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Hip arthroscopy: Pathologies, surgical techniques and complications

Edited by
Carlos Suarez-Ahedo and Anell Olivos

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Hip arthroscopy: Pathologies, surgical techniques and complications

Topic editors

Carlos Suarez-Ahedo — National Institute of Rehabilitation Luis Guillermo Ibarra Ibarra, Mexico

Anell Olivos — Hospital Médica Sur, Mexico

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EDITED AND REVIEWED BY
Dror Lindner,
Shamir Medical Center (Assaf Harofeh), Israel

*CORRESPONDENCE
Carlos Suarez-Ahedo
✉ drsuarezahedo@gmail.com

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Editorial: Hip arthroscopy: Pathologies, surgical techniques and complications

Carlos Suarez-Ahedo*

Adult Hip & Knee Reconstruction Department, National Institute of Rehabilitation Luis Guillermo Ibarra Ibarra, Tlalpan, Mexico

KEYWORDS

hip, arthroscopy, arthroplasty, hip joint, hip pain

Editorial on the Research Topic
Hip arthroscopy: Pathologies, surgical techniques and complications

In the beginning, hip arthroscopy was mainly diagnostic, but a better understanding of the pathology, better examination techniques, and better imaging have led to increasing numbers of therapeutic procedures being performed and also led to the recognition of new pathologies, in a case report **Jian et al.** will show a patient with lateral hip pain who failed with conservative treatment, hip endoscopy was performed on this patient, resulting in significant improvement to regular daily and social activities in the mid-term.

Hip arthroscopy has been recognized as a surgical technique to treat bone deformity, periarticular soft tissue pathologies, and complications. However, it is important to recognize that OA and ONFH can be induced by exosomes which may play an important role as an inducer and serve as a promising treatment for early intervention, just like **LV et al.** showed us in its interesting review. The original research by **Yu et al.** demonstrates that there is a strong association between blood lipid metabolism and coagulation function with IONFH, which opens the door for future research.

Unfortunately, when the damage around the Hip is severe, a total hip replacement can be the only available treatment option that we can offer. as we already know, total hip replacement is the most successful and cost-effective orthopedic surgery, however, leg length discrepancy is one of the most common causes of a lawsuit after THR in the U.S.A. that is why the study presented by **Chen et al.** is important because they show that the horizontal calibrator provides more accurate limb length and femoral offset. however, when THR fails, one of its causes can be secondary to an acetabular defect, and a revision THR will be needed. The Systematic Review by **Cheng et al.** showed that using a jumbo cup is a recommended method for acetabular reconstruction in rTHA with satisfying clinical outcomes and survivorship.

Regarding surgical techniques, Li et al. presented an RCS that shows the importance of reconstructing the joint capsule and conjoint tendon to enhance muscle strength for the patient's best recovery. In its case report, **Gebhardt et al.** show us the importance of capsule closure to avoid iliopsoas tendon entrapment intraarticular.

The remaining article by **Shen et al.** looks into postoperative delirium in the geriatric population after hip surgery. The study proposes a prediction score that will enable delirium risk stratification for hip fracture patients and facilitate the development of strategies for delirium prevention.

This article series provides the most current information in a rapidly evolving field, according to the editorial board of Hip Arthroscopy: Pathologies, surgical techniques, and

complications. In this series of articles, we will discuss hip pathology and the various treatment options available.

Author contributions

This author contributed with revision of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Accuracy of the Horizontal Calibrator in Correcting Leg Length and Restoring Femoral Offset in Total Hip Arthroplasty

*Xing Chen[1], Shuxing Xing[1], Zhiyong Zhu[2], Huisheng Wang[2], Zhongshen Yu[2], Xizhuang Bai[2] and Xi Li[2]**

[1] Department of Orthopedic Surgery, Chengdu Fifth People's Hospital, The Fifth People's Hospital of Chengdu University of TCM, Chengdu, China, [2] Department of Orthopedics and Sports Medicine and Joint Surgery, Liaoning Provincial People's Hospital, People's Hospital of China Medical University, Shenyang, China

Background: Limb length discrepancy (LLD) is one of the most common postoperative complications and can cause serious consequences. Poor recovery of femoral offset (OD) will result in weakness of the patient's external rotator muscles and affect the patient's postoperative function. The study is aimed to present a simple approach that compensates for the shortcomings of previous measuring devices and combines the advantages of different measuring devices to provide more accurate limb length and femoral offset restoration in total hip arthroplasty (THA).

Methods: This study was a prospective controlled trial involving 89 patients with THA. Group I ($n = 44$) was used for intraoperative measurement of THA with our self-designed horizontal calibrator. Group II ($n = 45$) was measured by a traditional freehand technique. The main outcome indicators were measured on the Neusoft PACS, including LLD, femoral offset deviation, and operative time. IBM SPSS 23.0 was used for data analysis.

Results: The independent sample *t*-test was performed for all the data. The operative time, preoperative radiographic LLD, and OD of Group I and Group II had no statistical significance. Postoperative LLD of Group I and Group II were 2.5 ± 2.1 mm (range −5.7 to 8.3 mm) and 6.2 ± 4.3 mm (range −18.0 to 15.2 mm), and the independent sample *t*-test data of both ($P < 0.001$; 95%CI = −5.1, −2.2) showed statistical significance. In Group I, there were 38 THAs with LLD <5 mm, accounting for 86% and there were 44 THAs with LLD <10 mm, accounting for 100%. In Group II, there were 20 THAs with LLD <5 mm, accounting for 44%. There were 36 THAs with LLD <10 mm, covering for 80%. There was no significant difference in postoperative femoral offset and OD.

Conclusion: The horizontal calibrator can provide more accurate limb length and femoral offset recovery in THA. It is a simple surgical technique that does not add additionally surgical costs and does not significantly increase operative time, providing a new solution for surgeons to resolve postoperative LLD and restore femoral offset.

Keywords: hip arthroplasty, leg length discrepancy, offset, intraoperative, calibrator

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Carlos Suarez-Ahedo, Hospital Médica Sur, Mexico

Reviewed by:
Giovanni Solitro, Louisiana State University Health Shreveport, United States
Tsung-Yuan Tsai, Shanghai Jiao Tong University, China

****Correspondence:***
Xi Li
lixiseki@gmail.com

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INTRODUCTION

Total hip arthroplasty (THA) is the most successful and cost-effective orthopedic surgery for patients with end-stage hip arthritis that relieves pain, restores function and improves quality of life (1). Limb length discrepancy (LLD) is one of the most common causes of lawsuit after THA in the United States (2). LLD may lead to biomechanical changes in the hip joint, gait dysfunction, low back pain, sciatica, instability, and increased risk of dislocation (3). The incidence of LLD after primary THA has been reported to be 1–27%, with an average of 3–17 mm and a range of 3–70 mm (1, 4). The research results of Fujita et al. (5) showed that 7 mm might be a reasonable threshold to reduce residual discomfort.

Although preoperative and postoperative LLD can be reliably measured by clinical examination and radiographs, intraoperative assessment of LLD is difficult (4). Various measurement techniques have been used to evaluate limb length intraoperatively. The freehand technique is a widely used technique, but it reveals great interobserver and intraobserver variability (6). Preoperative templates are also widely used, and digital templates have emerged to make the operation more convenient and the results more accurate (7, 8). But studies have shown that in up to 60% of the cases, the preoperative template cannot accurately predict the correct size of the implant (9). Some studies have also reported the use of intraoperative radiography to assess limb length and offset, but the postural requirements are greatly high (10, 11). Intraoperative navigation may yield satisfying results, but its application is limited by the difficulty of finding anatomical navigation points in obese patients and the high price (6). Also some studies reported no difference in leg length balance between computer-assisted and conventional THAs (1). Most surgeons use a variety of devices to accurately measure the length of the neck and the angle of the osteotomy, as well as devices that are attached to the pelvis to determine changes in the length of the implant after it has been placed (12, 13). However, there are limitations in obese patients, and the complications of pelvic fixation have been reported (3, 14).

The mechanical relationship between the abductor tissue and the direction of the femur is known as femoral offset (OD). OD is the distance from the center of the femoral head to the shaft axis of the femoral component. Inadequate reduction of OD results in decreased abductor tension and subsequent instability, thereby affecting gait symmetry. In addition, inappropriate OD may increase the risk of instability due to bone impingement. Fackler and Pose found that femoral displacement was significantly reduced in patients with postoperative dislocation and concluded that lateral rather than distal femoral stalk displacement enhanced stability. Since OD recovery is not physically obvious to patients, it receives less attention intraoperatively than LLD, and therefore less intraoperatively verified (15, 16).

The method based on the change of the position of the reference point of the pelvis and femur is an effective way to minimize LLD and OD recovery. Although there are many devices designed according to this idea at the present such as: Double-Stitch Technique (17), L-shaped caliper (18), LOOD device (14), calipers dual pin retractor (19), they also have obvious disadvantages, such as susceptibility to changes in limb position, complex operation, poor measurement accuracy, inconsistent anchor points, muscle contracture, and soft tissue effects (1, 3, 4). This article proposes a simple method that compensates for the shortcomings of previous measuring devices (12, 13, 16, 17, 19–23) and combines the advantages of different measuring instruments (14, 18, 24–30) to provide more accurate limb length and recovery of OD. This technique involves careful preoperative planning combined with the intraoperative use of the Horizontal Calibrator plus a double reverse "U" pad. According to a review of the literature (12–14, 16–26, 28–33), no studies on the device have been published. We conducted a prospective controlled study in our hospital to evaluate the efficacy of this technique in reducing LLD and restoring OD after THA.

MATERIALS AND METHODS

Patients

This study was a prospective controlled study. Since there were no blind surgeons, so the use of a single blind. Due to measurement tool design, production, validation, and other reasons, the study was not randomized, yet was grouped according to the time of admission. All patients were informed of the risks and benefits of the trial, gave their consent and signed an informed consent. Inclusion criteria: hip osteoarthritis, development displasia hip, osteonecrosis of the femoral head. Exclusion criteria: proximal femur/acetabular fracture, hemorrhage, malignant tumor, local infection, lower limb bone dysplasia, scoliosis, hip revision, or body intolerance to surgery. This study was approved by the Ethics Committee of Liaoning Provincial People's Hospital and was registered in the Chinese Clinical Trial Registry (ChiCTR2000038040) on 09/09/2020, retrospectively registered. Between 2019 and 2021, we collected 89 THAs, all performed by the same orthopedic surgeon. All acetabular prostheses were Trilogy IT (Zimmer, Warsaw, In, USA), and all femoral prostheses were M\L Taper (Zimmer, Warsaw, In, USA), with a modular head. The choice of femoral prosthesis affects the judgment of limb length and femoral offset during operation. Different types of implants have different penetration depths and femoral offset, so the type and manufacturer of femoral implants need to be controlled so that they are not variable factors.

Measuring Technique

Radiological examination included an anteroposterior pelvic radiograph with 15° internal rotation of both lower extremities. Depending on the results of the physical examination, a lateral radiograph of the hip and plain radiographs of the spine from other perspectives may be required to detect rigid scoliosis. For LLD measurement, a reliable method is used to measure the vertical distance from the line connecting the lower edge of the two tear drops to the innermost edge of the small rotor. The difference between the measured values of the two sides is the LLD (10). OD is measured by the distance between the axis of femur and the center of the femoral head (**Figure 1**) (1, 12). To achieve the accuracy of the measurement, all the

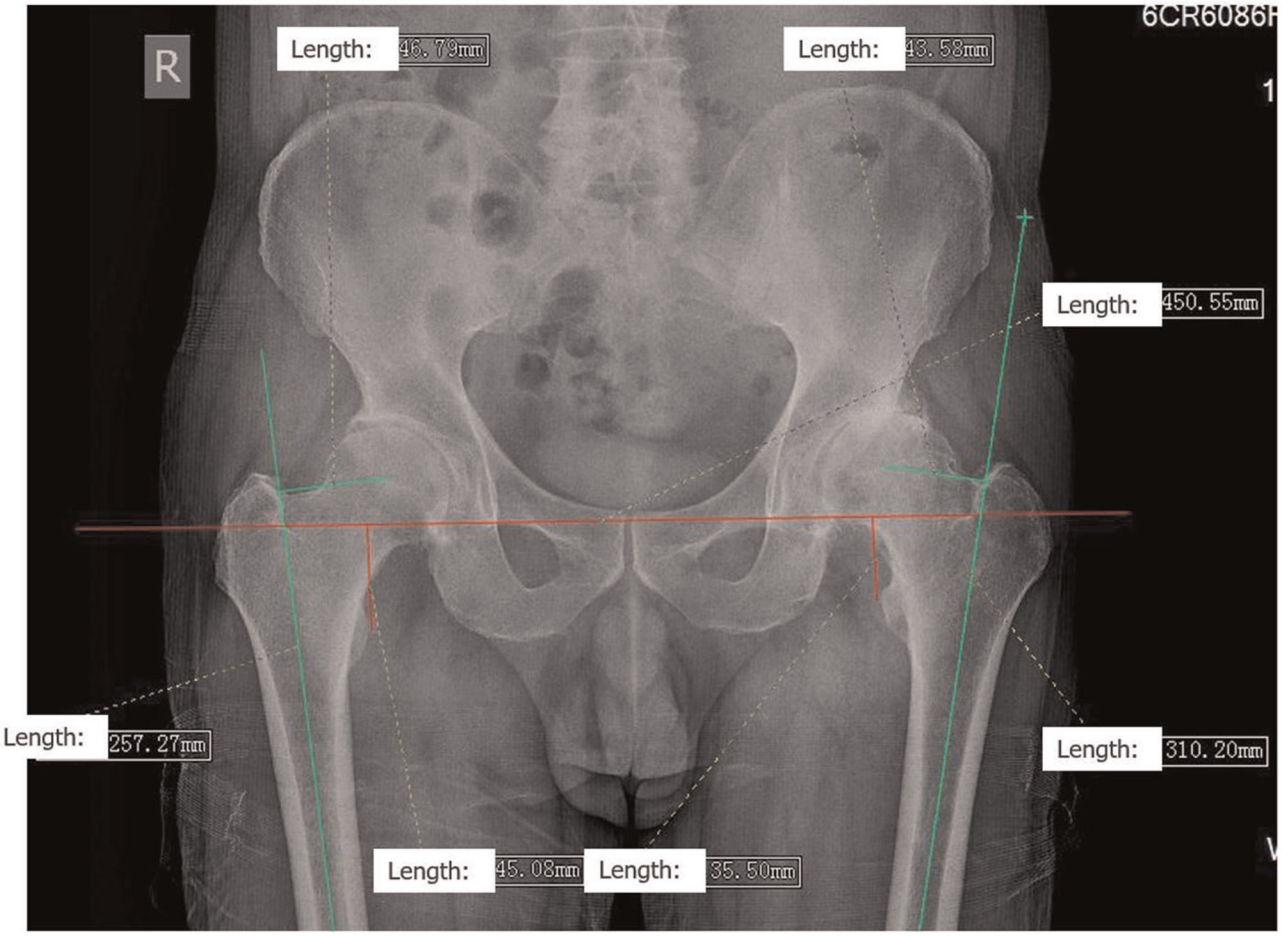

FIGURE 1 | Preoperative X-ray templating All data measurements were made on Neusoft PACS. An anteroposterior (AP) positive view of the pelvis was obtained with both lower extremities internally rotated at 15°. For LLD measurement, a reliable method is to measure the vertical distance from the line connecting the lower edge of the two teardrops to the innermost edge of the small rotor. The difference between the measured values of the two sides is the LLD. OD is measured by the distance between the axis of the femur and the center of the femoral head. In the figure, the LLD was 9.58 mm, the OD on the right was 46.79 mm, and the OD on the left was 43.58 mm.

measurements were carried out on Neusoft PACS (Neusoft Corp., China).

Surgical Technique

To achieve the ideal limb length during the operation, we used the horizontal calibrator plus a double-reverse "U" pad technique to measure the limb length (**Figures 3**, **4**). All operations were performed in the posterior lateral decubitus position. Before the surgery, the double-reverse "U" pad is placed between the legs so that the healthy leg is placed into the lower groove. After sterilizing the towel, the other parts except the acetabular side of the Steinman pin are installed and connected and then set aside (**Figure 4b**). After exposing and incising the pelvis–trochanter muscles, the limb is placed in an extended position with the affected leg in the upper groove, aligned with the axis of the body and parallel to the ground in order to reproduce this position as much as possible during surgery. At this point, the acetabular side of the Steinman pin was driven into the acetabulum 3–5 cm above the greater trochanter at 1 o'clock (right hip) or 11 o'clock (left hip) as a static reference point (**Figure 5a**). The surgeon looked for a bony projection in the middle of the intertrochanteric spine of the axis of the femur as a reference point, extending toward the most lateral part of the greater trochanter perpendicular to the axis of the femur for diathermic or suture mark (**Figure 5b**). The first connection is linked to the upper pelvis side of the Steinman pin, and then another Steinman pin is fixed to the second connection at the femoral side using the marker as a reference. The surgeon reconfirmed that both the legs were in the grooves of the double reverse "U" pad. The bubble level and extension rod were adjusted so that the bubble of the level is centered and the extension rod is parallel to the affected limb and the longitudinal axis of the body (**Figure 5c**). The locking screw was fixed sequentially, and the values were read and recorded (**Figure 5d**). The other parts except the lateral acetabular wire were removed and placed aside without disassembling, and the operation was continued. After the installation of the test model,

the measurement according to the above steps was repeated. If the limb needs to be lengthened or shortened, it can be adjusted directly according to the preoperative plan. The operative key is to select the correct size of the combination of the femoral component and the modular head so that this distance will be exactly or as close as possible to the differential length measured preoperatively.

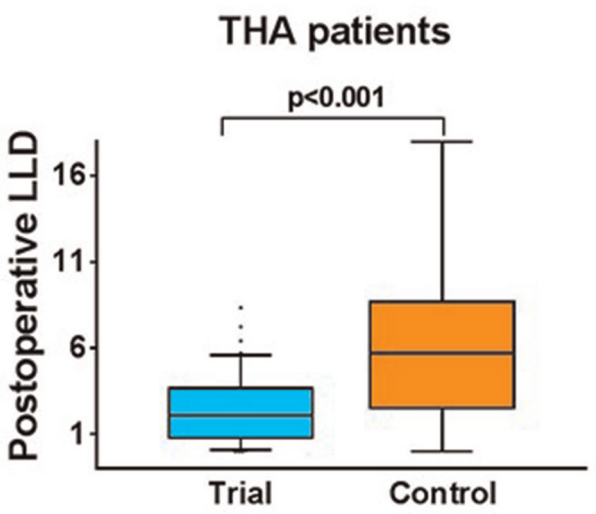

FIGURE 2 | Comparison of postoperative LLD between group I and group II.

Data Collection and Analysis

The basic information of the patients, the operation time, the anteroposterior radiographs of the pelvis before and 1–6 weeks after the operation were collected, and the femoral deviation and the difference and the LLD were measured and calculated (**Figure 1**). Pelvic radiographs were reviewed within 6 weeks after surgery because limb length had not been compensated and muscle strength had not been fully restored 1–6 weeks after surgery. Therefore, the data obtained are relatively real, avoiding the influence of other factors. All difference in the measurements were recorded as absolute values; however, compared to the opposite side, the range of values also includes negative values for shortening and positive values for lengthening. Two independent observers recorded all the data before and after the operation, respectively, and the final data was the average of the data recorded by them, which was statistically calculated by the third independent observer. SPSS 23.0(IBM Corp., USA) software was used for independent sample *T*-test for statistical analysis.

RESULTS

A total of 44 cases of THA were involved in Group I. About 59% of the patients were female, whose age and body mass index were 58.6 ± 9.4 years and 25.3 ± 3.3 kg/m^2, respectively. A total of 45 THAs were included in Group II, 78% of the patients were female, whose age and body mass index were 61.1 ± 11.5 years and 24 ± 3.4 kg/m^2, respectively. Age of both ($p = 0.483$; 95%CI = −6.9, 2.0) and body mass index ($p = 0.979$; 95%CI = −0.1, 2.7) were not statistically significant. The operative time of Group I and

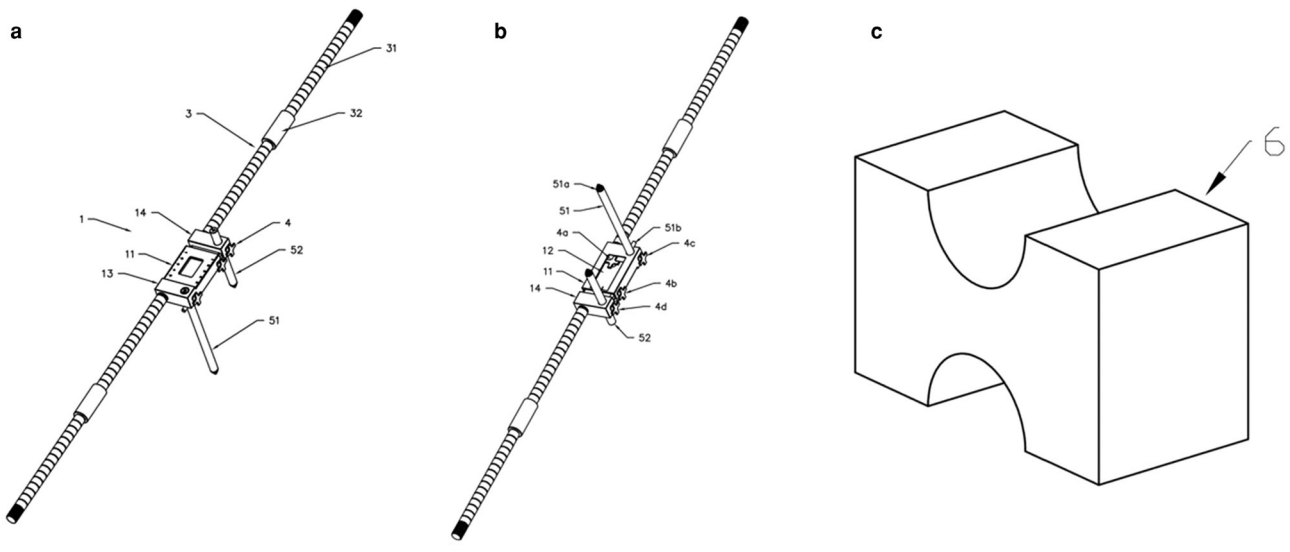

FIGURE 3 | Structure diagram of the horizontal calibrator **(a)** is the front structure diagram of the horizontal calibrator, and **(b)** is the reverse structure diagram. 1—Sliding Scale, 2—Bubble Level, 3—Extension Rod, 4—Lock Screw, 5—Steinman pin, 6—Limb Fixture; 11—first main ruler, 12—second main ruler; 13—First connecting part, 14—Second connecting part;111—0–6 cm ruler scale, 112—rectangular groove, 113—open accommodating groove, 114-lock hole; 121—6–12 cm ruler scale, 122—lock hole groove; 131—first horizontal hole groove, 132—first three-way hole; 141—second horizontal hole groove, 142—second three-way hole; 31—extension rod, 32—connecting cylinder; 41—Threaded joint, 42—Holding part; 51—Lateral pelvic long Steinman pin, 52—Femoral Steinman pin. **(c)** Double reverse "U" pad.

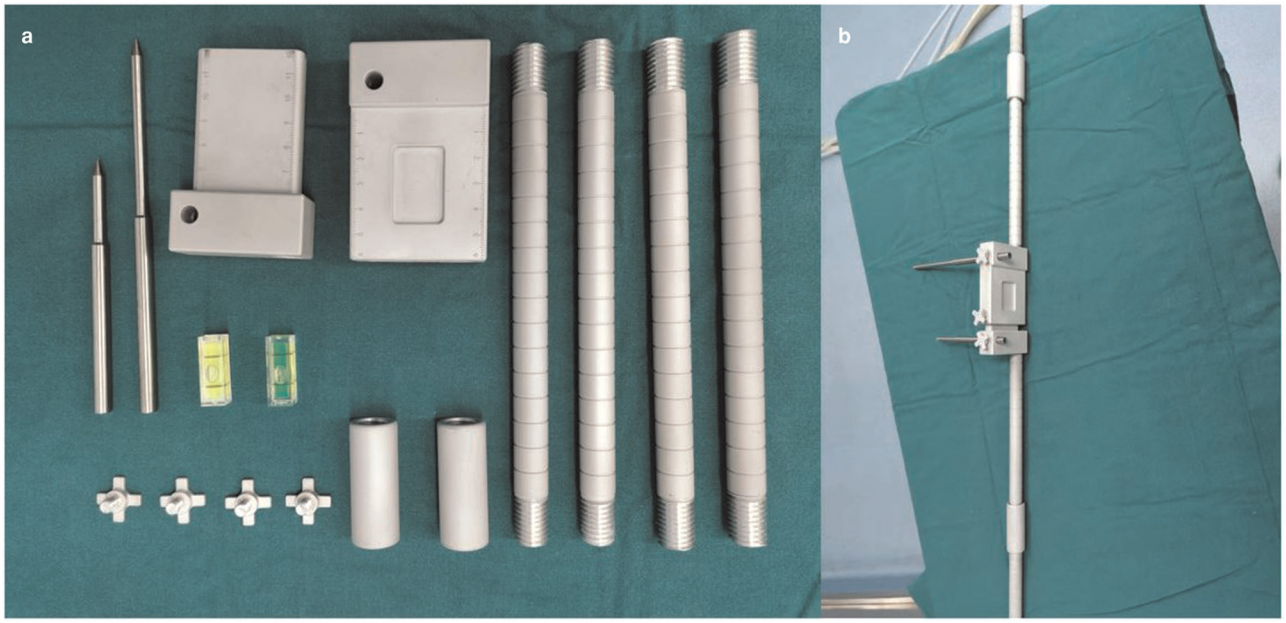

FIGURE 4 | Physical diagram of the horizontal calibrator. **(a)** Shows all the components of the horizontal calibrator. See **Figure 3** for details. **(b)** Shows the complete connected physical diagram of the horizontal calibrator, which was reserved preoperatively.

Group II ($p = 0.08$; 95%CI = −5.7, 12.9) were 83.4 ± 24.3 min and 79.8 ± 19.5 min, respectively, without statistical significance (**Table 1**). The preoperative radiographic LLD of Group I (mean ± SD = 9.6 ± 7.1 mm, range −51.0 to 19.7 mm) and Group II (mean ± SD = 10.0 ± 8.8 mm, range −21.9 to 32.0 mm) were examined by the independent *T*-test, and the data ($p = 0.686$; 95%CI = −3.8, 3.0) showed no statistically significant difference. There were 14 THAs with LLD <5 mm in Group I preoperatively, accounting for 32%. There were 29 cases with LLD <10 mm, accounting for 66%. In Group II, there were 17 cases with LLD <5 mm before operation, accounting for 38%. There were 26 cases with LLD <10 mm, accounting for 58%. Therefore, there was no significant difference in preoperative radiographic LLD between Group I and Group II. Postoperative LLD of Group I and Group II were 2.5 ± 2.1 mm (range −5.7 to 8.3 mm) and 6.2 ± 4.3 mm (range −18.0 to 15.2 mm), respectively. Independent *t*-test data of the two groups ($p < 0.001$; 95% CI = −5.1, −2.2) showed statistical significance (**Figure 2**). In Group I, 38 THAs with LLD <5 mm, covering for 86% and LLD <10 mm in 44 cases, covering for 100% were observed. In Group II after surgery, there were 20 THAs in LLD <5 mm, accounting for 44% and there were 36 cases with LLD <10 mm, accounting for 80% (**Table 2**).

After independent *T*-test of preoperative imaging OD of Group I (mean ± SD: 36.3 ± 6.2 mm, range 23.8–48.5 mm) and Group II (mean± SD: 36.3 ± 9.0 mm, range 17.8–57.3 mm), the data ($p = 0.052$; 95%CI = −3.2, 3.3) was not statistically significant. The imaging OD of Group I and Group II were (mean ± SD: 42.0 ± 6.1 mm, range 31.0–53.1 mm) and (mean ± SD: 43.9 ± 6.8 mm, range 30.4–56.7 mm), respectively. The independent *t*-test data of the two groups ($p = 0.548$; 95%CI = −4.6, 0.8) showed no statistical significance. In addition, we also conducted independent *t*-test analysis of the OD difference before and after surgery. Results of Group I (mean ± SD: 7.6 ± 5.9 mm, range −17.5 to 21.3 mm) and Group II (mean ± SD: 9.4 ± 7.1 mm, range −9.8 to 29.0 mm) showed no statistical significance ($p = 0.171$; 95%CI = −4.6, 1.0) (**Table 3**).

