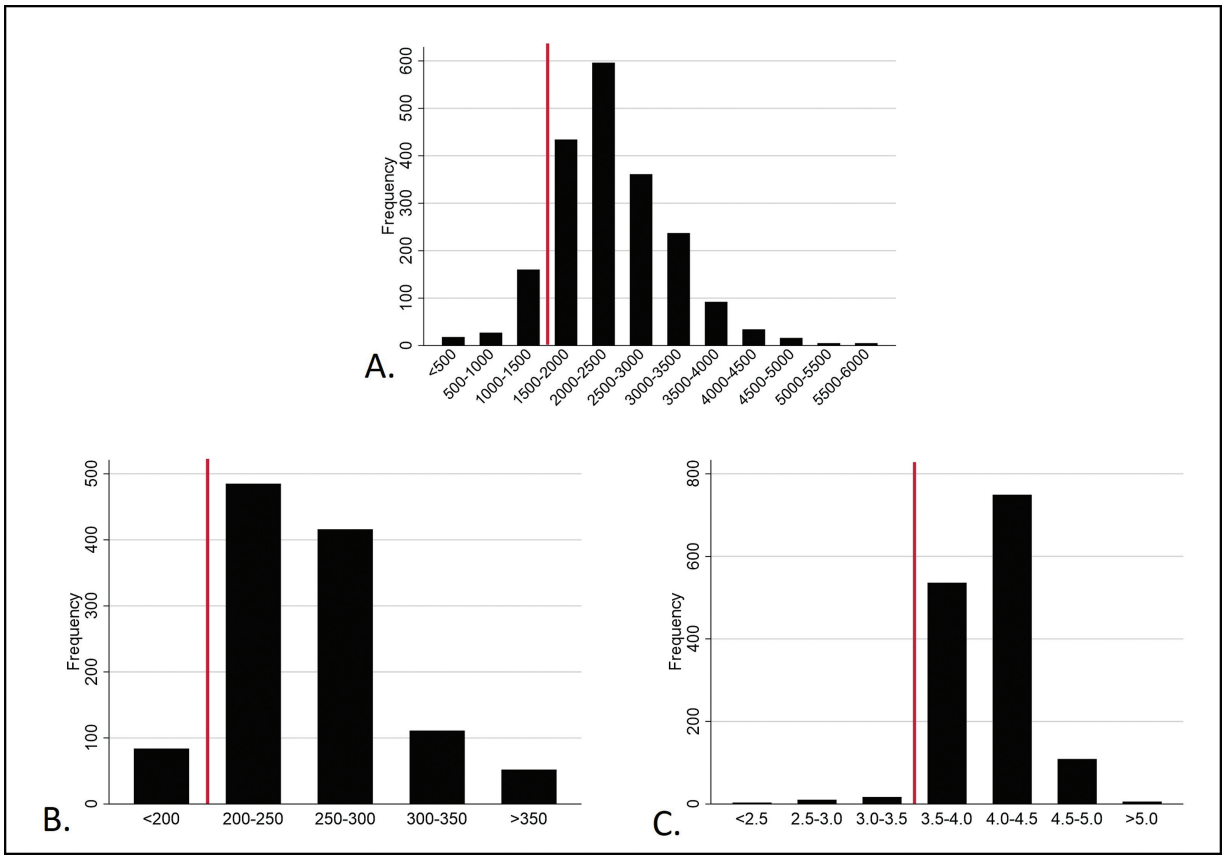


Fig. 2 Distribution of laboratory markers of malnutrition, measured up to 180 days before primary total knee arthroplasty. The red line on each graph denotes the cutoff point for the malnutrition criterion.[3] A. Lymphocyte count ($n = 1{,}988$): 205 participants with dosage below 1,500 cells/mm3; B. Transferrin dosage ($n = 1{,}149$): 84 participants with dosage below 200 mg/dL; C. Albumin dosage ($n = 1{,}433$): 30 participants with dosage below 3.5 g/dL.

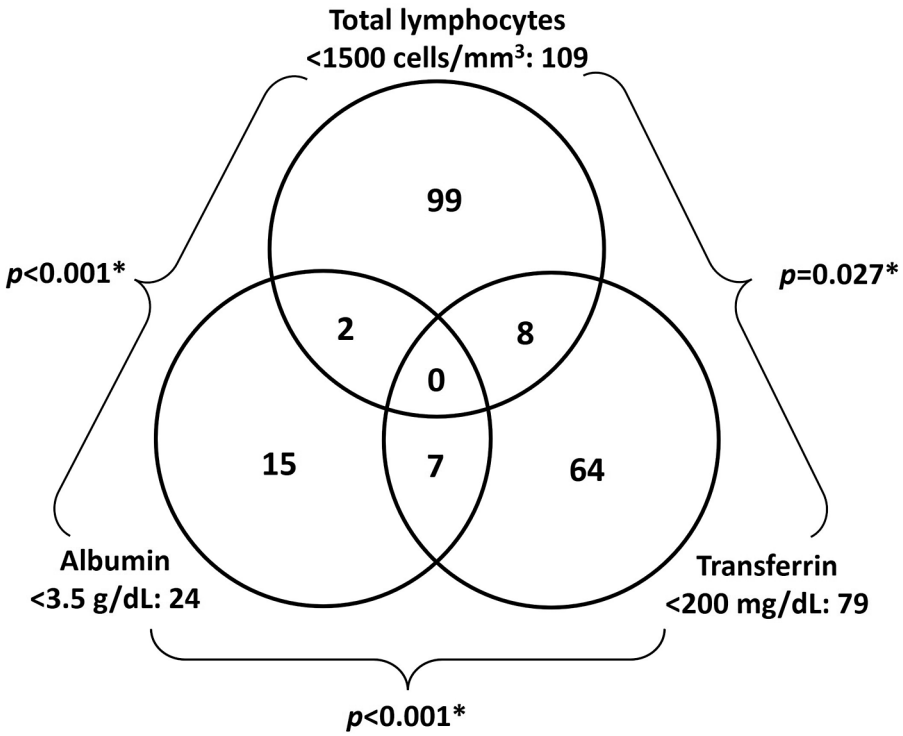


Fig. 3 Distribution of the 195 patients classified as malnourished (among the 1,099 with the 3 available and valid laboratory parameters), according to the laboratory-defined malnutrition.

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Table 1 Analysis of demographic and laboratory characteristics between malnourished and non-malnourished patients undergoing primary total knee arthroplasty ($n = 1099$)

	Not Malnourished ($n = 904$)		Malnourished ($n = 195$)		Total		Odd Ratio	95% CI	p-valor
Gender – N(%)									
Female	678	(75.0%)	133	(68.2%)	811	(73.8%)			
Male	226	(25.0%)	62	(31.8%)	288	(26.2%)	1.40	(1.00, 1.96)	0.051
BMI (OMS/OPAS)– N(%)									
Obesity	480	(57.7%)	73	(42.2%)	553	(55.0%)	1.00	–	–
Overweight	139	(16.7%)	33	(19.1%)	172	(17.1%)	1.56	(0.99, 2.45)	0.054
Normal Weight	188	(22.6%)	53	(30.6%)	241	(24.0%)	1.85	(1.25, 2.74)	**0.002**
Underweight	25	(3.0%)	14	(8.1%)	39	(3.9%)	3.65	(1.83, 7.41)	**<0.001**
ASA – N(%)									
I	143	(21.3%)	30	(21.3%)	173	(21.3%)	1.00	–	–
II	523	(77.9%)	110	(78.0%)	633	(78.0%)	1.00	(0.64, 1.56)	0.991
III	5	(0.7%)	1	(0.7%)	6	(0.7%)	0.95	(0.11, 8.46)	0.966
Arterial Hypertension – N(%)									
No	219	(24.3%)	61	(31.3%)	280	(25.5%)			
Yes	683	(75.7%)	134	(68.7%)	817	(74.5%)	0.70	(0.50, 0.99)	**0.043**
Diabetes mellitus – N(%)									
No	669	(74.0%)	167	(85.6%)	836	(76.1%)			
Yes	235	(26.0%)	28	(14.4%)	263	(23.9%)	0.48	(0.31, 0.73)	**0.001**
Heart Disease – N(%)									
No	852	(94.2%)	185	(94.9%)	1037	(94.4%)			
Yes	52	(5.8%)	10	(5.1%)	62	(5.6%)	0.89	(0.44, 1.77)	0.732
Dyslipidemia – N(%)									
No	853	(94.4%)	187	(95.9%)	1040	(94.6%)			
Yes	51	(5.6%)	8	(4.1%)	59	(5.4%)	0.72	(0.33, 1.53)	0.389
Rheumatoid arthritis – N(%)									
No	858	(94.9%)	180	(92.8%)	1038	(94.5%)			
Yes	46	(5.1%)	14	(7.2%)	60	(5.5%)	1.45	(0.78, 2.70)	0.239

Table 1 (*Continued*)

	Not Malnourished (*n* = 904)		Malnourished (*n* = 195)		Total		Odd Ratio	95% CI	p-valor
Anemia – N(%)									
No	632	(77.4%)	118	(68.2%)	750	(75.8%)			
Yes	185	(22.6%)	55	(31.8%)	240	(24.2%)	1.59	(1.11, 2.28)	**0.011**
Blood transfusion – N(%)									
No	777	(86.6%)	154	(79.0%)	931	(84.7%)			
Yes	127	(14.1%)	41	(21.0%)	168	(15.3%)	1,63	(1.10, 2.41)	0.015
Age (years) – median (IIQ)	67	(63–73)	70	(64–76)	68	(63–74)	–	–	0.001
Hematocrit (%)– median (IIQ)	39,0	(36.6–41.9)	38.2	(35.6–41.1)	38.9	(36.4–41.7)	–	–	0.012
Hemoglobin (g/dL) – median (IIQ)	12,9	(12.1–13.9)	12.9	(11.9–13.8)	12.9	(12.0–13.9)	–	–	0.113
White Blood Cell (cel./mm^3) – median (IIQ)	7300	(6300–8600)	5900	(4900–7700)	7200	(6000–8500)	–	–	<0.001
BMI (kg/m^2) – median (IIQ)	30,8	(27.5–34.7)	29.2	(26.0–32.7)	30.6	(27.3–34.5)	–	–	<0.001
Blood transfusion Volume (ml) – median (IIQ)	290	(256–513)	288	(261–511)	290	(257–512)	–	–	0.973

The prevalence of hypoalbuminemia was lower than reported in the literature, with only 2.1% of patients meeting the malnutrition criterion. Nelson et al. (2015)[19] found that 4.2% of over 37,000 patients undergoing primary TKA in the USA had low serum albumin. In South Korea, Morey et al. (2016)[20] reported 7.1% malnutrition based on albumin levels. This variation may be due to geographic differences in dietary profiles, as global data show higher total and animal protein intake in Brazil compared with the USA and South Korea.[21]

Using transferrin serum levels, malnutrition was identified in 7.3% of the sample. Huang et al. (2013)[22] found 6.6% malnutrition in patients undergoing elective arthroplasty. While their study linked malnutrition to higher complication rates, our findings differed. They also reported low overlap between albumin and transferrin, with 4.9% of malnourished patients showing both markers altered, similar to our study's 3.6%.

Total lymphocyte count was the most common malnutrition marker in our cohort (10.3%). This aligns with previous studies, such as Morey et al. (2016),[20] who found a 16% incidence. Overlap between lymphocyte and albumin markers was rare, occurring in just 1% of cases in our study and 7.7% in theirs. The lack of overlap among nutritional markers is notable, as malnutrition typically affects protein synthesis and immunity together, yet concurrent changes in albumin, transferrin, and lymphocytes were not observed here or in previous studies.[20,22]

Our study found a small, yet statistically significant, association between malnutrition and advanced age, likely due to factors such as reduced appetite, food intake, comorbidities, polypharmacy, and functional decline.[23] Family isolation also plays a role, as increased dependence, loss of autonomy, and lack of home support negatively impact nutrition.[24] These issues were common in our population, often due to mobility loss from orthopedic conditions.

Anemia indicates poor nutritional status, especially in the elderly.[25] In our study, transferrin levels were used to assess malnutrition, but these vary based on anemia type: they increase in iron deficiency to optimize metal absorption and decrease in chronic disease along with that of other proteins.[26] Thus, the link between anemia and malnutrition may not be solely due to nutrient deficiencies but also chronic disease conditions associated with malnutrition.[27] Additionally, iron deficiency anemia can lower lymphocyte counts, explaining the independent association between anemia and malnutrition.[28]

We found an association between malnutrition and lower BMI categories ("underweight" and "normal weight"), with higher risk compared with obese participants (BMI $\geq$ 30 kg/m^2). The prevalence of malnutrition in the underweight group was expected, as a BMI below 18.5 kg/m^2 is often a diagnostic criterion. However, even normal-weight individuals had higher rates of laboratory malnutrition. This may be due to osteoarthritis-related inactivity, leading to chronic conditions, lean mass loss, and fat replacement, contributing to malnutrition despite a normal BMI. In arthroplasty patients, normal-weight individuals showed a higher risk

Table 2 Result of the multivariate logistic regression model of factors associated with malnutrition in patients ($n = 901$) undergoing primary total knee arthroplasty

	Odds Ratio	95% CI	p
Age (years)	1.03	(1.01, 1.05)	0.014
BMI (OMS/OPAS)			
Obesity	1.00	–	–
Overweight	1.61	(0.99, 2.62)	0.057
Normal Weight	1.85	(1.21, 2.82)	0.005
Underweight	3.13	(1.50, 6.50)	0.002
Diabetes mellitus	0.60	(0.38, 0.96)	0.031
Anemia	1.55	(1.05, 2.28)	0.028
Intercept	*0.02*	*(0.00, 0.10)*	*0.000*

of malnutrition than overweight and obese patients (51% versus 27% and 32%, $p = 0.0012$ and 0.0023).[29] Age-related changes also support using the PAHO's BMI classification for the elderly, which better identifies underweight individuals at nutritional risk and is linked to higher mortality.[30]

Interestingly, diabetes appears to be a protective factor against malnutrition. In lumbar spine surgery patients, insulin-dependent diabetes was linked to higher hypoalbuminemia rates, while non-insulin-dependent diabetes had similar rates to nondiabetics.[31] Studies on diabetes and malnutrition show mixed results. An Austrian survey of hospitalized and geriatric patients found diabetes to be a protective factor using the MUST score, nearing statistical significance (OR = 0.883, $p = 0.06$).[32] Conversely, diabetes was an independent risk factor for malnutrition in kidney carcinoma patients assessed by the SGA scale.[33] Most studies found no significant association between diabetes and malnutrition risk.[34,35] In our population, factors such as greater focus on dietary protein and stricter nutritional monitoring in high-risk diabetic patients may have contributed to better nutritional status. Additionally, diagnostic bias could play a role, as individuals with higher socioeconomic status may have better nutrition, greater healthcare access, and a higher likelihood of having or reporting a diabetes diagnosis.

Neither malnutrition nor serum marker levels were independent risk factors for complications after TKA. The only associations noted were between malnutrition and transferrin levels with postoperative length of stay, observed only in bivariate analysis, likely due to confounding factors like age and anemia. Fu et al.[13] found that hypoalbuminemia (albumin < 3.5 g/dL) was associated with total length of stay, but only in bivariate analysis. However, the independent link between anemia and malnutrition prevalence, along with increased postoperative length of stay, highlights that preoperative anemia is a modifiable yet often overlooked risk factor.[14]

Several studies indicate that malnutrition increases the risk of both infectious and noninfectious complications after arthroplasty. In a study with 9,001 arthroplasty patients, those with albumin concentration < 3.5 g/dl were more likely to develop deep PJI (adjusted odds ratio 4.69, $p < 0.001$).[36] The infection rate in patients with low albumin (7.3%) was significantly higher than in our study (3.3%). This discrepancy may be due to the inclusion of hip arthroplasties, particularly urgent surgeries for proximal femur fractures, which carry a higher risk of early PJI compared with elective procedures.[37]

Bohl et al.[14] identified serum albumin concentration as a potential risk marker for periprosthetic joint infection (PJI), perioperative complications, and readmission. They found an association between hypoalbuminemia, extreme BMI (<18.5 kg/m^2 and >40 kg/m^2), and advanced age (>70 years). These results were supported by Fu et al.,[13] who reported higher septic and aseptic complication rates in patients undergoing TKA. However, Morey et al.[20] found no impact of malnutrition on infection rates or functional outcomes in 3,169 TKA patients, suggesting that nutritional assessment through laboratory parameters may not effectively stratify the risk of post-TKA infection.

A 2019 systematic review with meta-analysis evaluated 20 studies on the effects of laboratory-defined malnutrition in patients undergoing primary or revision total knee arthroplasty (TKA) and total hip arthroplasty (THA). Among the 11 studies involving over 100,000 patients with primary TKA, the combined prevalence of laboratory malnutrition was 11.6%. Only one study found no link between malnutrition and postoperative complications. The meta-analysis included eight comparable studies, which revealed a significant association between an albumin level < 3.5 g/dL and operative wound complications in arthroplasty patients (OR: 2.176, 95% CI: 1.916–2.471). However, the review did not address publication bias or article heterogeneity. Limitations included inconsistencies in malnutrition definitions, variations in assessed outcomes, and limited data on the timing of malnutrition marker collection.[38]

This study has several limitations. We obtained analyzable results for albumin, transferrin, and lymphocytes in 68.9%, 55.2%, and 95.7% of the sample, respectively. Similar studies have reported 30% to 70% losses, a common limitation in this study design.[19,36] Despite the significant sample size, only 18 early PJI cases were identified, limiting the analysis of infection risk factors. The lack of other malnutrition

Table 3 Analysis of malnutrition and nutritional serologic markers as a risk factor for unfavorable outcomes after primary total knee arthroplasty

	Early Periprosthetic Joint Infection				Hospital Readmission				Hospital Readmission for Wound Complications				Days from surgery to Hospital Discharge	
		OR	CI 95%	p		OR	CI 95%	p		OR	CI 95%	p	Median (IIQ)	p
Malnourished ($n = 195$)	3 (1.5%)	0.93	0.17- 3.32	0.904	17 (8.7%)	0.91	0.49- 1.59	0.730	8 (4.1%)	0.70	0.28- 1.52	0.358	4 (3–5)	**0.025**
Nonmalnourisehd ($n = 904$)	15 (1.7%)				86 (9.5%)				52 (5.8%)				3 (3–5)	
Albumin <3,5 g/dL ($n = 30$)	1 (3.3%)	2.16	0.51–14.35	0.447	3 (10.0%)	1.15	0.22–3.81	0.825	2 (6.7%)	1.26	0.14–5.18	0.751	4 (3–6)	0.149
Albumin >3,5 g/dL ($n = 1403$)	22 (1.6%)				124 (8.8%)				75 (5.4%)				3 (3–5)	
Transferrin <200mg/dL ($n = 84$)	1 (1.2%)	0.66	0.02–4.28	0.689	5 (6.0%)	0.62	0.19–1.55	0.304	4 (4.8%)	0.88	0.23–2.48	0.816	4 (3–6)	**0.021**
Transferrin >200mg/dL ($n = 1065$)	19 (1.8%)				99 (9.3%)				57 (5.4%)				3 (3–5)	
Lymphocytes <1.500 cell/mm^3 ($n = 205$)	6 (2.9%)	1.51	0.51–3.68	0.358	22 (10.7%)	1.19	0.71–1.93	0.458	12 (5.9%)	1.1	0.54–2.07	0.752	4 (3–5)	0.055
Lymphocytes >1.500 cell/mm^3 ($n = 1783$)	35 (2.0%)				163 (9.1%)				95 (5.3%)				3 (3–5)	

Table 4 Multivariate analysis of factors associated with primary total knee arthroplasty and hospital discharge interval

	Hazard Ratio	95% CI	p
Age (years)	0.995	(0.980, 1.000)	0.056
Anemia	0.843	(0.754, 0.941)	**0.002**
Intercept	*0.352*	*(0.248–0.499)*	*<0.001*

assessments, such as nutritional questionnaires and body composition analysis, may have led to classification bias, misclassifying malnourished patients as eutrophic and vice versa. However, strengths include the focus on TKA, the use of the PAHO classification to assess nutritional risk by BMI in older adults, and the restriction of laboratory exam dates to six months before the procedure. Additionally, we utilized the three most recognized laboratory parameters for malnutrition —albumin, transferrin, and lymphocytes—enabling evaluation of each criterion's individual and combined effectiveness.

Conclusions

The prevalence of altered lymphocyte count, serum albumin, and transferrin levels in patients undergoing TKA was 17.7%, with higher rates observed in older patients, anemic patients, and individuals with normal or low BMI. Identifying these groups could enhance preoperative management through nutritional interventions for partial or complete correction before surgery. Further studies with greater statistical power are needed to evaluate the association between malnutrition—regardless of the definition used—and adverse outcomes post-TKA.

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

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Medial Thigh Cutaneous Flap Irrigated by Perforating Vessels of the Secondary Pedicle of the Gracilis Muscle: Anatomical Study and Clinical Case Report

Retalho cutâneo medial da coxa irrigado por vasos perfurantes do pedículo secundário do músculo grácil: Estudo anatômico e relato de caso clínico

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Abstract

Objective To analyze the anatomy of the perforating vessels irrigating the skin of the medial aspect of the thigh and originating from the secondary vascular pedicle of the gracilis muscle.

Methods We dissected 33 thighs from cadavers of both sexes to record and analyze the characteristics of the blood vessels irrigating the gracilis muscle in the middle third of the thigh.

Results All thighs (100%) had a secondary vascular pedicle in the intermuscular septum between the gracilis and vastus medialis/sartorius muscles, with branches irrigating the overlying skin on the medial aspect. The pedicle presented an arterial diameter ranging from 1.3 to 4.6 mm (mean: 2.3 mm) and a length ranging from 28 to 84 mm (mean: 50.6 mm). In 87.8% of the cases, the pedicle irrigated the gracilis muscle and presented vessels to the overlying skin.

Conclusion Based on the data found, we conclude that it is feasible to obtain a reliable flap from the medial aspect of the middle third of the thigh.

Keywords
- gracilis muscle
- surgical flaps
- thigh

Resumo

Objetivo Estudar a anatomia dos vasos perfurantes que irrigam a pele da face medial da coxa, provenientes do pedículo vascular secundário do músculo grácil.

Métodos Foram dissecadas 33 coxas de cadáveres de ambos os sexos, e registradas e analisadas as características dos vasos sanguíneos que irrigam o músculo grácil no terço médio.

Study performed at the Department of Orthopedics and Traumatology, Irmandade da Santa Casa da Misericórdia de São Paulo (DOT/ISCMSP), São Paulo, SP, Brazil.

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Resultados Em todas as coxas (100%) foi evidenciada a presença de um pedículo vascular secundário no septo intermuscular entre os músculos grácil e vasto medial/sartório, com ramos que irrigam a pele suprajacente na face medial. O pedículo apresentou um diâmetro arterial que variou de 1,3 a 4,6 mm (média de 2,3 mm) e comprimento entre 28 e 84 mm (média de 50,6 mm). Em 87,8% dos casos, o pedículo irrigava o músculo grácil e apresentava vasos para a pele suprajacente.

Conclusão Com base nos dados encontrados, podemos concluir que é possível obter um retalho confiável da face medial do terço médio da coxa.

Palavras-chave
- coxa
- músculo grácil
- retalhos cirúrgicos

Introduction

Injuries resulting from high-energy trauma, mainly traffic accidents, often involve soft tissue loss and exposure of essential structures, such as bones, tendons, vessels, and nerves.[1] These therapeutic situations are difficult to manage and challenging for the reconstructive surgeon.

The improvements in surgical techniques have increased treatment success rates. Today, free flaps are an effective option among reconstructive techniques. Perforator flaps are an evolution of microsurgical flaps, enabling the creation of thinner flaps and resulting in better functional and esthetic outcomes.[2]

In 1967, Fujino[3] documented the distribution of perforating arteries to supply the interstitium, similar to axial arteries. In 1988, Koshima et al.[4] pioneered perforating artery-based flaps exclusively consisting of skin and subcutaneous tissue. Wei et al.[5] defined perforating artery-based flaps as those supplied by arteries crossing the adjacent deep fascia and making it feasible to dissection through the muscle or the intermuscular septum to their vessel of origin, with no need for muscle inclusion in the flap.

Focusing on the medial aspect of the thigh, certain authors, such as Peek et al.[6] and Eom et al.,[7] described, in anatomical studies and case reports, a flap from this region based on the perforating arteries originating from the main vascular pedicle of the gracilis muscle. This flap has been widely studied and may be used in its pedicled or free form to cover different defects in the inguinal region or distant areas.

Feng et al.,[8] Scaglioni et al.,[1] and Zheng et al.[9] also described, through anatomical studies and some clinical cases, the anteromedial thigh flap or lower medial thigh flap based on perforating branches from muscular arteries irrigating the vastus medialis muscle. In 1984, Song et al.[10] described the perforating flap from the deep femoral artery, harvested from the posteromedial aspect of the thigh.

The gracilis muscle, in the medial region of the thigh, is commonly used as a functional free muscle flap. Mathes and Nahai[11] classified its irrigation pattern as type 2, that is, muscle irrigation occurs by a dominant vascular pedicle, able to supply the entire muscle, but with the contribution of several smaller secondary pedicles. Some branches of these vessels cross the deep fascia in the medial region of the thigh and irrigate the subcutaneous tissue and overlying skin. In an anatomical study with arteriography, Peek et al.[6] identified the presence of a secondary pedicle in the intermediate region of the thigh with multiple intramuscular anastomoses with the main vascular pedicle.

The objective of the present study was to evaluate the anatomical parameters of the vessels irrigating the skin and fascia of the medial region of the thigh, originating from the secondary vascular pedicle of the gracilis muscle in the middle third of the thigh, defining its location, diameter, distribution pattern, and anatomical variations, showing the feasibility of obtaining a reliable flap based on this vascular pedicle.

Materials and Methods

The institutional Ethics Committee approved the study under number CAAE: 15621319.1.0000.5479.

We performed microsurgical dissection of 33 thighs from 18 cadavers. In total, 19 thighs were from male cadavers, and 14, from female cadavers. We recorded biometric data of the cadavers, such as age, height, and weight. We excluded cadavers with peripheral vascular disease as the known cause of death and those with scars in the dissection region.

The same surgeon performed all dissections using a surgical magnifying glass with 3.5x magnification. We recorded anatomical parameters of the vascular pedicle, such as vessel length, diameter, location, origin, and distribution, in addition to their relationship with thigh length. We obtained the measurements using a millimeter tape and a digital four-dimensional 150-mm caliper (Digimess Instrumentos de Precisão Ltda.).

The Kolmogorov-Smirnov test assessed the normal distribution of the quantitative outcome variables. The analysis of quantitative variables used the equality of two proportions and Pearson's correlation tests. The statistical confidence interval was of 95%.

Dissection

Initially, we drew a line on the medial aspect of the thigh, from the ischiopubic ramus to the medial femoral epicondyle (►**Fig. 1**). This line coincided with the anterior border of the gracilis muscle. At the midpoint of this line, we drew a circle with a 3-cm radius divided into quadrants. Next, we made the incision following the circle contour. Then, we identified the perforating arteries by gentle dissection of the

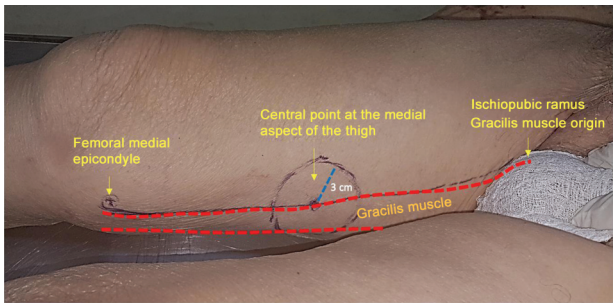


Fig. 1 Medial aspect of the right thigh with a drawing showing the location of the vascular pedicle.

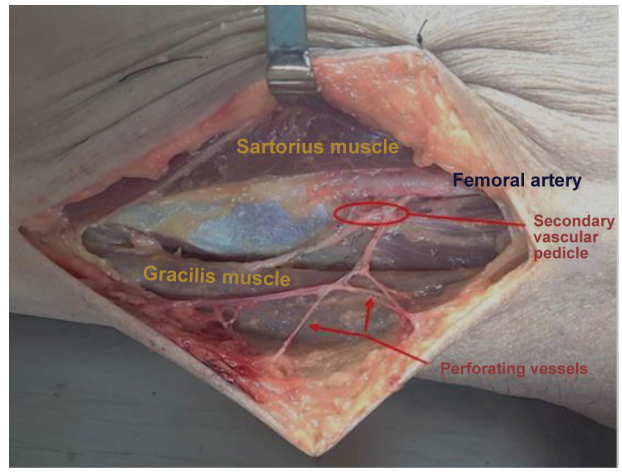


Fig. 2 Dissection of the secondary vascular pedicle of the gracilis muscle with its perforating vessels.

subcutaneous tissue, following them to the septum between the gracilis muscle and the vastus medialis/sartorius muscle. Most vessels identified in the intermuscular septum had muscular branches to the gracilis muscle and, in a few cases, to the sartorius muscle. These septal vessels gave off perforating branches to irrigate the skin and overlying subcutaneous tissue. The dissection continued deep into the femoral artery, which was identified as the arterial origin in all cases (►**Fig. 2**). The veins, usually two, were tributaries of the femoral vein, not of the great saphenous vein, which was close to the dissection site. The branch leading to the gracilis or sartorius muscle underwent ligation, preserving its proximal part. We did the same thing with the perforating veins leading to the skin, increasing the length of the vessels. We selected and documented vessels with an external diameter greater than 0.5 mm.

Table 1 Anthropometric data

Thigh number	Age (years)	Side	Sex	Height (cm)	Weight (kg)	Thigh length (inguinal-medial femoral condyle) (cm)
1	56	Right	Male	176	70	38
2	56	Left	Male	176	70	38
3	62	Right	Male	174	66	36
4	62	Left	Male	174	66	36
5	56	Right	Male	165	88	36
6	52	Right	Male	172	78	35
7	52	Left	Male	172	78	35
8	56	Right	Male	176	84	35
9	52	Right	Male	150	43	35
10	52	Left	Male	150	43	35
11	64	Right	Male	167	61	30
12	64	Left	Male	167	61	30
13	58	Right	Male	170	70	30
14	58	Left	Male	170	70	30
15	59	Right	Female	169	95	30
16	59	Left	Female	169	95	30
17	42	Right	Male	182	76	35
18	42	Left	Male	182	76	35
19	66	Left	Male	175	74	26
20	58	Right	Male	175	86	34
21	58	Left	Male	175	86	34
22	92	Right	Female	164	68	28

(*Continued*)

Table 1 (*Continued*)

Thigh number	Age (years)	Side	Sex	Height (cm)	Weight (kg)	Thigh length (inguinal-medial femoral condyle) (cm)
23	92	Left	Female	164	68	28
24	47	Right	Female	160	65	29
25	47	Left	Female	160	65	29
26	36	Right	Female	165	70	33
27	36	Left	Female	165	70	33
28	92	Right	Female	163	55	32
29	92	Left	Female	163	55	32
30	85	Right	Female	157	42	29
31	85	Left	Female	157	42	29
32	38	Right	Female	160	62	29
33	38	Left	Female	160	62	29
Mean	**57.8**			**162.5**	**66.5**	**31.3**
Maximum	**92**			**182**	**95**	**38**
Minimum	**36**			**150**	**42**	**26**

Table 2 Vascular pedicle features

Thigh number	Pedicle length (mm)	Artery diameter (mm)	Vein diameter (mm)	Origin	Irrigated muscle	Quadrant	Variation
1	53	3.8	3	Femoral	Gracilis	Anterosuperior	
2	48	3.4	3.2	Femoral	Gracilis	Anterosuperior	
3	83	4.2	3.2	Femoral	Gracilis	Anterosuperior	
4	76	4.6	3.6	Femoral	Gracilis	Anterosuperior	
5	32	2.1	1.8	Femoral	None	Anteroinferior/ Anterosuperior	No muscular branch
6	41	3.6	3.4	Femoral	Gracilis	Anteroinferior	
7	38	3.4	3.2	Femoral	Gracilis	Anteroinferior	
8	63	3.2	2.8	Femoral	Sartorius	Anterosuperior	Branch to the sartorius muscle
9	38	2	2	Femoral	Gracilis	Anterosuperior	
10	32	2.2	1.8	Femoral	Gracilis	Anterosuperior	
11	32	1.3	1	Femoral	Gracilis	Anterosuperior	
12	28	1.5	1.2	Femoral	Gracilis	Antroinferior	
13	78	1.6	1.4	Femoral	Gracilis	Anterosuperior	
14	45	2.5	2	Femoral	Gracilis	Anterosuperior	
15	84	1.8	1.8	Femoral	Gracilis	Anterosuperior	
16	76	1.6	1.6	Femoral	Gracilis	Anterosuperior	
17	38	1.3	1.2	Femoral	Gracilis	Anterosuperior	
18	40	1.4	1.2	Femoral	Gracilis	Anterosuperior	
19	32	1.6	1.4	Femoral	Gracilis	Anterosuperior	
20	40	2.2	2	Femoral	Sartorius	Anterosuperior	Branch to the sartorius muscle
21	38	2	2	Femoral	Sartorius	Anterosuperior	

Table 2 (*Continued*)

Thigh number	Pedicle length (mm)	Artery diameter (mm)	Vein diameter (mm)	Origin	Irrigated muscle	Quadrant	Variation
							Branch to the sartorius muscle
22	62	1.5	1.5	Femoral	Gracilis	Anterosuperior	
23	60	1.3	1.5	Femoral	Gracilis	Anterosuperior	
24	58	2	1.8	Femoral	Gracilis	Antroinferior	
25	61	2.4	1.9	Femoral	Gracilis	Anteroinferior	
26	64	2.7	2.2	Femoral	Gracilis	Anterosuperior	
27	68	2.4	2.3	Femoral	Gracilis	Anterosuperior	
28	56	1.8	1.6	Femoral	Gracilis	Anterosuperior	
29	42	2.8	2	Femoral	Gracilis	Anterosuperior	
30	56	2.8	2.3	Femoral	Gracilis	Anterosuperior	
31	58	2.5	2.2	Femoral	Gracilis	Anterosuperior	
32	52	2	1.8	Femoral	Gracilis	Anterosuperior	
33	50	1.8	1.6	Femoral	Gracilis	Anterosuperior	
Mean	**50.6**	**2.3**	**2.0**				
Maximum	**84**	**4.6**	**3.6**				
Minimum	**28**	**1.3**	**1**				

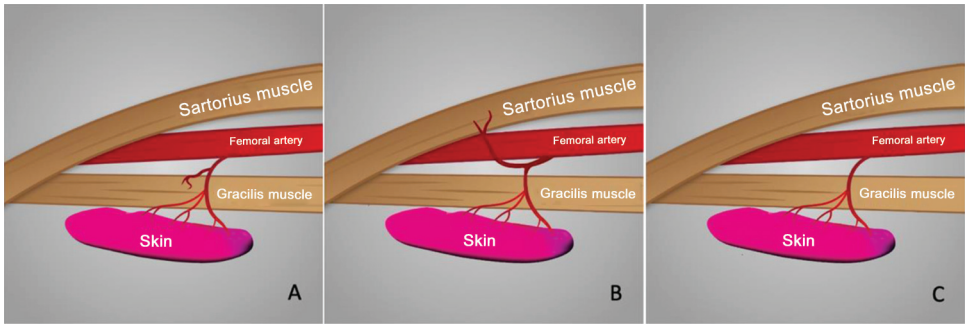


Fig. 3 Arterial distribution patterns. Vessels with branches to the gracilis muscle (**A**). Vessels with branches to the sartorius muscle (**B**). Direct perforating vessels, with no muscular ramifications (**C**).

Results

►**Table 1** shows the anthropometric data of the dissected cadavers, and ►**Table 2** shows the flap vessel features.

In all dissections (100%), we identified at least 1 artery accompanied by 2 veins and considered them viable for flap creation. All of these vessels were in the intermuscular septum between the gracilis and vastus medialis/sartorius muscles. In 29 (87.8%) of the 33 thighs, the main vessel was a septocutaneous artery with branches to the gracilis muscle; in 3 (9.1%) thighs, the septocutaneous arteries provided branches to the sartorius muscle; and 1 thigh (3%) had two direct septocutaneous arteries with no muscular branches (►**Fig. 3**).

All cases had at least 1 artery and 1 vein with an external diameter greater than 0.5 mm. The largest diameter was of 4.6 mm, and the smallest, of 1.3 mm. The mean artery diameter was of 2.3 mm. In general, there were 2 veins for each artery. The largest vein diameter was of 3.6 mm, and the smallest, of 1.0 mm, with a mean of 2.0 mm (►**Fig. 4**). The length of the vessels, from their origin in the femoral vessels to the smaller branches in the subcutaneous tissue, ranged from 28 mm to 84 mm, with a mean of 53.2 mm.

The statistical analysis started with the Kolmogorov-Smirnov parametric test to assess the normality of the distribution of the quantitative variables, and we concluded that there was a normal distribution. Regarding the distribution of the relative frequency (percentages) of qualitative factors, by applying the equality of two proportions test, we observed that the pedicle was in the anterosuperior quadrant in 84.8% of the dissected thighs. In addition, we noted that the gracilis was the muscle most commonly irrigated by this pedicle, corresponding to 87.9% ($p < 0.001$) of the cases (►**Tables 3**, **4**, respectively).

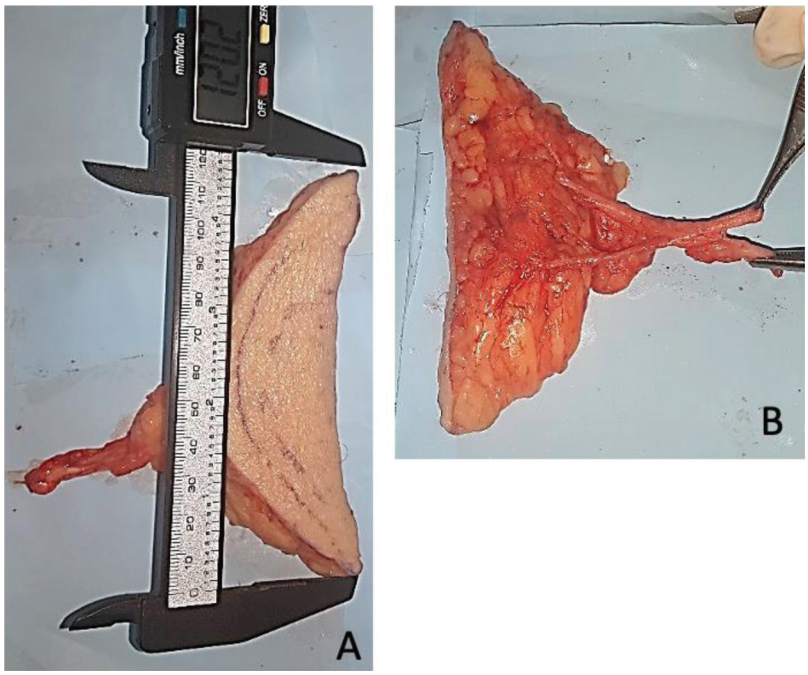


Fig. 4 Isolated flap with an approximate length of 12 cm (**A**). Vascular pedicle (**B**).

Table 3 Pedicle location at anteroinferior and anterosuperior quadrants

		n	%	*p*-value
Quadrant	Anteroinferior Anterosuperior	5 28	15.2% 84.8%	< 0.001

Table 4 Muscles irrigated by the vascular pedicle

		n	%	*p*-value
Irrigated muscle	Gracilis None Sartorius	29 1 3	87.9% 3.0% 9.1%	< 0.001 < 0.001

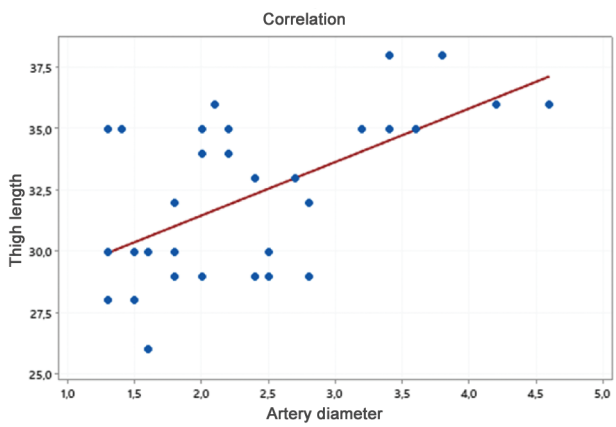


Fig. 5 Relationship between thigh length and artery diameter.