DISCUSSION

In our design, several aspects stand out. First, the design of the double-reverse "U" shape pad is added to solve the problem that the body position is susceptible to change during the measurement process. It refers to the idea of adding a cotton pad between the two legs by Huddleston (24). This design only replaces the bench that is normally placed between the calves and does not increase the time and complexity of the operation. Second, the position of the reference points on the pelvis and the femur is different, and the line between the two reference points is generally not parallel to the extension axis of the limb. Therefore, the limb elongation determined by previous methods does not match the real limb elongation. In our design, extension bars are added on both sides of the calibrator, which can effectively keep the limb in the same horizontal position during the intraoperative measurement. The extension rod has been attached before the skin is cut and does not increase the time spent in the position. Shiramizu et al. (18) also expressed similar views. Third, to avoid changes in the position of the pelvis and the femur side, we chose the two points as fixed points. On the pelvic side, the insertion point of the Steinman pin was selected at 1 o'clock (right hip) or 11 o'clock (left hip) of the acetabulum, and it was 3–5 cm above the greater trochanter, which was close to the center of hip rotation. Many studies have shown that the closer

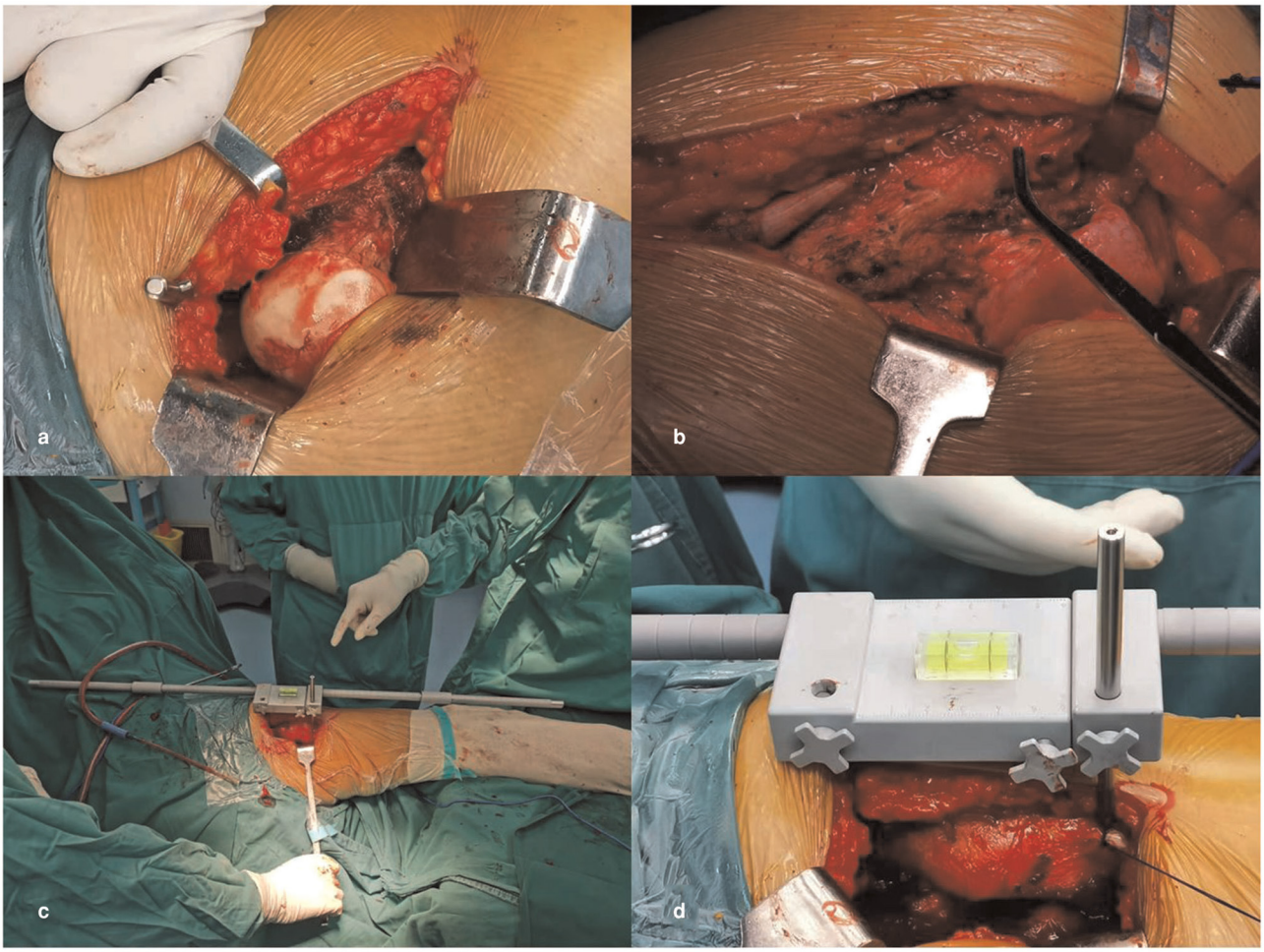

FIGURE 5 | Intraoperative measurement of the horizontal calibrator. A lateral acetabular wire was inserted 3–5 cm above the greater trochanter at 1 o 'clock (right hip) or 11 o 'clock (left hip) as a static reference point in **(a)**. The surgeon looks for a bony projection in the middle of the intertrochanteric spine of the femoral shaft as a reference point in **(b)**. It was made sure that both lower legs are in the grooves of the double reverse "U" pad. The bubble level and extension rod were adjusted so that the bubble of the level is centered and the extension rod is parallel to the affected limb and the longitudinal axis of the body **(c)**. The locking screw was fixed sequentially, the values were read and recorded **(d)**.

TABLE 1 | Baseline table of patients.

Types	Group I ($n = 44$)	Group II ($n = 45$)	p	95%CI
Age (years)	58.61± 9.37	61.07± 11.54	0.483	−6.89, 1.98
Female (%)	59%	78%		
Body mass index (Kg/m^2)	25.27 ± 3.32	24± 3.35	0.979	−0.14, 2.67
Operation time (minutes)	83.39± 24.3	79.8± 19.52	0.08	−5.69, 12.86

the acetabular measurement point is to the center of rotation, the smaller the measurement error (13, 34). Ranawat et al. (25) also described placing the Steinmann pin vertically in the groove below the ischium of the acetabulum and thus close to the center of rotation. This has been shown to reduce measurement error, even though small changes in limb position, result in a mean postoperative LLD of 2.6 mm. The selected point on the femoral side is a bony process in the middle of the intertrochanteric spine as the reference point and the intersection point extending to the most lateral part of the greater trochanter perpendicular to the axis of the femur. Fourth, in the sliding body part of the calibrator, we have a scale with an accuracy of 1 mm so that the increased or decreased limb length during the operation can be directly viewed, and also the measurement process can be fully quantified. LOOD device described by Barbier et al. (14) and L-shaped calipers described by Shiramizu et al. (18), although they also have scales, have a poor accuracy and can only roughly estimate the measured length. Fifth, a bubble level is placed above the main body of the calibrator so that the calibrator is always parallel to the ground during the measurement process, which adds a second insurance for the measurement. Rice et al. (30) also described that the horizontal bubble meter can make the measurement more accurate. Sixth, to avoid the loosening of the needle, we added a thread at the end. Takigami et al. (19) adopted

TABLE 2 | Comparison of radiographic LLD.

Groups	Mean ± SD (mm)	Range (mm)	<5 mm	<10 mm	*P*	95%CI
Preoperative Group I	9.55 ± 7.05	−51.03–19.68	*n* = 14(32%)	*n* = 29(66%)	0.686	−3.76, 2.95
Preoperative Group II	9.95 ± 8.76	−21.94–32	*n* = 17(38%)	*n* = 26(58%)		
Postoperative Group I	2.51 ± 2.09	−5.71–8.34	*n* = 38(86%)	*n* = 44(100%)	<0.001	−5.07, −2.21
Postoperative Group II	6.15 ± 4.29	−17.98–15.16	*n* = 20(44%)	*n* = 36(80%)		

TABLE 3 | Comparison of radiographic OD.

Groups	Mean ± SD (mm)	Range (mm)	*P*	95%CI
Preoperative Group I	36.29 ± 6.2	23.8–48.45	0.052	−3.23, 3.29
Preoperative Group II	36.26 ± 8.99	17.8–57.27		
Postoperative Group I	41.99 ± 6.1	30.98–53.1	0.548	−4.62, 0.82
Postoperative Group II	43.89 ± 6.79	30.44–56.73		
Difference Group I	7.61 ± 5.94	−17.47–21.29	0.171	−4.56, 0.97
Difference Group II	9.4 ± 7.12	−9.78–28.99		

a triangular-shaped design with double needles and screw ends to avoid intraoperative loosening of the measuring device, but at the same time increased surgical trauma.

Preoperative planning and surgical precision are important factors for THA success. How to minimize LLD while maintaining hip stability is a common challenge. Many studies (11, 13, 14, 16–25, 27–37) have been published to describe techniques for LLD management. Freehand techniques are widely used, including intraoperative clinical assessment of soft tissue tension and comparison with contralateral leg position. The literature has identified 933 cases of primary THA in which the freehand technique was used for intraoperative limb balance, with a mean postoperative LLD of 4.42 mm (16). Intraoperative procedures assessing soft tissue tension as an indicator of limb length, such as the Shuck or Dropkick test, may be biased by the patient's position or even the type of anesthesia (38). The dependent position is reproduced when compared to the contralateral leg, and a single palpation marker through asepsis may be inaccurate (39).

The method (12–14, 16–26, 28–33) based on the change of the position of the reference point of the pelvis and femur is an effective way to minimize LLD. A review by Desai et al. (4) concluded that intraoperative calipers combined with preoperative templates is a reliable method to overcome postoperative LLD after THA. The average LLD calculated using intraoperative calipers in literature was 2.89 mm. Shiramizu et al. (18) reported straight calipers and improved L-calipers, and conducted a prospective study of 100 THAs. The results showed that the mean value of L-calipers group was 1.7 ± 1.6 mm, and the mean value of the straight calipers group was 6.2 ± 4.1 mm. Enke et al. (16) made a single incision on the ilium and the most lateral margin of the greater trochanter as a reference point, and conducted a retrospective study of 101 cases of unilateral THA. The results showed that the mean absolute difference (LLD) of the leg length after surgery was 2.51 mm, and the mean deviation difference was 2.39 mm. Nevertheless, this method is far from the center of acetabular rotation, which increases measurement error and additional trauma. Gupta and Papadopoulos et al. (12, 17) described a double-stitch technology, that is, tie a knot with silk thread on the skin about 10 cm from the proximal end of the great trochanter, and then draw the other end with vascular forceps to make a diathermic mark on the most lateral edge of the great trochanter. They performed 60 THAs using this technique and showed a mean postoperative LLD of 1.58 mm (range −8 mm to 7 mm). The technique is simple but susceptible to soft tissue and 3D space.

Inadequate OD reduces soft tissue tension and increases the risk of dislocation. Restoring this soft tissue tension by increasing the length of the femoral neck may increase the length of the leg. A large offset increases the risk of rotor bursitis and adduction tendinitis. The average cervical stem angle of adult males was 129.6°(range 113.2°-148.2°) and that of adult females was 131.9°(range 107.1°-151.9°). Patients with cervical stem value significantly lower than this value could have hip varus, and vice versa (3). Woolson et al. (40) argued that excessive leg lengthening to increase stability was unacceptable. Contrary to the rationalization of the theory that inadequate soft tissue tone leads to increased postoperative stability, their study found that patients with short legs did not have an increased incidence of postoperative dislocation compared with patients with long or similar legs. Studies have confirmed that abnormal lever arms increase the wear of polyethylene in the prosthesis, which may lead to aseptic loosening (12). Kurtz (13) described the *in situ* femur measurement technique, which refers to the implantation of the femoral prosthesis before the femoral neck osteotomy without dislocation of the hip joint so that the implanted femoral prosthesis can be used to measure the LLD and OD. Ninety-three patients (100 hips) were treated with this technique and the difference between the *in situ* measurements and the preoperative and postoperative radiographic measurements was a mean leg length of 0.1 mm and a OD of 0.4 mm. This method is as close as possible to the rotation center of the hip joint, and the fixation pins on the acetabulum are not easy to come off. But the technology's complexity has limited its widespread use. Although our technique did not show statistically significant differences in the recovery of OD, our Group I patients performed better than Group II after surgery. Next, we will continue to improve the device by installing

a vortex-like structure on the measuring body to accurately measure the femoral offset.

There are some flaws in our study. First of all, the outcome indicators in our study only collected imaging and basic patient information, without measuring structural limb length and functional scoring. We simply pursued the absolute equality of the limbs in imaging, ignoring the patient's feelings. The study of Fujita et al. (5) showed that patients with little or no LLD after THA still felt uncomfortable with their leg length due to residual pelvic inclination. Secondly, although we added extension rods and double-reverse "U" shaped pads to ensure that the patient's position did not change, for some obese patients, it was still not possible to ensure that their position did not change during the operation because the side stopper could not be fixed. Finally, our technique still requires a learning curve, adding 3–5 min to the traditional method.

CONCLUSION

The horizontal calibrator can provide more accurate limb length and femoral offset recovery in THA. It is a simple surgical technique that does not add additional surgical costs and does not significantly increase operative time, providing a new solution for surgeons to resolve postoperative LLD and restore femoral offset.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Liaoning Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

1. Sculco PK, Austin MS, Lavernia CJ, Rosenberg AG, Sierra RJ. Preventing leg length discrepancy and instability after total hip arthroplasty. *Instr Course Lect*. 65:225–41 (2016).
2. Bokshan SL, Ruttiman RJ, DePasse JM, Eltorai AEM, Rubin LE, Palumbo MA, Daniels AH. Reported litigation associated with primary hip and knee arthroplasty. *J Arthroplasty*. (2017) 32:3573–7 e3571. doi: 10.1016/j.arth.2017.07.001
3. Kayani B, Pietrzak J, Hossain FS, Konan S, Haddad FS. Prevention of limb length discrepancy in total hip arthroplasty. *Br J Hosp Med*. (2017) 78:385–90. doi: 10.12968/hmed.2017.78.7.385
4. Desai AS, Dramis A, Board TN. Leg length discrepancy after total hip arthroplasty: a review of literature. *Curr Rev Musculoskelet Med*. (2013) 6:336–41. doi: 10.1007/s12178-013-9180-0
5. Fujita K, Kabata T, Kajino Y, Tsuchiya H. Optimizing leg length correction in total hip arthroplasty. *Int Orthop*. (2020) 44:437–43. doi: 10.1007/s00264-019-04411-0
6. Nossa JM, Munoz JM, Riveros EA, Rueda G, Marquez D, Perez J. Leg length discrepancy after total hip arthroplasty: comparison of 3 intraoperative measurement methods. *Hip Int*. (2018) 28:254–8. doi: 10.5301/hipint.5000577
7. Grobler G, Nortje M, Dower B, Chivers D. A Vertical measurement system to predict the change in leg length in total hip arthroplasty. *Arthroplasty today*. (2020) 6:330–7. doi: 10.1016/j.artd.2020.04.008
8. Jassim SS, Ingham C, Keeling M, Wimhurst JA. Digital templating facilitates accurate leg length correction in total hip arthroplasty. *Acta Orthopaedica Belgica*. (2012) 78:344–9
9. Knight JL, Atwater RD. Preoperative planning for total hip arthroplasty. Quantitating its utility and precision. *J Arthroplasty*. (1992) 7:403–9. doi: 10.1016/S0883-5403(07)80031-3
10. Debbi EM, Rajaee SS, Mayeda BF, Penenberg BL. Determining and achieving target limb length and offset in total hip arthroplasty using intraoperative digital radiography. *J Arthroplasty*. (2020) 35:779–85. doi: 10.1016/j.arth.2019.10.003
11. Ezzet KA, McCauley JC. Use of intraoperative X-rays to optimize component position and leg length during total hip arthroplasty. *J Arthroplasty*. (2014) 29:580–5. doi: 10.1016/j.arth.2013.08.003
12. Papadopoulos DV, Koulouvaris P, Aggelidakis GC, Tsantes AG, Lykissas MG, Mavrodontidis A. Intraoperative measurement of limb lengthening during total hip arthroplasty. *Indian J Orthop*. (2017) 51:162–7. doi: 10.4103/0019-5413.201716
13. Kurtz WB. In situ leg length measurement technique in hip arthroplasty. *J Arthroplasty*. (2012) 27:66–73. doi: 10.1016/j.arth.2011.02.003
14. Barbier O, Ollat D, Versier G. Interest of an intraoperative limb-length and offset measurement device in total hip arthroplasty. *Orthop Traumatol Surg Res*. (2012) 98:398–404. doi: 10.1016/j.otsr.2012.02.004
15. Fackler CD, Poss R. Dislocation in total hip arthroplasties. *Clin Orthop Relat Res*. (1980) (151):169–78. doi: 10.1097/00003086-198009000-00023
16. Enke O, Levy YD, Bruce WJ. Accuracy of leg length and femoral offset restoration after total hip arthroplasty with the utilisation of an intraoperative calibration gauge. *Hip Int*. (2020) 30:296–302. doi: 10.1177/1120700019836383
17. Gupta R, Pathak P, Singh R, Majumdar KP. Double-stitch technique: a simple and effective method to minimize limb length discrepancy after total hip arthroplasty. *Indian J Orthop*. (2019) 53:169–73. doi: 10.4103/ortho.IJOrtho_188_18
18. Shiramizu K, Naito M, Shitama T, Nakamura Y, Shitama H. L-shaped caliper for limb length measurement during total hip arthroplasty. *J Bone Joint Surg Br Vol*. (2004) 86:966–9. doi: 10.1302/0301-620X.86B7.14587
19. Takigami I, Itokazu M, Itoh Y, Matsumoto K, Yamamoto T, Shimizu K. Limb-length measurement in total hip arthroplasty using a calipers dual pin retractor. *Bull NYU Hosp Joint Dis*. 66:107–10 (2008)
20. Knight WE. Accurate determination of leg lengths during total hip replacement. *Clin Orthop Relat Res*. (1977) 123:27–8. doi: 10.1097/00003086-197703000-00010
21. Bose WJ. Accurate limb-length equalization during total hip arthroplasty. *Orthopedics*. (2000) 23:433–6
22. Desai AS, Connors L, Board TN. Functional and radiological evaluation of a simple intra operative technique to avoid limb length discrepancy

in total hip arthroplasty. *Hip Int.* (2011) 21:192–8. doi: 10.5301/hip.2011.6514
23. Woolson ST, Harris WH, A. method of intraoperative limb length measurement in total hip arthroplasty. *Clin Orthop Relat Res.* (1985) 194:207–10. doi: 10.1097/00003086-198504000-00032
24. Huddleston HD. An accurate method for measuring leg length and hip offset in hip arthroplasty. *Orthopedics.* (1997) 20:331–2. doi: 10.3928/0147-7447-19970401-10
25. Ranawat CS, Rao RR, Rodriguez JA, Bhende HS. Correction of limb-length inequality during total hip arthroplasty. *J Arthroplasty.* (2001) 16:715–20. doi: 10.1054/arth.2001.24442
26. Naito M, Ogata K, Asayama I. Intraoperative limb length measurement in total hip arthroplasty. *Int Orthop.* (1999) 23:31–3. doi: 10.1007/s002640050298
27. Ng VY, Kean JR, Glassman AH. Limb-length discrepancy after hip arthroplasty. *J Bone Joint Surg Am Vol.* (2013) 95:1426–36. doi: 10.2106/JBJS.L.00433
28. Desai A, Barkatali B, Dramis A, Board TN, A. simple intraoperative technique to avoid limb length discrepancy in total hip arthroplasty. *Surgeon.* (2010) 8:119–21. doi: 10.1016/j.surge.2009.10.023
29. McGee HM, Scott JH, A. simple method of obtaining equal leg length in total hip arthroplasty. *Clin Orthop Relat Res.* (1985) (194):269–70. doi: 10.1097/00003086-198504000-00042
30. Rice IS, Stowell RL, Viswanath PC, Cortina GJ. Three intraoperative methods to determine limb-length discrepancy in THA. *Orthopedics.* (2014) 37:e488–495. doi: 10.3928/01477447-20140430-61
31. Ranawat CS, Rodriguez JA. Functional leg-length inequality following total hip arthroplasty. *J Arthroplasty.* (1997) 12:359–64. doi: 10.1016/S0883-5403(97)90190-X
32. Itokazu M, Masuda K, Ohno T, Itoh Y, Takatsu T, Wenyi Y. A simple method of intraoperative limb length measurement in total hip arthroplasty. *Bulletin* 56:204–5 (1997).
33. Matsuda K, Nakamura S, Matsushita T, A. simple method to minimize limb-length discrepancy after hip arthroplasty. *Acta Orthop.* (2006) 77:375–9. doi: 10.1080/17453670610046280
34. Tagomori H, Kaku N, Tabata T, Tsumura H, A. new and simple intraoperative method for correction of leg-length discrepancy in total hip arthroplasty. *J Orthopaedics.* (2019) 16:405–8. doi: 10.1016/j.jor.2019.04.007
35. Sarin VK, Pratt WR, Bradley GW. Accurate femur repositioning is critical during intraoperative total hip arthroplasty length and offset assessment. *J Arthroplasty.* (2005) 20:887–91. doi: 10.1016/j.arth.2004.07.001
36. Halai M, Gupta S, Gilmour A, Bharadwaj R, Khan A, Holt G. The Exeter technique can lead to a lower incidence of leg-length discrepancy after total hip arthroplasty. *Bone Joint J.* (2015) 97-B:154–9. doi: 10.1302/0301-620X.97B2.34530
37. Alazzawi S, Douglas SL, Haddad FS, A. novel intra-operative technique to achieve accurate leg length and femoral offset during total hip replacement. *Ann R Coll Surg Engl.* (2012) 94:281–2. doi: 10.1308/rcsann.2012.94.4.281a
38. Sathappan SS, Ginat D, Patel V, Walsh M, Jaffe WL, Di Cesare PE. Effect of anesthesia type on limb length discrepancy after total hip arthroplasty. *J Arthroplasty.* (2008) 23:203–9. doi: 10.1016/j.arth.2007.01.022
39. Xue E, Su Z, Chen C, Wong PK, Wen H, Zhang Y. An intraoperative device to restore femoral offset in total hip arthroplasty. *J Orthop Surg Res.* (2014) 9:58. doi: 10.1186/s13018-014-0058-7
40. Della Valle CJ, Di Cesare PE. Complications of total hip arthroplasty: neurovascular injury, leg-length discrepancy, and instability. *Bulletin.* (2001) 60:134–42.

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CORRECTION
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Corrigendum: Accuracy of the Horizontal Calibrator in Correcting Leg Length and Restoring Femoral Offset in Total Hip Arthroplasty

*Xing Chen[1], Shuxing Xing[1], Zhiyong Zhu[2], Huisheng Wang[2], Zhongshen Yu[2], Xizhuang Bai[2] and Xi Li[2]**

[1]Department of Orthopedic Surgery, Chengdu Fifth People's Hospital, The Fifth People's Hospital of Chengdu University of TCM, Chengdu, China, [2]Department of Orthopedics and Sports Medicine and Joint Surgery, Liaoning Provincial People's Hospital, People92s Hospital of China Medical University, Shenyang, China

Keywords: hip arthroplasty, leg length discrepancy, offset, intraoperative, calibrator

A Corrigendum on

Accuracy of the Horizontal Calibrator in Correcting Leg Length and Restoring Femoral Offset in Total Hip Arthroplasty

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***Correspondence:**
Xi Li
lixiseki@gmail.com

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1. In the original article, there was an error in "MATERIALS AND METHODS " section, "Measuring Technique" sub-section, Paragraph one, Line 10–12 : "OD is measured by the distance between the axis of femur and the center of the femoral head (**Figures 1**, **2**) (1, 12)."

A correction has been made to "MATERIALS AND METHODS " section, "Measuring Technique" sub-section, Paragraph one, Line 10–12 : "OD is measured by the distance between the axis of femur and the center of the femoral head (**Figure 1**) (1, 12)."

2. In the original article, there was an error in "RESULTS " section, Paragraph one, Line 24–26 : "Independent *t*-test data of the two groups ($p < 0.001$; 95% CI = −5.1, −2.2) showed statistical significance (**Figure 5**)."

A correction has been made to "RESULTS "section, Paragraph one, Line 24–26 : "Independent *t*-test data of the two groups ($p < 0.001$; 95% CI = −5.1, −2.2) showed statistical significance (**Figure 2**)."

3. In the original article, there was a mistake in the legend for "**FIGURE 4**" as published : "Physical diagram of the horizontal calibrator. (**a**) Shows all the components of the horizontal calibrator. See **Figure 2** for details. (**b**) Shows the complete connected physical diagram of the horizontal calibrator, which was reserved preoperatively."

The correct legend appears below:

"Physical diagram of the horizontal calibrator. (**a**) Shows all the components of the horizontal calibrator. See **Figure 3** for details. (**b**) Shows the complete connected physical diagram of the horizontal calibrator, which was reserved preoperatively."

The authors apologize for these errors and state that these do not change the scientific conclusions of the article in any way. The original article has been updated.