The Pearson test analyzed the correlation among these variables. It revealed a significant and directly-proportional association between vessel diameter and thigh length ($p < 0.001$) (►**Fig. 5**).

Discussion

According to Giordano et al.[12] and Peek et al.,[6] the gracilis muscle receives blood supply from a proximal main pedicle originating from the medial circumflex femoral artery and at least two distal secondary pedicles originating from the femoral or popliteal artery. Most of these primary and secondary pedicles have branches piercing the deep fascia and irrigating a considerable skin area over the gracilis muscle, corresponding to at least twice the width of this muscle. The anatomical characteristics of the main pedicle are well-known, resulting in reliable parameters to create gracilis or musculocutaneous flaps. However, the literature is scarce on secondary pedicles and their potential use as fasciocutaneous flaps.

The most common flaps are the proximal fasciocutaneous flaps of the thigh, irrigated by branches of the main pedicle of the gracilis muscle. Gracilis flaps are used widely in their pedicled and free forms. However, they compromise the main pedicle of the gracilis muscle and require care with the branches of the obturator nerve at the dissection site. The main vascular pedicle flap, harvested from the proximal medial region of the thigh, is in an area more susceptible to contamination and with limited access to postoperative dressings.[6]

Scaglioni et al.[1] described some flaps of the anteromedial region in the distal region of the thigh based on the perforating musculocutaneous vessels crossing the vastus medialis. However, an adequate-length pedicle requires



Fig. 6 Primary closure of the donor area.

intramuscular dissection, and the scar area is more exposed compared with the main pedicle flap. Song et al.[10] and Algan and Tan[13] described a reliable flap originating from perforators of the deep femoral artery in this region, but often the patient's positioning makes it impossible to harvest it.

The proposed flap is on the medial side of the middle third of the thigh. After flap removal, primary closure of the donor area can be performed without the need for a skin graft. The scar is in a region of little exposure. The donor area is further away from the inguinal and perineal regions when compared with the main pedicle flap. Dressing change is more comfortable, and the prevention of contamination and infection is more reliable.

The mean arterial diameter in the current study was of 2.3 mm. According to Jacobson and Suarez,[14] this value is safe for vascular anastomoses in free flaps. The mean length of the pedicle was of 50.6 mm, which is adequate for free or pedicled flaps. However, in one of the dissections, we identified a pedicle shorter than 30 mm (28 mm), that is, a relatively short pedicle that would hinder anastomosis and depend on the area and the recipient's vessel.

Some interesting parameters found in the dissection included the following: all vascular pedicles were in the central region of the medial aspect of the thigh, within a circle with 6 cm in diameter, whose central point coincided with the anterior border of the gracilis muscle; the arterial origin was in the anterosuperior quadrant of the circle in 87.8% of the cases, and most of the vessels (87.8%) were septocutaneous vessels, with branches to the gracilis muscle. The greater saphenous vein requires care, as it is often included in the flap design and should be ligated and included in the flap if it is impossible to isolate.

According to Giordano et al.,[12] the width of the skin irrigated by the perforating vessels would correspond to at least twice the width of the underlying gracilis muscles. Closure of the donor area closure could be performed primarily, with relative ease, with no need for skin grafting (►**Fig. 6**).

The parameters found will enable the safe dissection and removal of a microsurgical flap. The skin of the medial region of the thigh is thinner and more versatile. A flap from this region is appropriate for covering small and medium-sized defects (shorter than 15 cm in diameter).

Case series[15,16] conducted in recent years have demonstrated the advantages of using perforating vessel flaps to obtain less bulky and malleable flaps; however, the flap herein presented was not described in any of these studies.

To demonstrate flap viability, we performed surgery on a young male patient who had been involved in a traffic accident and, in addition to multiple fractures on his right foot, had lost skin on the medial surface extending to the plantar surface, exposing tendons and the plantar aponeurosis (►**Fig. 7**). We performed microsurgical coverage with the flap described, with anastomosis of its vessels in branches and tributaries of the posterior tibial vessels. The procedure was successful, thus demonstrating technical viability (►**Fig. 7** and ►**Fig. 8**).

In our opinion, one of the best indications for this flap would be upper limb skin coverage, which requires thin and malleable skin and donor vessels of smaller caliber. We

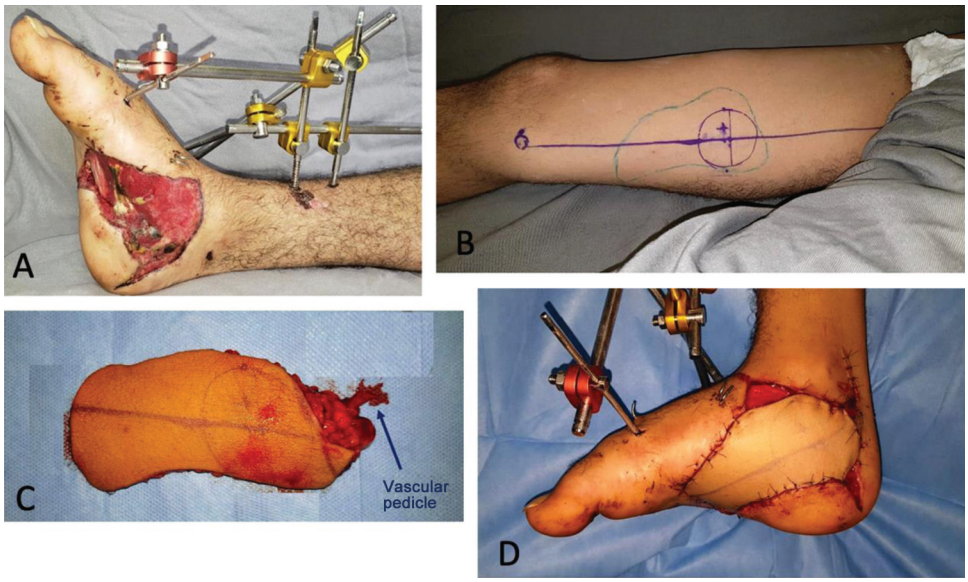


Fig. 7 Operated case. Right foot with inferomedial defect coverage (**A**). Medial aspect of the right thigh with a drawing of the flap and location of the vascular pedicle (**B**). Isolated flap (**C**). Defect coverage with anastomosis in the posterior tibial vessels (**D**).



Fig. 8 Operated case at three months of postoperative follow-up.

intend to perform a series of cases using this flap type for later publication of the outcomes, showing the positive and negative points.

Conclusion

We found the secondary pedicle of the gracilis muscle, which provides septocutaneous and perforating branches to the skin of the medial thigh, in all dissected thighs (100%). Therefore, this is a reliable option to obtain a fasciocutaneous flap from this region.

Authors' Contributions

Each author contributed individually and significantly to the development of the present article. GVV: writing – original draft, cadaveric dissection, clinical case surgery, and data collection and analysis. ACC: clinical case surgery, methodology, formal analysis, and writing – review & editing. DFF: statistical analysis, validation, and writing – review & editing, and formal analysis. YAA: methodology, conceptualization, and writing – review & editing.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Demonstration of the Relationship between Sociodemographic Characteristics and Depression in Patients with Carpal Tunnel Syndrome

Demonstração da relação entre características sociodemográficas e depressão em pacientes com síndrome do túnel do carpo

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Abstract

Objective To present the clinical, epidemiological, and socioeconomic characteristics of individuals with symptoms of carpal tunnel syndrome (CTS) and depression.

Methods The Beck Depression Inventory (BDI) was administered to 100 patients diagnosed with CTS, and its relationship between anxiety and depression was investigated alongside the sociodemographic characteristics of the patients.

Results Depression was identified in 30.9% of the 68 patients, the majority of whom were women. The BDI scores were found to be significantly higher in patients with low socioeconomic status, poor nutrition, and smoking ($p < 0.05$). Furthermore, the frequency of depressive symptoms was found to be significantly higher in patients who had chronic low back and neck pain along with CTS, with regular use of analgesics, and who had previously undergone any surgery ($p < 0.05$).

Conclusion Depression and anxiety are prevalent among individuals diagnosed with CTS. Effective treatment, including the management of comorbid depression and anxiety, is crucial for optimal patient outcomes.

Keywords
- anxiety
- carpal tunnel syndrome
- depression

Resumo

Objetivo Apresentar as características clínicas, epidemiológicas e socioeconômicas de indivíduos com sintomas de síndrome do túnel do carpo (STC) e depressão.

Métodos O Inventário de Depressão de Beck (IDB) foi administrado a 100 pacientes diagnosticados com STC e sua relação entre ansiedade e depressão foi investigada juntamente com as características sociodemográficas dos pacientes.

Study developed at Kayseri City Hospital, University of Health Sciences, Kayseri, Republic of Türkiye.

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Resultados A depressão foi identificada em 30,9% dos 68 pacientes, em sua maioria mulheres. As pontuações no IDB foram significativamente maiores em pacientes com condição socioeconômica baixa, má nutrição e tabagismo ($p < 0,05$). Além disso, a frequência de sintomas depressivos foi significativamente maior em pacientes com dor lombar e cervical crônica além da STC, com uso regular de analgésicos e que já haviam sido submetidos a alguma cirurgia ($p < 0,05$).

Conclusão Depressão e ansiedade são prevalentes entre indivíduos diagnosticados com STC. O tratamento eficaz, incluindo o controle da depressão e ansiedade comórbidas, é crucial para bons desfechos.

Palavras-chave
- ansiedade
- depressão
- síndrome do túnel do carpo

Introduction

Carpal tunnel syndrome (CTS) is a condition that arises as a consequence of compression of the median nerve at various levels within the carpal tunnel at the wrist. It represents the most prevalent peripheral neuropathy in the upper extremity.[1] Despite the lack of clarity surrounding its pathogenesis, it is observed with greater frequency in the middle-aged and women. It is also possible for occupational CTS to occur in individuals who are subjected to pressure on the flexor retinaculum, located on the inner aspect of the hand. However, it is important to note that the prevalence of this condition is also high in individuals with obesity, pregnancy, diabetes, chronic alcohol use, and rheumatological diseases.

Occupational CTS is a rare phenomenon, and it is essential to exclude all other potential causes, particularly factors such as obesity, before attributing the condition to occupational factors. The most prevalent mechanisms in the pathogenesis of this condition are mechanical compression, microvascular insufficiency and vibration theories. The mechanical compression theory posits that the symptoms of CTS are caused by compression of the median nerve within the carpal tunnel.[1]

The prevalence of CTS and its distribution in society can vary considerably, with estimates ranging from 0.125 to 1% and 5 to 16%. The etiology or underlying cause is also a significant factor in determining its incidence.[2] The two principal forms of CTS are acute and chronic. The former is less common and arises when the pressure within the carpal tunnel increases rapidly. The condition was first described by Sir James Paget in 1854, in the context of a fractured radius.[3] In their study, Silverstein et al. investigated the correlation between high-force/repetitive movements and CTS among a cohort of 652 workers across 39 occupations, in 7 distinct industrial sectors. Their findings indicated that repetitive movements may represent a significant risk factor for CTS. However, they also suggested that high force and repetition alone may not be sufficient to induce the condition.[4]

The classic symptoms of CTS include paresthesia, numbness and tingling in the areas innervated by the median nerve, particularly at night. Several tests are employed in the diagnosis of CTS, including the Tinel, Phalen, square wrist, closed fist, and flick signs, as well as the Katz hand diagram, the wrist flexion and extension test, the pressure provocation test, and the tourniquet test.

The symptoms may vary depending on the severity of the disease. During the initial phase, symptoms manifest as a result of the involvement of the median nerve's sensory component. In contrast, during the subsequent phase, symptoms emerge as a consequence of the involvement of motor fibers. The most frequently observed symptom is burning pain accompanied by paresthesia and numbness in the distribution of the median nerve in the distal wrist. The affected fingers are the thumb, index finger and middle finger, and the radial half of the ring finger. Patients frequently report nocturnal pain and paresthesia, with attempts to alleviate their symptoms by squeezing their hands or changing positions. The diagnosis can be established through the use of electromyography (EMG), ultrasound (US), and magnetic resonance imaging (MRI).[5]

A variety of surgical and nonsurgical treatment options are available. Nonsurgical methods are effective in patients with mild to moderate CTS. Corticosteroid injections into the wrist is a frequently employed method by physical therapy or algology physicians. Although symptoms may temporarily worsen, the treatment can provide complete or significant pain relief for weeks to years in 60 to 70% of patients.[6–8] In surgical procedures, the transverse carpal ligament is incised and the nerve is relaxed, thereby performing a decompression operation.

Individuals diagnosed with CTS may perceive their condition as a barrier to continued employment, which could potentially lead to financial challenges. Additionally, they may experience physical discomfort and a sense of diminished strength, which could contribute to a range of emotional and psychological difficulties. These may include depressive symptoms such as anxiety, reduced interest and engagement in daily activities, as well as feelings of dissatisfaction and sadness. It has been documented that individuals afflicted with physical ailments are more prone to experiencing feelings of anxiety and depression.[9] Also, it has been demonstrated that mental health conditions, such as depression and anxiety, can result in functional limitations among patients with upper extremity musculoskeletal disorders.[10]

The objective of this study is to examine the relationship between anxiety and depression status and the disease in CTS patients using the Beck Depression Inventory (BDI).

Materials and Methods

This study was conducted by the hospital's Neurosurgery Clinic between March and June 2024. Those presenting to the outpatient clinic with CTS were first informed about the study and their written consent was obtained, in accordance with the principles of the Declaration of Helsinki. The study was approved by our hospital's Ethical Committee under the number 76397871, dated March 15th, 2024.

Study Design

The sample of the study was obtained as 100, using literature information and the Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 statistical softwares (NCSS LLC., Kaysville, UT, USA). The study population comprised 100 CTS patients aged between 18 and 72 years, including those with mild, moderate and severe disease, irrespective of gender. A questionnaire was administered to the patients, comprising 21 questions. These enquired about sociodemographic data, including age, gender, place of residence, schooling, and economic status. Four of the questions were open-ended and focused on behavior regarding smoking and alcohol use, exercise and nutrition. Additionally, we included the 21-question Beck depression Inventory (BDI). The data were collected by a single researcher using the face-to-face interview method. Patients' height (in centimeters), body weight (in kilograms), and body mass index (BMI) were calculated on a weighing and measuring scale with 0.01 kg precision, with the subject barefoot and wearing sports clothes.

Exclusion Criteria

The study's population comprises individuals with neurological conditions affecting the central nervous system, resulting in neurological deficits in the upper extremity. Additionally, the cohort includes individuals diagnosed with polyneuropathy.

Beck Depression Inventory

The BDI is frequently employed in our country. It comprises 21 questions, is a survey instrument with four response options, yielding scores between 0 and 3. The Turkish validity and reliability of the BDI were established by Hisli.[11]

Statistical Analysis

The data were recorded using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) software, version 22.0, and the analyses were performed using the same program. Descriptive statistics included frequency, percentage, mean, standard deviation (SD), median, and range values. To conduct a statistical analysis of categorical data, a Yates correction was applied to values below 25, and a Fisher's exact test was employed for values below 5. The Kolmogorov-Smirnov test was employed to ascertain whether the data exhibited a normal distribution. In binary groups where the quantitative data did not conform to a normal distribution in independent groups, the Mann-Whitney U-test was utilized. For groups comprising more than two categories, the Kruskall-Wallis test (post hoc Dunn's) was applied. The statistical significance of the observed difference was deemed to be $p < 0.05$.

Results

The mean age of the 100 CTS patients who participated in the study was 44.76 ± 13.45 (range: 18–72) years, with 68% of the cohort being female. The mean BDI score of the patients was 11.99 ± 7.42 (range: 0–34). When the cut-off point was taken as 17 and above, the frequency of depressive symptoms was found to be 26%. While BDI scores were relatively low among university graduates, they were significantly higher among those who defined their economic situation as poor, residing in rural areas, and unemployed ($p < 0.05$), as shown in ►**Table 1**. In our study, the frequency of depressive symptoms was significantly higher in CTS patients who described their diet as irregular, did not engage in regular physical activity, had previously received psychological help, and had previous antidepressant use ($p < 0.05$). Furthermore, BDI scores were found to be significantly lower in smokers and alcohol users ($p < 0.05$). However, the observed difference was not statistically significant ($p > 0.05$), as shown in ►**Table 2**.

The prevalence of depressive symptoms was significantly higher in patients with CTS who had chronic low back and neck pain, used regular analgesics for this pain, and had previously undergone any surgery ($p < 0.05$), as shown in ►**Table 3**.

Discussion

The present study revealed that the prevalence of depressive symptoms was 26%. Notably, BDI scores were observed to be relatively low among university graduates. However, they were found to be significantly elevated among individuals who self-identified as economically disadvantaged, rural area residents, and unemployed.

In patients with CTS, pain, paresthesia and tingling sensations in the area innervated by the nerve have a detrimental impact on quality of life. This condition has a profound impact on physical function in individuals with persistent hypoesthesia and motor impairment. It can also give rise to mental health problems, such as anxiety or depression.[12] McCallum et al. showed a link between anxiety and depression levels and the presence of pain in their study.[13] This is corroborated by prior research examining the incidence of mental health illnesses in individuals with chronic pain.[14] Additionally, it has been demonstrated that social circumstances and physical activities that influence health may be linked to mental health in many musculoskeletal and neurological disorders.[15,16]

In accordance with the findings of Adjibade et al.,[17] patients who exhibited multiple healthy lifestyle behaviors

Table 1 Sociodemographic findings and BDI scores of CTS patients

Variables		n	BDI score			*p*-value	Depression frequency		*p*-value
			Median	Range	Mean ± SD		Positive: n (%)	Negative: n (%)	
Gender	Female	68	10.5	0–37	12.0 ± 7.3	0.827*	21 (30.9)	47 (69.1)	0.168***
	Male	32	11.0	0–34	11.9 ± 7.3		5 (15.6)	27 (84.4)	
Age (years)	≤ 40	42	11.0	0–26	11.4 ± 6.5	0.622*	8 (19.0)	34 (81.0)	0.264***
	> 40	58	10.0	0–34	12.4 ± 8.0		18 (31.0)	40 (69.0)	
Schooling	Under high school	66	12.5	0–34	12.8 ± 7.8	**0.029****	20 (30.3)	46 (69.7)	0.144****
	High school	25	11.0	3–26	11.8 ± 6.5		6 (24.0)	19 (76.0)	
	University	9	6.0	0–13	6.1 ± 4.0		0 (0.0)	9 (100.0)	
Economic status	Good	35	8.0	0–27	10.5 ± 7.2	**0.032****	6 (17.1)	29 (82.9)	**0.037****
	Medium	61	11.0	0–29	12.2 ± 7.1		17 (27.9)	44 (72.1)	
	Bad	4	20.5	13–34	22.0 ± 8.7		3 (75.0)	1 (25.0)	
Family type	Small	69	10.0	0–34	11.8 ± 7.8	0.488*	17 (24.6)	52 (75.4)	0.828***
	Big	31	13.0	0–26	12.5 ± 6.7		9 (29.0)	22 (71.0)	
Habitation	City	68	9.0	0–34	10.9 ± 7.3	**0.013***	13 (19.1)	55 (80.9)	**0.041****
	Town	32	14.5	0–27	14.4 ± 7.2		13 (40.6)	19 (59.4)	
Working Status	Yes	39	8.0	0–26	9.2 ± 6.3	**0.001***	4 (10.3)	35 (89.7)	**0.008****
	No	61	13.0	0–34	13.8 ± 7.6		22 (36.1)	39 (63.9)	

Abbreviations: BDI, Beck Depression Inventory; CTS, carpal tunnel syndrome; SD, standard deviation.
Notes: *Mann-Whitney U-test. **Kruskal-Wallis test. ***Chi-squared Yates correction. ****Fisher's exact test.

Table 2 Health and behavioral status and BDI scores in CTS patients

Variables		n	BDI score			*p*-value	Depression frequency		*p*-value
			Median	Range	Mean ± SD		Positive: n (%)	Negative: n (%)	
Chronic disease	Yes	**44**	**11.5**	**0–34**	**12.9 ± 8.5**	**0.470***	**15 (34.1)**	**29 (65.9)**	**0.160*****
	No	56	10.0	0–26	11.3 ± 6.4		11 (19.6)	45 (80.4)	
Regular medication	In use	42	12.0	0–29	12.9 ± 7.9	0.314*	15 (35.7)	27 (64.3)	0.098***
	No	58	10.0	0–34	11.3 ± 7.0		11 (19.0)	47 (81.0)	
Chronic disease in family members	Var	28	11.0	0–29	11.3 ± 7.4	0.612*	6 (21.4)	22 (78.6)	0.692***
	Yok	72	10.5	0–34	12.3 ± 7.5		20 (27.8)	52 (72.2)	
Nutritional status	Regular	74	10.0	0–27	11.1 ± 6.7	0.105*	15 (20.3)	59 (79.7)	**0.028*****
	Irregular	26	13.0	0–34	14.4 ± 8.8		11 (42.3)	15 (57.7)	
Regular Exercise	Yes	22	9.0	3–24	9.7 ± 5.5	0.122*	2 (9.1)	20 (90.9)	**0.041*****
	No	78	12.0	0–34	12.6 ± 7.8		24 (30.8)	54 (69.2)	
Tobacco use	In use	38	8.5	0–34	10.4 ± 7.8	**0.049***	7 (18.4)	31 (81.6)	0.264***
	No	62	13.0	0–29	12.9 ± 7.1		19 (30.6)	43 (69.4)	
Alcoholism	In use	12	8.5	0–34	9.6 ± 6.2	0.203*	1 (8.3)	11 (91.7)	0.177****
	No	88	12.0	3–26	12.3 ± 7.5		25 (28.4)	63 (71.6)	
Previous psychological treatment	Yes	9	18.0	5–27	16.4 ± 8.1	0.082*	5 (55.6)	4 (44.4)	**0.049*****
	No	91	10.0	0–34	11.5 ± 7.3		21 (23.1)	70 (76.9)	
Previous antidepressant use	Yes	9	23.0	8–27	19.3 ± 7.0	**0.003***	6 (66.7)	3 (33.3)	**0.009*****
	No	91	10.0	0–34	11.3 ± 7.1		20 (22.0)	71 (78.0)	
BMI (kg/m^2)	< 25	16	12.0	0–34	12.9 ± 9.4	0.148**	3 (18.8)	13 (81.3)	0.123
	25–29.9	44	9.0	0–24	10.3 ± 6.6		8 (18.2)	36 (81.8)	
	≥ 30	40	13.0	0–29	13.4 ± 7.3		15 (37.5)	25 (62.5)	

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; CTS, carpal tunnel syndrome; SD, standard deviation.
Notes: *Mann-Whitney U-test. **Kruskal-Wallis test. ***Chi squared Yates correction. ****Fisher's exact test.

Table 3 Chronic low back-neck pain and BDI scores in CTS patients

Variables		n	BDI score			*p*-value	Depression frequency		*p*-value
			Median	Range	Mean ± SD		Positive: n (%)	Negative: n (%)	
Chronic neck pain	Yes	47	13.0	0–34	14.2 ± 8.2	**0.009***	21 (44.7)	26 (55.3)	**< 0.001****
	No	53	9.0	0–29	10.0 ± 6.1		5 (9.4)	48 (90.6)	
Chronic back pain	Yes	41	11.0	0–34	13.4 ± 8.7	0.232*	17 (41.5)	24 (58.5)	**0.007****
	No	59	11.0	0–29	11.0 ± 6.3		9 (15.3)	50 (84.7)	
Analgesic for low back and neck pain	Yes	50	12.5	0–27	13.1 ± 7.2	0.102*	18 (36.0)	32 (64.0)	**0.040****
	No	50	9.5	0–34	10.8 ± 7.5		8 (16.0)	42 (84.0)	
Previous surgery	Yes	49	13.0	0–34	13.8 ± 8.2	**0.029***	18 (36.7)	31 (63.3)	**0.030****
	No	51	9.0	0–24	10.2 ± 6.2		8 (15.7)	43 (84.3)	

Abbreviations: BDI, Beck Depression Inventory; CTS, carpal tunnel syndrome; SD, standard deviation.
Notes: *Mann-Whitney U-test.**Fisher's exact test.

(i.e., nonsmoking, low alcohol intake, regular physical activity, a healthy diet, and a normal BMI) demonstrated a reduced likelihood of experiencing depressive symptoms in comparison to those with two or fewer healthy lifestyle behaviors. In our study, the frequency of depressive symptoms was significantly higher in subjects who described their diet as irregular, did not engage in regular physical activity, had previously received psychological help,

and had previously used antidepressants. Additionally, BDI scores were significantly lower in smokers.

In a study conducted in 2020, Paiva Filho et al.[18] evaluated the prevalence of anxiety and depression in CTS patients. Although no association was found between BMI and higher depression or anxiety index when considered alone, almost ⅔ of the patients exhibited values above the normal range. In their study, the characteristics that were statistically associated with both anxiety and depression symptoms in patients with CTS, independent of other characteristics, were gender, smoking status, and family income. In our study, lower BDI values were also correlated with alcohol intake, but the difference was not statistically significant.

The relationship between depressive symptoms and surgical outcomes in CTS is of particular interest, given the high prevalence of both conditions, particularly in women.[19] In the present study, depression was identified in 30.9% of the 68 female patients. The BDI scores were relatively low among university graduates, but significantly higher among those who described their economic situation as poor, who resided outside the city (in towns and villages), and who were unemployed. Once more, the existing literature indicates a statistically significant association between smoking and family income and anxiety in patients with CTS.[19] Depression alone was found to have a statistically significantly association with family income in CTS patients. Studies have shown that conditions such as depression and anxiety may contribute to functional limitations in patients with upper extremity musculoskeletal disorders.[20]

Furthermore, our study demonstrated that the prevalence of depressive symptoms was markedly elevated in patients presenting with chronic lower back and neck pain in conjunction with CTS, with regular analgesic use, and who underwent prior surgical procedures ($p < 0.05$).

It is of great importance to gain an understanding of the sociodemographic characteristics of CTS individuals with mood disorders, particularly anxiety and depression, to provide optimal treatment and facilitate healing following surgical intervention. The present study is informed by a small number of articles published on similar topics, as well as by the broader literature on the subject. The aim was to examine the clinical, epidemiological and socioeconomic characteristics of individuals presenting with CTS, anxiety, and depression symptoms.

Conclusion

People with CTS had a high prevalence of symptoms of depression and anxiety. Treatment is of utmost importance for the recovery of patients. More research is needed aimed at demonstrating the effectiveness of approaches that address organic and pathological causes, as well as psychosocial stressors, anxiety, and depression, on relieving CTS symptoms.

Authors' Contributions

YG contributed to detailing the work; project preparation, data collection, and writing of the article. ŞG contributed to the collection of data, and writing and proofreading of the article. BO contributed to the statistical analysis, and preparing the tables and graphics. EB contributed to the statistical analyses and proofreading of the article.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Postoperative Outcomes with and without Neoadjuvant Denosumab in Grade-III Giant Cell Tumor of the Proximal Femur: A Comparative Retrospective Study

Desfechos pós-operatórios com ou sem denosumabe adjuvante em tumores de células gigantes de grau III do fêmur proximal: Um estudo retrospectivo comparativo

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Abstract

Objective To retrospectively compare the impact of using neoadjuvant denosumab for Campanacci grade-III giant cell tumor (GCT) of the proximal femur involving the hip joint.

Methods We retrospectively reviewed 18 cases of Campanacci grade-III GCT of the proximal femur receiving surgery between January 2014 and December 2019 from our hospital. One group of 10 patients received weekly neoadjuvant denosumab 120 mg for 4 weeks, while the other group of 8 patients did not receive denosumab before surgery. Two patients were subjected to intralesional curettage while the others received resection and hip arthroplasty. Comparisons were made using unpaired *t*-test and Fisher's exact test. Functional outcomes were assessed by revised Musculoskeletal Tumor Society (MSTS) score and Harris Hip Score (HHS) at 6 weeks, 6 months, and 12 months of follow-up, as well as incidence of recurrence.

Results The comparison of the mean MSTS scores of the denosumab and non-denosumab groups was as follows: 24.0 ± 6.5 versus 20.0 ± 6.0 ($p = 0.04$) at 6 weeks respectively; 26.0 ± 5.0 versus 23.0 ± 0.67 ($p = 0.04$) at 6 months respectively; and 28.8 ± 1.7 versus 29.5 ± 0.33 ($p = 0.35$) at 12 months respectively. The comparison of

Keywords
- bone neoplasms
- denosumab
- giant cell tumor
- hip
- proximal femoral fractures

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HHSs between the denosumab and non-denosumab groups was as follows: 61.02 ± 7.36 versus 48.52 ± 3.97 ($p = 0.03$) at 6 weeks respectively; 81.1 ± 2.97 versus 79.15 ± 3.24 ($p = 0.82$) at 6 months respectively; and 89.84 ± 3.75 versus 90.05 ± 3.00 ($p = 0.38$) at 12 months respectively. There was no recurrence.

Conclusion Denosumab was clinically effective in improving the short-term functional outcomes, but long-term functional outcomes remained similar between the groups. We did not find an increased recurrence rate in the denosumab group.

Resumo

Objetivo Comparar retrospectivamente o impacto do uso de denosumabe neoadjuvante em tumores de células gigantes (TCG) de grau III de Campanacci no fêmur proximal com acometimento da articulação do quadril.

Métodos Avaliamos retrospectivamente 18 casos de TCG de grau III de Campanacci do fêmur proximal que foram submetidos à cirurgia entre janeiro de 2014 e dezembro de 2019 em nosso hospital. Um grupo de 10 pacientes receberam denosumabe neoadjuvante em dose de 120 mg uma vez por semana por 4 semanas, enquanto outro grupo, com 8 pacientes, não recebeu denosumabe antes da cirurgia. Dois pacientes foram submetidos à curetagem intralesional e os demais, à ressecção e artroplastia de quadril. As comparações foram feitas usando o teste *t* não pareado e o teste exato de Fisher. Os resultados funcionais foram avaliados pelo escore revisto da *Musculoskeletal Tumor Society* (MSTS) e pelo escore de quadril de Harris (Harris Hip Score, HSS) em 6 semanas, 6 meses e 12 meses de acompanhamento. A incidência de recidiva também foi determinada.

Resultados A comparação das médias dos escores MSTS entre os grupos com e sem denosumabe foi de 24,0 ± 6,5 *versus* 20,0 ± 6,0 ($p = 0,04$) em 6 semanas, respectivamente; 26,0 ± 5,0 *versus* 23,0 ± 0,67 ($p = 0,04$) em 6 meses, respectivamente; e 28,8 ± 1,7 *versus* 29,5 ± 0,33 ($p = 0,35$) em 12 meses, respectivamente. A comparação das médias das pontuações no HSS entre os grupos com e sem denosumabe foi de 61,02 ± 7,36 *versus* 48,52 ± 3,97 ($p = 0,03$) em 6 semanas, respectivamente; 81,1 ± 2,97 *versus* 79,15 ± 3,24 ($p = 0,82$) em 6 meses, respectivamente; e 89,84 ± 3,75 *versus* 90,05 ± 3,00 ($p = 0,38$) em 12 meses, respectivamente. Não houve recidiva.

Conclusão O denosumabe foi clinicamente eficaz na melhora dos desfechos funcionais em curto prazo, mas os desfechos funcionais em longo prazo foram semelhantes entre ambos os grupos. Não observamos aumento na taxa de recidiva no grupo com denosumabe.

Palavras-chave
- denosumab
- fraturas proximais do fêmur
- neoplasias ósseas
- quadril
- tumores de células gigantes

Introduction

Giant cell tumor (GCT) of the bone is a benign but locally aggressive tumor of the end of a long bone. It is characterized by mononuclear stromal cell growth and the presence of many multinucleated giant cells with a homogenous distribution.[1] The distal femur, proximal tibia, and distal radius are the most frequent sites for GCTs in the metaphyseal-epiphyseal region.[1] Giant cell tumor of the proximal femur is a rare entity with higher morbidity due to changes in gait, lifestyle disturbances, risk of pathological fractures, and limitations in daily activities. Moreover, the disease is associated with the younger population, which may be at increased risk of longer poor quality of life. Therefore, GCT of the proximal femur warrants special attention. It has a slight female prevalence and occurs more frequently in the third and fourth decades of life.[2] Grade III is ascribed to GCT with poorly defined margins, cortical bone loss, and invasion of the surrounding soft tissues according to the Campanacci grading system.[3]

Denosumab is the only US Food and Drug Administration (FDA)-approved drug for the treatment of GCT.[4] Denosumab decreases the number of multinucleated giant cells in the bone matrix and accelerates the development of the mature rim around the tumor by blocking the receptor activator of nuclear factor-κB (RANK)/RANK-ligand (RANKL) pathway. Denosumab has been employed as a neo-adjuvant therapy method in prior trials. However, the studies showed a substantially larger number of denosumab cycles preoperatively.[5]

The present study is the first that aims to investigate the functional and oncological outcomes of neoadjuvant

denosumab for Campanacci grade III GCT of proximal femur with surgery. Previously conducted trials on GCT of proximal femur mainly focused upon resection and replacement of proximal femur with endoprosthesis, Wagner prosthesis, total hip arthroplasty, and hemiarthroplasty of the hip.[6,7] These studies did not consider intralesional curettage as an option, except for Wijsbek et al. who performed intralesional curettage for 10 patients but did not use neoadjuvant denosumab.[8] Considering the average age of the population, a joint salvage approach would be more appropriate than prosthetic replacements as these have limited duration, after which loosening of prosthesis may occur.[9] All of the studies performed to date assessed the oncological outcomes by Musculoskeletal Tumor Society (MSTS) score without utilizing other hip scores to evaluate the functional outcome and quality of life after surgery.

Materials and Methods

Study Design

The data used in the present study was acquired retrospectively from the record files of the patients who were treated from January 2014 to December 2019 at a tertiary hospital. The patients' data included the name, age, diagnosis with radiographs and biopsy reports, bone involved, management plan, status on last follow-up and contact for correspondence. The patients were individually contacted by the second author for signed informed consent before registration, following the Declaration of Helsinki. The present work received our approval Institutional Review Board under number CHK/DMC/Ortho/Dated 11–22/001.

Inclusion and Exclusion Criteria

The patients having a diagnosis of Campanacci grade III GCT of proximal femur confirmed on imaging and had received surgery were included in the study. The GCT of the proximal femur included GCT of anatomical landmarks of the head, neck, trochanteric, and subtrochanteric areas. The study population included was stratified into two cohorts according to the use of preoperative subcutaneous denosumab 120 mg injections given once weekly for 4 weeks before proximal femur surgery. All patients who were treated by surgery but did not receive denosumab were stratified into the non-denosumab group, while those who underwent surgery and received denosumab were included in the denosumab group.

Exclusion was done based on skeletal immaturity and missing age from records. Patients who had primary and secondary malignant GCT, grade-I or - GCT, follow-up for less than 12 months, non-compliance with postoperative rehabilitation, less than 4 doses of denosumab, and previous curettage for GCT as well as those who did not provide consent were also excluded from the study.

Surgical Technique

Selection of any one of the following two methods were made after discussion in the preoperative meeting of the multidisciplinary team of the tumor board, where GCT tumors were reassessed after 4 doses of denosumab.

- Intralesional curettage with hemicortical resection
- Resection and hip arthroplasty.

Intralesional Curettage with Hemicortical Resection

After consent and counseling and under aseptic measures, through a lateral approach, skin, subcutaneous tissue, and fascia were incised, and the tumor was located. Under the C arm, a cortical window was made by resection of the margins, including the lateral wall of the neck and the greater trochanter. The residual tumor at the medial wall was curetted, and burring was used to clear the remaining tumor and to level the surface. Once the surface became smooth and tumor free, cauterization and hydrogen peroxide were used to burn the micro tumor particles. A dynamic hip screw was placed, and the defect was reconstructed with bone cement. Holes were created in the bone cement and the abductors were reattached. The surgical techniques are shown in ►**Fig. 1**.

After final washing, the wound was closed in layers. Early hip movement was encouraged postoperatively, and weight bearing was resumed once the patients were able to tolerate it. Stitches were removed after 2 weeks, and patients were followed-up fortnightly for 3 months, then monthly for 6 months, thereafter, every 3 months for 2 years and then, biannually afterwards. On each visit, hip movements were assessed and documented on follow-up charts.

Resection and Hip Arthroplasty

Under general anesthesia with patient's consent and antiseptic measures, a longitudinal lateral incision in lateral position was made on the skin after evaluation of the radiographs. After incising through the subcutaneous tissue and fascia, the muscles were reflected. Afterwards, the measurements were obtained, and the femur was cut 2 to 3 cm from the margin of the tumor. Wide margin resection of the GCT was performed, and the specimen was obtained for histopathology of specimen margins. After resection, the site was assessed for suitability of Wagner prosthesis.

- Bipolar hemiarthroplasty was performed in patients with pathological femoral neck fracture or damaged calcar femorale.
- We used the Wagner prosthesis with bipolar head in tumors extended into intertrochanteric or subtrochanteric area in cases in which acetabulum cartilage was not involved.
- Total hip arthroplasty with Wagner prosthesis was used in patients with damaged cartilage and calcar femorale.

The surgical site was then washed, and the wound was closed in layers. Sterile dressings were applied on alternate days, and sutures were cut after two weeks. Patients were followed-up fortnightly for 3 months, then monthly for 6 months, thereafter, every 3 months for 2 years, and then, biannually afterwards. On each visit, hip movements were

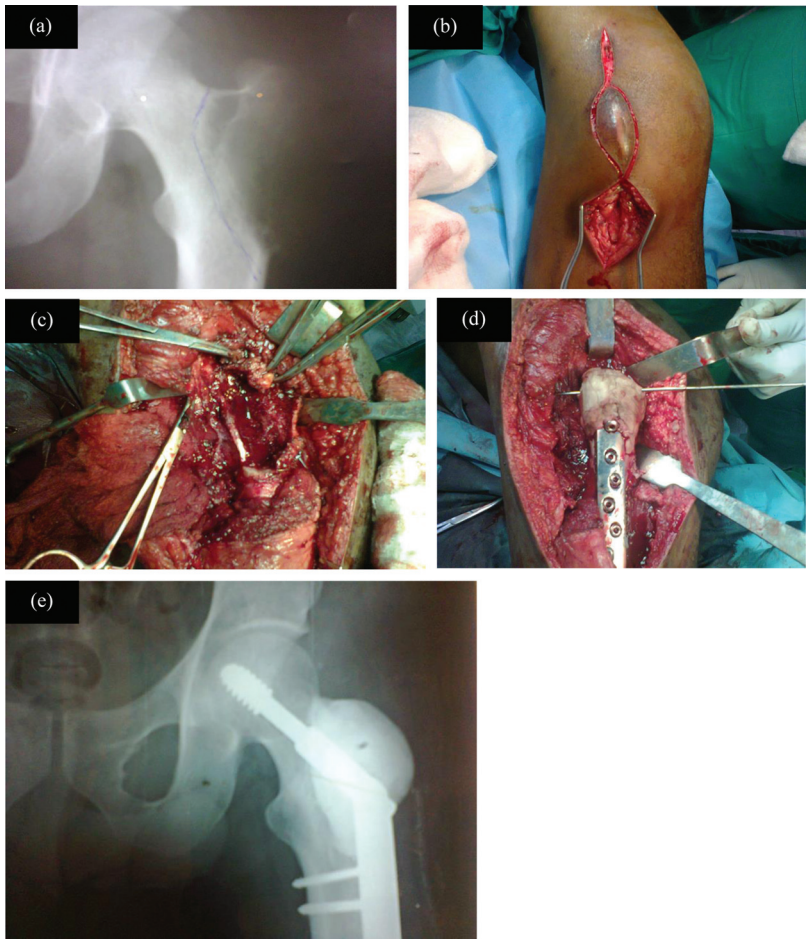


Fig. 1 Surgical methods (**A**) preoperative X-ray after denosumab therapy (**B**) boat-shaped incision (**C**) after creating cortical window and high-speed burring curettage (**D**) filling with bone allograft, cement with DHS (**E**) postoperative X-ray showing DHS and allograft with bone cement.

assessed and documented on follow-up charts. The surgical techniques are shown in ►**Fig. 2**.