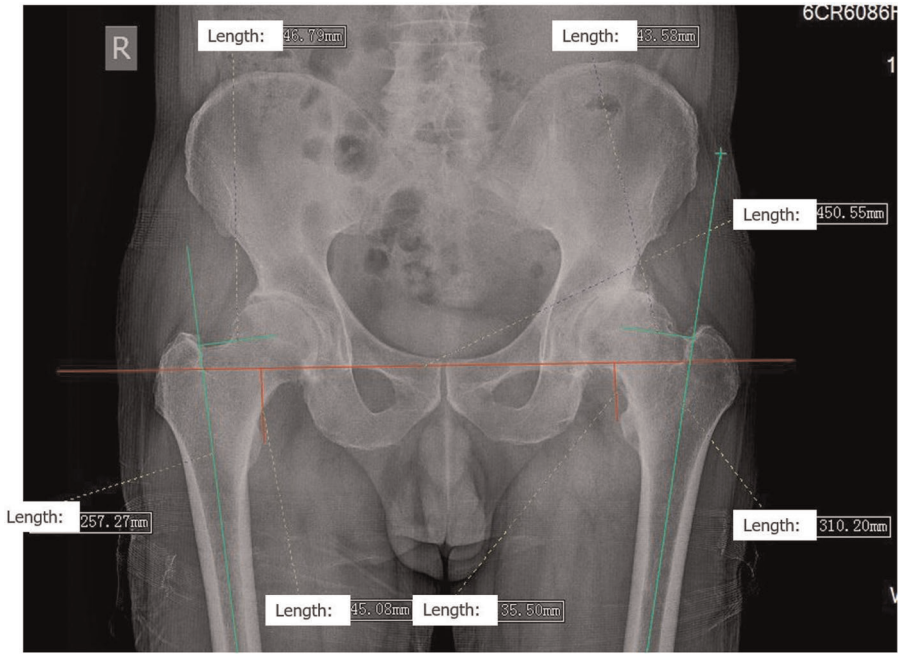

FIGURE 1 |

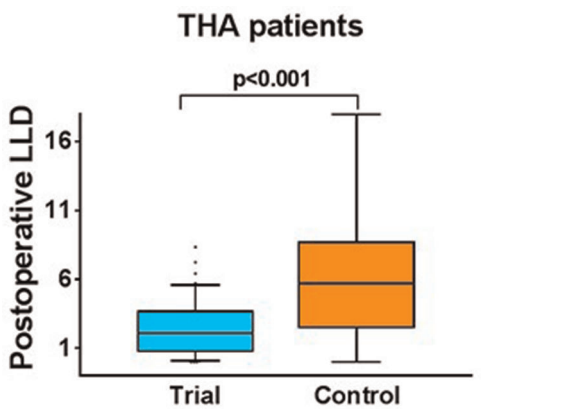

FIGURE 2 |

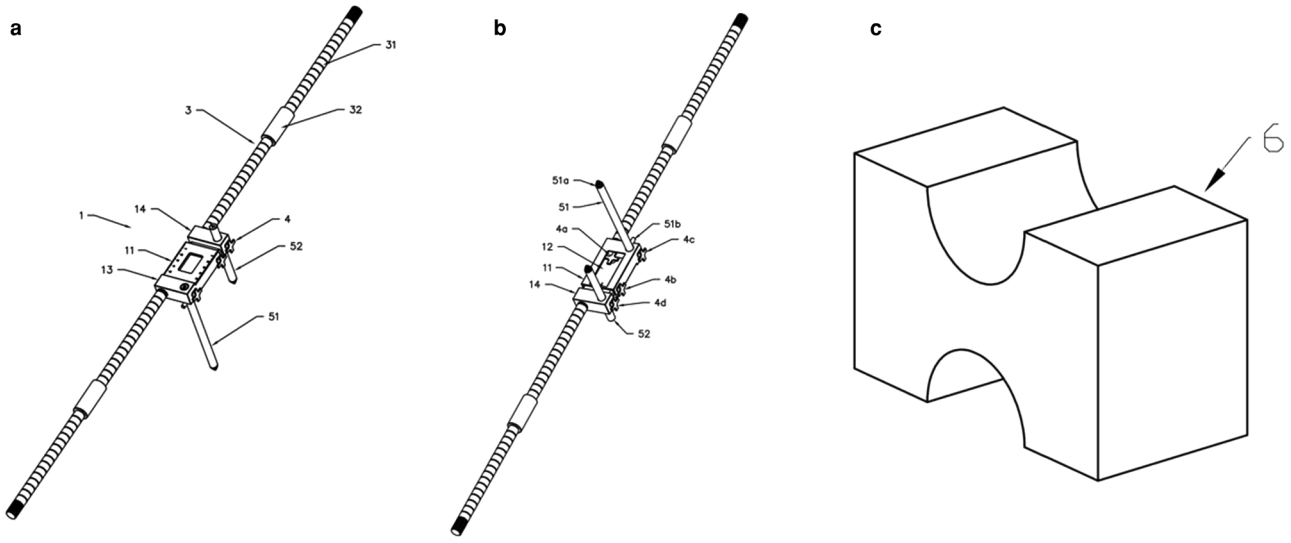

FIGURE 3 |

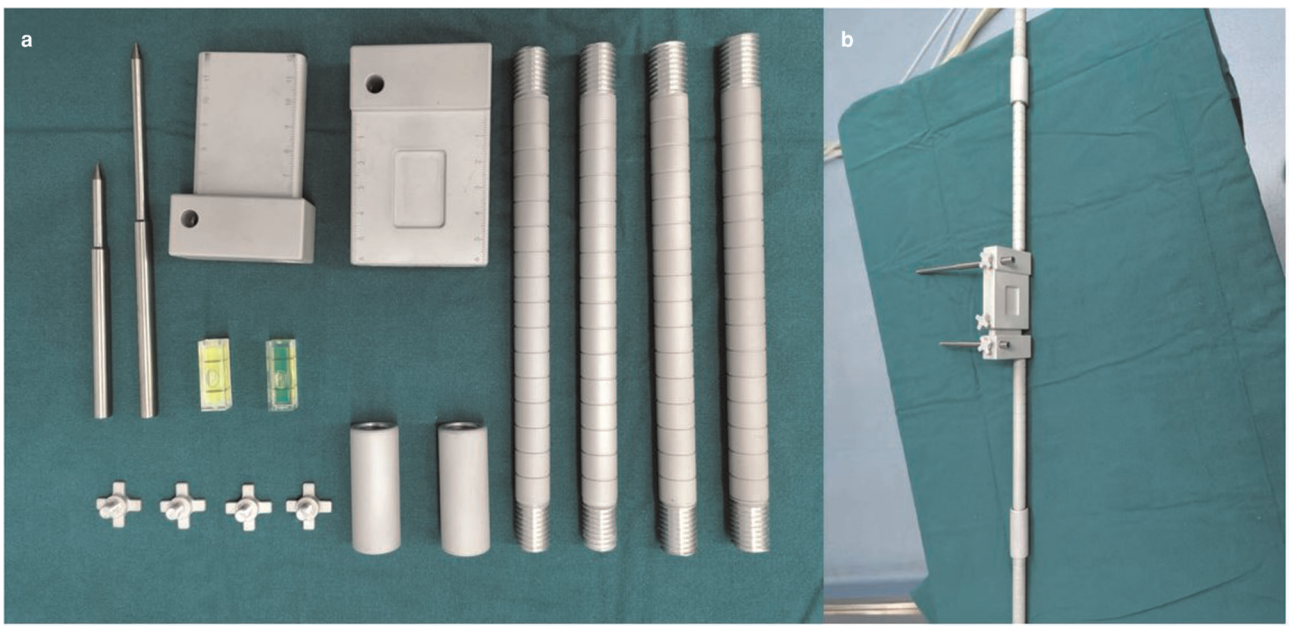

FIGURE 4 |

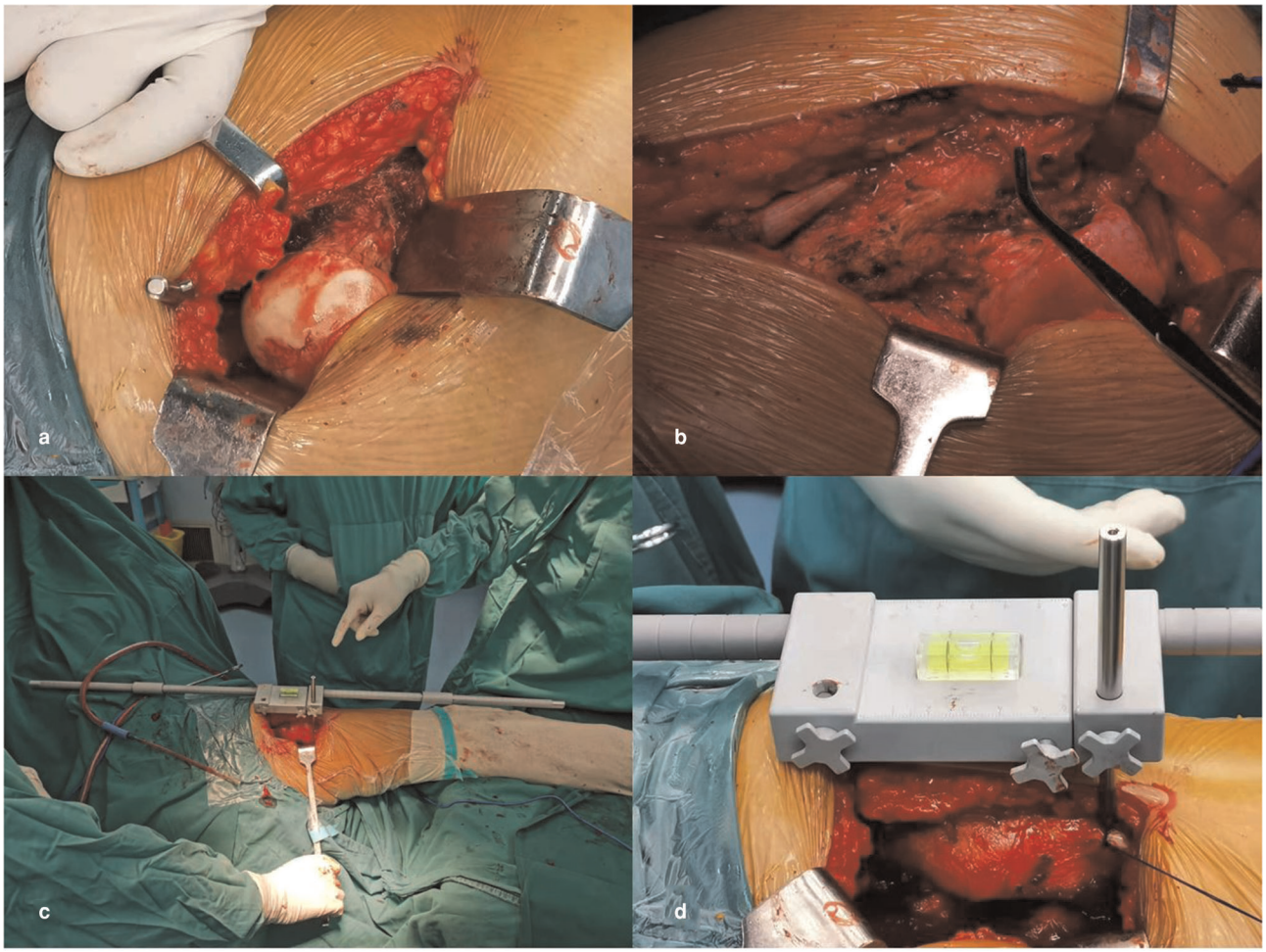

FIGURE 5 |

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Randomized Clinical Study on the Efficacy of Direct Anterior Approach Combined With Tendon Release and Repair After Total Hip Arthroplasty

*Guanbao Li, Qiuan Chen, Wei Zhou, Pinquan Li, Peng Ma, Tongyuan Liu and Hai Tang**

Department of Orthopaedics, The First Department of Hip Joint, Yulin Orthopedic Hospital of Chinese and Western Medicine, Yulin, China

Background: To study the effect of reconstruction of the joint capsule and conjoint tendon on the functional recovery of the hip joint during direct anterior approach (DAA) total hip arthroplasty.

Methods: A total of 60 patients who underwent their first total hip arthroplasty surgery were selected. According to the set criteria, the selected patients were divided into observation group A ($n = 30$) and control group B ($n = 30$). In group A, the joint capsule and conjoint tendon (superior muscle, internal obturator muscle, and inferior muscle) were repaired *in situ*, while in group B, only the joint capsule was repaired *in situ*, and the conjoint tendon was not repaired. The surgical indicators, including hip joint function and clinical efficacy of the two groups, were compared.

Results: After 6 months of follow-up in groups A and B, no dislocation occurred. The Harris Hip scores of group A were higher than those of group B at 1-month post-operation, i.e., $p < 0.05$, as well as the valid muscle strength and conjoint tendon valid tension, were higher in group A than group B at 1-month postoperative follow-up, i.e., $p < 0.05$.

Conclusion: DAA for total hip arthroplasty on the premise of reconstructing the joint capsule structure can rebuild the tension of the conjoint tendon, enhance its muscle strength, and significantly improve the joint stability and function of the patient early stage. It is beneficial for the patient's rapid recovery and is worth implementing.

Keywords: direct anterior approach (DAA), THA—total hip arthroplasty, conjoint tendon, joint capsule, repair

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****Correspondence:***
Hai Tang
tanghai6996@sina.com;
tanghai6996@gmail.com
orcid.org/0000-0001-6087-5026

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INTRODUCTION

Total hip arthroplasty (THA) is an effective orthopedic operation that has evolved significantly in surgical methods and procedures since its inception (1–3). THA was initially reserved for the elderly and feeble patients with locomotor impairments and comorbidities (1). However, patients undergoing THA are increasingly opting for renowned, high-performance hip implants to meet their postoperative demands.

The posterolateral and mini posterior methods, the lateral approach, and the anterolateral approach are traditional surgical procedures for THA; the posterior approach is the most often utilized internationally and has survived the test of time (4–6). The disinsertion of the external

rotators is the fundamental disadvantage of the posterior approach (PA), which is the most often utilized method in the United States and possibly worldwide (5, 7). Although newer studies have shown no higher risk when sufficient capsulorrhaphy or improved posterior soft tissue healing is achieved, posterior dislocation is possible for this method (8–11). Recently, there has been a trend toward minimally invasive surgical methods for a quick recovery; in this sense, orthopedic surgeons and patients worldwide have been paying close attention to the direct anterior approach (DAA).

The direct anterior approach (DAA) to the hip tends to have a longer shelf life in terms of popularity. The DAA employs a genuine internervous, intermuscular plane to expose the hip using the Hueter interval between the tensor fascia lata (TFL) and sartorius muscle. The strategy, according to proponents, is linked to reduced muscle injury and discomfort, as well as a faster recovery following hip arthroplasty. Despite the extensive research on the DAA and conventional techniques for primary THA, there is still disagreement over which technique is the most effective or desirable (6, 12).

However, exposing the femur can be challenging, and early users of the procedure have reported a high rate of early sequelae, including trochanteric and femoral fractures (13, 14). The conjoint tendon may need to be loosened during the DA approach to provide surgeons access to the hip joint. The conjoined external rotators tendon (CERT; conjoined tendons of the gemellus superior, obturator internus, and gemellus inferior) has been proposed as one of the critical active stabilizers of the hip, and it, along with the internally rotating gluteus minimus, is often referred to as the "rotator cuff" of the hip (15). The CERT can help with external hip rotation and hip joint stability (16), and it is also vital for avoiding posterior hip dislocation after THA (10, 17). Although the anterior or anterolateral minimally invasive method is touted as a muscle-sparing THA, surgeons may need to release more soft tissue for femur canal preparation, such as the capsular ligament or the insertion of muscles around the hip, including the CERT. These releases make it possible to properly prepare the canal, insert the broach, and test it.

Even though external rotation is thought to be significant for patient satisfaction (18), no investigation on repairing the conjoint tendon has been done. The purpose of this study was to investigate the effect of repairing the conjoint tendon on the postoperative hip joint function on the premise of reconstructing the joint capsule during the DAA for THA.

The objective of the study was to answer the following clinical question: Among patients with THA ($n = 60$), does the repairing of the conjoint tendon along with joint capsule, when compared with the repairing of joint capsule only, improve the Harris Hip Score (HHS) and manual muscle testing score (MMT), and decrease the frequency of postoperative complications, i.e., postoperative dislocation, infection, hematoma, and deep vein thrombosis?

The investigators hypothesized that repairing the conjoint tendon with a joint capsule improves the HHS and MMT scores and decreases the incidence of postoperative complications, i.e., postoperative dislocation, infection, hematoma, and deep vein thrombosis in the treatment of the control group.

MATERIALS AND METHODS

The study is a clinical randomized controlled trial comprising of patients who were selected for THA. The patients who visited the Department of Orthopedics from July 2020 to July 2021 were recruited for the present study. The present study was approved by the institute's ethical committee (Yulin Orthopedic Hospital of Chinese and Western Medicine) and was performed according to the Helsinki Declaration. Furthermore, the study's authors confirm that this trial has been registered (protocol YOHGU #IRB/2020/522), and all patients enrolled in the study have signed the written informed consent.

In this study, adult patients without any systemic complications, who strictly met the inclusion criteria, were engaged. The study's inclusion criteria were unilateral symptomatic hip osteoarthritis, Dorr's femur classification A/B, American Society of Anaesthesiologists Score (ASA) 3 or less, a body mass index (BMI) <40 kg/m^2, and age between 40 and 80 years, the general condition of body is good, and there is no serious organic disease or infectious disease, total hip arthroplasty for the first time, piriformis muscle and external obturator muscle must be kept intact.

If a subject had a Dorr's femur classification of C, had previous hip surgery (excluding arthroscopy), refused to accept randomization and blinding, or had severe pathology that would affect postoperative participation, such as neurologic, psychiatric, or other confounding pre-existing musculoskeletal disorders, they were excluded from the study. In addition, those with cardiopulmonary insufficiency or cardiovascular and cerebrovascular illnesses, those with a history of trauma, tumor, or infection at the site, those who are contraindicated in surgery, those with insufficient follow-up data, and those who have insufficient follow-up data which are mentally ill were also excluded.

Study Sampling

The patient sample size was calculated using (19):

$$n = \frac{N}{1 + N(e)^2} \tag{1}$$

Where N is the population size and e is the level of precision. For the present study, the population's size was determined based on the previous number of patients seen because of osteoarthritis, N is 60 patients for 6 months, and e is 0.05 at 95% confidence interval $n = 60$. The two groups received equal patients.

Irrespective of age and gender, randomization of consecutive patients was done using the concealed method. An independent researcher not involved in participant recruitment, treatment, or assessment prepared the randomization sequence with allocation prepared in sequentially numbered opaque envelopes. The surgeon and the primary investigator were blinded to the approach until the preoperative planning meeting, while participants were blinded pre-operatively. The patients were divided into group A (Experimental group, i.e., repairing the joint capsule and conjoint tendon) and group B (Control group, i.e., repairing the joint capsule only). A single surgeon who was

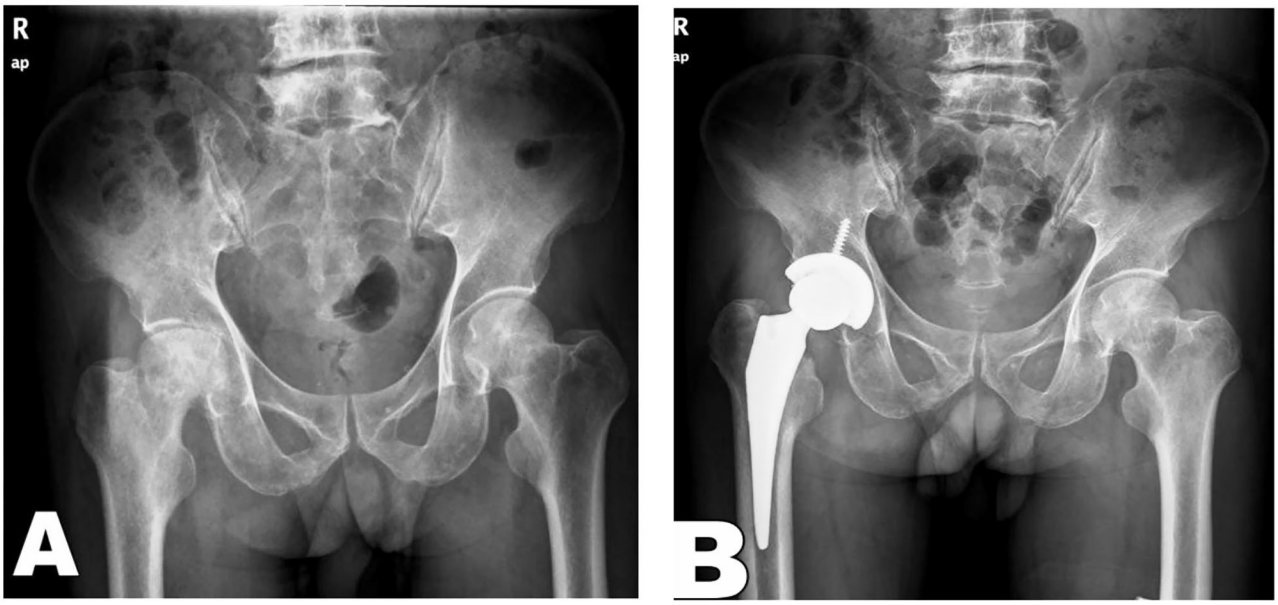

FIGURE 1 | Preoperative X-rays indicated Ficat stage IV of hip avascular necrosis of the right femoral head and subjected to DAA for total hip arthroplasty. **(A)** Preoperative orthographic X-ray; **(B)** Postoperative orthographic X-ray.

an experienced senior surgeon had operated on all the patients under standard aseptic conditions and protocol to remove bias.

The artificial joint used in operation was all biologically fixed prostheses. Group A was sutured *in situ* on the loosened joint capsule and conjoint tendon (superior muscle, internal obturator muscle, inferior muscle). Meanwhile, only the joint capsule was sutured *in situ* in group B but not the conjoint tendon. The surgical indicators, including hip joint function and clinical efficacy of the two groups, were compared.

Operative Procedure

Both group patients underwent intraspinal anesthesia in a supine position and with DAA incisions. The skin incision was 1 cm down from the anterior superior iliac spine and 2 cm behind the anterior superior iliac spine. Furthermore, the incision extended toward the head of the fibula following the direction of the tensor fascia lata muscle. Then, a peel hook was used to open and cut the fat layer on the fascia surface to make a blunt separation to the inside. After that, the ascending branch of the lateral femoral circumflex artery was ligated to expose the hip joint capsule through the gap of superficial Hueter between the lateral edge of the sartorius muscle and the anterior fascia of the tensor fascia lata muscle, followed by the gap of deeper Hueter between the lateral edge and the rectus femoris and the anterior edge of the gluteus medius. The joint capsule was cut from the upper edge of the femoral neck to the intertrochanteric line in an "L" shape, leaving the joint capsule opened, and absorbable thread was used to pull the joint capsule upwards to expose the joints and perform the artificial joint replacement. Group A: To obtain the optimal lifting height of the proximal femur during the operation and achieve a smooth operation of femoral medullary cavity shaping and prosthetic stem placement, Ethibond suture 2-0 was used to mark the conjoint tendon. It was cut off at the medial surface of the proximal femur of the greater trochanter (leave 2–3 mm at the stump of the greater trochanter) after the prosthesis was installed, and the conjoint tendon was sutured *in-situ* to close the entire incision site layer by layer after repairing the joint capsule according to the marked point. Group B: The conjoint tendon relaxation was performed with a similar method. After the prosthesis was installed, the conjoint tendon was not sutured. After the joint capsule was repaired, the entire incision was closed layer by layer. A drainage tube was placed in the two groups when the wound was sutured, and it was removed 24 h later (**Figures 1**, **2**).

Both DAA groups utilized comparable intra-operative local infiltration anesthetic regimens based on a version of Kerr's technique. A 0.25% Bupivacaine, 20 mg ketorolac, and 1% adrenaline were used in the procedure.

Moreover, the individuals with symptoms of renal failure were not administered ketorolac. For the first 24 h following surgery, continuous infusion pumps were utilized on the ward. All patients received prophylactic antibiotics (Ceftriaxone) and thromboprophylaxis, as required by the hospital service.

All of the patients were able to move about the day after surgery. The DAA group's hip mobility was unaffected. The goal for discharge to home or rehabilitation was set for the 3rd postoperative day. On a daily basis, physiotherapists and physicians accompanying the orthopedic team monitored this. Patients who did not meet the criteria for release were sent to a rehabilitation facility.

Outcome Variables

Participants were assessed pre-operatively and 2 weeks, 1, 3, and 6 months after THA. The same investigator was in charge of the follow-up.

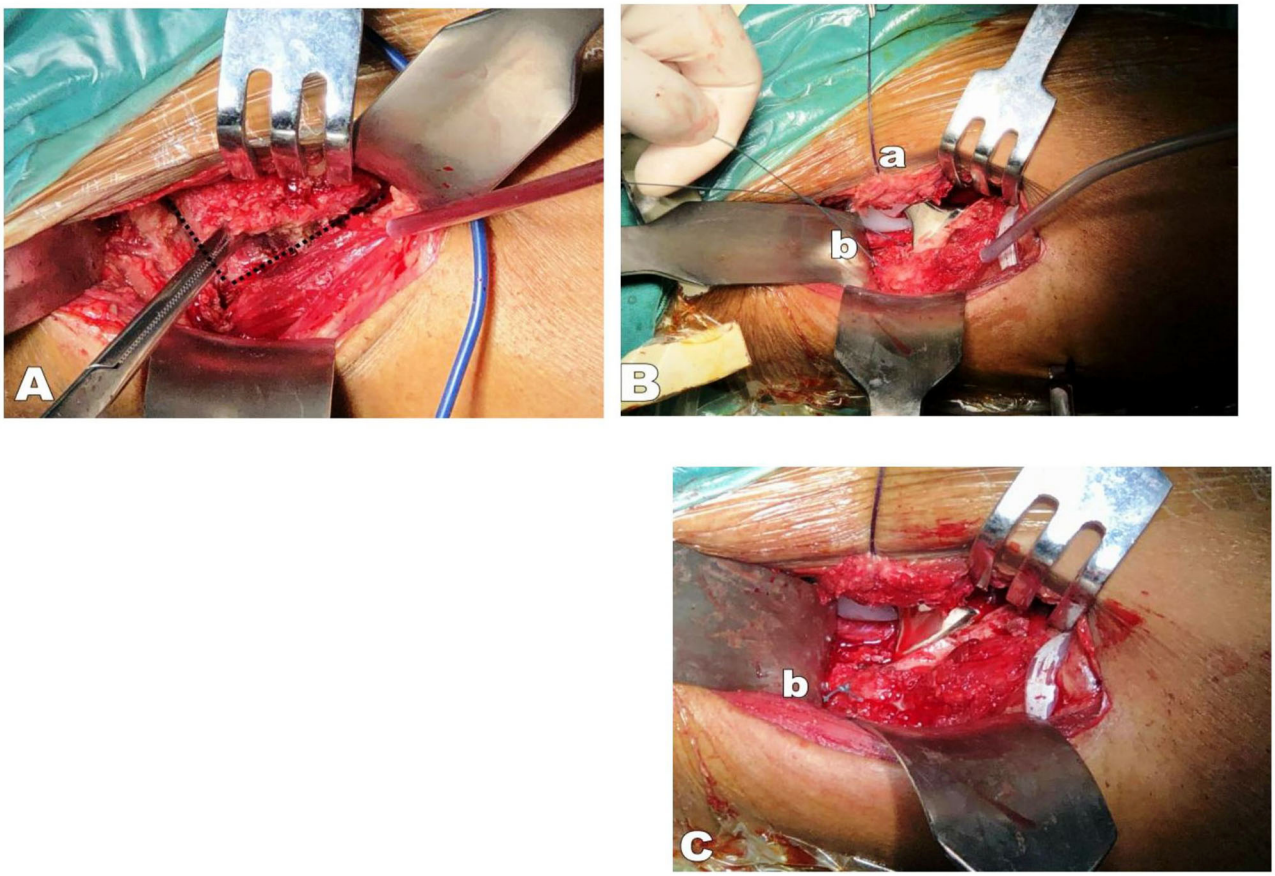

FIGURE 2 | (A) The black dotted line indicates the cut from the upper edge of the femoral neck to the intertrochanteric line in an "L" shape, with a margin of 2–3 mm at the edge to facilitate the joint capsule reparation; **(B)** The loosened joint capsule was pulled (a) upward to expose the hip joint; Ethibond suture two was used to mark the conjoint tendon (b) in the proximal femur before it was cut off at the medial surface of the proximal femur of the greater trochanter (leave 2–3 mm at the stump of the greater trochanter to facilitate reconstruction); **(C)** The conjoint tendon was repaired *in-situ* after the prosthesis was installed (b); **(D)** Completed repair of the joint capsule (a).

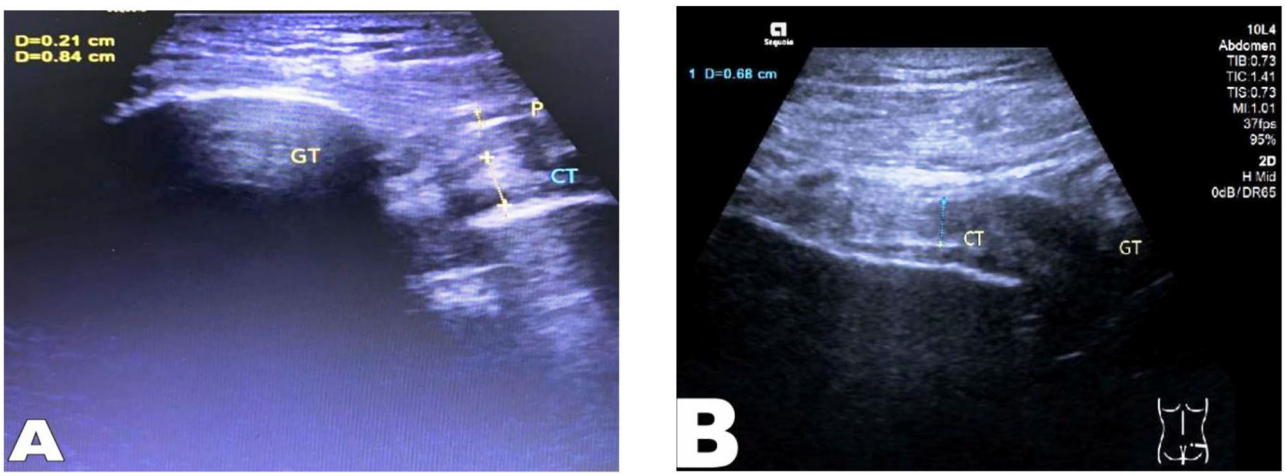

FIGURE 3 | Musculoskeletal ultrasound examination, **(A)** "CT" indicates the preoperative conjoint tendon morphology; "GT" indicates the greater trochanter of femur; **(B)** "CT" indicates the conjoint tendon morphology after repaired, with good tendon tension.

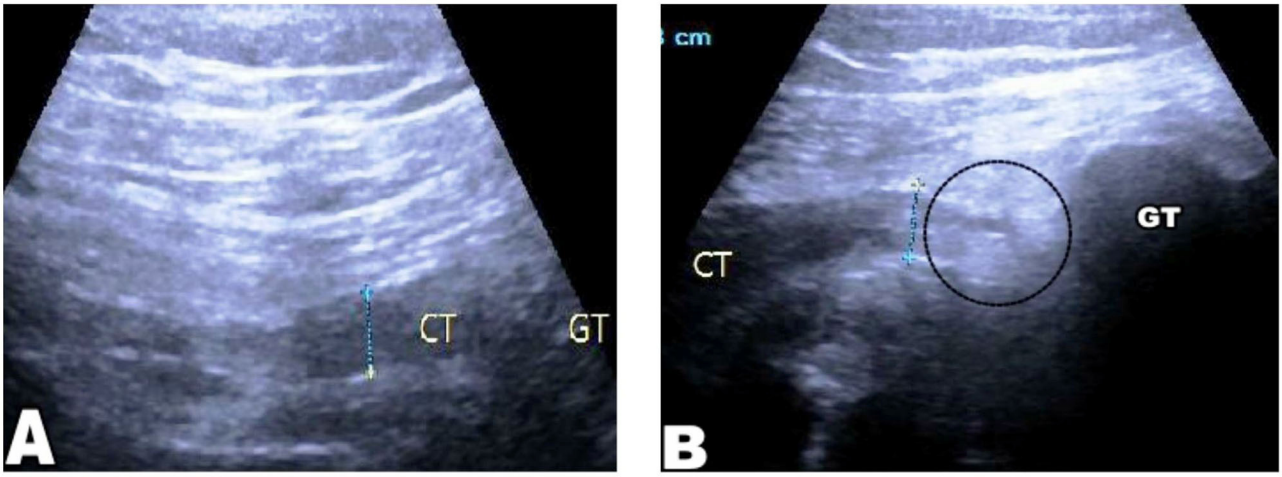

FIGURE 4 | Musculoskeletal ultrasound examination, **(A)** "CT" indicates the preoperative conjoint tendon morphology; "GT" indicates the greater trochanter of the femur; **(B)** "CT" indicates the conjoint tendon morphology after lysis; the continuity of the tendon is interrupted, slightly tortuous, and has poor tension. The black circle indicates the position of the interrupted conjoint tendon.

The Harris Hip Score (HHS) was used to evaluate the hip joint function before and after the operation, divided into four aspects: pain, function, deformity, and joint mobility. The total score is 100 points; a score $\geq$90 is excellent, 89–80 is good, 79–70 is fair, and a score lower than 70 is poor.

The manual muscle test (MMT) was used to detect the abductor muscle strength of the two groups of patients. The evaluation method was divided into six grades, and the valid muscle strength is not lower than the 3rd grade.

The tension of the conjoint tendon of the two groups was compared by musculoskeletal ultrasound examination. A good continuity without tortuosity in a conjoint tendon represents valid tension. However, a discontinuous conjoint tendon with tortuosity, shortening, or unclear display represents invalid tension (**Figures 3**, **4**).

The operation time, intra-operative and postoperative total blood loss, and related complications of the two groups of patients were recorded.

Statistical Analysis

SPSS 22.0 (SPSS, Inc., Chicago, IL) statistical software was used to analyze the data. Measurement data were expressed as mean $\pm$ standard deviation ($\chi^2 \pm$ S) and paired t-test was used to compare groups. Count data is expressed as an example (percentage), and the comparison between groups uses the χ^2-test. Statistical significance was assigned to findings with p-values of $<$0.05.

RESULTS

Group A comprised 18 males and 12 females aged 45–81 years old, average (64.7 $\pm$ 3.1) years old. Meanwhile, Group B consisted of 16 males and 14 females ranging from 48 to 80 years old, average (64.5 $\pm$ 3.0) years old. Comparison of general data such as gender, age, and disease diagnosis between the two groups of patients was not statistically significant ($p > 0.05$), and they were comparable. **Figure 5** demonstrates the flow diagram for patient recruitment and selection.

There was no significant difference in operation time and blood loss between the two groups ($p > 0.05$) (**Table 1**).

One month after the surgery, the Harris Hip score of group A was higher than that of group B, and the difference between the groups was statistically significant ($p = 0.012$, $p < 0.05$). Furthermore, three to 6 months after the surgery, the HHS of the two groups was not statistically significant ($p = 0.23$, $p > 0.05$) (**Table 2**).

The valid muscle strength of group A was significantly higher than that of group B, and the difference was statistically significant ($p = 0.045$, $p < 0.05$). In addition, the valid tension of the conjoint tendon was significantly higher in group A than in group B, and the difference was statistically significant ($p = 0.042$, $p < 0.05$). However, there was no significant difference in the incidence of complications such as postoperative dislocation, infection, hematoma, and deep vein thrombosis between the two groups ($p > 0.05$) (**Table 3**).

DISCUSSION

The main objective behind this study is to examine the effect of repairing of conjoint tendon and join capsule vs. repairing of joint capsule only; on the improvement of HHS and MMT scores and the incidence of postoperative complications, i.e., postoperative dislocation, infection, hematoma, and deep vein thrombosis. The results of this research confirm the hypothesis, i.e., a significant difference exists among group A and group B in terms of HHS and MMT scores ($p < 0.05$), i.e., group A shows a significant improvement in the HHS and MMT score at 1-month follow-up and reduced incidence of postoperative complications,

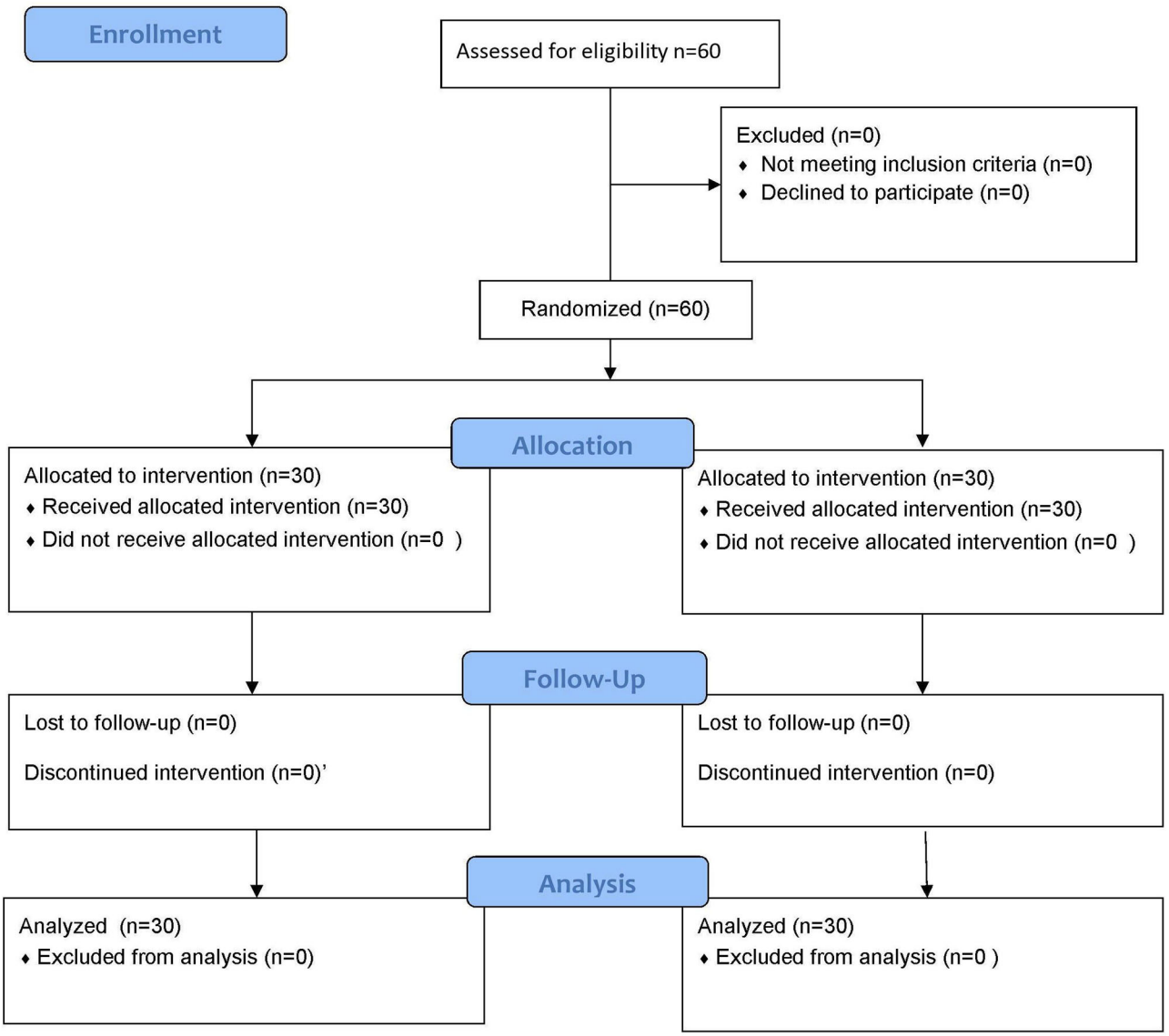

FIGURE 5 | Demonstrates the flow diagram for patient recruitment and selection.

i.e., postoperative dislocation, infection, hematoma, and deep vein thrombosis as compared to group B. However, at 3- and 6-month follow-up, the difference between groups A and B in terms of HHS and MMT is insignificant, i.e., $p > 0.05$.

Early dislocation is a severe complication after the first total hip arthroplasty, and this incidence is preceded only by the aseptic loosening of the joint prosthesis. Surgical factors are considered to be one of the critical factors affecting the incidence of early dislocation, and they are also the most concerned the researchers. Surgical factors include prosthetic factors and surgical operating factors, while surgical operating factors include replacement approach, soft tissue imbalance reconstruction, the design and placement of the prosthesis, patient compliance, history of previous hip surgery. Dislocations usually occur within 3 months after the replacement, and late dislocations are predominant (20). With the development of hip arthroplasty and the maturity of the replacement experience of the surgeon, the dislocation issue caused by the poor positioning of the prosthesis is gradually reduced, and the soft tissue imbalance has gradually become the main factor of the dislocation of the prosthesis. Studies have shown (21) that the soft tissue around the hip has an important influence on the stability of the prosthesis.

The stability of the hip joint after the conventional total hip arthroplasty through the posterolateral approach is partly maintained by the tension of the hip girdle muscle and the repair of the fibrous scar around the prosthesis. However, the early postoperative joint prosthesis lacks the protection of the joint

TABLE 1 | Comparison of surgical indicators between the two groups ($\chi^2 \pm S$).

Groups	Intraoperative blood loss (ml)	Operation time (min)	Incision length (cm)	Postoperative drainage volume (ml)
A	180.4 ± 35.9	63.1 ± 15.4	9.34 ± 2.0	180.8 ± 31.7
B	179.7 ± 35.5	61.8 ± 13.9	9.35 ± 1.8	196.7 ± 22.2
t-value	0.550	0.576	0.250	8.788
P-value	>0.05	>0.05	>0.05	<0.05

TABLE 2 | Comparison of Harris Hip scores between the two groups pre- and post-operation ($\chi^2 \pm S$, score/min).

Groups	Pre-operation	1-month post-operation	3–6 months post-operation
A	45.7 ± 7.0	85.3 ± 11.3	90.2 ± 2.4
B	45.1 ± 7.2	80.4 ± 11.7	90.4 ± 2.9
t-value	0.33	2.35	0.27
P-value	>0.05	$p = 0.012$; $p < 0.05$	$p = 0.23$; $p > 0.05$

capsule. The antagonistic muscle strength balance between the external and internal obturator muscles (the anterior fiber of the gluteus medius and minimus) is more prone to posterior hip dislocation. Therefore, the patient must be required to strictly control the range of motion of the affected hip to prevent hip dislocation. Therefore, retaining the joint capsule and the anatomical structure of the small supinator muscle group during the process of total hip arthroplasty will help to restore the soft tissue balance of the hip joint and increase the joint stability (22). Wu et al. (23) believe that since soft tissue acts as an essential stable structure of the hip joint, it is crucial to restoring the balance of the soft tissue around the hip to maintain the stability of the hip joint after the replacement. Lu et al. (24) believe that low soft tissue tension, especially the abductor muscle weakness, is the most crucial cause of total hip arthroplasty dislocation. Hideki et al. (25) repaired the external obturator muscle before soft tissue enhancement can reduce the risk of prosthesis dislocation during the posterior total hip arthroplasty.

White et al. (26) performed total hip arthroplasty *via* the posterior approach. During the operation, the posterior joint capsule was trimmed into a tissue flap with a 30–50% circumference of the acetabular. After the prosthesis was implanted, the joint capsule and the external obturators were sutured within the same layer onto the 2.7 mm diameter bone hole on the greater trochanter of the femur. Six-month follow-up showed three out of 437 cases (0.7%) had a post-traumatic dislocation, and another 4 had asymptomatic avulsion fractures in the greater trochanter. The dislocation rate was as high as 4.8% in the other patients who did not undergo this repair. Sioen et al. (27) have performed posterior total hip arthroplasty on both hips of 3 fresh cadavers to observe the stability of the hip joint using different repair methods on the posterior joint capsule (no repair, soft tissue repair, muscle, and bone repair). Research suggests that the bone repair of the composite tissue flap of the posterior joint capsule and external obturator muscle group can significantly increase the stability of the hip joint. Zhang et al. (28) reported that using suture anchors to anchor the piriformis and external obturator muscle to the greater trochanter can reduce the dislocation. Browne et al. (29) reported a repair method in which the posterior joint capsule and short external obturator compound tissue flaps were directly sutured on the posterior edge of the gluteus minimus and its deep anterior and superior joint capsule. This method involves joint capsule repair and soft tissue end-to-end suture eliminating the dead space and significantly reducing early dislocation incidence.

Researchers have confirmed the vital role of repairing the joint capsule and short external rotators in the THA of the posterolateral approach to maintain the early stability of the hip joint. In recent years, with the continuous development of minimally invasive techniques, there have been more methods of the THA surgical approach. Among them, the direct anterior approach (DAA) is a new minimally invasive surgical technique that is currently widely available and clinically applied in total hip arthroplasty (30). This technology uses the muscle gap between the tensor fascia lata and sartorius muscles as well as the rectus and gluteus medius muscles to expose the hip joint, hence, avoiding damage to the abductor muscles around the hip joint and ensuring the integrity of the soft tissues on the back of the hip joint. Hence, people named it the "Hueter" approach (31). Most studies have shown that this method has a lower incidence of complications such as minimal damage to muscle, mild pain, and dislocation and can enable patients to undergo total hip arthroplasty surgery and recover more quickly after the surgery. Therefore, it is widely used in clinical orthopedic applications.

Although the DAA has apparent advantages, it has limitations too. This approach enters the hip joint through the muscle gap. Since the intraoperative incision is small, the surgical field and operation space are narrow; thus, the femoral treatment is more complicated. In addition, if there is a lack of traction bed, unique prosthesis, operating tools, or immature surgical technique, complications such as iatrogenic fractures, nerve and muscle damage often occur during the operation. Therefore, the conventional DAA approach requires the hospital to be equipped with a traction bed, unique prosthesis, and operating tools.

Last but not least, strict screening is needed in every case. For instance, patients with high BMI indexes and obesity will be excluded. This method also increases the cost and difficulty of the surgery and the financial burden of patients. Fujii et al. have confirmed that relaxation of the conjoint tendon (internal obturator muscle, superior and inferior muscles) helps achieve the optimal lifting height of the proximal femoral (25) and ease the operation of the femoral medullary cavity shaping and prosthetic stem implantation. It will significantly reduce the surgical cost and difficulty of the DAA approach, which is conducive to promoting the DAA-THA approach. We have known that suturing the external obturator muscles in the posterolateral THA and repairing the posterior joint capsule can effectively provide strong support for the fragile posterior structure of the hip after THA. It will reduce postoperative joint dislocation (32, 33).

TABLE 3 | Valid muscle strength, conjoint tendon valid tension, and post-operative complications.

Groups	Joint dislocation	Infection	Hematoma	Deep vein thrombosis	Valid muscle strength	Conjoint tendon valid tension
Observation group ($n = 30$)	0 (0)	0 (0)	1 (3.33)	1 (3.33)	28 (82.50)	26 (86.7)
Control group ($n = 30$)	0 (0)	1 (3.33)	2 (6.67)	1 (3.33)	23 (62.50)	21 (70.0)
χ^2-value	0.0	0.556	0.346	0.721	4.013	4.011
P-value	0.0	0.456	0.556	0.396	0.045	0.042

On the other hand, from the perspective of biomechanics, suturing the external obturator muscles and repairing the posterior joint capsule can promote the artificial hip joint of the body to be closer to the physiological state of the human body, thereby achieving an excellent soft-tissue balance, which is beneficial to the functional recovery of the hip joint of patients in the later stage. Based on this, we also found that in the DAA-THA approach, by comparing group A with both joint capsule and conjoint tendon repairs and group B with only joint capsule repair, the drainage rate of group A was significantly less than that of group A group B. Furthermore, the Harris score of group A was higher than that of group B 1-month post-operation. In addition, the valid muscle strength of group A was significantly higher than that of group B. Also, the musculoskeletal ultrasound showed that the valid tension of the conjoint tendon in group A was significantly higher than that in group B. Our research confirms that repairing the conjoint tendon on the premise of reconstructing the joint capsule during THA surgery through the DAA approach can indeed reduce postoperative complications and restore hip joint function faster.

Analyzing the reasons, we believe that it may be related to the following: Firstly, From the histological Analysis, reconstruction of the joint capsule and conjoint tendon can compensate for the weakness of the front joint structure after total hip arthroplasty, thereby effectively reducing the incidence of postoperative dislocation; In addition, from biomechanical Analysis, reconstruction of the joint capsule and conjoint tendon can bring the hip joint closer to the physiological state, thereby obtain a better soft tissue balance, and better restoring the joint function after the replacement.

LIMITATIONS

The minimal number of patients included in the study is one of the study's shortcomings. On the other hand, most studies on long-term results after orthopedic surgeries have utilized a similar sample size. Patients were not evenly distributed in terms of sex between the two groups, and neither had a preoperative VAS score. Furthermore, the trial's follow-up was not designed to record the precise day when gait assistance was stopped. Observing bias might develop when data is gathered and analyzed by a single investigator.

In summary, THA surgery through the DAA approach to repair the conjoint tendon on the premise of reconstructing the joint capsule structure can rebuild its tension, enhance its muscle strength, and improve the patient's hip joint function, with a definite effect. Furthermore, combined with the advantages of the DAA approach, it can significantly reduce complications such as dislocation, bleeding, and infection after total hip arthroplasty, and it is worthy of clinical promotion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study protocol was reviewed and approved by [Yulin Orthopedic Hospital of Chinese and Western Medicine, Guangxi University], approval number [YOHGU #IRB/2020/522]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GL and QC: concept and designed the study. WZ: analyzed data. PL and PM: collected the data and helped in data analysis. TL and HT: drafting the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Patel NN, Shah JA, Erens GA. Current trends in clinical practice for the direct anterior approach total hip arthroplasty. *J Arthroplasty*. (2019) 34:1987–93.e3. doi: 10.1016/j.arth.2019.04.025
2. Malviya A, Abdul N, Khanduja V. Outcomes following total hip arthroplasty: a review of the registry data. *Indian J Orthop*. (2017) 51:405–13. doi: 10.4103/ortho.IJOrtho_177_17
3. Charnley J. Arthroplasty of the hip. A new operation. *Lancet*. (1961) 1:1129–32. doi: 10.1016/S0140-6736(61)92063-3

4. Jia F, Guo B, Xu F, Hou Y, Tang X, Huang L, et al. comparison of clinical, radiographic and surgical outcomes of total hip arthroplasty between direct anterior and posterior approaches: a systematic review and meta-analysis. *Hip Int.* (2019) 29:584–96. doi: 10.1177/1120700018820652
5. Waddell J, Johnson K, Hein W, Raabe J, FitzGerald G, Turibio F. Orthopaedic practice in total hip arthroplasty and total knee arthroplasty: results from the Global Orthopaedic Registry (GLORY). *J Orthop*. (2010) 39(Suppl.):5–13.
6. Taunton MJ, Trousdale RT, Sierra RJ, Kaufman K, Pagnano MW. John Charnley Award: randomized clinical trial of direct anterior and miniposterior approach THA: which provides better functional recovery? *Clin Orthop Relat Res.* (2018) 476:216–29. doi: 10.1007/s11999.0000000000000112
7. Chechik O, Khashan M, Lador R, Salai M, Amar E. Surgical approach and prosthesis fixation in hip arthroplasty world wide. *Arch Orthop Trauma Surg.* (2013) 133:1595–600. doi: 10.1007/s00402-013-1828-0
8. Kwon MS, Kuskowski M, Mulhall KJ, Macaulay W, Brown TE, Saleh KJ. Does surgical approach affect total hip arthroplasty dislocation rates? *Clin Orthop Relat Res.* (2006) 447:34–8. doi: 10.1097/01.blo.0000218746.84494.df
9. Kim YS, Kwon SY, Sun DH, Han SK, Maloney WJ. Modified posterior approach to total hip arthroplasty to enhance joint stability. *Clin Orthop Relat Res.* (2008) 466:294–9. doi: 10.1007/s11999-007-0056-8
10. Iorio R, Specht LM, Healy WL, Tilzey JF, Presutti AH. The effect of EPSTR and minimal incision surgery on dislocation after THA. *Clin Orthop Relat Res.* (2006) 447:39–42. doi: 10.1097/01.blo.0000218750.14989.ef
11. Zhou Y, Cao S, Li L, Narava M, Fu Q, Qian Q. Is soft tissue repair a right choice to avoid early dislocation after THA in posterior approach? *BMC Surg.* (2017) 17:60. doi: 10.1186/s12893-017-0212-3
12. Barrett WP, Turner SE, Leopold JP. Prospective randomized study of direct anterior vs postero-lateral approach for total hip arthroplasty. *J Arthroplasty.* (2013) 28:1634–8. doi: 10.1016/j.arth.2013.01.034
13. Spaans AJ, van den Hout JA, Bolder SB. High complication rate in the early experience of minimally invasive total hip arthroplasty by the direct anterior approach. *Acta Orthop.* (2012) 83:342–6. doi: 10.3109/17453674.2012.711701
14. Jewett BA, Collis DK. High complication rate with anterior total hip arthroplasties on a fracture table. *Clin Orthop Relat Res.* (2011) 469:503–7. doi: 10.1007/s11999-010-1568-1
15. Yoo S, Dedova I, Pather N. An appraisal of the short lateral rotators of the hip joint. *Clin Anat.* (2015) 28:800–12. doi: 10.1002/ca.22568
16. Tubbs, R. S. (2016). "Pelvic girdle and lower limb 1316-1382," in *Gray's Anatomy*, 41st Edn, eds T. P. Pick and R. Howden (New York, NY: Fall River Press).
17. Goldstein WM, Gleason TF, Kopplin M, Branson JJ. Prevalence of dislocation after total hip arthroplasty through a posterolateral approach with partial capsulotomy and capsulorrhaphy. *J Bone Joint Surg Am*. (2001) 83(Suppl.2):2–7. doi: 10.2106/00004623-200100021-00002
18. Yao R, Howard JL, Lanting BA. Conjoint tendon release in direct anterior total hip arthroplasty: no impact on patient outcomes. *Orthopedics.* (2017) 40:e971–e4. doi: 10.3928/01477447-20170918-05
19. Ellen S. *Slovin's Formula Sampling Techniques*. sciencing.com. Available online at: https://sciencing.com/slovins-formula-sampling-techniques-5475547.html (accessed December 5, 2021).
20. Xu LM, Zhu BB, Jiang Y, Yu HP. Analysis of the causes of early post-dislocation after total hip arthroplasty. *China Orthoped Traumatol.* (2010) 23:187–8.
21. Bender B, Nogler M, Hozack W J. Direct anterior approach for total hip arthroplasty. *Orthoped Clin North America.* (2009) 40:321–8. doi: 10.1016/j.ocl.2009.01.003
22. Huang Z. Minimally invasive procedure, minimally invasive surgery—the main theme of surgery in the 21st century. *Chinese J Surg.* (2002) 40:9.
23. Wu X, Lou LM, Li SH, Wu WP, Cai ZD. Soft tissue balancing in total hip arthroplasty for patients with adult dysplasia of the hip. *Orthop Surg.* (2009) 1:212–5. doi: 10.1111/j.1757-7861.2009.00034.x
24. Lu Y, Xiao H, Xue F. Causes of and treatment options for dislocation following total hip arthroplasty. *Exp Ther Med.* (2019) 18:1715–22. doi: 10.3892/etm.2019.7733
25. Hideki F, Takuya O, Yasuhiko K, Tetsuo H, Toshiomi A, Motoi T, et al. Preventing postoperative prosthetic joint dislocation by repairing obturator externus in total hip arthroplasty performed *via* the posterior approach. *Arthroplasty.* (2020) 2:33. doi: 10.1186/s42836-020-00054-4
26. White RE Jr, Forness TJ, Allman JK, Junick DW. Effect of posterior capsular repair on early dislocation in primary total hip replacement. *Clin Orthop Relat Res.* (2001) (393):163–7. doi: 10.1097/00003086-200112000-00019
27. Sioen W, Simon JP, Labey L, Van Audekercke R. Posterior transosseous capsulotendinous repair in total hip arthroplasty: a cadaver study. *J Bone Joint Surg Am.* (2002) 84:1793–8. doi: 10.2106/00004623-200210000-00009
28. Zhang Y, Tang Y, Zhang C, Zhao X, Xie Y, Xu S. Modified posterior soft tissue repair for the prevention of early postoperative dislocation in total hip arthroplasty. *Int Orthop.* (2013) 37:1039–44. doi: 10.1007/s00264-013-1874-9
29. Browne JA, Pagnano MW. Surgical technique: a simple soft-tissue-only repair of the capsule and external rotators in posterior-approach THA. *Clin Orthop.* (2012) 2:511–5. doi: 10.1007/s11999-011-2113-6
30. Yang XT, Huang HF, Sun L, Yang Z, Deng CY, Tian XB. Direct anterior approach versus posterolateral approach in total hip arthroplasty: a systematic review and meta-analysis of randomized controlled studies. *Orthop Surg.* (2020) 12:1065–73. doi: 10.1111/os.12669
31. Jie L, Jinwei C, Jinzhong M. Research progress of direct anterior total hip arthroplasty. *Int J Orthopaed.* (2014) 35:94-9.
32. Cheng L, Heng W, Lei L. Evaluation of reconstruction of external obturator muscles to prevent posterior joint dislocation after the first total hip replacement. *Chinese General Practice*. (2014) 12:1763–5.
33. Chen C, Yin Y, Juncai L, Chen G. The direct anterior approach for simultaneous bilateral total hip arthroplasty: a short-term efficacy analysis. *Arthroplasty.* (2020) 2:21. doi: 10.1186/s42836-020-00040-w

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CASE REPORT
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Case Report: Intraarticular Iliopsoas Tendon causes Groin Pain Following Periacetabular Osteotomy

*Sebastian Gebhardt, Lars Nonnenmacher, Georgi I. Wassilew and Alexander Zimmerer**

Center for Orthopaedics, Trauma Surgery and Rehabilitation Medicine, University Medicine Greifswald, Greifswald, Germany

A 43-year-old female patient reported persistent iliopsoas-related groin pain following periacetabular osteotomy (PAO) combined with femoroplasty *via* a direct anterior approach due to CAM morphology. Concomitantly with the planned removal of screws, hip arthroscopy was performed, and the iliopsoas tendon was found to run intraarticularly, resulting in the tendon being impaired in its mobility and being entrapped. The tendon was arthroscopically released. The patient reported relief of the groin pain after the arthroscopic tendon debridement. During PAO combined with capsulotomy, the postoperatively observed intraarticular position of the iliopsoas tendon should be prevented by careful closure of the joint capsule.

Keywords: PAO, femoroplasty, iliopsoas tendon, impingement, pain

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Anell Olivos, Hospital Médica Sur, Mexico

****Correspondence:***
Alexander Zimmerer
alexander.zimmerer@gmail.com

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INTRODUCTION

Periacetabular osteotomy (PAO), first described by Ganz et al. in 1988 (1), is a well-established technique for treating hip pain caused by inadequate acetabular coverage of the femoral head. To address an existing CAM morphology that may lead to femoroacetabular impingement syndrome (FAIS) in a supplementary manner, arthroscopy of the hip joint or an open approach *via* the direct anterior approach (DAA) can be performed.

Good results are reported for PAO, with significantly increased patient-related outcome measurements (PROMs) (2), and survivor rates are 90, 60, and 30% after 10, 20, and 30 years, respectively (3, 4). However, up to 10% of patients are reported to have postoperative iliopsoas-related pain besides satisfying bony correction of the acetabulum (5). To our knowledge, this is the first report of an intraarticular position of an iliopsoas tendon after PAO with additional femoroplasty using a DAA involving a capsulotomy. Thus, this report offers feasible rationale and treatment option regarding the observed complication associated with groin pain after successful bone correction by PAO.

CASE REPORT

Patient Information

A 43-year-old female patient presented to our clinic with persistent left groin pain 1 year after PAO and femoroplasty *via* the DAA for acetabular retroversion and combined FAIS. Despite taking daily nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy, she was unable to work and was restricted in her leisure activities. In particular, she complained of pain with active hip flexion. Other than the significant groin pain, her postoperative course had been unremarkable with adequate wound healing and postoperative recovery.

Clinical Findings

On clinical examination after the PAO, the wound was unremarkably healed, and neuromuscular function was found to be intact. The patient showed a positive flexion-adduction-internal-rotation (FADIR) test and iliopsoas tendon-related pain especially with active flexion of the hip against resistance. The internal rotation of the hip was increased to 30° compared to the 20° before PAO. Further range of motion was unchanged with external rotation 50°, extension/flexion 10-0-100°, and abduction/adduction 60-0-30°.

Timeline

The patient reported having hip pain for years. Initial conservative measures failed; thus, given typical radiological findings, she was scheduled for PAO and concomitant femoroplasty. According to our standard of care, femoroplasty was performed through the DAA without closure of the capsule after trimming of the femoral neck. In the postoperative course, besides unremarkable wound-healing and mobilization, she reported persistence of groin pain. Consequently, we proposed concomitant hip arthroscopy with the removal of screws 1 year after the operation.

Diagnostic Assessment

Initial anterior-posterior (AP) pelvis and left 45°-Dunn-view radiographs before the PAO showed a crossover sign (COS), posterior wall sign (PWS), ischial spine sign, and a lateral center edge angle (LCEA) of 38° (**Figure 1A**). The initial magnetic resonance imaging (MRI) of the left hip showed a lesion of the labrum and an anterolateral subchondral acetabular edema, while the course of the psoas tendon was clearly extraarticular (**Figure 2**). The post-PAO radiograph of the pelvis obtained showed satisfying bony correction (COS and PWS not observed, LCEA 38°) and correct placement of osteosynthesis screws as well as complete consolidation of the osteotomy (**Figure 1B**).

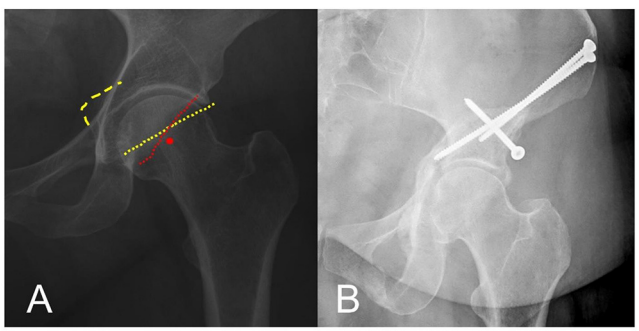

FIGURE 1 | (A) Anterior-posterior (AP) radiograph of the left hip: signs of acetabular retroversion are present; posterior wall sign (PWS), red circle; crossover sign (COS), dotted red and yellow line; ischial spine sign, dashed yellow line. **(B)** AP radiograph of the left hip: satisfying bony correction and correct screw placement after anteverting periacetabular osteotomy (PAO) of the left hip.

An MRI post PAO, besides being compromised by metal artefacts, showed an intraarticular position of the psoas tendon and subsequent edema (**Figure 3**).

Therapeutic Intervention

The patient was recommended to undergo hip arthroscopy in the process of operative screw removal to verify the hypothesis of iliopsoas impingement. Intraoperatively, the iliopsoas tendon was found to run intraarticularly, causing it to be trapped and limiting its mobility. The labrum showed adhesions that were locally inflamed (**Figure 4**). An arthroscopic release of the inflamed adhesions and debridement of the iliopsoas tendon was performed by the senior author (AZ).

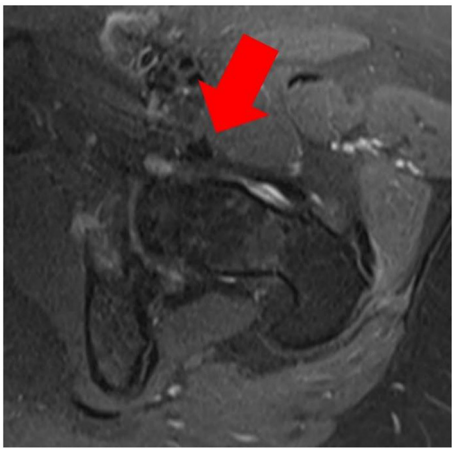

FIGURE 2 | Pre-PAO MRI of the left hip shows the iliopsoas tendon running extracapsularly (red arrow).

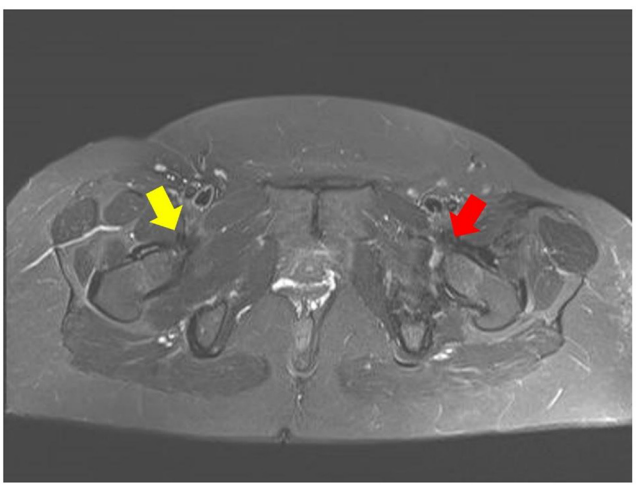

FIGURE 3 | Follow-up MRI after minimal invasive PAO with anteversion of the acetabulum showing normal anatomy of the right psoas tendon (yellow arrow) and intraarticular position of the left iliopsoas tendon (red arrow).

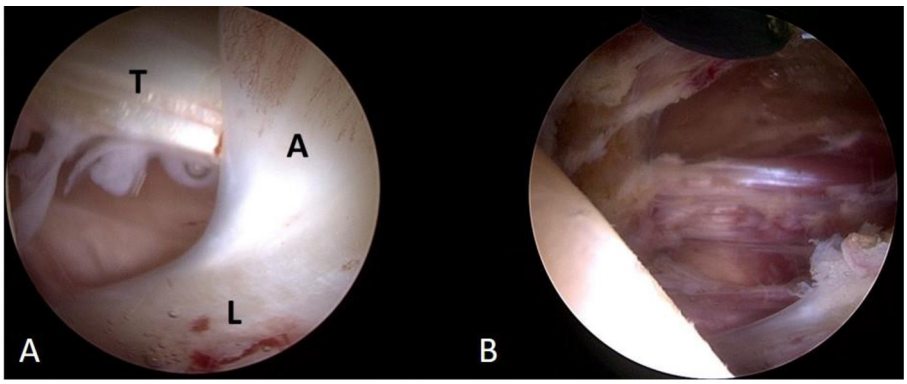

FIGURE 4 | (A) Intraopertive view showing the labrum (L), locally inflamed adhesion (A), and intraarticular position of the iliopsoas tendon (T). **(B)** View after the arthroscopic release of the adhesion and iliopsoas tendon to prevent further impingement.