Comparative Outcomes Analysis

Our primary end point was postoperative outcomes of hip joint, which were assessed at 6 weeks, 6 months and 12 months of follow-ups by the Harris Hip Score (HHS) and the revised MSTS. According to the HHS, 0 to 25% means a poor result, 26 to 50% means a fair result, 51 to 75% means a good result, and 76 to 100% means an excellent result. According to the revised MSTS score for the lower extremities, 0 to 7 means a poor result, 8 to 14 means a fair result, 15 to 22 means a good result, and above 22 means an excellent result, after 6 weeks, 6 months, and 12 months of follow-up; the secondary outcome was incidence of recurrence.

Statistical Analysis

All descriptive statistics are represented as means with standard deviations for continuous variables. Categorical variables are included as frequencies with percentages. Comparison of baseline characteristics between the two groups was made by either the unpaired *t*-test for the continuous variables or the Fisher's exact test for proportions of two categorical variables as it is more suitable for lower sample-sized studies with a 95% CI for both. The data were analyzed using the IBM SPSS Statistics for Windows software (IBM Corporation), version 22.0. The HHS and the MSTS score are continuous variables, while the incidence of recurrence and complications are categorical variables.

Results

None of the study characteristics differ significantly between the denosumab and non-denosumab groups, including mean age (28.6 ± 5.85 versus 29.5 ± 2.96 respectively; $p = 0.81$), sex (4:6 [40%:60%] versus 0:8 [0%:100%] respectively; $p = 0.09$), pathological fractures (8 [80%] versus 4 [50%] respectively; $p = 0.32$), recurrent GCT (2 [20%] versus 0 [0%] respectively; $p = 0.47$), and mean follow-up in months (21.62 ± 5.13 versus 26.82 ± 9.48 respectively; $p = 0.38$). The parts of the proximal femur involved in denosumab and non-denosumab groups were head (0 [0%] versus 0 [0%] respectively; $p = 1$), neck (2 [20%] versus 2 [25%] respectively; $p = 1$), intertrochanteric area (4 [40%] versus 2 [25%]



Fig. 2 Surgical methods showing (**A**) preoperative X-ray after denosumab therapy (**B**) boat shaped incision (**C**) incision of skin, subcutaneous, and fascia to expose the tumor (**D**) Resected specimen of proximal femur (**E**) insertion of Wagner prothesis and total hip arthroplasty.

respectively; $p = 0.64$), and subtrochanteric area (4 [40%] versus 4 [50%] respectively; $p = 1$). All patients in the non-denosumab group had resection and arthroplasty, while 2 (20%) patients had curettage in the denosumab group only, and others had resection & arthroplasty. Intralesional curettage (20% versus 0%; $p = 0.48$) and resection and arthroplasty (80% versus 100%; $p = 0.48$) remained statistically similar between the denosumab and non-denosumab groups respectively. The results are shown in ►**Table 1**, and the inclusion and exclusion criteria are shown in a flowchart as ►**Fig. 3**.

MSTS Score

The mean MSTS scores of the the denosumab and non-denosumab groups after 6-weeks (24 ± 6.5 versus 20.0 ± 6.0 respectively; $p = 0.04$) and 6-months (26.0 ± 5 versus 23.0 ± 0.67 respectively; $p = 0.04$) of surgery showed a statistically significant difference. On the 6-week analysis of the MSTS score, the results showed good-results in the non-denosumab group while excellent results were seen in the denosumab group. The MSTS score was excellent in both groups in the 6-month analysis and onwards. However, we have seen better pain relief and emotions ranging from the immediate postoperative phase to 6 months of follow-up after denosumab therapy, in which the mean pain score was 3.9 ± 0.4 in the denosumab group versus 2.1 ± 0.6 in the non-denosumab group. However, the mean MSTS scores were similar between the two groups at 12 months follow-up (28.8 ± 1.7 versus 29.5 ± 0.33 respectively ; $p = 0.35$). These findings are summarized in ►**Table 2**.

Harris Hip Score

The difference in the mean HHS remained statistically non-significant and excellent in the denosumab and non-denosumab groups after 6 months (81.1 ± 2.97 versus 79.15 ± 3.24 respectively ; $p = 0.82$) and 12 months (89.84 ± 3.75 versus 90.05 ± 3.00 respectively; $p = 0.38$) of follow-ups postoperatively. However, the results were considerably different between the groups at the 6-week follow-up (61.02 ± 7.36 versus 48.52 ± 3.97 respectively; $p = 0.03$), at which point good results were obtained in the denosumab

Table 1 Baseline study characteristics comparison of denosumab with non-denosumab group

	Denosumab	Non-denosumab	*p*-value
Number of patients	10	8	–
Age in years: mean ± standard deviation	28.6 ± 5.85)	29.5 ± 2.96)	0.81
Sex: n (%)			
Male	4 (40%)	0 (0%)	0.09
Female	6 (60%)	8 (100%)	
Pathological fractures: n (%)	8 (80%)	4 (50%)	0.32
Follow-up in months: mean ± standard deviation	21.62 ± 5.13	26.82 ± 9.48	0.38
Surgical procedure: n (%)			
Intralesional curettage with hemicortical resection	2 (20%)	0 (0%)	0.48
Resection and hip arthroplasty	8 (80%)	8 (100%)	
Recurrent giant cell tumor: n (%)	2 (20%)	0 (0%)	0.47
Part of proximal femur involved: n (%)			
Head	0 (0%)	0 (0%)	1
Neck	2 (20%)	2 (25%)	1
Intertrochanteric	4 (40%)	2 (25%)	0.64
Subtrochanteric	4 (40%)	4 (50%)	1

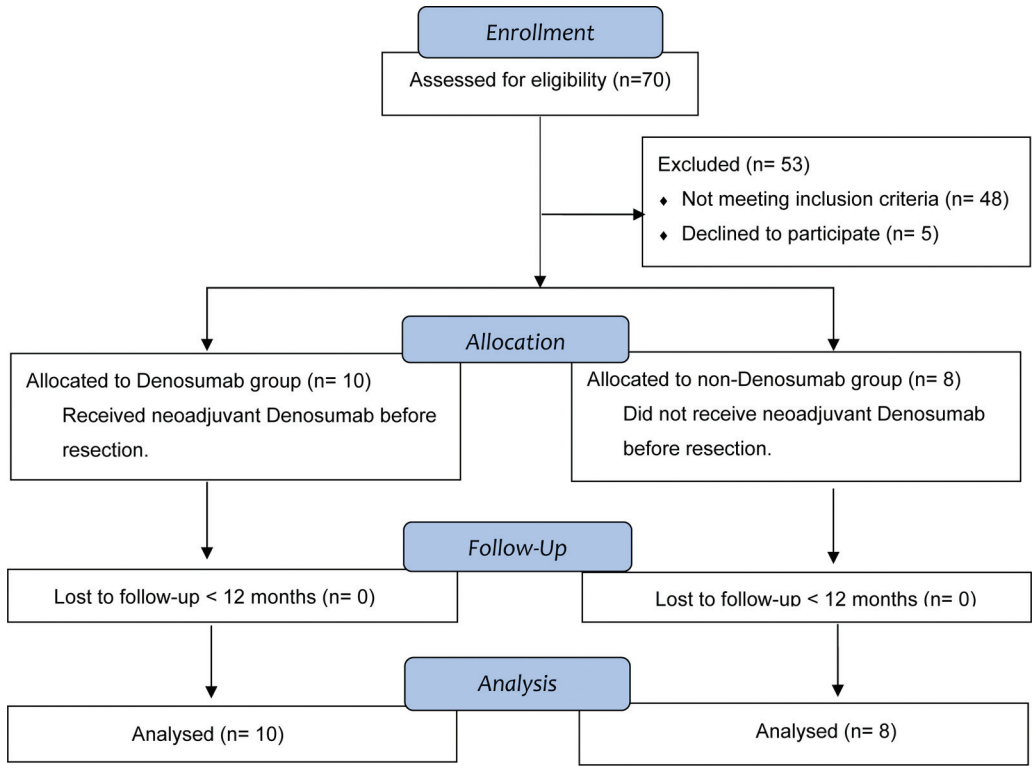


Fig. 3 Flowchart for inclusion/exclusion of patients.

group, while fair results were obtained in the non-denosumab group. Considering the pain scale of the HHS, significantly higher pain was observed in the non-denosumab group than in the denosumab group in the first 6 months postsurgery, which may be attributed to higher hip dysfunction in the non-denosumab group. However, the difference in pain became non-significant after 12 months of follow-up. These findings are summarized in ►**Table 2**.

Table 2 Postoperative comparison of outcomes between the denosumab and non-denosumab groups

	Denosumab	Non-denosumab	*p*-value
MSTS score: mean ± standard deviation			
6 weeks	24.0 ± 6.5	20.0 ± 6.0	0.04
6 months	26.0 ± 5.0	23.0 ± 0.67	0.04
12 months	28.8 ± 1.7	29.5 ± 0.33	0.35
Harris Hip score: mean ± standard deviation			
6 weeks	61.02 ± 7.36	48.52 ± 3.97	0.03
6 months	81.1 ± 2.97	79.15 ± 3.24	0.82
12 months	89.84 ± 3.75	90.05 ± 3.00	0.38
Recurrence: n (%)	0 (0%)	0 (0%)	1
Infections	0 (0%)	1 (12.5%)	0.44
Hip dislocation	0 (0%)	1 (12.5%)	0.44

Abbreviation: MSTS, Musculoskeletal Tumor Society.

Recurrence

None of the patients in any of the groups experienced recurrence ($p = 1$), as shown in ►**Table 2**.

Discussion

GCT of proximal femur has not been discussed in depth in the scientific literature. According to our literature search, this study is the first study focusing upon the role of denosumab in GCT of proximal femur. Majority of the previously published articles focused upon the different types of reconstructions after resection of GCT of proximal femur.[7] We further focused upon grade III GCT of proximal femur only excluding cases of grade I and II GCT. The study was designed as a comparative study to compare the results with and without neoadjuvant denosumab. We also utilized denosumab in significantly lower dosage preoperatively as recent studies have utilized higher and longer dosing regimens for downstaging of tumor that included a loading regimen at day 0, 8, 15, then once monthly or fortnightly.[10]

Surgical downstaging of GCT with the neoadjuvant denosumab and its correlation with the future choice of surgery has been discussed in the literature. Rutkowski et al.[11] concluded in their results that denosumab proved to be successful in surgical downstaging and to defer surgery in 48% participants. However, the recurrence rate was 15% while monthly doses of denosumab were used for a long time.[11] The long-term utility of denosumab has been proposed as risk factor for sarcomatous malignant changes in GCT.[12] Therefore, short-term use of neoadjuvant denosumab coupled with surgery remains the optimal and safer modality. But, the choice of surgical procedure remains the most crucial step for management.

Previously, major focus was kept on considering intralesional curettage for GCTs as a less morbid procedure, but it led to higher rates of recurrence.[13] Errani et al.[14] concluded that intralesional curettage for the proximal femur was a risk factor for recurrence. Therefore, we performed resection in 16 out of 18 patients and intralesional curettage in 2 patients. We tried curettage in 3 cases, but in 1 candidate, the calcar femorale was unsalvageable; thus, we converted to resection and arthroplasty with Wagner prosthesis. Wijsbek et al. performed a study in which they found better result with curettage than joint replacement for GCT of the proximal femur.[8] In another study by Khan et al.,[6] they included customized endoprosthesis for GCT of the proximal femur. From our point of view, the site of the tumor remains a better indicator for selection between resection or curettage rather than the downstaging after denosumab.

To assess the functional and oncological outcomes, we performed analysis at 6 weeks, 6 months, and 12 months. We wanted to see gradual improvement in patients with the passage of time. The HHS has been traditionally used in sports surgery and arthroplasty.[15] According to our results, the HHS and MSTS score have remained significantly better in the denosumab group during the immediate postoperative phase. However, a rapid increase in hip functions was observed according to the HHS, thereby producing similar results after 6 months of follow-up. Significant pain improvement was reported by all candidates who used denosumab. Petranova et al.[16] proposed that significant pain relief has been reported in 53.6% of GCT candidates. Hence, pain improvement preoperatively led to better rehabilitation and functional outcome for hip joint in the denosumab group in our study.

Recently conducted studies have associated the neoadjuvant use of denosumab with increased incidence of recurrences.[17] However, it is noteworthy to mention that these studies have used denosumab with curettage where increased recurrences were reported.[13] Agarwal et al.[18] performed a study where they proposed that recurrence after denosumab and curettage might be prevented by in-depth curettage of the tumor to pretreatment margins according to pretreatment radiographs. The osteosclerotic rim provides

protection to certain remnants of giant cells while curettage that leads to recurrence within first 2-years after the primary surgery. Therefore, our results have shown no incidence of recurrence in any cohort signifying that denosumab is not associated with recurrence.

Denosumab primarily forms an osteosclerotic rim around the tumor that leads to easier handling and resection of tumor that decreases the intraoperative duration as shown by Sahito et al.[19] and Muller et al.[20] The decrease in intraoperative duration lowers the chances of microbial growth, as shown by Cheng et al.[21] and Teo et al.[22] Hence, in our study, one case of deep infection developed in which revision surgery has been performed in the non-denosumab group. Moreover, the primary surgery was performed in 108 minutes, which was the longest duration among all 18 operated cases.

Conclusion

In conclusion, denosumab has proven to be beneficial for GCT of the proximal femur by providing early rehabilitation and better surgical and oncological outcomes. However, the downstaging of GCT of the proximal femur for joint salvage of hip remains questionable, and further research is needed. Moreover, those candidates who are not willing or have certain serious adverse effects to denosumab must be counseled about slower progress and rehabilitation and early postoperative difficulties, especially pain. We also concluded that once-weekly dosing of denosumab for 4 weeks is the optimal dosage in the month preceding surgery, and higher dosage may not be necessary.

Authors' Contributions

Each author contributed individually and significantly to the development of this article: MUA and SMEA: conceptualization, data collection, writing – review & editing, study design, data interpretation, and writing – original draft; BS: conceptualization, data collection, and writing – review & editing; and HK and AA: study design, data interpretation, and writing – original draft. All authors approved the final draft and stand accountable for the validity of the data.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Iatrogenic Pectus Deformities after Sternotomy in Patients with Down Syndrome

Pectus iatrogênico após esternotomia em pacientes com síndrome de Down

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Abstract

Objective To evaluate the incidence of pectus deformity after sternotomy in patients with Down syndrome, in addition to the clinical and radiographic characteristics.

Methods There were 20 patients with sternotomy history during childhood and a control group ($n = 20$). The chest was clinically evaluated for the presence and type of pectus deformity, severity, and the clinical sternal body length. Radiographic examinations were used to evaluate any abnormalities.

Results From the total, 85% ($n = 17$) presented with pectus deformities (41% lateral pectus carinatum, 65% mild severity, and 29% little flexibility). In the control group, deformity occurred in 5% ($n = 1$). In the sternotomy group, 40% ($n = 8$) had a clinically shortened sternum, which did not occur in the control group ($p = 0.01$). Radiographic examination of the sternotomy with pectus group showed posterior angulations in the manubrium (10%), sternal shortening (38%), and irregularities in the sternal body (70%); furthermore, 36% of the children had all sternal growth plates closed, and 10% had early sterno-manubrial fusion, which did not occur in the control group.

Conclusion Patients presented a high incidence of pectus deformity after sternotomy (mostly mild and of the lateral carinatum type), with radiographic changes suggestive of abnormal sternal growth.

Keywords
- deformity
- Down syndrome
- iatrogenic disease
- pectus carinatum
- pectus excavatum
- sternotomy

Study performed at the Department of Orthopedic Surgery, Hospital de Base do Distrito Federal, and Centro Clínico Orthopectus, Brasília, DF, Brazil.

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Resumo

Objetivo Avaliar a incidência de deformidade *pectus* após esternotomia em pacientes com síndrome de Down, além das características clínicas e radiográficas.

Métodos Foram estudados 20 pacientes com histórico de esternotomia durante a infância e um grupo controle ($n = 20$). O tórax foi avaliado clinicamente quanto à presença e tipo de deformidade *pectus*, gravidade e comprimento clínico do corpo esternal. Exames radiográficos foram utilizados para avaliar quaisquer anormalidades.

Resultados Do total, 85% ($n = 17$) apresentaram deformidades *pectus* (41% *carinatum* lateral, 65% gravidade leve e 29% pouca flexibilidade). No grupo controle, a deformidade ocorreu em 5% ($n = 1$). No grupo de esternotomia, 40% ($n = 8$) apresentaram esterno clinicamente encurtado, o que não ocorreu no grupo controle ($p = 0{,}01$). O exame radiográfico do grupo com *pectus* mostrou angulações posteriores no manúbrio (10%), encurtamento esternal (38%) e irregularidades no corpo esternal (70%); além disso, 36% das crianças tinham todas as placas de crescimento esternal fechadas, e 10% apresentaram fusão esterno-manubrial precoce, o que não ocorreu no grupo controle.

Conclusão Os pacientes apresentaram uma alta incidência de deformidade *pectus* após esternotomia (principalmente leve e do tipo *carinatum* lateral), com alterações radiográficas sugestivas de crescimento esternal anormal.

Palavras-chave

- deformidades
- doença iatrogênica
- esternotomia
- pectus carinatum
- pectus excavatum
- síndrome de Down

Introduction

Pectus deformities are idiopathic in most cases, but may also be iatrogenic,[1,2] congenital, or pathological (such as, Marfan syndrome).[3] It is mostly noticed at around 10-years-old, often worsening during puberty.[4]

Sternal growth occurs through endochondral ossification[5,6] and presents as growth plates between its osseous segments and the costochondral junctions, which was originally described by Haje and Bowen.[4] The onset of sternal growth disorders during the prenatal and developmental periods can result in a disproportion between the sternum and the ribs.

Haje et al.[7] described that lesions in the sternal growth plates of rats can generate pectus deformities. Primary lesions or anatomical disarrangements of the sternal growth plates resulting from sternotomy during cardiac surgery seemed to have caused deformities during children's growth period.[2,8,9] Another possible cause would be the persistence of a macroscopic gap between the growth plates or the two halves of the sternal body after closing the sternotomy.[9]

Lateral radiographic views revealed early closure of sternal growth plates in patients with pectus, especially in the superior carinatum or Currarino type, resulting in shortened and curved sternal bodies.[10]

The first reported case of iatrogenic pectus deformity in the literature was in 1995, involving pectus carinatum after sternotomy for the treatment of cardiac malformation, which was satisfactorily treated with the Dynamic Chest Compressor 1 (DCC 1) brace,[8] first described by Haje and Raymundo in 1979.[11] Another case of iatrogenic pectus carinatum has been described.[12] However, the number of cases is possibly underreported, especially those with mild deformity, which may not be prioritized by attending physicians or family members.

Haje et al.[9] have also classified idiopathic pectus deformities in terms of clinical type, severity, and flexibility;[1,4,9] but these factors have not been analyzed in the setting of iatrogenic pectus deformities.

The objective of this study was to evaluate the prevalence of iatrogenic pectus deformity in skeletally immature patients with Down syndrome who underwent sternotomy during surgical treatment for congenital heart disease. The secondary objectives were to evaluate the deformity's type, flexibility, severity, and radiographic changes in these patients.

Materials and Methods

The clinical data for assembling groups with and without sternotomy were collected from the medical records of patients with Down syndrome. All legal guardians were informed about the study and provided informed consent. The evaluation protocol was approved by the Institutional Ethics Committee (37229014.0.1001.5553).

The study included 434 medical records of Down syndrome patients, of which 43 had a history of sternotomy during childhood for cardiac repair. ►**Fig. 1** shows the flowchart of patient selection for the study. There were 20 patients classified as the sternotomy group (8 males and 12 females; mean age 12.51, 1–24 years, standard deviation [SD]: 7.16) of whom 11 were children or growing adolescents and 9 were adults. Of the 391 remaining patients, 20 without a history of sternotomy were randomly selected as the control group (8 males and 12 females; mean age 14.67 years, 1–34 years, SD: 9.04), with 11 children or growing adolescents and 9 adults.