Follow-Up and Outcomes

The early postoperative course was unremarkable. The patient reported relief of the groin pain earlier described. In particular, she was able to actively flex her hip without pain within 2 weeks after iliopsoas tendon debridement.

DISCUSSION

The most common indication of PAO is hip dysplasia. Hip dysplasia is defined by insufficient coverage of the femoral head by the acetabulum and is considered a risk factor for the development of groin pain and early onset of arthritis of the hip. The indication for surgical treatment of hip dysplasia in adults consists of clinical and radiological findings. Patients with LCEA <2 5°, hip osteoarthritis < Tönnis grade 2, body mass index (BMI) < 30 kg/m^2, age <45, and persistence of groin pain for > 3 month have been shown to be especially eligible for surgical treatment (6). Further indications for PAO can be pathologic acetabular retroversion resulting in FAIS. Compared with other pelvic osteotomies, PAO has been postulated to have a lower pseudarthrosis rate, which could be attributed to increased postoperative pelvic stability and larger cancellous contact surfaces (7).

The initial cohort of 75 consecutive dysplastic hips treated by Ganz showed encouraging long-term results at 11 years follow-up with 73% good to excellent results and an overall preservation rate of the joint of 82%. Major complications were only observed in the very first 18 patients (8). Recently research focused on patient-related outcome scores for younger and active patients which showed that despite significant improvement in pain level and function after PAO the average scores remained lower than for healthy age-related counterparts. A remarkably high proportion of 35% of patients experienced persistence of groin pain after PAO (6). While there is no obvious explanation for this postoperative complication, it is interesting that similar observations were made after total hip arthroplasty (THA). In patients who experienced groin pain after THA, among other factors like implant loosening, impingement of the iliopsoas tendon was identified as source of the pain (9).

The standard approach used for PAO in our clinic aims not to open the joint capsule (10); however, the capsule can either be opened accidently when preparing the osteotomy of the ilium by bluntly releasing structures off the capsule with a Hohman's retractor or intentionally for concomitant treatment of intraarticular pathologies *via* capsulotomy. The latter mentioned is similar to the DAA for THA. In this case, we hypothesize that because of the capsulotomy for femoroplasty, the iliopsoas tendon was transposed intraarticularly, and that the resulting entrapment led to the observed groin pain. As recent reports had found good results for arthroscopic iliopsoas release in cases with iliopsoas impingement after THA (11), the indication for diagnostic hip arthroscopy and iliopsoas tendon release was made in this case. The necessity of closure of the hip capsule for biomechanical reasons and superior clinical outcomes of hip joint preservation surgery have recently been discussed controversially with recommendation for closure of the hip capsule in young and active patients (12, 13). Considering the findings and the pathology presented in this case report, closure of the hip joint capsule after PAO with concomitant femoroplasty is recommended.

CONCLUSION

The intra-articular position of the Iliopsoas tendon may be a cause of groin pain after PAO with concomitant open treatment of intra-articular pathology. In PAO without open hip treatment, the capsule could accidently be opened in the process of preparation of the ilium. In both cases, careful closure of the joint capsule is recommended to prevent iliopsoas impingement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

1. Ganz. (1988). A new periacetabular osteotomy for the treatment of hip dysplasias. Technique and preliminary results. *Clin Orthop Relat Res.* 232:26. doi: 10.1097/00003086-198807000-00006
2. Clohisy JC, Ackerman J, Baca G, Baty J, Beaulé PE, Young-Jo K. et al. Patient-reported outcomes of periacetabular osteotomy from the prospective ANCHOR cohort study. *J Bone Joint Surg Am*. (2017) 99:33–41. doi: 10.2106/JBJS.15.00798
3. Büchler L, Beck M. Periacetabular osteotomy: a review of swiss experience. *Curr Rev.* (2014) 7:330–6. doi: 10.1007/s12178-014-9232-0
4. Lerch TD, Simon SD, Emanuel LF, Tannast M, Siebenrock KA. One-third of hips after periacetabular osteotomy survive 30 years with good clinical results, no progression of arthritis, or conversion to THA. *Clin Orthop Relat Res*. (2017) 475:1154–68. doi: 10.1007/s11999-016-5169-5
5. Thiagarajah S, Verhaegen J, Balijepalli P, Bingham J, Grammatopoulos G, Witt J. Iliopsoas Tendon related pain following minmally invasive periacetabular osteotomy. *Orthop Proc*. (2019) 101-B. Available online at: https://online.boneandjoint.org.uk/doi/abs/10.1302/1358-992X.2019.6.003
6. Jacobsen JS, Kjeld S, Thorborg K, Bolvig L, Storgaard J, Hölmich P. Patient-reported outcome and muscle-tendon pain after periacetabular osteotomy are related: 1-year follow-up in 82 patients with hip dysplasia. *Acta Orthopaedica*. (2019) 90:40–5. doi: 10.1080/17453674.2018.1555637
7. Wassilew GI, Janz V, Renner L, Perka C, Pruss A. Reduced rates of non-union with modified periacetabular osteotomy using peracetic-acid sterilized cancellous allografts. *Cell Tissue Bank*. (2016) 17:713–20. doi: 10.1007/s10561-016-9587-0
8. Siebenrock KA, Schöll E, Lottenbach M, Ganz R. Bernese periacetabular osteotomy. *Clin Orthop Relat Res.* (1999) 363:9–20. doi: 10.1097/00003086-199906000-00003
9. O'Sullivan M, Tai CC, Richards S, Skyrme AD, Walter WL, Walter WK. Iliopsoas tendonitis a complication after total hip arthroplasty. *J Arthroplasty*. (2007) 22:166–70. doi: 10.1016/j.arth.2006.05.034
10. Löchel J, Janz V, Carsten P, Hofer A, Zimmerer A, Wassilew GI. a new rectus and sartorius sparing approach for periacetabular osteotomy in patients with developmental dysplasia of the hip. *J Clin Med*. (2021) 10. doi: 10.3390/jcm10040601
11. Zimmerer A, Hauschild M, Nietschke R, Schneider MM, Wassilew G, Sobau C, et al. Results after arthroscopic treatment of iliopsoas impingement after total hip arthroplasty. *Arch Orthop Trauma Surg*. (2020) 142:189–95. doi: 10.1007/s00402-020-03623-z
12. Frank RM, Lee S, Bush-Joseph CA, Kelly BT, Salata MJ, Nho SJ. Improved outcomes after hip arthroscopic surgery in patients undergoing T-capsulotomy with complete repair versus partial repair for femoroacetabular impingement: a comparative matched-pair analysis. *Am J Sports Med*. (2014) 42:2634–42. doi: 10.1177/0363546514548017
13. Bolia IK, Fagotti L, Briggs KK, Philippon MJ. Midterm outcomes following repair of capsulotomy versus nonrepair in patients undergoing hip arthroscopy for Femoroacetabular Impingement With Labral Repair. *Arthrosc J Arthrosc Relat Surg*. (2019) 35:1828–34. doi: 10.1016/j.arthro.2019.01.033

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EDITED BY
Carlos Suarez-Ahedo,
Hospital Médica Sur, Mexico

REVIEWED BY
Yuan Xiao,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Yukun Zhang
zhangyukuncom@126.com
Cao Yang
caoyangunion@hust.edu.cn
Kangcheng Zhao
zhao_uh@hust.edu.cn
Bin Lv
dr_lvbin@sina.com

†These authors have contributed equally to this work

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Therapeutic perspectives of exosomes in glucocorticoid-induced osteoarthrosis

Bin Lv*†, Zhangrong Cheng†, Yajie Yu†, Yuhang Chen, Weikang Gan, Shuai Li, Kangcheng Zhao*, Cao Yang* and Yukun Zhang*

Department of Orthopaedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Exosomes are widely involved in a variety of physiological and pathological processes. These important roles are also hidden in the physiological processes related to bone. Chondrocytes, osteoblasts, synovial fibroblasts, and bone marrow mesenchymal stem cells produce and secrete exosomes, thereby affecting the biology process of target cells. Furthermore, in the primary pathogenesis of osteoarthrosis induced by steroid hormones, mainly involve glucocorticoid (GC), the exosomes have also widely participated. Therefore, exosomes may also play an important role in glucocorticoid-induced osteoarthrosis and serve as a promising treatment for early intervention of osteoarthrosis in addition to playing a regulatory role in malignant tumors. This review summarizes the previous results on this direction, systematically combs the role and therapeutic potential of exosomes in GC-induced osteoarthrosis, discusses the potential role of exosomes in the treatment and prevention of GC-induced osteoarthrosis, and reveals the current challenges we confronted.

KEYWORDS

Exosomes, glucocorticoid, osteonecrosis, femoral head, treatment

Introduction

Glucocorticoids are a class of steroid hormones that play an important role in regulating the body's development, growth, metabolism and immune function, and are also the most widely used and effective anti-inflammatory and immunosuppressive agents in clinical practice. However, long-term use of glucocorticoids can induce osteocyte apoptosis, sustained bone destruction, injury and apoptosis of bone microvascular endothelial cells (BMECs) in the femoral head, and inhibit angiogenesis accompanied by microcirculation disorders (1, 2). Therefore, long-term use of glucocorticoids can lead to Glucocorticoid-induced osteoporosis (GIOP), Osteonecrosis of the femoral head (ONFH) and other osteoarthrosis.

GIOP (Glucocorticoid osteoporosis) is one of the most common and serious adverse reactions associated with glucocorticoid use, as considered to be the most common iatrogenic cause of secondary osteoporosis, leading to early and progressive bone loss, causing osteoarthritis pain and even pathological fractures, with postmenopausal women and men over 50 years of age at high risk (3). GC mainly acts directly on

osteoblasts, osteoclasts and osteocytes. GC can reduce the formation of osteoblasts, promote the apoptosis of osteoblasts and osteoblasts, and prolong the life span of osteoclasts, means inhibit bone formation and promote bone resorption. It also reduces vascular endothelial growth factor bone vessels, interstitial fluid, and bone strength (4). At present, the clinical treatment of GIOP mainly includes the combined use of calcium and vitamin D, and the treatment of anti-osteoporosis drugs, including bone resorption inhibitors: bisphosphonates, sex hormone replacement therapy and thyrocalcitonins, when necessary. And bone formation promotors: parathyroid hormone amino-terminal fragment (PTHl-34), fluorine preparations, etc. But long-term use of these drugs can also lead to adverse reactions such as gastrointestinal reactions, osteonecrosis of the jaw, musculoskeletal pain, elevated blood pressure, and kidney stones (3, 5). Therefore, we need new effective drugs to treat GIOP. ONFH (Osteonecrosis of the femoral head) is a disease of mesenchymal cells or bone cells characterized by impaired subchondral microcirculation, bone necrosis, and accumulation of microfractures (6, 7). As a disabling and progressive disease, ONFH is caused by the destruction or interruption of the blood circulation of the femoral head at the initial stage, followed by cell necrosis, which eventually leads to hip joint dysfunction (8, 9). The pathogenic factors of ONFH mainly involve traumatic (such as femoral neck fracture, hip dislocation) and non-traumatic (such as corticosteroids, alcoholism, coagulopathy) risk factors (7, 10–12). As the most common type of ONFH, steroid-induced osteonecrosis of the femoral head (SONFH) accounts for 46.03% of the 15,000–20,000 new ONFH cases in China each year (6, 12). If early intervention is not provided, about 80% of patients will develop femoral head collapse, hip joint dysfunction, and permanent disability (13). The exact mechanism of GC (glucocorticoid)-induced ONFH involves cell death, vascular damage, or insufficient bone repair (14, 15). As we all know, GC directly induces apoptosis and inhibits angiogenesis, so it plays a vital role in destroying bone tissue formation and the occurrence of ONFH (14, 16–23). ONFH is a chronic disease that seriously affects the life quality of patients. ONFH, which usually occurs in young patients, may cause the femoral head to collapse and even require the replacement of all hip joints, accompanied by systemic functional defects and serious defects (24–26). So far, a variety of surgical methods have been used for total hip replacement and autologous cell transplantation. However, no treatment can completely cure the disease (27, 28). Besides, non-surgical treatments for ONFH (such as acetaminophen and cortisone injection) are not sufficient to prevent joint damage, and traditional drugs cannot restore the normal structure and function of the damaged musculoskeletal system (29). Therefore, it is imperative to explore the pathogenesis of ONFH in depth and find a new type of treatment that contribute to delaying the progression of the disease and repairing the damage of the bone marrow microenvironment. Luckily, the discovery of exosomes may have great potential and multiple advantages in the pathogenesis, prevention, and treatment of GC-induced osteoarthrosis (30–33).

Exosomes are naturally derived 50–150 nm nanocapsules that are secreted by cells and commonly found in blood, urine, saliva, cerebrospinal fluid, pleural fluid, and milk. Exosomes play an important paracrine effector role in cell-to-cell and/or cell-to-tissue communication and cross-species communication by transferring proteins and genetic material to target cells (34, 35). Exosomes usually contain various biologically active molecules, such as protein, RNA (mRNA, microRNA, and other non-coding RNA), DNA (mitochondrial DNA [mtDNA], double-stranded DNA [dsDNA], single-stranded DNA, and viral DNA), Lipids, amino acids, and metabolites. These different components play a key role in signal transduction between cells and regulate the microenvironment of nearby or distant cells (36–38). As a new type of biological vesicles, Exosomes have multiple advantages and are considered to be suitable tools for the treatment of various diseases including cancer. First of all, most cells can secrete exosomes and retain the characteristics of parental cells. Secondly, unlike a single protein or small molecule, exosomes contain molecules with heterogeneous functions but lack the complexity of cells and organs. In addition, exosomes show many benefits in terms of biocompatibility, immunogenicity, stability, pharmacokinetics, biodistribution, and cellular uptake mechanisms. Bone-derived exosomes are believed to be essential for intercellular communication between bone cells. The exosome-mediated transfer of nucleic acid or protein cargo between bone cells can bypass the space barriers between different cells and play a vital role in the crosstalk between bone cells that regulate bone homeostasis. Since exosomes are a new biological vesicle that regulates the bone formation, we summarized the characteristics of exosomes, listed the known functions of exosomes in bone homeostasis, and discussed the clinical potential.

In this article, we will mainly through the example of GC-induced GIOP and ONFH introduce the mechanism of exosomes in GC-induced osteoarthrosis and describes the latest achievements in the treatment of GC-induced osteoarthrosis by exosomes. Then, we introduced how exosomes act on GC-induced osteoarthrosis in different aspects. Finally, we discussed the problems that must be solved in the clinical application of these methods and the future research direction of exosomes in the treatment of GC-induced osteoarthrosis.

As a new and potential substance that can be used for early intervention and treatment of GC-induced osteoarthrosis, exosomes have been found to play an important role in the pathogenesis of osteoarthrosis caused by GC. We summarized the roles of exosomes in the three main mechanisms of GC-induced osteoarthrosis (**Figure 1**).

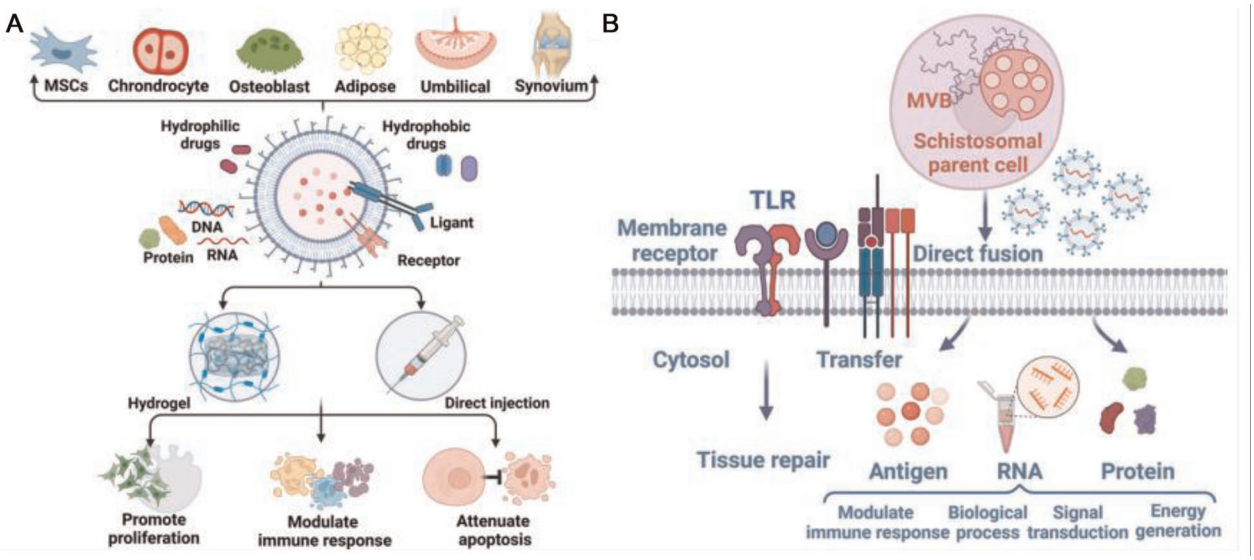

FIGURE 1
(A) Exosome-deriving cells and application of exosome to defect sites, achieving promotion of cell proliferation, modulation of immune response, and attenuation of apoptosis. (B) Biology and functions of exosomes in Glucocorticoid-induced Osteonecrosis of the Femoral Head (ONFH). Exosomes can be regarded as vehicles for delivering antigens, proteins and RNA to modulate immune responses, gene expression, and metabolic processes. Exosomes are also involved in the transfer of lipids to recognize TLRs, thus participating in tissue repair.

The role of exosomes in GC-induced apoptosis

Studies have shown that GC can directly act on osteoblasts, osteoclasts and osteocytes, reduce the formation of osteoblasts and promote the apoptosis of osteoblasts and osteoblasts. For osteoblasts, activation of glucocorticoid receptors up-regulates the expression level of P53 in mouse osteoblast cell line Mc3t3-e1, thereby enhancing the transcriptional activity of P53 and leading to up-regulation of pro-apoptotic genes P21, PUMA and NOXA. Finally, Mc3t3-e1 cells were induced apoptosis and cell cycle arrest (39). Deng's study found that dexamethasone can down-regulate the expression of P-PI3K and P-Akt to inhibit the activation of PI3K/AKT signaling pathway. The expression of Bax, caspase3, caspase9 and bcl-2 could be decreased and the expression of Bcl-2 could be increased to reduce dexamethasone induced osteoblast apoptosis by removing the expression of GSK3β, the downstream target of PI3K/AKT (40). In addition, GCs' dose has different effects on bone cells. Low dose GC treatment can lead to autophagy of bone cells, while under high dose GC stress, bone cells may undergo apoptosis or necrosis (41).

Accumulated studies have shown that GC leads to the occurrence and development of ONFH through a variety of mechanisms, and GC-induced bone cell apoptosis is one of the most important ways (42, 43). Under the action of GC, a large number of bone cells undergo apoptosis, leading to loss of bone strength, and disease progression eventually leads to the collapse of the femoral head (8). The research of Hamamura and Saito et al. showed that the increase of bone cell apoptosis is related to endoplasmic reticulum (ER) stress. Specifically, the accumulation of misfolded or unfolded proteins induces phosphorylation of protein kinase-like endoplasmic reticulum kinase (PERK), activates the unfolded protein response (UPR), and helps cells adapt to ER under mild ER stress conditions Stress (44). Among the three main signal pathways of ER stress, the PERK (protein kinase RNA-like ER kinase)/CHOP (CCAATenhancer-binding protein homologous protein) pathway is considered to be closely related to apoptosis. CHOP can inhibit the expression of Bcl-2, increase the level of lytic caspase-3, and cause cell apoptosis.

More and more studies have shown that exosomes play a crucial physiological and pathological role by influencing cell apoptosis, and the same role also occurs in bone physiology (45, 46). For example, exosomes from human umbilical cord mesenchymal stem cells (HUCMSC) can reduce apoptosis of bone marrow mesenchymal stem cells (BMSC) in osteoporotic rats through Mir-1263/Mob1/Hippo signaling pathway (47). In another study, EXOs derived from adipose-derived MSCs (ADSCs-EXOs) prominently reduced H/SD (hypoxia and serum deprivation)-induced apoptosis in the osteocyte-like cell line MLO-Y4 cells by increasing the ratio of Bcl-2/Bax, reducing the production of reactive oxygen species and cytochrome c, and activating caspase-9 and caspase-3 subsequently (48). A research report from S3 shows that

exosomes (PRP-EXOS) derived from PRP (Platelet-rich plasma) promote the expression of BCL-2 under ER stress through the AKT/BAD/BCL-2 signaling pathway. The ability to prevent GC-induced apoptosis in ONFH rats (49). PRP-exos significantly enhances the activation of the AKT and ERK signaling cascade, on the one hand, it promotes the angiogenesis of the bone microenvironment; on the other hand, it promotes the expression of anti-apoptotic proteins such as bcl-2 (50). Secondly, the study of S. Zhang et al. observed that exosomes were activated by CD73-mediated AKT and ERK signals to increase the expression of chondrocyte proliferation and anti-apoptotic related genes (51). Guo et al. discovered for the first time that exosomes secreted by human synovial-derived mesenchymal stem cells (SMSC-Exos) can be internalized into bone marrow-derived stromal cells (BMSCs) and enhance their proliferation and anti-apoptotic ability. In in vivo experiments, they found that infusion of SMSC-Exos can reduce GC-induced trabecular bone loss, bone marrow necrosis, and fat cell accumulation. The infusion of SMSC-Exos can effectively prevent GC-induced ONFH in the rat model. At the same time, in vitro cell experiments also found that SMSC-Exos can reverse the anti-proliferative effect induced by GC (52). According to reports, SMMSC-Exos derived from SMMSC significantly reduced glucocorticoid (GC)-induced adipocyte aggregation, bone marrow necrosis, and trabecular bone loss, and to a certain extent reversed bone cell proliferation arrest and BMSC cells apoptosis (52). Micro-CT analysis also showed that SMMSC-Exos significantly improved the trabecular bone microstructure and mineral density of ONFH (ONFH) induced by GC in rats (52).In addition, exosomes produced by MSC can prevent bone cell apoptosis in hypoxia/serum deficiency models and glucocorticoid-induced osteonecrosis models (48, 53) (**Figure 2**).

The numerous pieces of evidence indicate that exosomes from various sources can inhibit GC-induced apoptosis of osteoblasts and bone cells, and reverse osteonecrosis to a certain extent, which shows the great potential of exosomes in the early treatment of osteoarthrosis caused by GC.

The role of exosomes in GC-induced vascular damage

In the pathogenesis of osteoarthrosis caused by GC, GC damage to vascular endothelial cells is another main way. A considerable number of studies have shown that: glucocorticoids can induce injury and apoptosis of bone microvascular endothelial cells (BMECs) of the femoral head,

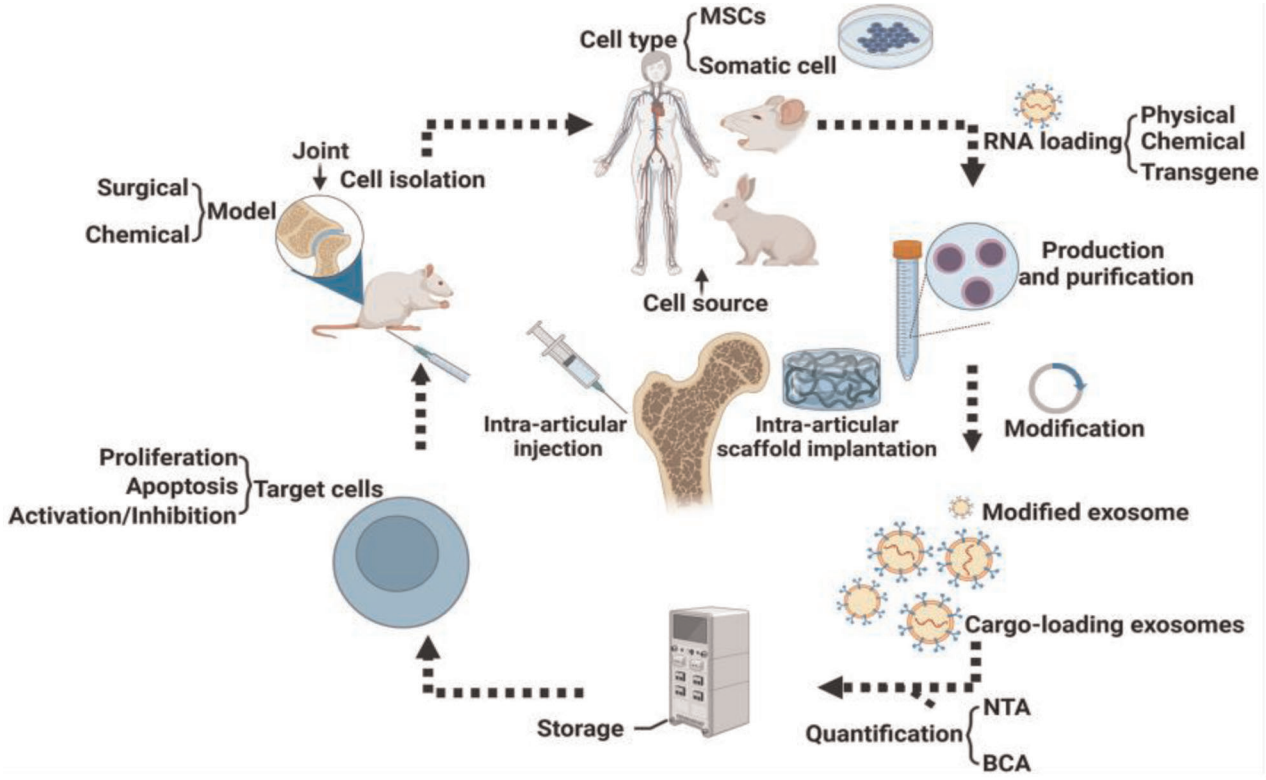

FIGURE 2
Procedures for preparation of exosomes.

which is closely related to the development of osteonecrosis and osteoporosis, leading to a hypercoagulable state and abnormal microthrombosis in the area of ONFH, and severely reducing the blood supply of trabecular bone (22, 54–58). The work of Greenberger et al. 2010 found that: GC treatment can inhibit the expression of VEGF-a in ECS and subsequent angiogenesis (59). Vascular damage is manifested by decreased function of circulating angiogenic cells, decreased migration function, and VEGF protein secretion (60).

Therefore, inhibition of endothelial cell (EC) apoptosis is necessary to maintain the integrity of blood vessels and prevent the further development of GC-induced osteoarthrosis (61). Similarly, exosomes also play an important role in the physiological and pathological processes related to endothelial cells. The study by Hu GW et al. pointed out that exosomes secreted by mesenchymal stem cells derived from human induced pluripotent stem cells can reduce limb ischemia by promoting angiogenesis in mice (62). Anderson et al. reported that MSC-derived exosomes contained abundant angiogenesis-related proteins that promote endothelial cell proliferation and angiogenesis (63, 64). And the team also detected the promotion of angiogenesis and tissue repair (including bone formation) by exosomes in both in vivo and in vitro experiments (65).In an animal experiment with osteoporotic rats as the experimental object, eight weeks after implantation of MSC-derived exosomes, the experimental group of rats detected the strong formation of blood vessels and bone tissue that was not in the control group (62). In addition, Yokota et al. proved that exosomes can accelerate the surgical angiogenesis of vascular implantation into the necrotic bone by injecting PRP-containing exosomes (66). In addition, activated platelets can also promote the proliferation and migration of bone mesenchymal stem cells (BMSCs) and ECS, thereby promoting bone formation and capillary formation (67). Qi et al and other studies have also shown that in ovariectomized rat models, exosomes secreted by iPS-derived MSCs can promote the regeneration of bone defects by enhancing angiogenesis and bone formation (68). Zuo et al. used miR-26a transfected human CD34 + stem cell-derived exosomes and found that miR-26a-CD34+-exosome enhanced the ability of human umbilical vein endothelial cells to migrate and form blood vessels, indicating that this kind of exosomes can prevent glucocorticoid-induced necrosis of the femoral skull by promoting angiogenesis and osteogenesis (69). These findings provide a novel method for vascular remodeling and bone cell proliferation in soft tissues to enhance early tissue repair.