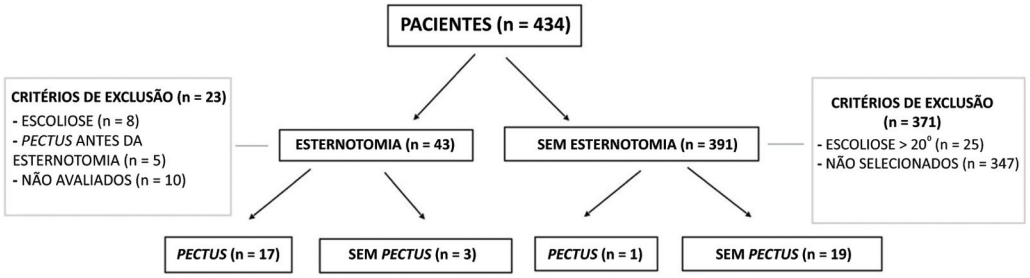


Fig. 1 Flowchart of patient selection for the study groups (sternotomy and control groups).

The mean age of sternotomy patients was 24.35 months. The patient who underwent sternotomy later was 96-months-old at the time of the sternotomy.

After the grouping of patients, clinical evaluations were initiated at the orthopedic outpatient clinic.

The patients' relatives were asked about the date of previous sternotomy, presence of pectus deformity prior to operation, time of pectus onset after , family history of chest deformities, and previous pectus treatment. The clinical evaluations were performed by a single pediatric orthopedist specialized in the noninvasive treatment of thoracic deformities. The analyses involved thoracic deformity type, severity (mild, moderate, or severe) and flexibility, sternal length (normal or short, with "short" being considered when the sternum or xiphoid process terminated proximal to the nipple line), and the presence of exacerbated thoracic kyphosis or scoliosis.

Deformities were classified as superior pectus carinatum (SPC), inferior pectus carinatum (IPC), lateral pectus carinatum (LPC), broad pectus excavatum (BPE), and localized pectus excavatum (LPE), as described in previous studies.[1,10,11,13]

The evaluation of the sternal length is shown in ►**Fig. 2**. The pectus carinatum flexibility was evaluated by manual compression of the deformity at the apex in the anteroposterior direction. Pectus excavatum flexibility was evaluated by manual compression at the lower costal edge protrusions in the anteroposterior direction, with the patient simultaneously performing a Valsalva maneuver with arm adduction against resistance, while observing the effects on the depression area.[4] Patients who could not perform the Valsalva maneuver were instructed to either blow a balloon or exempt from this evaluation component.

For both pectus carinatum and excavatum, the deformity was classified as very or moderately flexible when there was a significant or complete reversal of the deformity, respectively. Alternatively, it was classified as less flexible when the pectus presented little change, or rigid when there was none with the provocative maneuvers performed,.

The chest imaging findings of all patients of the sternotomy and control groups were documented. Radiographs were taken in the lateral and oblique views of the sternum.

The presence of latero-lateral irregularity of the sternal body was evaluated in the oblique view.[9] The radiographic parameters observed in the lateral view were the number of open sternal growth plates (0 to 3), total number of sutures in the growth plate, sternum sagittal angulation pattern,[14] and sternal body-manubrium (BM) or xiphoid-manubrium (BxM) indexes (►**Fig. 3**).[5] A previous study demonstrated that these two indexes were constant in normal patients, regardless of age, with values ranging from 2.16 ± 0.24 (BM)

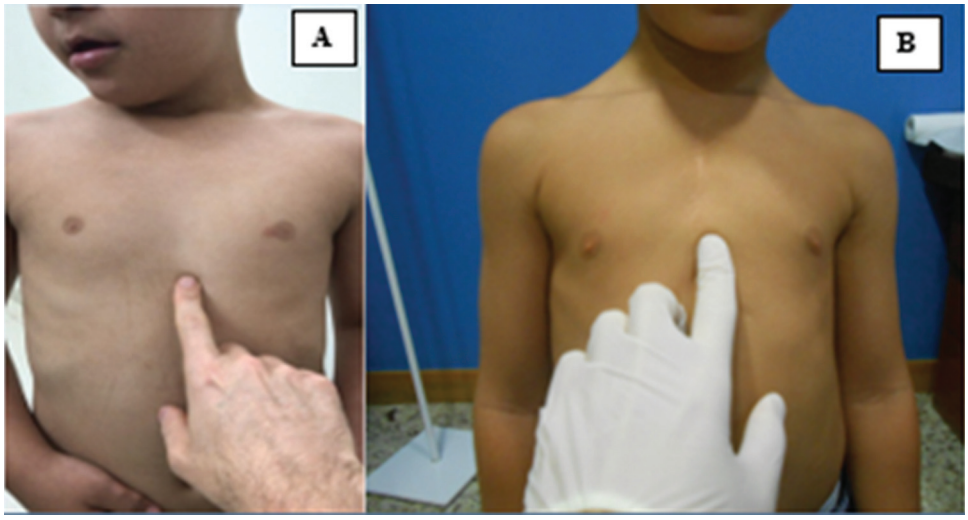


Fig. 2 Evaluation of the sternal length in a patient with a sternal of normal length (A), and in a patient with shortened sternum (B).

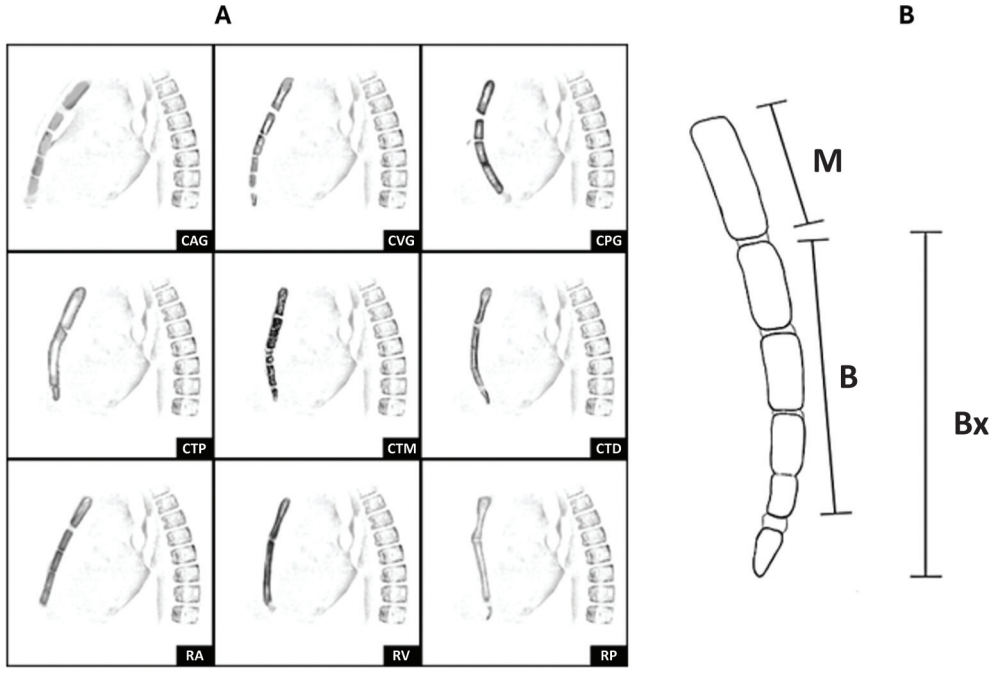


Fig. 3 (A) Illustration of the sternal patterns: gradual anterior curve (GAC), gradual vertical curve (GVC), gradual posterior curve (GPC), proximal third curve (PTC), middle third curve (MTC); distal third curve (DTC), anterior rectilinear (AR), vertical rectilinear (VR), and posterior rectilinear (PR)[14]. (**B**) Diagram of measurements taken from the lateral view of the sternum of a child with a normal chest, around 10-years-old, with two open growth plates. The length of the manubrium (M) and the body of the sternum (B), and the straight line drawn from the proximal end of the sternal body to the distal end of the xiphoid (Bx) were measured in centimeters. The result obtained by dividing the length of the sternal body (B) by the length of the manubrium (M) was called the BM index. When the xiphoid process was ossified, the BxM index was measured, represented by the division of Bx by M [5].

to 2.73 ± 0.31 (BxM). These normal ranges were applied in the present study.[5]

Additional abnormal radiographic findings were noted. Although computed tomography (CT) chest scans were not requested, patients who underwent this examination for other reasons had their images analyzed.

Total spine radiographs in the orthostatic position were requested for patients with clinical examination findings suggestive of scoliosis or exacerbated kyphosis to determine the severity of the curve by the Cobb angle.

The Shapiro-Wilk test was used for the comparative statistical analysis between numerical variables of each group that followed normal distribution. When the hypothesis of normality was not rejected, the *t* test for independent samples was used to compare the groups. When the hypothesis of normality was rejected, the nonparametric Mann-Whitney test was used. The chi-squared test (x2) was used to compare categorical variables between groups.

The number of open sternal growth plates (0–3) and the presence of sutures variables were not compared for either group, as they were age-related and the number of children and adolescents in both groups was insufficient for a statistical analysis.

Results

In the group of 20 patients who underwent sternotomy, 85% ($n = 17$) presented with pectus deformities after the procedure. The mean time of onset was 5 months (median $= 3$ months), and 25% of the cases happened soon after ($n = 5$); 15% ($n = 3$) in 3 months; 5% ($n = 1$) in 4 months; 5% ($n = 1$) in 6 months; and 5% ($n = 1$) in 36 months. In 30% ($n = 6$) of the cases, family members failed to recall.

The mean age of pectus onset in our group was 27.47 months (2.29 years).

In the control group, the only patient with deformity presented with localized pectus excavatum at 6-months-old, with mild severity and moderate flexibility. None of the patients from either group had a family history of pectus deformities.

►**Table 1** shows the pectus types, severity, and flexibility in the sternotomy group.

Mild scoliosis was found in 40 ($n = 8$) and 20% ($n = 4$) of patients from the sternotomy and the control groups, respectively, with statistical difference ($p < 0.001$). All patients in both groups had postural kyphosis.

All control patients had a clinically normal sternal length, while 40% ($n = 8$) of the sternotomy group presented with a clinically shortened sternum; significant difference was observed between groups ($p = 0.01$). ►**Fig. 4** shows a patient in the sternotomy group with IPC and termination of the sternum at the level of the nipple, which represented sternal shortening (►**Fig. 4A,B**), with a lateral radiographic view of the sternum showing several changes (►**Fig. 4C**).

The measurement of the BM index showed normal sternal length in all patients without a history of sternotomy. In 38% ($n = 6$) of the sternotomy group, the BM and BxM indexes

Table 1 Pectus types, severity, and flexibility in the sternotomy group

Pectus type	Severity			Flexibility		
	Mild	Moderate	Severe	Moderate or high	Rigid or little	Total
IPC	11.8% (n = 2)	5.9% (n = 1)	11.8% (n = 2)	23.6% (n = 4)	5.9% (n = 1)	29.5% (n = 5)
LPC	29.5% (n = 5)	11.8% (n = 2)	0.0% (n = 0)	35.3% (n = 6)	5.9% (n = 1)	41.1% (n = 7)
SPC	5.9% (n = 1)	0.0% (n = 0)	0.0% (n = 0)	0.0% (n = 0)	5.9% (n = 1)	5.9% (n = 1)
LPE + LPC*	0.0% (n = 0)	5.9% (n = 1)	0.0% (n = 0)	0.0% (n = 0)	5.9% (n = 1)	5.9% (n = 1)
LPE	17.6% (n = 3)	0.0% (n = 0)	0.0% (n = 0)	11.8% (n = 2)	5.9% (n = 1)	17.6% (n = 3)
Total	64.8% (n = 11)	23.6% (n = 4)	11.8% (n = 2)	70.7% (n = 12)	29.5% (n = 5)	100.0% (n = 17)

Abbreviations: IPC, inferior pectus carinatum; LPE, localized pectus excavatum; LPC, lateral pectus carinatum; SPC, superior pectus carinatum.
Notes: * Mixed type of pectus.

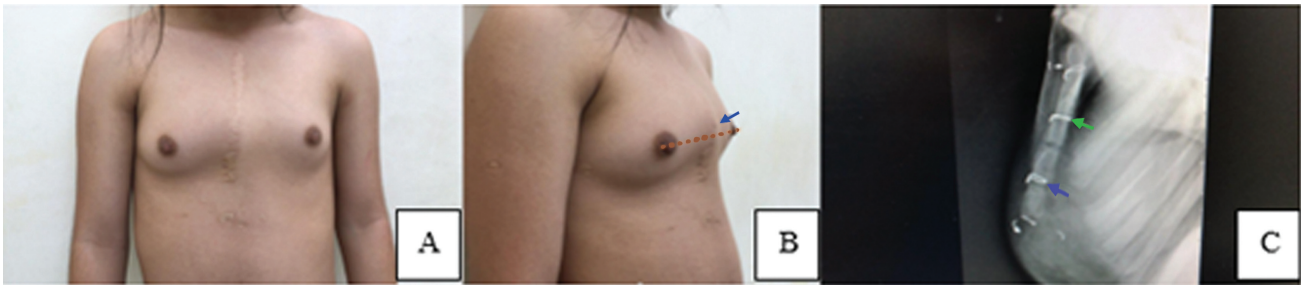


Fig. 4 (**A**) Anterior view of a 13-year-old patient who underwent sternotomy at 18 months of age. Right oblique view showing IPC. (**B**) The distal end of the sternum or xiphoid (apex of the deformity – arrow 1) was proximal to the nipple line (dashed line), showing clinical shortening of this bone. (**C**) Lateral view of the sternum showing the posterior angulation of the manubrium bone (arrow 1), metallic suture at the sterno-manubrial junction with incipient fusion (arrow 2), two open growth plates, metallic suture on the distal growth plate (arrow 3) with a rectilinear sternal pattern and BM index < 2.

showed a radiographically shortened sternum, which was significantly higher when compared with the control group (38 vs. 0%, $p = 0.05$). Oblique radiographic assessment of the sternum showed that latero-lateral irregularities were significantly higher in the sternotomy group (70 vs. 20%, $p = 0.01$), as shown in ►**Fig. 5**.

As for the presence of metallic sutures in the growth plates, they were found in sternotomy patients who were still growing and with sternal growth plates still open ($n = 11$). Of them, 36% ($n = 4$) presented with sutures in the growth plates: two patients with sutures in two growth plates and two with sutures in one growth plate. One of these patients underwent CT in another hospital (►**Fig. 5**). All patients without pectus deformities in the sternotomy group ($n = 3$) were already adults during radiographic evaluation, rendering it impossible to determine whether the metal sutures were previously placed on the referred growth plates. The BM and BxM indexes, the presence of latero-lateral irregularities, and the number of open sternal growth plates in the sternotomy and control groups are detailed in ►**Table 2**.

In the sternotomy group, 2 patients (10%) presented with posterior angulation of the manubrium in the middle third segment (none in control group), one of whom associated with ossification in the anterior region, 20.0% ($n = 4$) had sternomanubrial fusion (only two were children with pectus deformities, the others were adults, one without deformity), and 10.0% ($n = 2$) presented with additional acute angulation of the sternum in the distal third portion, one of whom had anterior and posterior angulation. In the control group, 25% ($n = 5$) presented with sternomanubrial fusion, all of them adults.

About the type of sternal curvature, the sternotomy group presented with 25% ($n = 5$) of GAC, 5% ($n = 1$) of posterior gradual, 30% ($n = 6$) of GVC, 25% ($n = 5$) of AR, 5% ($n = 1$) of PR, and 10% ($n = 2$) of vertical rectilinear curve. In the control group, 50% ($n = 10$) had GVC, 40% ($n = 8$) AR, and 10% ($n = 2$) PR. The X2 test showed no significant difference regarding the type of sagittal angulations among and between the groups ($p = 0.20$).

Of the sternotomy group patients who developed pectus deformities, three were treated using an orthosis (►**Fig. 6**).

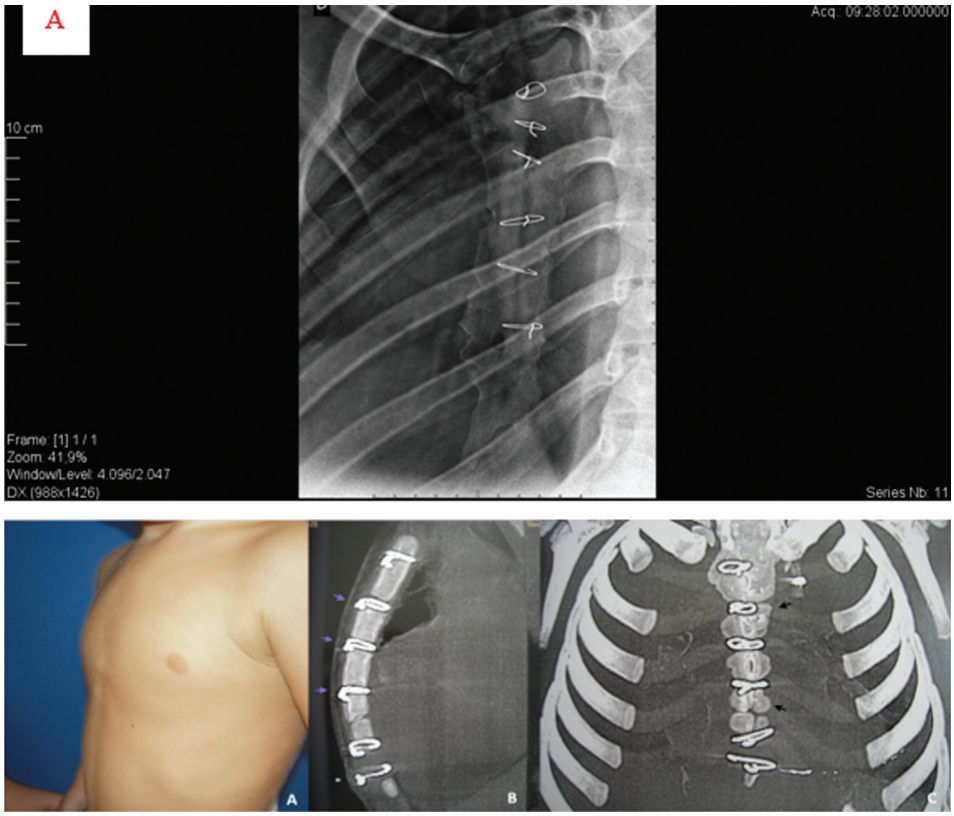


Fig. 5 (A) Oblique view of a 24-year-old patient with mild lateral pectus carinatum who underwent sternotomy at 96 months of age, with sterno-manubrial fusion and latero-lateral irregularities (asymmetries in the lateral contours on both sides of the sternum). (**B**) Computed tomography imaging of a two-year-old patient with IPC who underwent sternotomy (**a**). Sagittal image showing metallic structures in the two proximal growth plates and in the sterno-manubrial junction, with a GPC sternal pattern (arrows) (**b**). Coronal reformatted image showing irregular proximal growth plates and latero-lateral irregularity or asymmetry when comparing the two external sides (arrows) (**c**).

Table 2 Results of the BM index

Radiograph findings		Group		
		Control	Sternotomy	Total
BM/BxM indexes	< 2.16 or < 2.73*	0% (n = 0/15)	38% (n = 6/16)** s	20% ($n = 6/31$)
	< 2.16 or < 2.73*	100% (n = 15/15)**	63% (n = 10/16)** s	80% ($n = 25/31$)
Latero-lateral irregularity	Yes	20% (n = 4/20)	70% (n = 12/17)***	43% ($n = 16/37$)
	No	80% (n = 16/20)	30% (n = 5/17)***	57% ($n = 21/37$)
Growth plates open****	1	15% (n = 3/20)	0% (n = 0/20)	7.5% ($n = 3$)
	2	10% (n = 2/20)	10,0% (n = 2)	10% ($n = 4$)
	3	30% (n = 6/20)	20% (n = 4/20)	25% ($n = 10$)
Growth plates closed	(n = 20)	45% (n = 9/20) adults 0% (n = 0/20) children&	45% (n = 9/20) adults 25% (n = 5) children&	57.5% ($n = 23$)

Abbreviations: BM, body-manubrium; BxM, body xiphoid-manubrium. **Notes:** * $<$ or $>$ 2.16 values relative to the BM index and $<$ or $>$ 2.73 values relative to the BxM index[5]. ** 5 patients were excluded for presenting sterno-manubrial fusion causing inability to measure the BM or BxM indexes. **s 4 patients were excluded for presenting sterno-manubrial fusion causing inability to measure the BM or BxM indexes. *** Failure of analysis in three sternotomy patients due to bad quality radiographs. **** All patients with growth plates open were children. & Patients with all growth plates closed, 0% ($n = 0/9$) and 36% ($n = 5/14$) were children from the control and sternotomy group, respectively.