The role of exosomes in GC-induced insufficient bone repair

The pathogenesis of ONFH caused by GC is in addition to inducing osteoblast apoptosis, damage to vascular endothelial cells also involves its inhibition of bone formation (70–73). Previous research reports pointed out that GC has complex stimulating and inhibiting effects on bone metabolism. During normal bone formation, an appropriate amount of endogenous GC signal is necessary. For example, a study by Phillips JE showed that a small dose of dexamethasone (Dex) can promote the differentiation of several osteoblasts in the oval system. However, the use of high-dose GC significantly reduced the patient's bone mass and lowered bone density, which ultimately greatly promoted the occurrence and development of ONFH (73–75). Similarly, another study also showed that GCs down-regulated the expression of osteogenic marker molecules Runt-related transcription factor 2 (RUNX2) and alkaline phosphatase, and was associated with the decrease of bone density and the rupture of trabecular bone (75). Interestingly, the findings of Ekstrom et al. found that fusion of monocyte-derived exosomes with MSC can trigger the up-regulation of two osteogenic markers: RUNX2 and BMP-2. This phenomenon and two other studies both show that exosomes can interact directly with bone cells, thereby affecting the process of bone formation (76, 77). Of course, the evidence that exosomes play an important role in osteogenesis is not limited to this limited study. As we all know, bone remodeling is a complex process that mainly involves two steps: osteoclastogenesis (used to remove damaged bone tissue) and osteogenesis (used for bone formation). Current research reports have shown that exosomes play an important role in these two steps. Published reports indicate that the transfer of exosome-specific proteins, mRNA, and miRNA is the main mechanism of exosome-mediated bone remodeling. This crosstalk establishes a new network of cell-cell interactions during bone homeostasis (78). For example, the study of Cui, Y, and her colleagues found that mature osteoblast-derived exosomes may trigger the mutation of miRNA expression profile, and then cooperatively inhibit the expression of Axin1, the core component of the Wnt signaling pathway, and finally, β-catenin is up-regulation, leading to enhanced osteogenic differentiation (79). Besides, Let-7-rich exosomes derived from osteoblasts can also enhance osteogenic effects by regulating AT-hook 2 (HMGA2) and AXIN2 (79, 80). The proliferation induced by MSC-derived exosomes has also been reported, and the MAPK pathway may be a key factor in the activity of osteoblasts mediated by exosomes (81).In addition to physiological conditions, exosomes also exhibit important functions related to osteogenesis under pathological conditions. The research results of Furuta et al. showed that during fracture healing, exosomes derived from bone marrow stem cells express MCP-1, MCP-3, SDF-1, angiogenic factors, mRNA, and miRNA, and jointly promote bone Reshape (82).At the same time, exosomes may also increase osteoblast-related proteins (RUNX-2, ALP, OCN, and OPN) and some genes (miRNA-196a, miRNA-27a, and miRNA-206) to enhance the proliferation and differentiation of osteoblasts (83). In addition to the participation of osteoblasts

in bone remodeling, osteoclasts also play an important role, and the proper balance between the two is the key to complete thigh remodeling. Exosomes also play an important role in mutual signal communication between osteoblasts and osteoclasts. The inactivation of the RANK-RANKL signaling pathway in osteoblasts can release exosomes containing miR-503-3p, thereby inhibiting the formation of osteoclasts. In animal experiments, in the CD9−/− mouse femoral fracture model (in which the production of exosomes was inhibited), the formation of callus in the experimental group was significantly delayed compared with the control group. However, this delayed effect can be corrected by local injection of exosomes (82).Similar functions of exosomes in promoting fracture repair and bone remodeling have also been verified in a mouse model of osteoporosis (62). This series of research results suggest that exosomes may play an irreplaceable role in the process of bone remodeling and bone repair, and these phenomena may be occurring in the bone repair process of ONFH caused by GC. This hypothesis has also been confirmed by research by Zuo and his colleagues. Their experiments suggested that miR-26a-CD34+-exosome enhanced the osteogenic differentiation of BMSCs under the influence of GC. Finally, miR-26a-CD34+-exos increased the vascular density and small bone density of the femoral head in the GC-induced ONFH mouse model, thereby inhibiting the progression of ONFH and promoting bone repair (69). Shang-Chun Guo et al. also found that SMSC-Exos can improve bone mineral density and trabecular bone microstructure of GC-induced ONFH rats. Immunohistochemical staining for osteocalcin showed that MPS (methylprednisolone) was injected into the thigh The osteogenic response of bones is reduced, but SMSC-EXOS significantly inhibits this effect (52). Another study found that exosomes rich in miR-122-5 down-regulate SPRY2 through the RTK/Ras/mitogen-activated protein kinase (MAPK) signaling pathway, thereby delaying the development of ONFH (84).

In the past few decades, exosomes are involved in many biological processes related to bone metabolism, including angiogenesis, cell differentiation, immune regulation, metabolic balance, and development (36, 85–88). However, exosomes are not simple nucleic acid or protein molecules, but microvesicles containing a variety of substances including RNA, DNA, protein, and lipids. While there are extensive biological functions, exosomes are also highly heterogeneous, involving different sources and different contents. Therefore, since exosomes work through each of the molecules contained, understanding the mechanism of action of each content is crucial for further understanding and application of exosomes. We reviewed the roles played by different contents of exosomes derived from cells related to bone metabolism and the molecular mechanisms of their effects and summarized the possible roles of various substances in GC-induced osteoarthrosis (**Table 1**).

The role of miRNA

As one of the most studied contents in exosomes, miRNA released by exosomes has been shown to play an important

TABLE 1 Function of RNA family in glucocorticoid-induced osteonecrosis of the femoral head.

Class	Molecule	Vitro study	Vivo study	Biological effects	Ref.
miRNA	miR-26a	BMSCs	GC-induced ONFH rats	promoted the osteogenic differentiation of BMSCs, increased the vessel density and trabecular bone integrity in the GC-induced ONFH	(69)
	miR-548d-5p	hBMSCs	/	suppressed the dexamethasone-induced adipogenic differentiation of hBMSCs, enhanced their osteogenic potential.	(99)
	miR-27a-3p	MC3T3-E1 cells	/	decreased adenomatous polyposis coli (APC) expression, activated β-catenin pathway	(89)
	miR-8485	BMSCs	/	activated Wnt/b-catenin pathways, promoted chondrogenic differentiation of BMSCs	(92)
	miRNA-122-5p	BMSCs	ONFH rabbits	down-regulated SPRY2, promoted the proliferation and differentiation of osteoblasts, attenuated ONFH development	(153)
lncRNA	lncRNA-KLF3-AS1	OA chondrocytes	OA mice	induced chondrocyte proliferation, inhibited chondrocyte apoptosis via miR-206/GIT1 axis.	(109)
	lncRNA HOTAIR	MSCs	/	Regulated osteogenic differentiation and proliferation, targeted gene SMAD7 in non-traumatic ONFH	(110)
	lncRNA-Miat	rMSCs	/	promoted osteogenesis of rMSCs while silencing, modulated the function of endothelial cells via VEGF	(114)
circRNA	circUSP45	BMSCs	SD rats	sponged miR-127-5p through PTEN/ AKT signal pathway, reduced osteogenesis in bone GIONFH	(126)
	circ19142/ circ5846	MC3T3-E1 cells	/	induced osteogenic differentiation	(127)
	circFOXP1	MSCs	Wistar rats	promoted proliferation and differentiation of MSCs, preserved the MSC multipotent state, modulated non-canonical Wnt and EGFR pathways	(128)
	circRNA0010729	HUVECs	/	regulated hypoxia-induced HUVECs via miR-186/HIF-1a axis	(130)
	circRNA0003575	HUVECs	/	promoted the proliferation and the angiogenesis ability of oxLDL-induced HUVECs while silencing	(131)

role in multiple physiological processes of bone metabolism. For example, exosomes derived from myoblasts enter pre-osteogenic cells and promote osteoblast differentiation through miR-27a-3p-mediated β-catenin pathway activation (89). Young MSC exosomes can rejuvenate senescent HSCs through autophagy-related miR-17 and miR-34a cell-to-cell transfer, while miR-23b and miR-92a can effectively treat OA (Osteoarthritis) (90, 91). Furthermore, the exosomes of chondrocytes may promote the chondrogenesis and differentiation of BMSCs by activating the Wnt/β-catenin pathway, which is related to the inhibition of GSK-3β expression by miR-8485 in the exosomes (92).

Besides, recent studies have also highlighted the importance and significance of microRNA (miRNA) in the pathogenesis, prevention, and treatment of GC-induced osteoarthrosis (31, 32). One study showed that exosomal miRNAs promote osteoarthrosis development by influencing osteoblasts, osteoclasts and bone matrix through oxidative stress (OS) mediation. Exogenous antioxidants can help prevent or delay the development of osteoarthrosis, while the antioxidant balance in the body is disrupted (93). But Chen et al. detected the expression of Mir-425-5p in bone marrow mesenchymal stem cells (MSC) by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) and the expression of TNF by ELISA, and the results showed that Mir-425-5p could regulate cell apoptosis, proliferation and differentiation induced by TNF. ANXA2 is a target of Mir-425-5p and is involved in TNF-induced apoptosis, proliferation and differentiation of MSC cells. It was concluded that Mir-425-5P could enhance osteoporosis in mice (94). The above studies indicate that the mechanism of miRNA action on osteoporosis still needs further study. The above study indicates that the current research on the mechanism of miRNA action on osteoporosis is limited, and it is necessary to conduct in-depth basic and clinical research.

Wu et al. verified three up-regulated miRNAs (miR-210-3p, miR-320e, and let-7c) by comparing the expression of miRNA in non-traumatic ONFH and femoral neck fractures (95).In previous research evidence, Let-7 in osteoblast-derived exosomes has been shown to enhance osteogenesis by regulating AT-hook 2 (HMGA2) and AXIN2 (79, 80). This indicates that there are still a large number of miRNA that may have a potentially important role in bone repair and bone remodeling in ONFH, waiting to be discovered and explained. ONFH caused by overuse of glucocorticoids accounts for the majority of non-traumatic ONFH. The decrease in the proliferation of mesenchymal stem cells is related to the pathogenesis of glucocorticoid-induced ONFH, and this mutual connection may be involved in the exosomes released by mesenchymal stem cells. Bian et al. compared the expression of miRNA in human mesenchymal stem cells treated with and without dexamethasone. The study found that 11 up-regulated (miR-16-5p, miR-103a-3p, miR-107, miR-196a/b-5p, miR-378d, miR-1268a/b/f/g, miR-4289) and 6 down-regulated (miR-24-3p, miR-378a/h/I, miR-4448, miR-4634) miRNA were found between the two different concentrations of dexamethasone treatment groups. For further analysis, they injected methylprednisolone (21 mg/kg) subcutaneously into C57BL/6J mice and found that miR-21-3p and miR-652-5p were up-regulated and miR-34b-3p, miR-34c-5p, miR-148a-3p, miR-196a-5p, and miR-206-3p are down-regulated, which are predicted to be involved in osteogenic differentiation (96). Hao et al. found that miR-708 may enhance the osteogenic effect of mesenchymal stem cells and inhibit their adipogenic differentiation ability by targeting Smad3 (8). Yamasaki et al. confirmed that miR-210 (angiogenic miRNA) is highly expressed in non-invasive ONFH and may regulate angiogenesis in ONFH (56, 97, 98). Sun et al. confirmed that miR-548d-5p promotes the osteogenic differentiation of mesenchymal stem cells by acting on PPARγ, and may inhibit glucocorticoid-induced ONFH (99). In addition, miR-27 has also been shown to inhibit adipogenesis and enhance bone formation by regulating the expression of GREM1 and PPARγ (83, 100–103). These findings indicate that miRNAs secreted in the bone marrow microenvironment play an irreplaceable role in the pathogenesis of steroid-induced ONFH and the balance between osteogenic differentiation and adipogenic differentiation of mesenchymal stem cells.

The role of lncRNA

As a regulatory RNA, long non-coding RNA (lncRNA) has been shown to play a key role in various cellular physiological functions including cell proliferation, invasion, metabolism, apoptosis, and stem cell differentiation. Recent studies have shown that lncRNA is directly involved in the pathogenesis of many orthopedic diseases and also plays an important role in the process of bone development and regeneration. For example, long non-coding RNA (lncRNA) has been shown to be an important exosomal content in OA, widely involved in the regulation of various pathological and physiological processes (103, 104). Exosomes from adipose-derived stem cells (ADSCs-EXOS) have been verified that play an effective part in the repair of different tissues and organs. ADSCs-EXOS have also been confirmed to help in the treatment of osteoporosis (105). However, Wang et al. believed that compared with ADSC-EXOS, KCNQ1OT1-ExOS, as a kind of lncRNA closely related to cell proliferation, migration and apoptosis, had a more significant inhibitory effect on TNF-α -induced cytotoxicity and apoptosis (106).

Recent research results indicate that lncRNA also plays an important regulatory role in the pathogenesis and repair of ONFH. LncRNA was found to be differentially expressed in ONFH tissues, bone marrow mesenchymal stem cells and bone microvascular endothelial cells which isolated from

ONFH patients (9, 107, 108). Functional research has further clarified its important role in the survival of osteoblasts closely related to ONFH and the osteogenic differentiation of bone marrow mesenchymal stem cells. Liu et al. reported that MSC-Exos mainly up-regulated Col2a1 and proteoglycan levels through lncRNA-KLF3-AS1.239 released from exosomes, and down-regulated the expression of MMP13 and Rux2, which promoted the survival of IL-1β-treated chondrocytes (109). According to reports, as a differentially expressed lncRNA isolated from steroid-induced ONFH patients, forced expression of RP11-154D6 can promote the increase in the expression of osteogenic differentiation markers (osteocalcin (OCN) and RUNX2) and reduce the expression of adipogenic differentiation markers (such as lipoprotein lipase (LPL) and peroxisome proliferator-activated receptor gamma (PPAR gamma)), these effects ultimately lead to enhanced bone formation (108). In another study, Wei et al. found that HOTAIR can negatively regulate the proliferation and osteogenic differentiation of mesenchymal stem cells by regulating the expression of miR-17-5p and Smad7, and can be used as a therapeutic target for non-invasive ONFH (110). Wang et al. used the reconstruction of the coding-noncoding gene co-expression (CNC) network to reveal the key role of two lncRNAs (HOTAIR and RP1-193H18.2) in regulating the osteogenic and adipogenic differentiation of bone marrow MSCs (111). In addition, Yu et al. analyzed the BMEC (bone microvascular endothelial cells) of patients who underwent a conventional total hip replacement and exposed the cells to hydrocortisone (0.1 mg/ml) for 24 h using the co-expression analysis technology of non-coding RNA and related mRNA, the results reveal that FoxO transcription factors are closely related to the regulation of angiogenesis (112, 113). Furthermore, the overexpression of MIAT in the bone marrow microenvironment may lead to steroid-related ONFH by inhibiting the osteogenic differentiation of MSC, and this process can be blocked by the epigenetic silencing of MIAT by HXTL (114). Fan and colleagues confirmed that MALAT1 can protect human osteoblasts from dexamethasone-induced cell death. Specifically, MALAT1 prevents steroid-induced ONFH by regulating PPM1E-AMPK-NRF2-oxidative stress and the miR-214-ATF4 axis (32).

The role of circRNA

Circular RNA (circRNA) is a member of the non-coding RNA family. Unlike linear RNAs such as miRNA or lncRNA, it forms a covalently closed continuous loop, making them resistant to digestion by RNA exonuclease. Accumulated evidence shows that circRNA can perform biological functions by acting as a microRNA sponge, encoding proteins, and binding to proteins (115–121). Research on circRNA is later than most linear RNAs, but in recent studies, circRNA has also been found to be involved in bone metabolism in many diseases (including GC-induced osteoarthrosis).

For instance, Feng et al. found that hsa_circ_0006859 in exosomes of osteoporosis patients can inhibit osteoblast differentiation and promote adipose decomposition of human bone marrow mesenchymal stem cells (hBMSCs). Hsa_circ_0006859 acts, as a competitive endogenous RNA (ceRNA) of Mir-431-5p, directly binds to Mir-431-5p and promotes the expression of ROCK1 which was confirmed as a novel target gene of Mir-431-5p (122).

Generally, the weakened osteogenic differentiation and increased adipogenic differentiation of BMSCs are closely related to the formation of ONFH (102). Xiang et al. have identified 90 up-regulated and 141 down-regulated differentially expressed circRNAs in steroid-induced ONFH (SONFH) BMSCs (123). Further functional studies have found that circRNA immunoglobulin superfamily member 11 can promote osteoblast differentiation in BMSC osteogenesis through glycogen synthase kinase 3β/β-catenin signaling pathway, and knocking down this circRNA can increase miR199b-5p expression (123–125). In addition, some studies have found that circRNA plays a key role in the regulation of bone metabolism mainly by acting as a molecular sponge of miRNA. For example, Kuang et al. proved that in the steroid-induced ONFH rat model, circRNA ubiquitin-specific protease 45 can upregulate phosphatase and tensin homologs by binding to miR-127-5p, thereby inhibiting the protein kinase B pathway and regulate the bone mass of rats (126). In addition, the mode of action of the miRNA-mRNA axis targeted by circ19142/circ5846, circ19142 and circ5846 have been shown to act as sponges for miR-7067-5p in osteoblast differentiation (127). Besides, circRNA FOXP1 has also been shown to play a key role by acting as a sponge for several miRNAs in the regulation of MSC differentiation, which is closely related to the pathogenesis of ONFH (128). Although there are few studies on another important pathogenic mechanism (adipogenic differentiation of mesenchymal stem cells) that affects osteogenesis, The above observation results also show that there is a close correlation between circRNA and SONFH, which can be used for follow-up research and clinical treatment, and provides a good guide for finding therapeutic targets. In another core pathogenic mechanism of ONFH, endothelial cell damage and angiogenesis disorder, circRNA has also been shown to play an important biological role (129). For example, CircRNA0010729 mediates the apoptosis and proliferation of vascular endothelial cells by targeting the miR-186/hypoxia-inducible factor-1α axis (130). Furthermore, circRNA0003575 is up-regulated in human umbilical vein endothelial cells (HUVEC) induced by oxidized low-density lipoprotein and promotes HUVEC proliferation and angiogenesis (131). Although there is no research on circRNA directly targeting endothelial cells in the bone

marrow microenvironment, these findings also indicate that circRNA may play an important role in the activation mechanism of ONFH. The above research results indicate that circRNA plays a unique role in the formation of ONFH, and due to its unique stability, may play an irreplaceable role in the treatment of ONFH.

The role of protein

As a kind of exosomal load, many types of specific cell proteins have been shown to contribute to the communication and signal transduction between cells (132–137). In the study of bone-related exosomal proteins, Tsuno et al. used 2D-DIGE and mass spectrometry to identify serum exosomal proteins extracted from the healthy group and the OA group. They found that the exosome between the OA group and the healthy group has 21 spots in the somatic protein profile with different intensities, such as cathepsin F and Igalpha-2 chain C region, indicating the potential role of these proteins in OA (138). At the same time, recent studies have also discovered the role of exosomal proteins in regulating the biological response of chondrocytes. Zhang et al. found the expression of CD73/ecto-5'-nucleotidase in MSC-derived exosomes and found that the CD73 inhibitor AMPCP or the non-selective adenosine receptor antagonist theophylline can reduce MSC Exosomes-induced phosphorylation of AKT and ERK in chondrocytes (139). The results above indicate that the role of the protein-loaded exosomes in the differentiation and development of bone cells still needs further exploration, although the existing evidence has suggested its regulation of cartilage and MSC.

The role of DNA

Since the study of exosomal DNA is later than the study of RNA, only a small amount of literature has reported that carrying cytoplasmic DNA in exosomes can prevent cell senescence and cell death caused by DNA damage (140, 141). Moreover, exosomal DNA can exert effects because cells can secrete exosomes and remove harmful DNA in the extracellular matrix. In addition to double-stranded DNA, exosomes also contain single-stranded DNA, but we still know little about the biological role of this DNA. Therefore, it is necessary to study the expression and function of these DNAs in the bone marrow microenvironment.

Conclusions and outlooks

Exosomes carrying contents like DNA or RNA family serve as crucial vehicles for intercellular communication. Although there is a broad range of potential applications and uses of exosomes, it still appears to be some problems of methods for exosome isolation and analysis. Primarily, the quantities of exosomes released by mammalian cells is relatively low and the purification of exosomes is burdensome. Enhancing the ability to load a variety of cargoes and targeting capabilities without corrupting exosomes is also very important for the utility of this delivery technology. It is hoped that more researchers will participate in the exploration of these problems from bench to bedside in the future. Exosomes show important regulatory effects in different stages and different pathological mechanisms in osteoarthrosis caused by GC, which shows the usefulness and potential of exosomes in the treatment of steroid-related osteoarthrosis. Up to now, take GC-induced ONFH's treatment for example, it has mainly relied on drug therapy, core decompression, interventional therapy, and cell therapy as early intervention methods, but usually, 65%–85% of patients will continue to develop femoral head collapse (85). Once it develops into the terminal stage of the disease, total hip replacement surgery becomes the only viable option, and this will bring tremendous pressure on the patient's economy and life. Furthermore, for those young patients, ONFH often means that multiple revision surgeries may be required in the future (because the life of the prosthesis is limited), which aggravates the patient's physical and psychological burden. Therefore, as a promising alternative to the traditional treatment of osteoarthrosis, exosomes have many incomparable advantages in the early intervention of osteoarthrosis, and they have received widespread attention as a new treatment for osteoarthrosis (34, 142, 143). Firstly, exosomes have multiple advantages in immunogenicity, and allogeneic exosome injection may not cause obvious complications and rejection in terms of immunogenicity (66). Secondly, exons show good stability and pertinence, because they maintain the properties of their parent cells for a long period and maintain their inherent integrity, which makes them more effective in the treatment of osteoarthrosis. Easily target cells without causing systemic adverse reactions (144–146). Finally, exosomes also show certain advantages in biodistribution and pharmacokinetics. Due to their small size, these nanoparticles can easily reach the wound site. Exosomes can be transformed to express specific surface molecules and can selectively bind to molecules overexpressed on target cells, and exosomes can use their unique functions to extend their half-life (147–152). However, exosomes still face many challenges before entering clinical applications, and the main resistance comes from the separation and purification of exosomes, the modification of exosomes, and the heterogeneity of exosomes. Concerning the role of exosomes in GC-induced osteoarthrosis, research on the underlying mechanism and diagnostic/therapeutic applications have just begun. Although there are still many

problems to be solved in this field, we speculate that technological advancement will give an optimistic outlook for the treatment of GC-induced osteoarthrosis based on exosomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

BL wrote the manuscript; ZRC revised the manuscript; YJY and YHC performed the literature search; WKG, SL, and KCZ compiled the graphs; CY and YKZ designed the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Li J, Ge Z, Fan L, Wang K. Protective effects of molecular hydrogen on steroid-induced osteonecrosis in rabbits via reducing oxidative stress and apoptosis. *BMC Musculoskelet Disord*. (2017) 18(1):58. doi: 10.1186/s12891-017-1431-6

2. Nan K, Zhang Y, Zhang X, Li D, Zhao Y, Jing Z, et al. Exosomes from miRNA-378-modified adipose-derived stem cells prevent glucocorticoid-induced osteonecrosis of the femoral head by enhancing angiogenesis and osteogenesis via targeting miR-378 negatively regulated suppressor of fused (Sufu). *Stem Cell Res Ther*. (2021) 12(1):331. doi: 10.1186/s13287-021-02390-x

3. Laurent MR, Goemaere S, Verroken C, Bergmann P, Body JJ, Bruyère O, et al. Prevention and treatment of glucocorticoid-induced osteoporosis in adults: consensus recommendations from the belgian bone club. *Front Endocrinol (Lausanne)*. (2022) 13:908727. doi: 10.3389/fendo.2022.908727

4. Walsh S, Jordan GR, Jefferiss C, Stewart K, Beresford JN. High concentrations of dexamethasone suppress the proliferation but not the differentiation or further maturation of human osteoblast precursors in vitro: relevance to glucocorticoid-induced osteoporosis. *Rheumatology (Oxford)*. (2001) 40(1):74–83. doi: 10.1093/rheumatology/40.1.74

5. Yang Y, Nian H, Tang X, Wang X, Liu R. Effects of the combined Herba Epimedii and Fructus Ligustri Lucidi on bone turnover and TGF-β1/Smads pathway in GIOP rats. *J Ethnopharmacol*. (2017) 201:91–9. doi: 10.1016/j.jep.2017.02.033

6. Moya-Angeler J, Gianakos AL, Villa JC, Ni A, Lane JM. Current concepts on osteonecrosis of the femoral head. *World J Orthop*. (2015) 6(8):590–601. doi: 10.5312/wjo.v6.i8.590

7. Shah KN, Racine J, Jones LC, Aaron RK. Pathophysiology and risk factors for osteonecrosis. *Curr Rev Musculoskelet Med*. (2015) 8(3):201–9. doi: 10.1007/s12178-015-9277-8

8. Hao C, Yang S, Xu W, Shen JK, Ye S, Liu X, et al. MiR-708 promotes steroid-induced osteonecrosis of femoral head, suppresses osteogenic differentiation by targeting SMAD3. *Sci Rep*. (2016) 6:22599. doi: 10.1038/srep22599

9. Huang G, Zhao G, Xia J, Wei Y, Chen F, Chen J, et al. FGF2 and FAM201A affect the development of osteonecrosis of the femoral head after femoral neck fracture. *Gene*. (2018) 652:39–47. doi: 10.1016/j.gene.2018.01.090

10. Cui L, Zhuang Q, Lin J, Jin J, Zhang K, Cao L, et al. Multicentric epidemiologic study on six thousand three hundred and ninety five cases of femoral head osteonecrosis in China. *Int Orthop*. (2016) 40(2):267–76. doi: 10.1007/s00264-015-3061-7

11. Lespasio MJ, Sodhi N, Mont MA. Osteonecrosis of the hip: a primer. *Perm J*. (2019) 23. doi: 10.7812/TPP/18-100

12. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV. The role of "cell therapy" in osteonecrosis of the femoral head. A systematic review of the literature and meta-analysis of 7 studies. *Acta Orthop*. (2016) 87(1):72–8. doi: 10.3109/17453674.2015.1077418

13. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest*. (1999) 104(4):439–46. doi: 10.1172/JCI6610

14. Sheng H, Sheng CJ, Cheng XY, Zhang G, Lee KM, Leung KS, et al. Pathomorphological changes of bone marrow adipocytes in process of steroid-associated osteonecrosis. *Int J Clin Exp Pathol*. (2013) 6(6):1046–50.

15. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature*. (2004) 428(6983):668–73. doi: 10.1038/nature02460

16. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest*. (1998) 102(2):274–82. doi: 10.1172/JCI2799

17. Wang X, Liu Y, Wang X, Liu R, Li J, Zhang G, et al. The role of (99 m)Tc-Annexin V apoptosis scintigraphy in visualizing early stage glucocorticoid-induced femoral head osteonecrosis in the rabbit. *Biomed Res Int*. (2016) 2016:7067259. doi: 10.1155/2016/7067259

18. Guo S, Mao L, Ji F, Wang S, Xie Y, Fei H, et al. Activating AMP-activated protein kinase by an α1 selective activator compound 13 attenuates dexamethasone-induced osteoblast cell death. *Biochem Biophys Res Commun*. (2016) 471(4):545–52. doi: 10.1016/j.bbrc.2016.02.036

19. Guo S, Xie Y, Fan JB, Ji F, Wang S, Fei H. α-Melanocyte stimulating hormone attenuates dexamethasone-induced osteoblast damages through activating melanocortin receptor 4-SphK1 signaling. *Biochem Biophys Res Commun*. (2016) 469(2):281–7. doi: 10.1016/j.bbrc.2015.11.104

20. Zhang C, Zou YL, Ma J, Dang XQ, Wang KZ. Apoptosis associated with Wnt/β-catenin pathway leads to steroid-induced avascular necrosis of femoral head. *BMC Musculoskelet Disord*. (2015) 16:132. doi: 10.1186/s12891-015-0606-2

21. Ogata K, Katagiri W, Osugi M, Kawai T, Sugimura Y, Hibi H, et al. Evaluation of the therapeutic effects of conditioned media from mesenchymal stem cells in a rat bisphosphonate-related osteonecrosis of the jaw-like model. *Bone*. (2015) 74:95–105. doi: 10.1016/j.bone.2015.01.011

22. Kerachian MA, Harvey EJ, Cournoyer D, Chow TY, Séguin C. Avascular necrosis of the femoral head: vascular hypotheses. *Endothelium*. (2006) 13 (4):237–44. doi: 10.1080/10623320600904211

23. Hao ZC, Lu J, Wang SZ, Wu H, Zhang YT, Xu SG. Stem cell-derived exosomes: a promising strategy for fracture healing. *Cell Prolif*. (2017) 50(5): e12359. doi: 10.1111/cpr.12359

24. Qi Y, Zhu Y, Cao Y, Wu H, Sun M, Wu H, et al. Association between MMP-3 polymorphisms among Chinese patients with osteonecrosis of the femoral head. *Oncotarget*. (2017) 8(65):108859–66. doi: 10.18632/oncotarget.22313

25. Gangji V, Hauzeur JP. Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. Surgical technique. *J Bone Joint Surg Am*. (2005) 87(Suppl 1(Pt 1)):106–12.