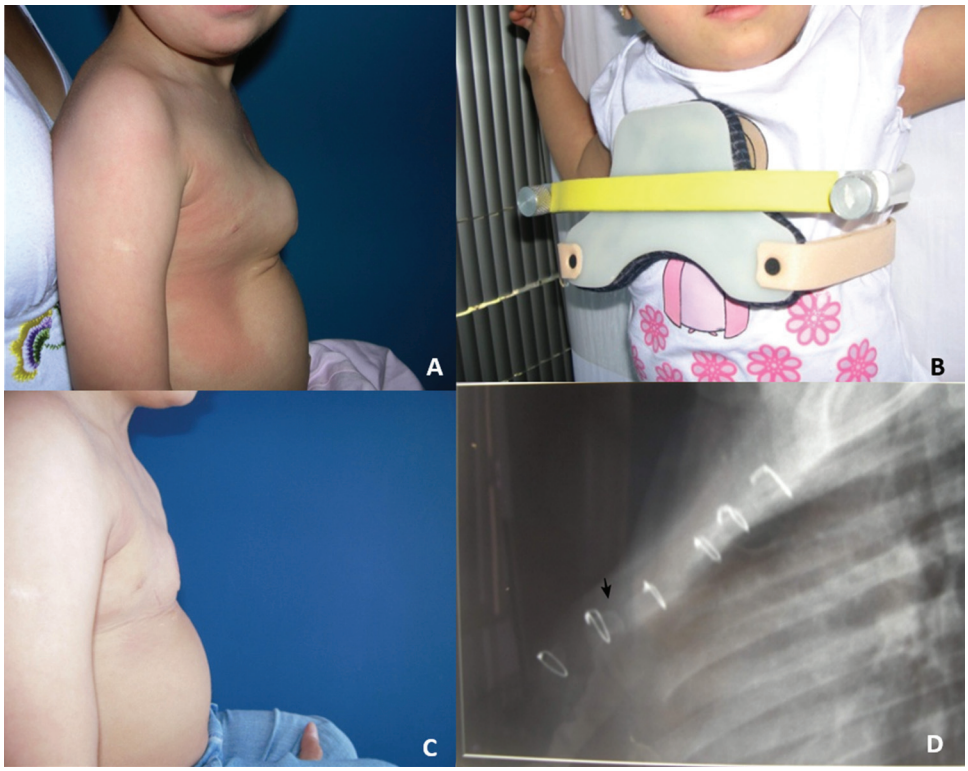


Fig. 6 Patient with Down syndrome who underwent sternotomy for cardiac repair at 6 months of age and again at 13 months of age presented with (**A**) severe inferior pectus carinatum at 2 years and 1 month of age, (**B**) being initiated the use of a DCC 1 orthosis, (**C**) with good partial correction after a 24-month follow-up. (**D**) Lateral radiography of the sternum showing an AR pattern with additional acute anterior angulation in its distal third portion (arrow) and early sterno-manubrial fusion.

Discussion

This is the first study to analyze the prevalence of pectus deformity in patients who underwent sternotomy. Our finding of the high prevalence of such deformities in sternotomy patients (85%) propose that families need to be informed about this risk before the referral to cardiac surgery needing sternotomy.

In the present study, 25.0% ($n = 5$) of the patients who underwent sternotomy were diagnosed with pectus deformity shortly after the procedure, inferring an immediate postsurgical change in the sternal bone. Additionally, the mean age of onset was 2.5 years in the patients' following sternotomy, which was much earlier than idiopathic cases which mostly appeared in the preadolescence period.[4,9]

According to Ellis, 40% of patients had a family history of pectus deformity.[15] However, these differed from the sample analyzed in our study, in which none of the patients with pectus deformity had a family history, reinforcing the iatrogenic etiology.

Pectus excavatum is the most frequently reported type in prevalence studies,[16] although a study by Haje et al.[17] on 4,012 patients reported that 79% had pectus carinatum (IPC: 45%, LPC: 28%, SPC: 5%, LPE: 13%, and BPE: 9%).[17] The comparison between this study series of iatrogenic cases with those reported by Haje and Haje[17] showed that LPC was the predominant pectus type, which can be justified by an eventual irregular apposition between the two sternal sides when surgically closing the sternum.

The study by Haje et al.[5] showed no sutures between the bone segments of the sternum as previously described by Currarino and Silverman,[5,18] but the presence of growth plates. The sternum length increases due to their action. These plates are also responsible for the growth of costal cartilages and ribs in the anterior chest wall. Any surgical aggression to these structures can result in disproportionate growth and, consequently, deformities.[1,5,7,10] In the present study, 70.0% of sternotomy pectus patients ($n = 12$) had latero-lateral irregularities, early growth plate closure, sternomanubrial fusion, and other changes that were not found in the control group, such as posterior angulation of the manubrium, acute angulation of the distal third of the sternum, and irregular ossification anterior to the sternal body.

A previous study had CT scans with coronal reconstruction showing that lateral sternal body irregularities were more frequent in pectus patients than in the control group ($n = 10$). Furthermore, these irregularities were more difficult to interpret and perform in oblique radiographs of the sternum. However, due to radiation concerns, chest CT for diagnosis was not routinely recommended.[10]

Sternomanubrial fusion occurred more frequently in adult patients but also occurred in two pediatric patients in the sternotomy group. Generally, this fusion does not occur in children, and is only found in10 to 30% of cases in

adulthood,[12] although an incidence of 55% was found in our adult control patients.

The present study included the clinical evaluation of sternal lengths, with 40.0% ($n = 8$) of sternotomy patients reporting a shortened sternum, unlike the control group, in which none reported such findings. This description of the clinical length of the sternum has not been previously reported in the literature and the authors believe it should be included in the physical examination of these patients.

The sternotomy group had more radiographically shortened sternums (abnormal BM index) than the control group, reinforcing the concept that surgical aggression to the sternal growth plates can shorten this bone, generating deformity, mostly mild severity. The BM (index was previously used to evaluate the radiographic shortening of the sternum, suggesting that a disproportion between the sternal and costal growths may result in a pectus deformity.[5]

This study also evaluated the number of open or closed sternal growth plates, which are scheduled to close according to age group, also varying individually. In the sternotomy group, five children with pectus deformity had all plates closed, which did not occur in the control group.

As for the treatment of pectus deformities, the use of DCCs and surgical correction have been described.[1,4,7–9,11] According to Haje et al.,[7,9] flexibility is the most important prognostic factor for conservative treatment. Idiopathic IPC and LPC are the most flexible types of carinatum, while SPC is more rigid and resistant to orthotic treatment.[9,17] However, two LPC and IPC cases in this study had rigidity during childhood, which was an unusual presentation. Therefore, iatrogenic pectus deformities tend to be more rigid than their idiopathic counterparts.

Aware that lesions in growth cartilage plates can cause deformity in the short and long term, orthopedic surgeons usually try to preserve them when operating on long bones in children and adolescents. Such care should be extended to surgeries performed on all bones in the thoracic region. Therefore, improved sternal suture techniques may decrease the onset of pectus deformity, saving the sternal growth plates or making their apposition as accurate as possible during sternal suturing.

Conclusion

In conclusion, sternotomy in Down syndrome patients was associated with a high prevalence of pectus deformity, most of which were mild and of the LPC type, with radiographic changes.

Authors' Contributions

Each author contributed individually and significantly to the development of this article. DPH: study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; and critical revision. JHCA: data acquisition, analysis, and interpretation; drafting of the manuscript. TVPS: data acquisition, analysis, and interpretation; drafting of the manuscript. FASA: data acquisition, analysis, and interpretation; drafting of the manuscript. All authors read and approved of the final manuscript.

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Conflict of Interests

The authors have no conflict of interests to declare.

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A Novel Invention of a 3D Printed Mould for Calcaneum Replacement Post Total Calcanectomy for a Recurrent Aggressive GCT of the Calcaneum

Novo molde impresso em três dimensões para substituição do calcâneo após calcanectomia total por um tumor de células gigantes agressivo recorrente do calcâneo

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Abstract

Advances in image processing have led to the clinical use of 3D printing technology, providing surgeons with realistic physical models of anatomy that enable them to recreate accurate bone structures. 3D-printed molds can play a central role in surgical replacements, offering both efficiency and cost-effectiveness. This case report describes the innovative creation of an anatomical calcaneum using a 3D printer. A patient presented with a recurrent aggressive stage of calcaneal giant cell tumor, which necessitated a complete resection, leaving a large void that required reconstruction. This paper outlines the 3D printing methodology used from pre-operative printing of the prototype, through the surgical procedure, to post-operative care. 3D images of the calcaneum were extracted from a CT scan and edited using 3D modelling software to print a hollow-shelled calcaneum. The printed prototype was created in two halves and sent for gas sterilization. After resecting the diseased calcaneum, the mold was filled with bone cement and clasped together with a proline mesh in between, for soft tissue attachment. Once the cement set, the shell was removed, and the shaped bone cement calcaneum was implanted into the patient with screws. The surrounding soft tissues and Achilles tendon were sutured to the mesh. Post-operatively, the patient was kept in a plaster dorsal slab for six weeks to allow for soft tissue incorporation. Six weeks after surgery, the patient began weight-bearing activities with an aesthetically shaped foot. This method for bone reconstruction is efficient, economical, and reproducible.

Keywords

- calcaneum
- giant cell tumors
- oncology
- printing, three-dimensional

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Resumo

Avanços no processamento de imagens levaram ao uso clínico da tecnologia de impressão tridimensional (3D), dando aos cirurgiões modelos físicos anatômicos realistas para recriação precisa de estruturas ósseas. Moldes impressos em 3D podem desempenhar um papel essencial em substituições cirúrgicas, oferecendo eficiência e boa relação custo-benefício. Este relato de caso descreve a criação inovadora de um calcâneo anatômico usando uma impressora 3D. Um paciente apresentou uma recidiva de tumor de células gigantes do calcâneo em estágio agressivo, com necessidade de ressecção completa, deixando um grande espaço vazio que exigia reconstrução. Este artigo descreve a metodologia utilizada desde a impressão 3D pré-operatória do protótipo, passando pelo procedimento cirúrgico, até os cuidados pós-operatórios. As imagens 3D do calcâneo foram extraídas de uma tomografia computadorizada e editadas usando um *software* de modelagem 3D para impressão do osso como uma concha oca. O protótipo impresso foi criado em duas metades e enviado para esterilização a gás. Após a ressecção do calcâneo acometido, o molde foi preenchido com cimento ósseo e as duas metades foram unidas, com uma tela de prolene entre elas, para fixação nos tecidos moles. Após a cura do cimento ósseo, a concha foi removida e o calcâneo moldado foi implantado no paciente com parafusos. Os tecidos moles circundantes e o tendão calcâneo foram suturados à tela. No pós-operatório, o paciente utilizou uma placa dorsal de gesso por 6 semanas para permitir a incorporação dos tecidos moles. Seis semanas após a cirurgia, o paciente iniciou atividades com suporte de peso no pé esteticamente moldado. Este método de reconstrução óssea é eficiente, econômico e reprodutível.

Palavras-chave

- calcâneo
- impressão tridimensional
- oncologia
- tumores de células gigantes

Introduction

Advances in image processing have led to an increasing clinical usage of 3D printing technology. The CT or MR images can be converted to 3D format files, giving a perfect anatomical model. This technology allows versatility in the design process and enables efficient production of both off-the-shelf and personalized anatomy that tailors to specificity.[1] In the field of orthopaedic oncology surgery, 3D-printed molds and instrumentation can be used to address bony restoration after a wide resection as part of tumor resection protocol. Although conventional metal implant replacements are available, costs can be exorbitant. In our case, the 3D anatomical shell is printed at minimal cost, and the bone cement used to fill it is also low in cost. This paper reviews the surgical technique and outlines the basics of 3D printing technology and its possible applications in orthopaedic surgery with its potential future impact.

Case Report

This innovative surgical treatment was performed on a patient who presented to our institution with a recurrent GCT of the calcaneum. The patient was initially treated 18 months prior with a series of Denosumab and an extended curettage. He presented with symptoms of swelling and pain over the left heel (►**Figs. 1** and **2**).

Technique Description 3D Printing

- Preoperative planning

Various methods of 3D printing exists, however all of them share the same principles and step-wise process.[1] Although 3D printing has gained traction over the years, it is not widespread given its steep learning curve and limited knowledge.[2] As the case was an oncological pathology – it is crucial that the high standards of oncological resection principles are upheld. Patient will have to go through the same standard clinical assessment with proper imaging: A CT scan and an MRI of the foot to delineate the soft tissue extension and neurovascular involvement. Once the diagnosis is established the surgical resection margins are determined: an anticipation of a significant void as a total calcanectomy was planned. The resected calcaneum will need to be replaced or reconstructed to facilitate weight bearing. A CT of the normal contralateral calcaneum was needed for the mold creation.

- Requirements for the surgery

A standard 3D printer was required. Examples were by Kokoni Smart, Bambulab, Creality and etc. A prior CT scan and MRI was required to obtain the 3D models. These 3D models were generated from Slicer (slicer.org) and then imported into a 3D modeling software (Fusion 360) (►**Fig. 3**). The final designs can be printed using several



Fig. 1 Radiograph imaging of the L pathological calcaneum in (**A**) AP view (**B**) axial (**C**) lateral.

printer-specific software. The model of the anatomical printing needs to be prepared prior to surgery and sterilized – the 3D model was sterilized with gas sterilisation as the PLA (Polylactic Acid) material used was heat labile.

- Indications and contraindications

This method of replacement follows a wide local excision of the underlying tumor avoiding the need for an amputation. Limb salvage surgery comprises surgical techniques designed to resect musculoskeletal extremity tumors and subsequently reconstruct a limb with an acceptable oncologic, functional, and cosmetic result.[3] Relative contraindications are pathologic fractures, neurovascular encasement, and a poorly placed biopsy tract. Limb salvage surgery is the preferred treatment of musculoskeletal extremity tumors in the modern era because limb salvage surgery has proven not to compromise survival or recurrence when compared with amputation.[3]

- Surgical anatomy

The calcaneus is an irregular, roughly cuboidal bone situated below the talus forming the core of the heel (►**Fig. 4**).[4] The posterior part of the calcaneus is circular, with three facets. The superior facet is separated from the calcaneal tendon by the retrocalcaneal bursa. The middle facet provides the attachment site for the Achilles tendon. The inferior facet is continuous with calcaneal tuberosity on the plantar surface. Superiorly is a cartilage-covered facet



Fig. 2 Clinical picture of the left pathological foot.

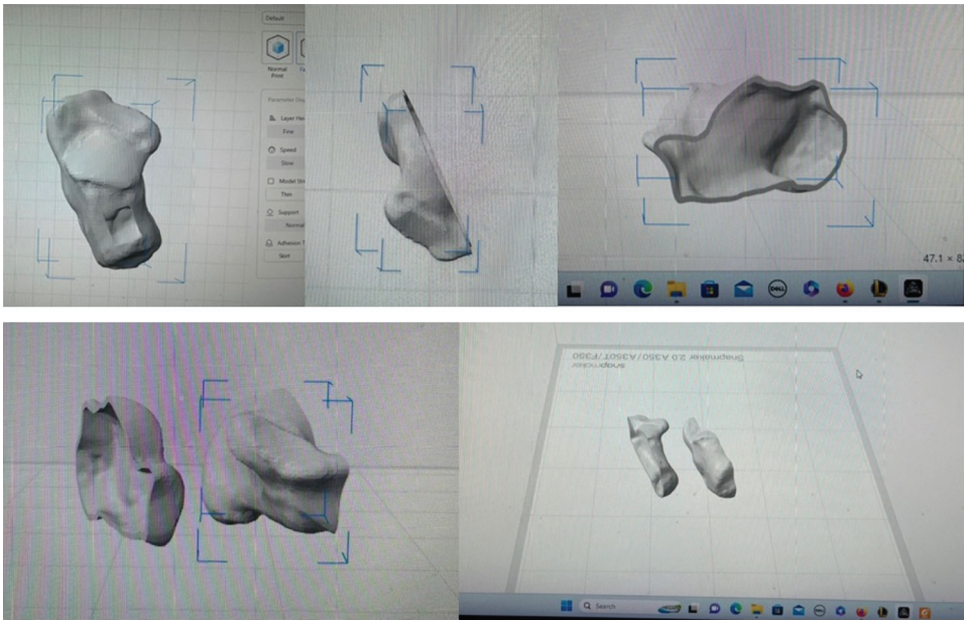


Fig. 3 (**A**) The creation of the 3D model from existing 3D reconstruction of the CT (**B**) superior view of the created halve of the calcaneum (**C**) the sagittal view of the created half of the calcaneum (**D**) creating a mirror image for printing (**E**) the final designs for printing in a 3D printer platform.

(middle talar articular facet) for the corresponding middle facet of the head of talus as part of the subtalar joint. The anterior surface has a convex articular facet for the cuboid bone articulation.

- Surgical technique

All patients will adhere to strict oncological resection principle of an en bloc resection with a clear resection margin. Surgical resection is crucial in the treatment of primary solid tumors, resection at tumor margins remains a concern, inadequately resected margins facilitating tumor recurrence.[5] Post excision of the tumor – ensure no macroscopic retainment of tumor. The operation was performed in the prone position using a Cincinnati incision[6] (►**Fig. 5**). The total calcanectomy was performed, via en bloc resection (►**Fig. 5**). The triceps surae were tagged for reconstruction later.

The sterilized printed mold is prepared for molding of the calcaneus for implantation. Each halves of the printed mold was lined with ioban and coated with liquid paraffin (►**Fig. 6**). Both the molds are then filled with one packet of standard bone cement each. The 2 molds are then clasped together with proline mesh in between. The prolene mesh serves to function as an anchor for the soft tissue reconstruction. The extruded cement upon clasping is removed while in liquid form before hardening (►**Fig. 6**).

Due to the physical properties of the polylactic acid, the hardened mold shell softens during the exothermic phase of the cement setting, enabling it to be peeled off easily (►**Fig. 6**). This molded calcaneum is then inserted to the resected calcaneal space. The Tricep surae was sutured to the posterior calcaneal aspect of the proline mesh. The proline mesh was trimmed to areas that required attachments. The Talocalcaneal joint is stabilized with the insertion of a partially treaded cancellous screws (►**Fig. 7**). Serial drill bits of increasing sizes were used to gradually dilate the tract to prevent cement from cracking.

Subsequently, after the insertion of the screws, the Tendon Achilles was sutured to the mesh over the posterior part

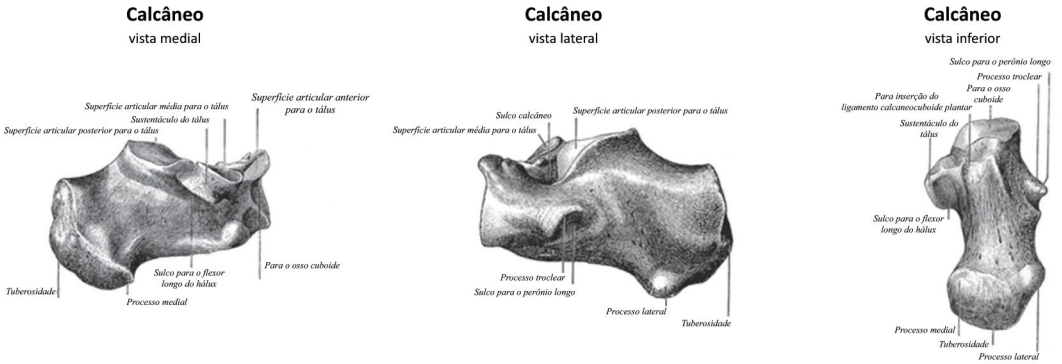


Fig. 4 Anatomy of calcaneum (**A**) medial (**B**) lateral (**C**) inferior. Source: Luijkx T, Elthokapy M, Gregory L, et al. Calcaneus. Reference article, Radiopaedia.org.

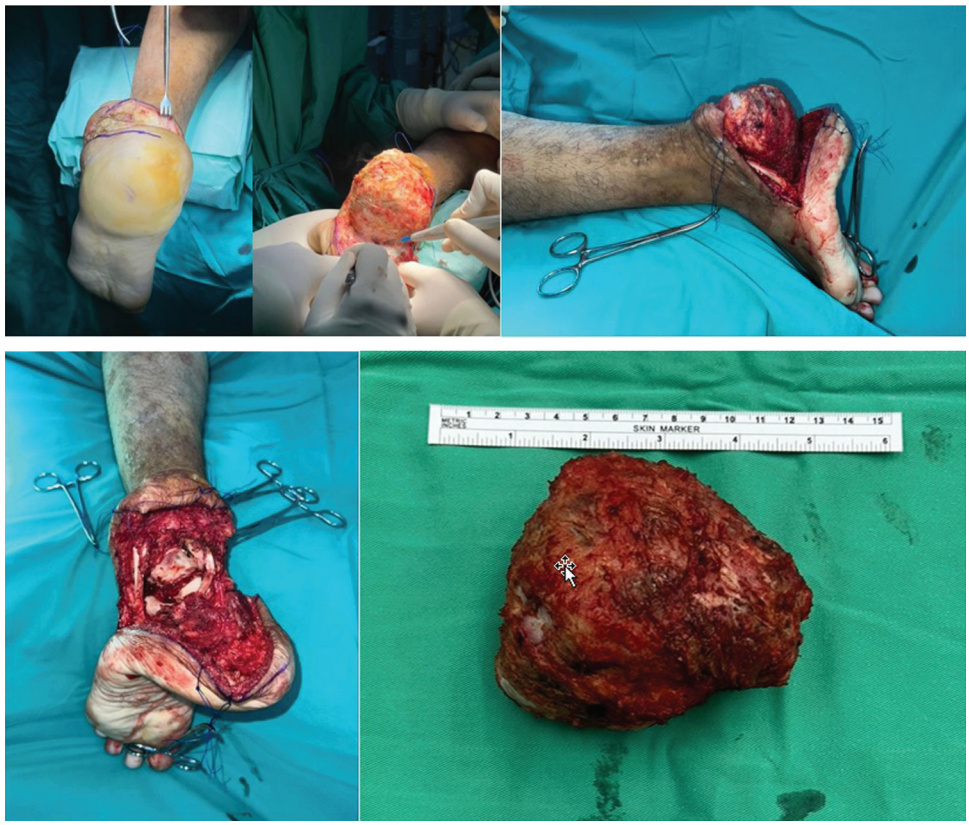


Fig. 5 Total calcanectomy with Cincinati approach to the calcaneum (**A**) Cincincati approach incision over the heel (**B**) Wide resection of the pathological calcaneum (**C**) sagittal view of the pathological calcaneum (**D**) Voided space post total calcanectomy (**E**) Excised recurrent Giant Cell Tumour of the calcaneus.

of the calcaneum with a size 2 Ethibond. The calcaneocuboid joint was reconstructed with the mesh around the joint with its surrounding ligament. Alternatively – another screw from posteriorly could be inserted across the calcaneocuboid joint (►**Fig. 7**).

A drain was applied and the subcutaneous tissue was closed with Vicryl 1 and skin with Dafilon 3/0. The wound is dressed with antibiotic cream and plaster and supplemented with fluffed gauze and bandaged.

- Postoperative management

The drainage tube is kept for 3–5 days till the wound was epithelised. Sutures were removed 2 weeks post-surgery. A postoperative below-knee dorsal slab was applied for 8 weeks. Subsequently, a progressive passive and active movement of the ankle without weight for an additional 6 weeks to allow Tendon Achilles to incorporate. Partial weight-bearing with crutches was allowed at 6 weeks after surgery and full weight-bearing at 3 months. This patient will be followed up with periodic clinical and radiological examinations. Functional results were evaluated according to the system proposed by the International Society of Limb Salvage and approved by the Musculoskeletal Tumor Society.[7]

- Result and Follow up

Patient was followed up post operatively in 2 weeks, 6 weeks, 3 months and 6 months after. The wound healed well without dehiscence or fat pad necrosis and patient started full ambulation after 3 months. Patient was able to walk with a fairly balanced gait and radiograph showed intact printed implant and screws (►**Fig. 8**). Patient was very satisfied with the result and rehabilitation.

- Pearls (Tip & tricks) and Pitfalls
  - Size and Morphology
    - Anatomically snug fit without interfering surrounding structures
    - Correct sizing
    - Printing a 2mm thick shell is sufficient for strength and also for malleability during the exothermic cement hardening.
  - Molding
    - Gauging the sufficient amount of cement required to fill the space without porosity within. The volume of the structure can be calculated with the 3D design software to estimate the amount of bone cement required.
    - Constant pressure and precision in maintaining the clasp awaiting the cement hardening
  - Mechanical strength
    - Implant integrity maintained to withstand load bearing
    - Stable fixation across the adjacent structures
  - Fixation

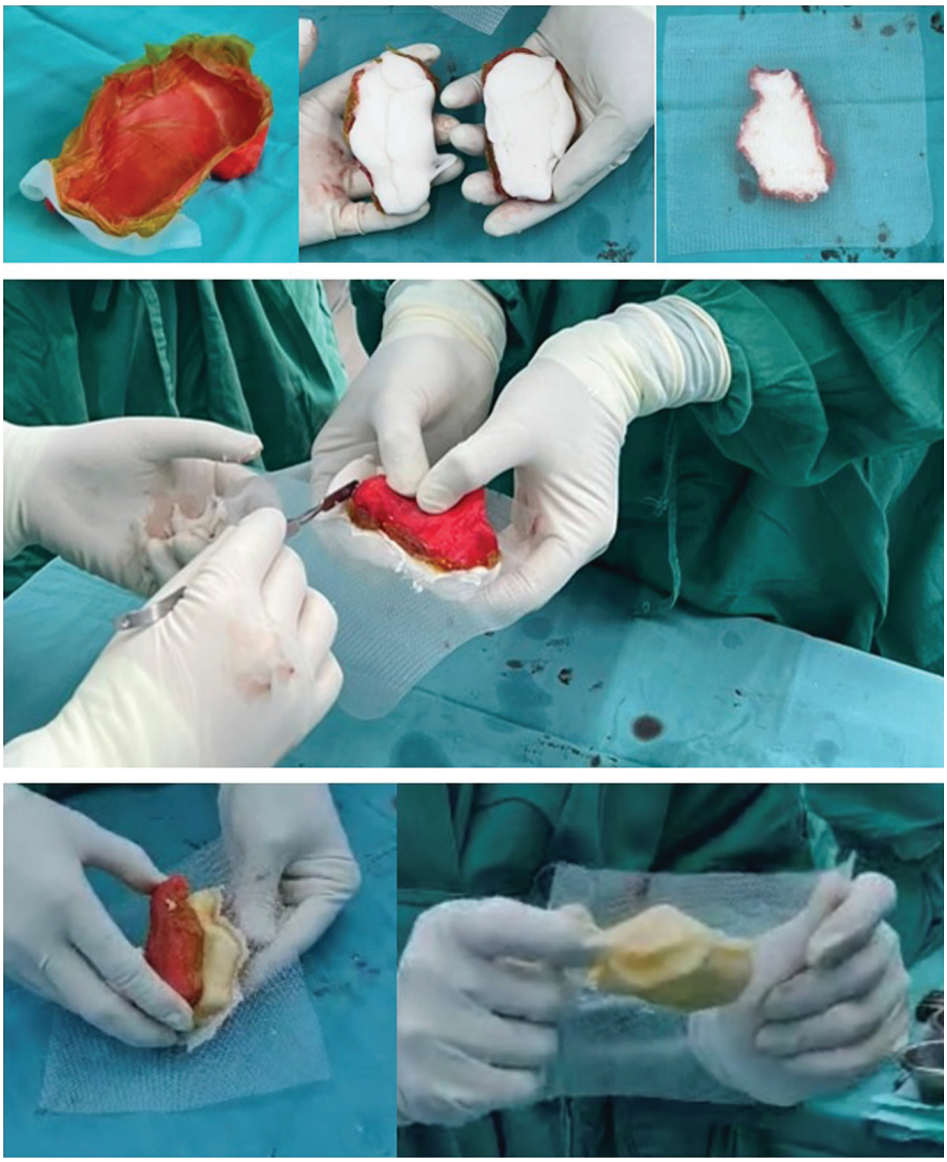


Fig. 6 Molding of the prototype calcaneal bone cement model (**A**) Mold lining with ioban and liquid paraffin (**B**) Both molds are then filled with a packet of standard bone cement each (**C**) A sheath of prolene mesh is placed between before clasping both together awaiting consolidation. (**D**) Clasping of both molds with cement and proline mesh while the assistant clears off the extruded cement. (**E**) Peeling the printed mold off the calcaneal cement (**F**) The cement calcaneum with the proline mesh incorporated in the center for soft tissue attachment.

    - Incremental drilling bit to avoid cement cracking
    - Use partially threaded screws without threads across the joint – to allow micro-gliding of the screws during ambulation
    - Prevent too many fixations surrounding the cement causing over rigidity
    - The quality, length, size, type and trajectories need to be pre-determined
    - Consider additional fixations to maintain good stability
  - Soft tissue reconstruction
    - Stable and strong fixation of the soft tissues, for example: Tendon Achilles and capsule over the calcaneo-cuboid joint.

- Complications
  - Infection: Both deep and superficial infection
  - Recurrence if margins are not clear
  - Skin flap necrosis
  - Implant fracture upon heavy weight bearing
  - Stiff joint leading to early onset of secondary osteoarthritis
  - Implant failure (screw fatigue)
- Uniqueness of the authors' technique compared with the standard technique

This method of indirect 3D printing can be reproduced and its cost is significantly less than that of direct metal 3D printing. The printing cost of the mold is minimal. The bulk of the cost is the bone cement used. This method enables an anatomical fit with near-physiological force distribution

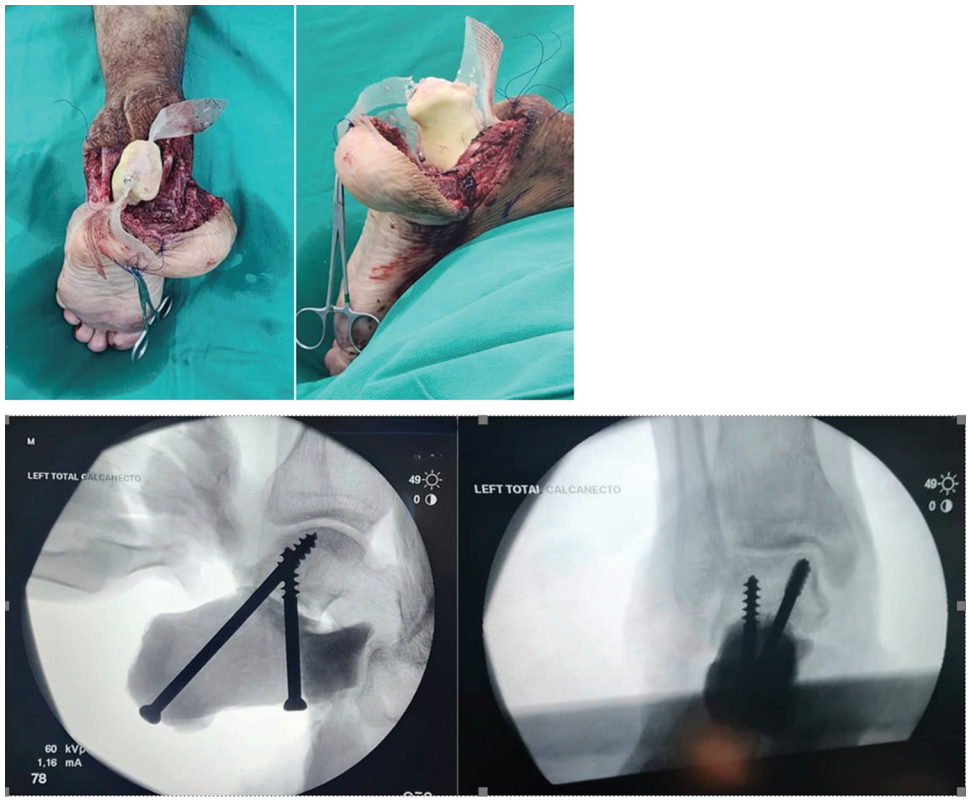


Fig. 7 The calcaneal cement inserted into the resected calcaneal space for reconstruction. (**A**) Posterior view (**B**) lateral view Intraoperative Image Intensifier images of both inserted cancellous screws. (**C**) Lateral view (**D**) AP view.



Fig. 8 Clinical picture of (**A**) bilateral foot from plantar (**B**) lateral view of foot and radiograph of (**C**) axial view of calcaneum and (**D**) lateral foot radiograph – at 9 months follow up post surgery.

during load bearing, rather than just an odd shaped cement spacer.

Discussion

A recurrence of a previously treated tumor, being malignant or an aggressive benign will necessitate a wider and more extensive resection – leaving behind a significant void. These voids will need to be filled to allow the distribution of forces for load bearing. The reconstruction requires a thorough 3D preoperative analysis for deformity or structural replacement, with the aim of restoring the hindfoot alignment allowing eventual ambulation via full load bearing. This complex void presents significant challenges, therefore the option of utilizing a 3D printing technology for the replacement aspect of the surgery. As replacement of the resected calcaneum is secondary, the primary importance is still maintaining clear margin resection of the recurrent tumor. Medical 3D printing was first introduced for an evaluation of intraarticular calcaneal fracture in 1997 by Kacl et al.[8] Despite the lapse of many years and the cost of production did reduce, however, the total cost in printing the entire calcaneum in titanium is still a significant financial burden to this age.[9] 3D printing has evolved over the years enabling pre-operative planning, pre-contouring plates, pre-shape plates, fabricating patient-specific guides etc.[9] Given the complexity of the foot and ankle – this method definitely helped in establishing a stable fixation and anatomical replacement without significant economical strain.

Final Considerations

This innovative approach not only promises functional recovery but also emphasizes patient comfort through reduced recovery times and enhanced anatomical fit. This is an efficient, economical and reproducible method for bony reconstruction after a complete or partial bony tumor resection. The evidence from a single case may not suffice to generate a conclusion – requires a series of cases, but this case throws light on a new novelty method that can be practiced effectively & economically. As this will set a precedent for future advancements in Orthopedic oncology worldwide especially in nations with financial constrain over health care.

Authors' Contributions

Each author contributed individually and significantly to the development of this article: GBHE, conceptualization, formal initiator, research, methodology, validation, visualization, writing of original draft, primary author, revision intrasubmission for publication. TKK, validation, editing, revision, 2nd read correction. AGP, validation, mentor, supervisor-trainer, editing, revision.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Letter to the Editor regarding "Anatomic Total Shoulder Arthroplasty Outcomes Were Not Negatively Affected by the COVID-19 Pandemic"

Carta ao editor sobre "Os desfechos da artroplastia anatômica total do ombro não foram afetados negativamente pela pandemia de COVID-19"

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Dear Editor,

The article "Anatomic Total Shoulder Arthroplasty Outcomes Were Not Negatively Affected by the COVID-19 Pandemic"[1] is the topic of discussion in this letter. In this study, the range of motion, strength, and results of physical therapy (PT) were compared in patients submitted to reverse total shoulder arthroplasty (RTSA) in 2019 and 2020. The findings demonstrated that forward elevation, external rotation, and internal rotation significantly improved in both groups. In contrast to the 2019 group, patients in 2020 underwent PT for a shorter period and completed fewer sessions. In 2020, however, at the last follow-up, patients reported a low mean pain score.

The comparatively small sample size of this study—24 patients in 2019 and 27 in 2020—is one of its shortcomings. This could induce bias and limit the application of the results. Furthermore, recall bias or the report of inaccuracies may result from the data collection strategy, namely due to the dependence on patient-reported measures during phone calls made in 2022.

In the future, it would be beneficial to carry out a bigger, randomized controlled trial to learn more about the variations in results among patients submitted to RTSA at different times. Furthermore, longitudinal research could be performed to evaluate the long-term impacts of PT duration and completion on patient outcomes. Future studies could investigate the causes of the decline in the number of completed PT sessions and their duration in 2020, as well as any effects this may have had on functional results and overall patient satisfaction. All things considered, this study offers insightful information on the results of RTSA patients and emphasizes how crucial it is to track PT length and completion to enhance outcomes.

Conflict of Interests

The authors have no conflict of interests to declare.

Reference

1 Stevens AJ, Patel AV, Gibbs D, Cvetanovich G, Bishop JY, Rauck RC. Anatomic Total Shoulder Arthroplasty Outcomes Were Not Negatively Affected by the COVID-19 Pandemic. Rev Bras Ortop 2024; 59(03):e429–e434

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MANUSCRIPT FORMAT

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Borges JLP, Milani C, Kuwajima SS, Laredo Filho J. Tratamento da luxação congênita de quadril com suspensório de Pavlik e monitorização ultra-sonográfica. Rev Bras Ortop 2002;37(1/2):5–12

2. Citing a chapter in a book:

Johnson KA. Posterior tibial tendon. In: Baxter D. The foot and ankle in sport. St Louis: Mosby; 1995. p. 43–51

3. Citing a book:

Baxter D. The foot and ankle in sport. St Louis: Mosby; 1995

4. Citing a thesis:

Laredo Filho J. Contribuição ao estudo clínico-estatístico e genealógico-estatístico do pé torto congênito equinovaro [thesis]. São Paulo: Universidade Federal de São Paulo colocar virgula Escola Paulista de Medicina; 1968

5. Citing a government publication:

Food and Drug Administration. Jin Bu Huan Herbal Tablets. Rockville, MD: National Press Office; April 15,

1994. Talk Paper T94-22

6. Citing na online article:

Lino Junior W, Belangero WD. Efeito do Hólmio YAG laser (Ho: YAG) sobre o tendão patelar de ratos após 12 e 24 semanas de seguimento. Acta Ortop Bras [periodical on the Internet] 2005 [cited 2005, Aug 27];13(2):[about 5 p.] Available from: http://www.scielo.br/ scielo

7. Citing a symposium article:

Eisenberg J. Market forces and physician workforce reform: why they may not work. Paper presented at: Annual Meeting of the Association of American Medical Colleges; October 28, 1995; Washington, DC

DIGITAL ARTWORK PREPARATION

General Guidelines

- It is best to use Adobe Photoshop to create and save images, and Adobe Illustrator for line art and labels.
- Do not submit art created in Microsoft Excel, Word, or PowerPoint. These files cannot be used by the typesetter.

- Save each figure in a separate file.
- Do not compress files.
- All black-and-white and color artwork should be at a resolution of 300 dpi (dots per inch) in TIFF format. Line art should be 1,200 dpi in EPS or TIFF format. Contact the Production Editor at Thieme if you are unsure of the final size.
- It is preferable for figures to be cropped to their final size (approximately 3½ inches for a single column and up to 7 inches for a double column), or larger, and in the correct orientation. If art is submitted smaller and then has to be enlarged, its resolution (dpi) and clarity will decrease.

  Note: Lower resolutions (less than 300 dpi) and JPEG format (.jpg extension) for grayscale and color artwork are strongly discouraged due to the poor quality they yield in printing, which requires 300 dpi resolution for sharp, clear, detailed images. JPEG format, by definition, is a lower resolution (compressed) format designed for quick upload on computer screens.

Black-and-White Art

- Black-and-white artwork can be halftone (or grayscale) photographs, radiographs, drawings, line art, graphs, and flowcharts. Thieme will only accept digital artwork.
- If possible, do not send color art for conversion to black-and-white. Do the conversion yourself so that you can check the results and confirm in advance that no critical details are lost or obscured by the change to black-and-white.
- For best results, line art should be black on a white background. Lines and type should be clean and evenly dark. Avoid screens or cross-hatching, as they can darken or be uneven in printing and lead to unacceptable printing quality.

Color Art

- All color artwork should be saved in CMYK, not RGB.

Art Labels

- Arrows, asterisks, and arrowheads (or other markers) should be white in dark or black areas and black in light or white areas, and large in size. If not, these highlighting marks may become difficult to see when figures are reduced in size during the typesetting process.
- Use 1-point (or thicker) rules and leader lines.
- Capitalize the first word of each label and all proper nouns. Consider using all capitals if you need a higher level of labels.
- Where there are alternate terms or spellings for a named structure, use the most common one and make sure it is consistent with what is used in the text.
- Avoid using multiple fonts and font sizes for the labels; use only one or two sizes of a serif font.

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