26. Mont MA, Etienne G, Ragland PS. Outcome of nonvascularized bone grafting for osteonecrosis of the femoral head. *Clin Orthop Relat Res*. (2003) (417):84–92. doi: 10.1097/01.blo.0000096826.67494.38

27. Kim SJ, Bahk WJ, Chang CH, Jang JD, Suhl KH. Treatment of osteonecrosis of the femoral head using autologous cultured osteoblasts: a case report. *J Med Case Rep*. (2008) 2:58. doi: 10.1186/1752-1947-2-58

28. Houdek MT, Wyles CC, Sierra RJ. Osteonecrosis of the femoral head: treatment with ancillary growth factors. *Curr Rev Musculoskelet Med*. (2015) 8 (3):233–9. doi: 10.1007/s12178-015-9281-z

29. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. *Bone Res*. (2016) 4:15040. doi: 10.1038/boneres.2015.40

30. Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone*. (2012) 50 (1):325–30. doi: 10.1016/j.bone.2011.11.002

31. Yuan HF, Von Roemeling C, Gao HD, Zhang J, Guo CA, Yan ZQ. Analysis of altered microRNA expression profile in the reparative interface of the femoral head with osteonecrosis. *Exp Mol Pathol*. (2015) 98(2):158–63. doi: 10.1016/j.yexmp.2015.01.002

32. Wang B, Yu P, Li T, Bian Y, Weng X. MicroRNA expression in bone marrow mesenchymal stem cells from mice with steroid-induced osteonecrosis of the femoral head. *Mol Med Rep*. (2015) 12(5):7447–54. doi: 10.3892/mmr.2015.4386

33. Cui Y, Guo Y, Kong L, Shi J, Liu P, Li R, et al. A bone-targeted engineered exosome platform delivering siRNA to treat osteoporosis. *Bioact Mater*. (2022) 10:207–21. doi: 10.1016/j.bioactmat.2021.09.015

34. De Jong OG, Van Balkom BW, Schiffelers RM, Bouten CV, Verhaar MC. Extracellular vesicles: potential roles in regenerative medicine. *Front Immunol*. (2014) 5:608. doi: 10.3389/fimmu.2014.00608

35. Wiklander OPB, Brennan M, Lötvall J, Breakefield XO, El Andaloussi S. Advances in therapeutic applications of extracellular vesicles. *Sci Transl Med*. (2019) 11(492):eaav8521. doi: 10.1126/scitranslmed.aav8521

36. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. *Nat Rev Immunol*. (2002) 2(8):569–79. doi: 10.1038/nri855

37. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. (2007) 9(6):654–9. doi: 10.1038/ncb1596

38. Skog J, Würdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol*. (2008) 10 (12):1470–6. doi: 10.1038/ncb1800

39. Li H, Qian W, Weng X, Wu Z, Li H, Zhuang Q, et al. Glucocorticoid receptor and sequential P53 activation by dexamethasone mediates apoptosis and cell cycle arrest of osteoblastic MC3T3-E1 cells. *PLoS One*. (2012) 7(6): e37030. doi: 10.1371/journal.pone.0037030

40. Deng S, Dai G, Chen S, Nie Z, Zhou J, Fang H, et al. Dexamethasone induces osteoblast apoptosis through ROS-PI3K/AKT/GSK3β signaling pathway. *Biomed Pharmacother*. (2019) 110:602–8. doi: 10.1016/j.biopha.2018.11.103

41. Yao W, Dai W, Jiang JX, Lane NE. Glucocorticoids and osteocyte autophagy. *Bone*. (2013) 54(2):279–84. doi: 10.1016/j.bone.2013.01.034

42. Plotkin LI, Manolagas SC, Bellido T. Glucocorticoids induce osteocyte apoptosis by blocking focal adhesion kinase-mediated survival. Evidence for inside-out signaling leading to anoikis. *J Biol Chem*. (2007) 282(33):24120–30. doi: 10.1074/jbc.M611435200

43. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest*. (1999) 104(10):1363–74. doi: 10.1172/JCI6800

44. Harding HP, Zhang Y, Zeng H, Novoa I, Lu PD, Calfon M, et al. An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell*. (2003) 11(3):619–33. doi: 10.1016/S1097-2765(03)00105-9

45. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat Cell Biol*. (2019) 21(1):9–17. doi: 10.1038/s41556-018-0250-9

46. Pluchino S, Smith JA. Explicating exosomes: reclassifying the rising stars of intercellular communication. *Cell*. (2019) 177(2):225–7. doi: 10.1016/j.cell.2019.03.020

47. Yang BC, Kuang MJ, Kang JY, Zhao J, Ma JX, Ma XL. Human umbilical cord mesenchymal stem cell-derived exosomes act via the miR-1263/Mob1/Hippo signaling pathway to prevent apoptosis in disuse osteoporosis. *Biochem Biophys Res Commun*. (2020) 524(4):883–9. doi: 10.1016/j.bbrc.2020.02.001

48. Ren L, Song ZJ, Cai QW, Chen RX, Zou Y, Fu Q, et al. Adipose mesenchymal stem cell-derived exosomes ameliorate hypoxia/serum deprivation-induced osteocyte apoptosis and osteocyte-mediated osteoclastogenesis in vitro. *Biochem Biophys Res Commun*. (2019) 508 (1):138–44. doi: 10.1016/j.bbrc.2018.11.109

49. Tao SC, Yuan T, Rui BY, Zhu ZZ, Guo SC, Zhang CQ. Exosomes derived from human platelet-rich plasma prevent apoptosis induced by glucocorticoid-associated endoplasmic reticulum stress in rat osteonecrosis of the femoral head via the Akt/Bad/Bcl-2 signal pathway. *Theranostics*. (2017) 7(3):733–50. doi: 10.7150/thno.17450

50. Ho L, Tan SY, Wee S, Wu Y, Tan SJ, Ramakrishna NB, et al. ELABELA is an endogenous growth factor that sustains hESC self-renewal via the PI3K/AKT pathway. *Cell Stem Cell*. (2015) 17(4):435–47. doi: 10.1016/j.stem.2015.08.010

51. Zhang S, Chu WC, Lai RC, Lim SK, Hui JH, Toh WS. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. *Osteoarthritis Cartilage*. (2016) 24(12):2135–40. doi: 10.1016/j.joca.2016.06.022

52. Guo SC, Tao SC, Yin WJ, Qi X, Sheng JG, Zhang CQ. Exosomes from human synovial-derived mesenchymal stem cells prevent glucocorticoid-induced osteonecrosis of the femoral head in the rat. *Int J Biol Sci*. (2016) 12 (10):1262–72. doi: 10.7150/ijbs.16150

53. Kuang MJ, Huang Y, Zhao XG, Zhang R, Ma JX, Wang DC, et al. Exosomes derived from Wharton's jelly of human umbilical cord mesenchymal stem cells reduce osteocyte apoptosis in glucocorticoid-induced osteonecrosis of the femoral head in rats via the miR-21-PTEN-AKT signalling pathway. *Int J Biol Sci*. (2019) 15(9):1861–71. doi: 10.7150/ijbs.32262

54. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. *Circ Res*. (2003) 92(1):81–7. doi: 10.1161/01.RES.0000050588.35034.3C

55. El Zaoui I, Behar-Cohen F, Torriglia A. Glucocorticoids exert direct toxicity on microvasculature: analysis of cell death mechanisms. *Toxicol Sci*. (2015) 143 (2):441–53. doi: 10.1093/toxsci/kfu243

56. Kerachian MA, Séguin C, Harvey EJ. Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action. *J Steroid Biochem Mol Biol*. (2009) 114(3-5):121–8. doi: 10.1016/j.jsbmb.2009.02.007

57. Williams TA, Verhovez A, Milan A, Veglio F, Mulatero P. Protective effect of spironolactone on endothelial cell apoptosis. *Endocrinology*. (2006) 147 (5):2496–505. doi: 10.1210/en.2005-1318

58. Zhang Q, Li T, Li Z, Lu J, Wu X, Gao F, et al. Autocrine activity of extracellular vesicles induced by icariin and its effectiveness in glucocorticoid-induced injury of bone microvascular endothelial cells. *Cells*. (2022) 11 (12):1921. doi: 10.3390/cells11121921

59. Greenberger S, Boscolo E, Adini I, Mulliken JB, Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med*. (2010) 362(11):1005–13. doi: 10.1056/NEJMoa0903036

60. Aschbacher K, Derakhshandeh R, Flores AJ, Narayan S, Mendes WB, Springer ML. Circulating angiogenic cell function is inhibited by cortisol in vitro and associated with psychological stress and cortisol in vivo. *Psychoneuroendocrinology*. (2016) 67:216–23. doi: 10.1016/j.psyneuen.2016.02.019

61. Nuttall ME, Gimble JM. Is there a therapeutic opportunity to either prevent or treat osteopenic disorders by inhibiting marrow adipogenesis? *Bone*. (2000) 27 (2):177–84. doi: 10.1016/S8756-3282(00)00317-3

62. Hu GW, Li Q, Niu X, Hu B, Liu J, Zhou SM, et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells attenuate

limb ischemia by promoting angiogenesis in mice. *Stem Cell Res Ther*. (2015) 6 (1):10. doi: 10.1186/scrt546

63. Anderson JD, Johansson HJ, Graham CS, Vesterlund M, Pham MT, Bramlett CS, et al. Comprehensive proteomic analysis of mesenchymal stem cell exosomes reveals modulation of angiogenesis via nuclear factor-kappaB signaling. *Stem Cells*. (2016) 34(3):601–13. doi: 10.1002/stem.2298

64. Salomon C, Ryan J, Sobrevia L, Kobayashi M, Ashman K, Mitchell M, et al. Exosomal signaling during hypoxia mediates microvascular endothelial cell migration and vasculogenesis. *PLoS One*. (2013) 8(7):e68451. doi: 10.1371/journal.pone.0068451

65. Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E. Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. *Stem Cells Dev*. (2015) 24(14):1635–47. doi: 10.1089/scd.2014.0316

66. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. (2020) 367(6478). doi: 10.1126/science.aau6977

67. Yuan T, Guo SC, Han P, Zhang CQ, Zeng BF. Applications of leukocyte- and platelet-rich plasma (L-PRP) in trauma surgery. *Curr Pharm Biotechnol*. (2012) 13(7):1173–84. doi: 10.2174/138920112800624445

68. Qi X, Zhang J, Yuan H, Xu Z, Li Q, Niu X, et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells repair critical-sized bone defects through enhanced angiogenesis and osteogenesis in osteoporotic rats. *Int J Biol Sci*. (2016) 12(7):836–49. doi: 10.7150/ijbs.14809

69. Zuo R, Kong L, Wang M, Wang W, Xu J, Chai Y, et al. Exosomes derived from human CD34(+) stem cells transfected with miR-26a prevent glucocorticoid-induced osteonecrosis of the femoral head by promoting angiogenesis and osteogenesis. *Stem Cell Res Ther*. (2019) 10(1):321. doi: 10.1186/s13287-019-1426-3

70. Hardy RS, Zhou H, Seibel MJ, Cooper MS. Glucocorticoids and bone: consequences of endogenous and exogenous excess and replacement therapy. *Endocr Rev*. (2018) 39(5):519–48. doi: 10.1210/er.2018-00097

71. Hartmann K, Koenen M, Schauer S, Wittig-Blaich S, Ahmad M, Baschant U, et al. Molecular actions of glucocorticoids in cartilage and bone during health, disease, and steroid therapy. *Physiol Rev*. (2016) 96(2):409–47. doi: 10.1152/physrev.00011.2015

72. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med*. (2011) 365(1):62–70. doi: 10.1056/NEJMcp1012926

73. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med*. (2001) 345(13):941–7. doi: 10.1056/NEJMoa002304

74. Phillips JE, Gersbach CA, Wojtowicz AM, García AJ. Glucocorticoid-induced osteogenesis is negatively regulated by Runx2/Cbfa1 serine phosphorylation. *J Cell Sci*. (2006) 119(Pt 3):581–91. doi: 10.1242/jcs.02758

75. Walsh LJ, Lewis SA, Wong CA, Cooper S, Oborne J, Cawte SA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. *Am J Respir Crit Care Med*. (2002) 166(5):691–5. doi: 10.1164/rccm.2110047

76. Helfrich MH, Nesbitt SA, Lakkakorpi PT, Barnes MJ, Bodary SC, Shankar G, et al. Beta 1 integrins and osteoclast function: involvement in collagen recognition and bone resorption. *Bone*. (1996) 19(4):317–28. doi: 10.1016/S8756-3282(96)00223-2

77. Crockett JC, Mellis DJ, Scott DI, Helfrich MH. New knowledge on critical osteoclast formation and activation pathways from study of rare genetic diseases of osteoclasts: focus on the RANK/RANKL axis. *Osteoporos Int*. (2011) 22 (1):1–20. doi: 10.1007/s00198-010-1272-8

78. Li J, Liu K, Liu Y, Xu Y, Zhang F, Yang H, et al. Exosomes mediate the cell-to-cell transmission of IFN-α-induced antiviral activity. *Nat Immunol*. (2013) 14 (8):793–803. doi: 10.1038/ni.2647

79. Cui Y, Luan J, Li H, Zhou X, Han J. Exosomes derived from mineralizing osteoblasts promote ST2 cell osteogenic differentiation by alteration of microRNA expression. *FEBS Lett*. (2016) 590(1):185–92. doi: 10.1002/1873-3468.12024

80. Wei J, Li H, Wang S, Li T, Fan J, Liang X, et al. let-7 enhances osteogenesis and bone formation while repressing adipogenesis of human stromal/mesenchymal stem cells by regulating HMGA2. *Stem Cells Dev*. (2014) 23 (13):1452–63. doi: 10.1089/scd.2013.0600

81. Zhao P, Xiao L, Peng J, Qian YQ, Huang CC. Exosomes derived from bone marrow mesenchymal stem cells improve osteoporosis through promoting osteoblast proliferation via MAPK pathway. *Eur Rev Med Pharmacol Sci*. (2018) 22(12):3962–70.

82. Furuta T, Miyaki S, Ishitobi H, Ogura T, Kato Y, Kamei N, et al. Mesenchymal stem cell-derived exosomes promote fracture healing in a mouse model. *Stem Cells Transl Med*. (2016) 5(12):1620–30. doi: 10.5966/sctm.2015-0285

83. Qin Y, Wang L, Gao Z, Chen G, Zhang C. Bone marrow stromal/stem cell-derived extracellular vesicles regulate osteoblast activity and differentiation in vitro and promote bone regeneration in vivo. *Sci Rep*. (2016) 6:21961. doi: 10.1038/srep21961

84. Liao W, Ning Y, Xu HJ, Zou WZ, Hu J, Liu XZ, et al. BMSC-derived exosomes carrying microRNA-122-5p promote proliferation of osteoblasts in osteonecrosis of the femoral head. *Clin Sci (Lond)*. (2019) 133(18):1955–75. doi: 10.1042/CS20181064

85. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, et al. B lymphocytes secrete antigen-presenting vesicles. *J Exp Med*. (1996) 183 (3):1161–72. doi: 10.1084/jem.183.3.1161

86. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, et al. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. *Nat Med*. (1998) 4(5):594–600. doi: 10.1038/nm0598-594

87. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles*. (2018) 7(1):1535750. doi: 10.1080/20013078.2018.1535750

88. Escola JM, Kleijmeer MJ, Stoorvogel W, Griffith JM, Yoshie O, Geuze HJ. Selective enrichment of tetraspan proteins on the internal vesicles of multivesicular endosomes and on exosomes secreted by human B-lymphocytes. *J Biol Chem*. (1998) 273(32):20121–7. doi: 10.1074/jbc.273.32.20121

89. Xu Q, Cui Y, Luan J, Zhou X, Li H, Han J. Exosomes from C2C12 myoblasts enhance osteogenic differentiation of MC3T3-E1 pre-osteoblasts by delivering miR-27a-3p. *Biochem Biophys Res Commun*. (2018) 498(1):32–7. doi: 10.1016/j.bbrc.2018.02.144

90. Kulkarni R, Bajaj M, Ghode S, Jalnapurkar S, Limaye L, Kale VP. Intercellular transfer of microvesicles from young mesenchymal stromal cells rejuvenates aged murine hematopoietic stem cells. *Stem Cells*. (2018) 36 (3):420–33. doi: 10.1002/stem.2756

91. Toh WS, Lai RC, Hui JHP, Lim SK. MSC exosome as a cell-free MSC therapy for cartilage regeneration: Implications for osteoarthritis treatment. *Semin Cell Dev Biol*. (2017) 67:56–64. doi: 10.1016/j.semcdb.2016.11.008

92. Li Z, Wang Y, Xiang S, Zheng Z, Bian Y, Feng B, et al. Chondrocytes-derived exosomal miR-8485 regulated the Wnt/β-catenin pathways to promote chondrogenic differentiation of BMSCs. *Biochem Biophys Res Commun*. (2020) 523(2):506–13. doi: 10.1016/j.bbrc.2019.12.065

93. Lu J, Zhang Y, Liang J, Diao J, Liu P, Zhao H. Role of exosomal microRNAs and their crosstalk with oxidative stress in the pathogenesis of osteoporosis. *Oxid Med Cell Longev*. (2021) 2021:6301433. doi: 10.1155/2021/6301433

94. Chen G, Huang G, Lin H, Wu X, Tan X, Chen Z. MicroRNA-425-5p modulates osteoporosis by targeting annexin A2. *Immun Ageing*. (2021) 18 (1):45. doi: 10.1186/s12979-021-00256-7

95. Wu X, Zhang Y, Guo X, Xu H, Xu Z, Duan D, et al. Identification of differentially expressed microRNAs involved in non-traumatic osteonecrosis through microRNA expression profiling. *Gene*. (2015) 565(1):22–9. doi: 10.1016/j.gene.2015.03.072

96. Bian Y, Qian W, Li H, Zhao RC, Shan WX, Weng X. Pathogenesis of glucocorticoid-induced avascular necrosis: a microarray analysis of gene expression in vitro. *Int J Mol Med*. (2015) 36(3):678–84. doi: 10.3892/ijmm.2015.2273

97. Yuan HF, Christina VR, Guo CA, Chu YW, Liu RH, Yan ZQ. Involvement of microRNA-210 demethylation in steroid-associated osteonecrosis of the femoral head. *Sci Rep*. (2016) 6:20046. doi: 10.1038/srep20046

98. Yamasaki K, Nakasa T, Miyaki S, Yamasaki T, Yasunaga Y, Ochi M. Angiogenic microRNA-210 is present in cells surrounding osteonecrosis. *J Orthop Res*. (2012) 30(8):1263–70. doi: 10.1002/jor.22079

99. Sun J, Wang Y, Li Y, Zhao G. Downregulation of PPARγ by miR-548d-5p suppresses the adipogenic differentiation of human bone marrow mesenchymal stem cells and enhances their osteogenic potential. *J Transl Med*. (2014) 12:168. doi: 10.1186/1479-5876-12-168

100. Aoyama T, Fujita Y, Madoba K, Nankaku M, Yamada M, Tomita M, et al. Rehabilitation program after mesenchymal stromal cell transplantation augmented by vascularized bone grafts for idiopathic osteonecrosis of the femoral head: a preliminary study. *Arch Phys Med Rehabil*. (2015) 96(3):532–9. doi: 10.1016/j.apmr.2014.09.040

101. Zhao D, Liu B, Wang B, Yang L, Xie H, Huang S, et al. Autologous bone marrow mesenchymal stem cells associated with tantalum rod implantation and vascularized iliac grafting for the treatment of end-stage osteonecrosis of the femoral head. *Biomed Res Int*. (2015) 2015:240506.

102. Wang C, Wang Y, Meng HY, Yuan XL, Xu XL, Wang AY, et al. Application of bone marrow mesenchymal stem cells to the treatment of osteonecrosis of the femoral head. *Int J Clin Exp Med*. (2015) 8(3):3127–35.

103. Zhao Y, Xu J. Synovial fluid-derived exosomal lncRNA PCGEM1 as biomarker for the different stages of osteoarthritis. *Int Orthop*. (2018) 42 (12):2865–72. doi: 10.1007/s00264-018-4093-6

104. Dragomir M, Chen B, Calin GA. Exosomal lncRNAs as new players in cell-to-cell communication. *Transl Cancer Res*. (2018) 7(Suppl 2):S243–52. doi: 10.21037/tcr.2017.10.46

105. Weiliang Z, Lili G. Research advances in the application of adipose-derived stem cells derived exosomes in cutaneous wound healing. *Ann Dermatol*. (2021) 33(4):309–17. doi: 10.5021/ad.2021.33.4.309

106. Wang SZ, Jia J, Chen CH. lncRNA-KCNQ1OT1: a potential target in exosomes derived from adipose-derived stem cells for the treatment of osteoporosis. *Stem Cells Int*. (2021) 2021:7690006. doi: 10.1155/2021/7690006

107. Luo H, Lan W, Li Y, Lian X, Zhang N, Lin X, et al. Microarray analysis of long-noncoding RNAs and mRNA expression profiles in human steroid-induced avascular necrosis of the femoral head. *J Cell Biochem*. (2019) 120(9):15800–113. doi: 10.1002/jcb.28850

108. Xiang S, Li Z, Weng X. The role of lncRNA RP11-154D6 in steroid-induced osteonecrosis of the femoral head through BMSC regulation. *J Cell Biochem*. (2019) 120(10):18435–45. doi: 10.1002/jcb.29161

109. Liu Y, Lin L, Zou R, Wen C, Wang Z, Lin F. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. *Cell Cycle*. (2018) 17(21–22):2411–22. doi: 10.1080/15384101.2018.1526603

110. Wei B, Wei W, Zhao B, Guo X, Liu S. Long non-coding RNA HOTAIR inhibits miR-17-5p to regulate osteogenic differentiation and proliferation in non-traumatic osteonecrosis of femoral head. *PLoS One*. (2017) 12(2):e0169097. doi: 10.1371/journal.pone.0169097

111. Harding C, Heuser J, Stahl P. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. *J Cell Biol*. (1983) 97 (2):329–39. doi: 10.1083/jcb.97.2.329

112. Yu QS, Guo WS, Cheng LM, Lu YF, Shen JY, Li P. Glucocorticoids significantly influence the transcriptome of bone microvascular endothelial cells of human femoral head. *Chin Med J (Engl)*. (2015) 128(14):1956–63. doi: 10.4103/0366-6999.160564

113. Potente M, Urbich C, Sasaki K, Hofmann WK, Heeschen C, Aicher A, et al. Involvement of Foxo transcription factors in angiogenesis and postnatal neovascularization. *J Clin Invest*. (2005) 115(9):2382–92. doi: 10.1172/JCI23126

114. Fang B, Li Y, Chen C, Wei Q, Zheng J, Liu Y, et al. Huo Xue Tong Luo capsule ameliorates osteonecrosis of femoral head through inhibiting lncRNA-Miat. *J Ethnopharmacol*. (2019) 238:111862. doi: 10.1016/j.jep.2019.111862

115. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*. (2013) 495(7441):333–8. doi: 10.1038/nature11928

116. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. *Nature*. (2013) 495(7441):384–8. doi: 10.1038/nature11993

117. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol*. (2015) 22 (3):256–64. doi: 10.1038/nsmb.2959

118. Kulcheski FR, Christoff AP, Margis R. Circular RNAs are miRNA sponges and can be used as a new class of biomarker. *J Biotechnol*. (2016) 238:42–51. doi: 10.1016/j.jbiotec.2016.09.011

119. Bretscher MS. Direct translation of a circular messenger DNA. *Nature*. (1968) 220(5172):1088–91. doi: 10.1038/2201088a0

120. Abe N, Matsumoto K, Nishihara M, Nakano Y, Shibata A, Maruyama H, et al. Rolling circle translation of circular RNA in living human cells. *Sci Rep*. (2015) 5:16435. doi: 10.1038/srep16435

121. Du WW, Zhang C, Yang W, Yong T, Awan FM, Yang BB. Identifying and characterizing circRNA-protein interaction. *Theranostics*. (2017) 7(17):4183–91. doi: 10.7150/thno.21299

122. Zhi F, Ding Y, Wang R, Yang Y, Luo K, Hua F. Exosomal hsa_circ_0006859 is a potential biomarker for postmenopausal osteoporosis and enhances adipogenic versus osteogenic differentiation in human bone marrow mesenchymal stem cells by sponging miR-431-5p. *Stem Cell Res Ther*. (2021) 12 (1):157. doi: 10.1186/s13287-021-02214-y

123. Zhang M, Jia L, Zheng Y. circRNA expression profiles in human bone marrow stem cells undergoing osteoblast differentiation. *Stem Cell Rev Rep*. (2019) 15(1):126–38. doi: 10.1007/s12015-018-9841-x

124. Zhao R, Li Y, Lin Z, Wan J, Xu C, Zeng Y, et al. miR-199b-5p modulates BMSC osteogenesis via suppressing GSK-3β/β-catenin signaling pathway. *Biochem Biophys Res Commun*. (2016) 477(4):749–54. doi: 10.1016/j.bbrc.2016.06.130

125. Huang L, Wang Y, Jiang Y, Wu Y, Hu C, Ouyang H. High levels of GSK-3β signalling reduce osteogenic differentiation of stem cells in osteonecrosis of femoral head. *J Biochem*. (2018) 163(3):243–51. doi: 10.1093/jb/mvx076

126. Kuang MJ, Xing F, Wang D, Sun L, Ma JX, Ma XL. CircUSP45 inhibited osteogenesis in glucocorticoid-induced osteonecrosis of femoral head by sponging miR-127-5p through PTEN/AKT signal pathway: Experimental studies. *Biochem Biophys Res Commun*. (2019) 509(1):255–61. doi: 10.1016/j.bbrc.2018.12.116

127. Qian DY, Yan GB, Bai B, Chen Y, Zhang SJ, Yao YC, et al. Differential circRNA expression profiles during the BMP2-induced osteogenic differentiation of MC3T3-E1 cells. *Biomed Pharmacother*. (2017) 90:492–9. doi: 10.1016/j.biopha.2017.03.051

128. Cherubini A, Barilani M, Rossi RL, Jalal MMK, Rusconi F, Buono G, et al. FOXP1 circular RNA sustains mesenchymal stem cell identity via microRNA inhibition. *Nucleic Acids Res*. (2019) 47(10):5325–40. doi: 10.1093/nar/gkz199

129. Boeckel JN, Jaé N, Heumüller AW, Chen W, Boon RA, Stellos K, et al. Identification and characterization of hypoxia-regulated endothelial circular RNA. *Circ Res*. (2015) 117(10):884–90. doi: 10.1161/CIRCRESAHA.115.306319

130. Dang RY, Liu FL, Li Y. Circular RNA hsa_circ_0010729 regulates vascular endothelial cell proliferation and apoptosis by targeting the miR-186/HIF-1α axis. *Biochem Biophys Res Commun*. (2017) 490(2):104–10. doi: 10.1016/j.bbrc.2017.05.164

131. Li CY, Ma L, Yu B. Circular RNA hsa_circ_0003575 regulates oxLDL induced vascular endothelial cells proliferation and angiogenesis. *Biomed Pharmacother*. (2017) 95:1514–9. doi: 10.1016/j.biopha.2017.09.064

132. Gross JC, Chaudhary V, Bartscherer K, Boutros M. Active Wnt proteins are secreted on exosomes. *Nat Cell Biol*. (2012) 14(10):1036–45. doi: 10.1038/ncb2574

133. Buschow SI, Liefhebber JM, Wubbolts R, Stoorvogel W. Exosomes contain ubiquitinated proteins. *Blood Cells Mol Dis*. (2005) 35(3):398–403. doi: 10.1016/j.bcmd.2005.08.005

134. Théry C, Regnault A, Garin J, Wolfers J, Zitvogel L, Ricciardi-Castagnoli P, et al. Molecular characterization of dendritic cell-derived exosomes. Selective accumulation of the heat shock protein hsc73. *J Cell Biol*. (1999) 147 (3):599–610. doi: 10.1083/jcb.147.3.599

135. Yuan D, Zhao Y, Banks WA, Bullock KM, Haney M, Batrakova E, et al. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. *Biomaterials*. (2017) 142:1–12. doi: 10.1016/j.biomaterials.2017.07.011

136. Whiteside TL. Exosomes carrying immunoinhibitory proteins and their role in cancer. *Clin Exp Immunol*. (2017) 189(3):259–67. doi: 10.1111/cei.12974

137. Goetzl EJ, Kapogiannis D, Schwartz JB, Lobach IV, Goetzl L, Abner EL, et al. Decreased synaptic proteins in neuronal exosomes of frontotemporal dementia and Alzheimer's disease. *Faseb J*. (2016) 30(12):4141–8. doi: 10.1096/fj.201600816R

138. Tsuno H, Arito M, Suematsu N, Sato T, Hashimoto A, Matsui T, et al. A proteomic analysis of serum-derived exosomes in rheumatoid arthritis. *BMC Rheumatol*. (2018) 2:35. doi: 10.1186/s41927-018-0041-8

139. Kawakami K, Fujita Y, Matsuda Y, Arai T, Horie K, Kameyama K, et al. Gamma-glutamyltransferase activity in exosomes as a potential marker for prostate cancer. *BMC Cancer*. (2017) 17(1):316. doi: 10.1186/s12885-017-3301-x

140. Takahashi A, Okada R, Nagao K, Kawamata Y, Hanyu A, Yoshimoto S, et al. Exosomes maintain cellular homeostasis by excreting harmful DNA from cells. *Nat Commun*. (2017) 8:15287. doi: 10.1038/ncomms15287

141. Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med*. (2009) 361(15):1475–85. doi: 10.1056/NEJMra0804615

142. Burger D, Viñas JL, Akbari S, Dehak H, Knoll W, Gutsol A, et al. Human endothelial colony-forming cells protect against acute kidney injury: role of exosomes. *Am J Pathol*. (2015) 185(8):2309–23. doi: 10.1016/j.ajpath.2015.04.010

143. Xin H, Li Y, Chopp M. Exosomes/miRNAs as mediating cell-based therapy of stroke. *Front Cell Neurosci*. (2014) 8:377. doi: 10.3389/fncel.2014.00377

144. Kalra H, Adda CG, Liem M, Ang CS, Mechler A, Simpson RJ, et al. Comparative proteomics evaluation of plasma exosome isolation techniques and assessment of the stability of exosomes in normal human blood plasma. *Proteomics*. (2013) 13(22):3354–64. doi: 10.1002/pmic.201300282

145. Mendt M, Kamerkar S, Sugimoto H, McAndrews KM, Wu CC, Gagea M, et al. Generation and testing of clinical-grade exosomes for pancreatic cancer. *JCI Insight*. (2018) 3(8). doi: 10.1172/jci.insight.99263

146. Koga Y, Yasunaga M, Moriya Y, Akasu T, Fujita S, Yamamoto S, et al. Exosome can prevent RNase from degrading microRNA in feces. *J Gastrointest Oncol*. (2011) 2(4):215–22. doi: 10.3978/j.issn.2078-6891.2011.015

147. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, et al. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature*. (2017) 546(7659):498–503. doi: 10.1038/nature22341

148. Grange C, Tapparo M, Bruno S, Chatterjee D, Quesenberry PJ, Tetta C, et al. Biodistribution of mesenchymal stem cell-derived extracellular vesicles in a model of acute kidney injury monitored by optical imaging. *Int J Mol Med*. (2014) 33(5):1055–63. doi: 10.3892/ijmm.2014.1663

149. Peinado H, Alečković M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, et al. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Nat Med*. (2012) 18 (6):883–91. doi: 10.1038/nm.2753

150. Kotmakçı M, Bozok Çetintaş V. Extracellular vesicles as natural nanosized delivery systems for small-molecule drugs and genetic material: steps towards the future nanomedicines. *J Pharm Pharm Sci*. (2015) 18(3):396–413. doi: 10.18433/J36W3X

151. Tian Y, Li S, Song J, Ji T, Zhu M, Anderson GJ, et al. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. *Biomaterials*. (2014) 35(7):2383–90. doi: 10.1016/j.biomaterials.2013.11.083

152. Ohno S, Takanashi M, Sudo K, Ueda S, Ishikawa A, Matsuyama N, et al. Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells. *Mol Ther*. (2013) 21(1):185–91. doi: 10.1038/mt.2012.180

153. Liao W, Ning Y, Xu H-J, Zou W-Z, Hu J, Liu X-Z, et al. BMSC-derived exosomes carrying microRNA-122-5p promote proliferation of osteoblasts in osteonecrosis of the femoral head. *Clin Sci*. (2019) 133(18):1955–75. doi: 10.1042/CS20181064

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EDITED BY
Carlos Suarez-Ahedo,
Hospital Médica Sur, Mexico

REVIEWED BY
Teresa Alvarez,
Instituto Nacional de Geriatría, Mexico
Anell Olivos,
Hospital Médica Sur, Mexico

*CORRESPONDENCE
Baoguo Jiang
jiangbaoguo@vip.sina.com
Peixun Zhang
zhangpeixun@bjmu.edu.cn

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Derivation and validation of a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty

Jiawei Shen[1], Youzhong An[2], Baoguo Jiang[1,3,4]* and Peixun Zhang[1,3,4]*

[1]Department of Orthopaedics and Trauma, Peking University People's Hospital, Beijing, China, [2]Department of Critical Care Medicine, Peking University People's Hospital, Beijing, China, [3]Key Laboratory of Trauma and Neural Regeneration, Peking University, Beijing, China, [4]National Center for Trauma Medicine, Beijing, China

Introduction: Postoperative delirium is a common complication of patients undergoing hip fracture surgery or arthroplasty and is related to decreased survival time and physical function. In this study, we aim to build and validate a prediction score of postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty.

Methods: A retrospective cohort of geriatric patients undergoing hip fracture surgery or hip arthroplasty was established. Variables of included patients were collected as candidate predictors of postoperative delirium. The least absolute shrinkage and selection operator (LASSO) regression and logistic regression were used to derive a predictive score for postoperative delirium. The accuracy of the score was evaluated by the area under the curve (AUC) of the receiver operating curve (ROC). We used bootstrapping resamples for model calibration. The prediction score was validated in an extra cohort.

Results: There were 1,312 patients in the derivation cohort, and the incidence of postoperative delirium was 14.33%. Of 40 variables, 9 were identified as predictors, including preoperative delirium, cerebrovascular accident (CVA) with the modified Rankin scale, diabetes with a random glucose level, Charlson comorbidity index (CCI), age, application of benzodiazepines in surgery, surgical delay ≥2 days, creatine ≥90 μmol/L, and active smoker. The prediction score achieved a mean AUC of 0.848 in the derivation cohort. In the validation cohort, the mean AUC was 0.833. The prediction model was well-calibrated in the two cohorts.

Conclusion: Based on retrospective data, a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty was derived and validated. The performance of the scoring system outperformed the models from previous studies. Although the generalization ability of the score needs to be tested in similar populations, the scoring

Abbreviations
ASA, American Anesthesia Society; AUC, area under the curve; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accidents; LASSO, least absolute shrinkage and selection operator; PE, pulmonary embolism; ROC, receiver operating curves

system will enable delirium risk stratification for hip fracture patients and facilitate the development of strategies for delirium prevention.

KEYWORDS

arthroplasty, complications, hip fracture, delirium, prognosis

Introduction

Hip fracture is a major cause of mortality, morbidity, and economic burden in geriatric patients (1). As the population ages, the total incidence of hip fracture is increasing globally despite a decline in age-adjusted incidence (2); it is predicted that the incidence will increase to 6.26 by the year 2050 (3). Although the surgical technique has improved in recent years, a high incidence of 1-year mortality still exists (4). On the other hand, functional impairments including cognitive decline and reduced production of hormones (e.g., vitamin D, pro-inflammatory cytokines, and estrogens) often complicate the preoperative status of geriatric patients, leaving the patients more vulnerable to various postoperative complications.

Delirium, defined as "an acute confusional state," is characterized by disturbance in attention and cognition (5). Postoperative delirium is a common complication with an incidence of 6.5%–55.9% in patients undergoing hip fracture surgery or hip arthroplasty (6). Delirium after surgery indicates a poor outcome with decreased survival time and impaired physical function (7). Moreover, postoperative delirium will increase hospital stay and postpone the functional recovery of patients (3). Preventing and controlling postoperative delirium are vital in clinical practice and have been set as a target for surgical quality improvement (8).

The early detection of postoperative delirium is important in delivering necessary care to patients at a higher risk. Although various prediction models have been developed for predicting postoperative delirium, previous studies were limited by a small sample size (9, 10) or a lack of patients who underwent hip arthroplasty (11, 12); in addition, there was no study with an appropriate sample size that had focused on the Chinese population (13) and most of the studies emphasized the evaluation of baseline mental or psychiatric presentations but omitted the disturbance of the microenvironment that may contribute to postoperative delirium (14, 15). As reported in previous studies, dysfunction of glucose metabolism and disturbance of microenvironments of neurons can contribute to the occurrence of delirium in geriatric patients (16, 17).

In the present study, by evaluating factors [electrolytes, albumin, blood urea nitrogen (BUN), etc.] that may affect the microenvironments of neurons and other possible predisposing factors of delirium, we aimed to derive and validate a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or arthroplasty.

Materials and methods

This retrospective noninterventional study was approved by the ethics committee of Peking University People's Hospital and was performed in compliance with the Declaration of Helsinki.

Study population

We retrospectively collected the electrical medical records of patients who were admitted to Peking University People's Hospital between January 2010 and December 2018. The inclusion criteria are as follows: (1) age ≥ 60 and (2) have received hip fracture surgery or hip arthroplasty. These patients were set as the derivation cohort of the prediction score. We further collected the medical records of patients who were admitted between January 2019 and March 2020 and included patients with the same criteria. These patients were set as the validation cohort.

Outcome assessment and variable collection

The primary outcome of this study was the occurrence of delirium after surgery (during the recorded hospitalization). Delirium was identified using a clinically validated chart-based tool (18, 19) (see **Supplementary Table S1**) by screening the electronic medical records. In detail, two experienced physicians screened all medical records (including progress notes, nursing notes, surgical and anesthetic records, consulting notes, etc.) to search for evidence of the acute onset of confusional state (e.g., described as delirium, inattention, mental status change, disorientation, hallucinations, agitation, inappropriate behavior, etc.), patients with any of the listed evidence had a suggested diagnosis of delirium.

The following variables are collected as candidates for predictors of postoperative delirium: age, sex, body mass index (BMI), Carlson comorbidity index (CCI); previous history of major fractures (lower limb, pelvic, spinal),

preoperative dementia, preoperative delirium, hearing loss, psychiatric disease, coronary heart disease, chronic heart failure, atrial fibrillation, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, acute kidney injury, pre-urgery dialysis, hepatic failure, malignancy, alcohol abuse, active smoker, cerebral vascular accidents (CVA, evaluated with the modified Rankin Scale), chronic obstructive pulmonary disease (COPD), symptomatic pulmonary embolism (PE), preoperative pneumonia, American Anesthesia Society (ASA) score; type of fracture (femoral neck, intertrochanteric, subtrochanteric, periprosthetic, multiple hip fractures), type of surgery (intramedullary nail, cancellous screw, hemiarthroplasty, total arthroplasty, revision of arthroplasty), duration of surgical delay, duration of surgery, general anesthesia; high risk medications in surgery (benzodiazepines, opioids, nonsteroidal anti-inflammatory drugs), serum levels of glucose, sodium, BUN, creatine, albumin; and white blood cell count, hemoglobin level. All lab tests were performed on admission.

Statistical analysis

Missing values were imputed when missing columns were less than 20%, and we used predictive mean matching for numeric variables, logistic regression for binary variables, and Bayesian polytomous regression for factor variables (>2 levels).

In the derivation cohort, candidate variables were selected using least absolute shrinkage and selection operator (LASSO) regression to minimize the overfitting and collinearity of variables. LASSO regression performs L1 regularization, in which a penalty value is equal to the magnitude of variable coefficients; larger penalties will force the smaller coefficients close to zero, thus resulting in a sparse model with fewer variables. These selected variables will enter logistic regression in the following analysis to build a prediction model. The significant predictors will be used to construct the prediction score for postoperative delirium with reference to a well-tested method (20); the accuracy of the prediction score was evaluated by the area under the curve (AUC) of the receiver operating curves (ROC). The accuracy of the prediction score was compared with the prediction models of two previous studies (12, 21).

We used 1,000 bootstrap resamples for model calibration (in both the derivation and validation cohort). Validation of the prediction score was performed by comparing the accuracy of the prediction in the derivation cohort and the validation cohort.

All statistical analyses were performed with R (version 4.0.2); R packages used were "MICE" (for processing missing values), "glmnet" (for LASSO regression), "glm" (for logistic regression), and "ggplot2" and "pROC" (for receiver operating characteristic curve depiction and calculation of the area under curves). $P < 0.05$ was considered statistically significant, and all statistical tests were two-sided.

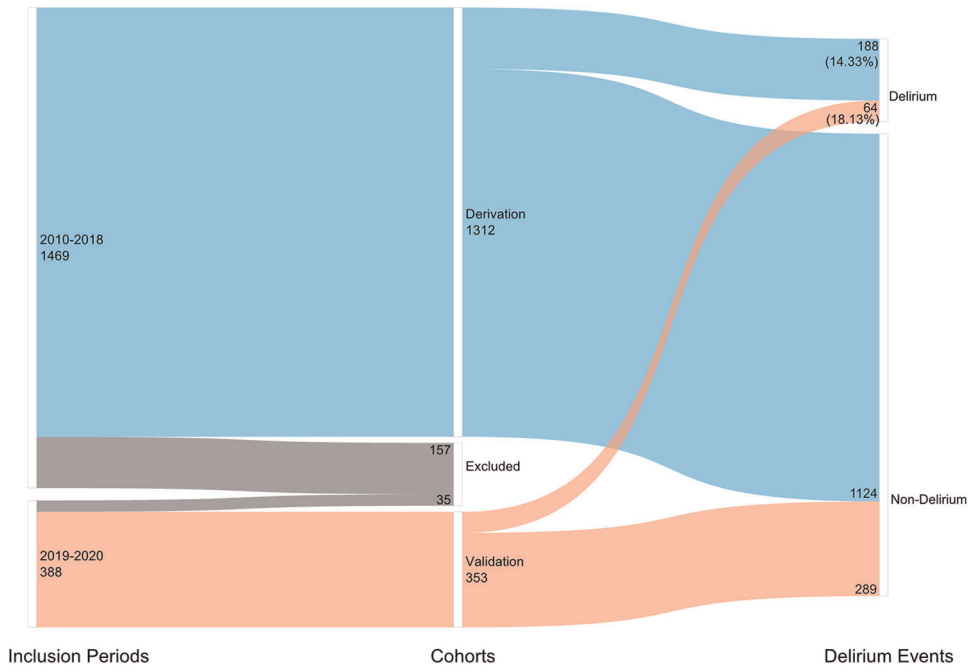

FIGURE 1
Number of included patients in different inclusion periods and the number of postoperative delirium cases.

TABLE 1 Baseline characteristics of patients in the derivation cohort who did or did not develop postoperative delirium.

Characteristic	Total	Delirium	
	$n = 1312$	No $N = 1124$ −85.67%	Yes $n = 188$ −14.33%
Age, years			
60–69	210(16.01)	204(18.15)	6(3.19)
70–79	375(28.58)	330(29.36)	40(21.28)
80–89	605(46.11)	502(44.66)	108(57.45)
≥90	122(9.30)	88(7.83)	34(18.09)
Sex			
Female (%)	896(68.29)	766(68.15)	130(69.15)
Male (%)	416(31.71)	358(31.85)	58(30.85)
BMI, kg/m^2			
<20	430(32.77)	376 (33.45)	54(28.72)
20–25	591(45.05)	502(44.66)	89(47.34)
25–30	246(18.75)	207(18.42)	39(20.74)
>30	45(3.43)	39(3.47)	6(3.10)
CCI score	5(3–7)	5(3–6)	7(4–9)
History of major fractures	354(26.98)	299(26.60)	55(29.25)
Preoperative dementia	35(2.67)	7(0.53)	28(2.13)
Preoperative delirium	102(7.77)	49(4.36)	53(28.19)
Hearing loss	104(7.93)	90(8.01)	14(7.45)
Psychiatric disease	46(3.51)	39(3.47)	7(3.72)
Coronary heart disease	340(25.91)	293(26.07)	47(25.00)
Chronic heart failure	26(1.98)	20(1.78)	6(3.19)
Atrial fibrillation	106(8.08)	67(5.96)	39(20.74)
Hypertension	793(60.44)	694(61.74)	99(52.66)
Peripheral vascular disease	60(4.57)	55(4.89)	5(2.66)
Diabetes	365(27.82)	299(26.60)	66(35.11)
Chronic kidney disease	131(9.98)	97(8.63)	34(18.09)
Acute kidney injury	14(1.10)	8(0.71)	6(3.19)
Presurgery dialysis	12(0.92)	9(0.80)	3(1.60)
Hepatic failure	6(0.46)	5(0.44)	1(0.53)
Malignancy	206(15.71)	167(14.86)	39(20.74)
Alcohol abuse	33(2.52)	27(2.43)	6(3.17)
Active Smoker	93(7.09)	75(6.67)	18(9.57)
CVA with the Rankin scale			
4–5	15(1.14)	4(0.36)	11(5.85)
2–3	100(7.62)	41(3.65)	59(31.38)
0–1	166(12.65)	91(8.10)	75(39.89)
COPD	46(3.506)	43(3.825)	3(1.60)
Symptomatic PE	7(0.51)	5(0.44)	2(1.06)
Preoperative pneumonia	228(17.38)	198(17.62)	30(15.96)
ASA score	2(1–2)	2(1–2)	2(2–3)
Type of fracture			
Femoral neck	722(55.03)	661(58.81)	61(32.45)
Intertrochanteric	516(39.33)	396(35.23)	120(63.83)
Subtrochanteric	28(2.13)	21(1.87)	7(3.72)
Periprosthetic	20(1.53)	16(1.42)	4(2.13)
Multiple hip fractures	26(1.98)	19(1.67)	7(3.72)
Type of surgery			
Intramedullary nail	614(46.81)	562(50.00)	52(27.66)
Cancellous screw	73(5.56)	59(5.25)	14(7.45)
Hemiarthroplasty	470(35.82)	421(37.41)	49(26.06)
Total hip arthroplasty	148(11.28)	135(12.01)	13(6.91)
Revision of arthroplasty	7(0.53)	6(0.53)	1(0.52)
Surgical delay			
<24 h	85(6.48)	67(5.96)	8(4.26)
24–48 h	1055(80.4)	927(82.47)	138(73.40)
>48 h	172(13.1)	130 (11.57)	42(22.34)
Duration of surgery (h)	3.11 ± 0.91	3.11 ± 0.5	3.49 ± 0.88
General anesthesia	161(12.27)	139(12.37)	22(11.7)
High-risk medications in surgery			
Benzodiazepines	103(7.85)	35(3.11)	68(36.17)
Opioids	332(25.30)	289(25.71)	43(22.87)
NSAIDs	258(19.66)	222(19.75)	36(19.14)
Glucose level for patients with diabetes (mmol/L)	8.77 ± 1.64	7.96 ± 2.55	8.43 ± 1.38
Sodium (mmol/L)	136.09 ± 16.21	135.53 ± 17.38	139.47 ± 3.67
BUN (mg/dL)	6.69(5.16–8.8)	6.41(5.00–8.41)	7.81(6.29–10.88)
Creatine (mmol/L)	69(56–94)	62(59–107)	70(55–95)
Albumin (mmol/L)	35.62 ± 4.89	35.82 ± 5.02	34.4 ± 4.85
White blood cell count (×10^9/L)	8.06 ± 2.73	8.00 ± 2.53	8.39 ± 3.66
Hemoglobin (g/L)	119(101–131)	110(92–130)	97(90–113)

Data are given as a number (%), mean + standard deviation, or median (interquartile range).

ADL, activities of daily living; BMI, body mass index; BUN, blood urea nitrogen; CCI, Carlson comorbidity index; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism.

Results

Characteristics of patients in the derivation cohort

A total of 535,037 records were screened in the electronic medical record system. Data of 1,312 patients were collected as the derivation cohort. Among these patients, 188(14.33%) had a suggested diagnosis of postoperative delirium (Figure 1). Baseline characteristics of patients are presented in Table 1. Most of the patients were in their 80s (46.1%) and women (896[68.29%]), with hypertension (793

TABLE 2 Multivariate regression of postoperative delirium.

Variable	OR	95% CI	*P*
Preoperative delirium	4.21	3.25–9.14	<0.001
CVA with the modified Rankin scale			
4–5	3.17	1.16–5.06	<0.001
2–3	2.25	1.26–4.29	
0–1[a]	–		
Diabetes with random glucose level			0.023
>13 mmol/L	2.43	1.32–2.99	
8–13 mmol/L	1.36	1.15–1.67	
<8 mmol/L[b]	–		
CCI score			0.008
≥9	2.32	1.69–4.83	
6–8	1.29	1.03–2.52	
≤5	–		
Age (years)			
≥80	1.87	1.25–2.50	0.021
70–79	1.11	1.07–2.19	
60–69	–		
Application of Benzodiazepines in surgery	1.44	1.24–3.17	0.036
Surgical delay ≥2 days	1.15	1.13–1.28	0.012
Creatine ≥90 μmol/L	1.09	1.02–1.13	0.034
Active smoker	1.05	1.04–1.94	0.042
General anesthesia	1.32	0.32–1.63	0.751
BUN >8.5 mmol/L	1.15	0.62–1.77	0.812
Albumin ≤30 g/L	1.08	0.86–1.26	0.623

[a]Without CVA.
[b]Without diabetes.
ADL, activities of daily living; BUN, blood urea nitrogen; CCI, Carlson comorbidity index; CI, confidence interval; CVA, cerebrovascular accident; OR, odds ratio.

[60.44%]), diabetes (365[27.82%]), and coronary heart diseases (340 [25.91%]) as the top three comorbidities.

A large majority of patients had femoral neck fracture (722 [55.03%]), followed by intertrochanteric (516[39.33%]), subtrochanteric (28[2.13%]), multiple locations of the hip (26 [1.98%]), and periprosthetic fractures (20[1.53%]). Most patients received intramedullary nail fixation (614[46.53%]), followed by hemiarthroplasty (470[35.82%]), total hip arthroplasty (148[11.28%]), cancellous screw (73[5.56%]), and revision of arthroplasty (7[0.53%]).

Selection of variables as predictors

With LASSO regression, 12 out of 40 variables were selected (see **Supplementary Figure S1**). The selected variables include pre-operative delirium, CVA with the modified Rankin scale, age, CCI, random glucose levels of patients with diabetes, application of benzodiazepines in surgery, surgical delay, creatine level, active smoker, general anesthesia, serum BUN level, and albumin level.

All 12 variables were then analyzed with the logistic regression model. There were nine variables that remained in the model: preoperative delirium (OR 4.21, 95% CI 3.25–9.14, $P < 0.001$), CVA with the modified Rankin scale (4–5, OR 3.17, 95% CI 1.16–5.06; 2–3, OR 2.25, 95% CI 1.26–4.29, $P < 0.001$), diabetes with a random glucose level (>13 mmol/L, OR 2.43, 95% CI 1.32–2.99; 8–13, OR 1.36, 95% CI 1.15–1.67, $P = 0.023$), CCI (≥9, OR 2.43, 95% CI 1.32–2.99; 6–8, OR 1.29, 95% CI 1.03–2.52, $P = 0.008$), age (≥80, OR 1.87, 95% CI 1.25–2.50; 70–79, OR 1.11, 95% CI 1.07–2.19, $P = 0.021$), application of benzodiazepines in surgery (OR 1.44, 95% CI 1.24–3.17, $P = 0.036$), surgical delay ≥2 days (OR 1.15, 95% CI 1.13–1.28, $P = 0.012$), creatine ≥90 μmol/L (OR 1.09, 95% CI 1.02–1.13, $P = 0.034$), and active smoker (OR 1.05, 95% CI 1.04–1.94, $P = 0.042$) (**Table 2**).

TABLE 3 Prediction score of postoperative delirium for patients after hip fracture surgery or hip arthroplasty.

Variable	Score
Preoperative delirium	4
CVA with the modified Rankin scale	
≥4	3
2–3	2
0–1[a]	0
Diabetes with random glucose level	
>13 mmol/L	2
8–13 mmol/L	1
<8 mmol/L[b]	0
CCI score	
≥9	2
6–8	1
≤5	0
Age (years)	2
≥80	1
70–79	0
60–69	
Application of benzodiazepines in surgery	1
Surgical delay ≥2 days	1
Creatine ≥90 μmol/L	1
Active smoker	1

[a]Without CVA.
[b]Without diabetes.
ADL, activities of daily living; CCI, Carlson comorbidity index; CVA, cerebrovascular accident.

Derivation of the prediction score

Using the nine variables selected in the last section, a prediction score was derived (**Table 3**). With bootstrapping,

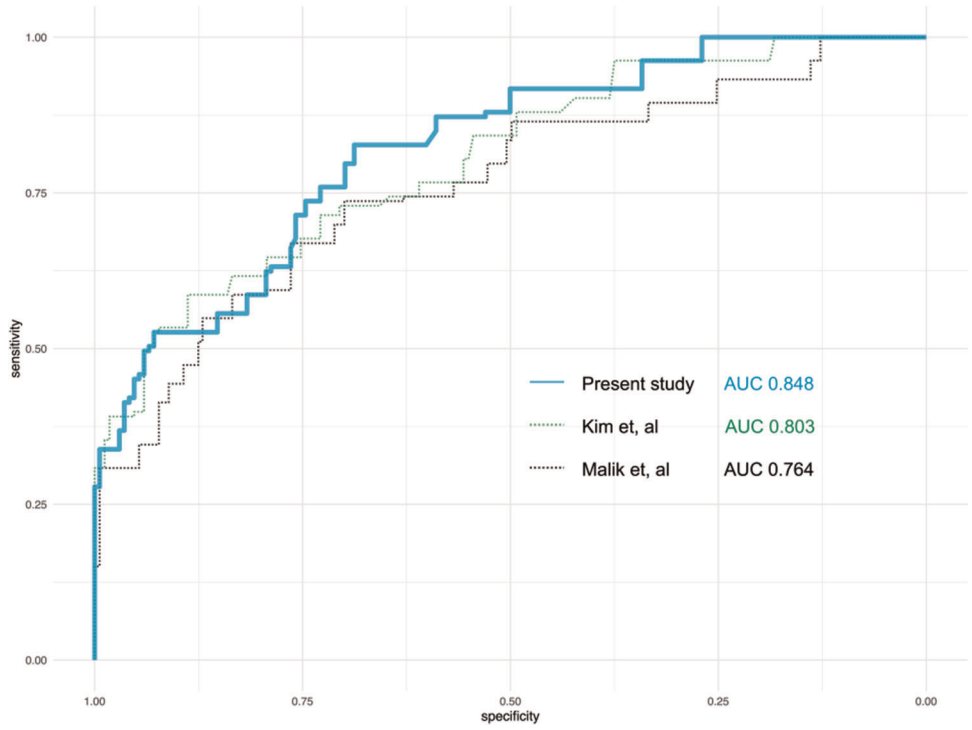

FIGURE 2
Comparison of the performance of the predicting models from the present study and two previous studies. AUC, area under the curve.

the mean AUC of the prediction score in the derivation cohort was 0.848 (95% CI 0.72–0.90), higher than the models of previous studies (Figure 2). The range of the score and the estimated probability of postoperative delirium were recorded in Supplementary Table S2.

Validation of the prediction score

We then use the validation cohort [with 353 patients and 64 (18.31%) with postoperative delirium] (Table 4) to test the performance of the prediction score model. Through 1,000 times bootstrapping, the mean AUC of the model was 0.833 (95% CI 0.68–0.89) (Figure 3), and the model was well-calibrated in both the derivation and validation cohorts (Figure 4). The prediction score had similar accuracy to postoperative delirium in the derivation and validation cohorts.

Discussion

Based on the retrospective data, a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty was derived and validated. In the derivation and validation cohorts, the accuracy of the score was satisfactory. The score consists of nine prediction factors (preoperative delirium, CVA with the modified Rankin scale, random glucose levels of patients with diabetes, CCI score, age, application of benzodiazepines in surgery, surgical delay, creatine level, active smoker) that are easily available in clinical practice. Moreover, the scoring system also included functional evaluation of CVA patients and disturbances of microenvironments (random glucose levels of diabetes, creatine levels), which were not reported in previous studies. In the derivation cohort, the suggested incidence of delirium was 14.33%, which was close to publications (9, 22) with similar patient composition; some of the predictors were consistent with previous studies (6, 12).

Predisposing factors that related to delirium

Preoperative delirium was identified as a significant predictor of postoperative delirium. As reported by a previous study, postoperative delirium had a high incidence in patients diagnosed with preoperative delirium (23) (up to 60%). However, in most of the related studies, preoperative delirium has been excluded in the process of patient selection (9, 24). This may be explained as an attempt to rule out prevalent delirium cases from new-onset postoperative delirium cases. However, excluding this group of patients will underestimate

TABLE 4 Baseline characteristics of patients in the validation cohort who did or did not develop postoperative delirium.

Characteristic	Total	Delirium	
	n = 353	No *N* = 289 −81.87%	Yes *n* = 64 −18.13%
Age, years			
60–69	51(14.45)	49(16.96)	2(3.13)
70–79	78(22.10)	66(22.84)	10(15.63)
80–89	165(46.74)	135(46.71)	30(46.88)
≥90	59(16.71)	39(13.49)	22(34.38)
Sex			
Female (%)	235(66.57)	196(67.82)	39(60.94)
Male (%)	118(33.43)	93(32.18)	25(39.06)
BMI, kg/m^2			
<20	116(32.86)	96(33.21)	20(31.25)
20–25	160(45.33)	131(45.33)	29(45.31)
25–30	64(18.13)	51(17.65)	13(20.31)
>30	13(3.68)	11(3.81)	2(3.13)
CCI score	6(3–6)	5(3–6)	5(3–9)
History of major fractures	89(25.21)	71(24.57)	18(28.13)
Preoperative dementia	29(8.22)	23(7.96)	6(9.38)
Preoperative delirium	16(4.53)	9(3.11)	7(10.94)
Hearing loss	21(5.95)	19(5.38)	2(3.13)
Psychiatric disease	13(3.68)	11(3.81)	2(3.13)
Coronary heart disease	82(23.23)	67(23.18)	15(23.44)
Chronic heart failure	6(1.70)	5(1.73)	1(1.56)
Atrial fibrillation	27(7.65)	18(6.23)	9(14.06)
Hypertension	207(58.64)	173(59.86)	34(53.13)
Peripheral vascular disease	16(4.53)	16(5.54)	0(0)
Diabetes	99(28.05)	70(24.22)	29(45.31)
Chronic kidney disease	34(9.63)	20(6.92)	14(21.88)
Acute kidney injury	8(2.27)	5(1.73)	3(4.69)
Presurgery dialysis	6(1.70)	4(1.38)	2(3.13)
Hepatic failure	5(1.42)	3(1.04)	2(3.13)
Malignancy	51(14.45)	39(13.49)	12(18.75)
Alcohol abuse	9(2.55)	7(2.42)	2(3.13)
Active smoker	26(7.37)	22(7.61)	4(6.25)
CVA with the Rankin scale			
4–5	9(2.55)	5(1.73)	4(6.25)
2–3	23(6.52)	7(2.42)	16(25.00)
0–1	11(3.12)	5(1.73)	6(9.38)
COPD	13(3.68)	6(2.08)	7(10.94)
Symptomatic PE	1(0.28)	1(3.45)	0(0)
ASA score	2(1–2)	2(1–2)	2(1–3)
Preoperative pneumonia	57(16.15)	34(11.76)	70(37.23)
Type of fracture			
Femoral neck	190(53.82)	172(59.52)	18(28.13)
Intertrochanteric	145(41.08)	101(34.95)	44(68.75)
Subtrochanteric	6(1.70)	4(1.38)	2(3.13)
Periprosthetic	5(1.42)	5(1.73)	0(0)
Multiple hip fractures	7(1.98)	7(2.42)	0(0)
Type of surgery			
Intramedullary nail	140(39.65)	102(35.29)	38(59.38)
Cancellous screw	45(12.75)	36(12.46)	9(14.06)
Hemiarthroplasty	121(34.28)	116(40.14)	5(7.81)
Total hip arthroplasty	42(11.90)	32(11.07)	10(15.63)
Revision of arthroplasty	5(1.42)	3(1.04)	2(3.13)
Surgical delay			
<24 h	22(6.23)	22(7.61)	0(0)
24–72 h	285(80.74)	34(11.76)	52(81.25)
>72 h	46(13.03)	233 (80.62)	12(18.75)
Duration of surgery	3.15 ± 0.93	3.08 ± 0.85	3.48 ± 0.81
General anesthesia	35(9.92)	27(9.34)	8(12.5)
High-risk medications in surgery			
Benzodiazepines	59(16.71)	26(8.99)	33(51.56)
Opioids	233(66.01) 78(22.10)	167(57.79) 63 (21.80)	12(18.75)
NSAIDs			15(23.44)
Glucose level for patients with diabetes (mmol/L)	8.69 ± 1.57	7.14 ± 3.44	8.85 ± 1.50
Sodium	134.02 ± 17.28	135.25 ± 18.72	136.39 ± 9.63
BUN	7.84(5.25–8.73)	6.38(5.02–8.08)	7.93(6.45–10.25)
Creatine	58(54–89)	67(55–85)	69(59.05–99)
Albumin	35.66 ± 4.42	35.95 ± 5.65	35.26 ± 4.92
White blood cell count	8.55 ± 2.97	7.98 ± 2.56	8.26 ± 3.77
Hemoglobin	119(99–127)	122(104–133)	105(88–104.8)

Data are given as a number (%), mean + standard deviation, or median (interquartile range).
ADL, activities of daily living; BMI, body mass index; BUN, blood urea nitrogen; CCI, Carlson comorbidity index; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

the incidence of postoperative delirium; on the other hand, preoperative delirium may not persist after surgery. In the derivation cohort, 102(7.77%) patients had preoperative delirium, and 53(51.96%) of these patients were in a delirium state postoperatively, while 48.04% of these patients had no delirium after the surgery. It is necessary to include patients with preoperative delirium in the prediction model to evaluate the risk of the postoperative state of delirium.

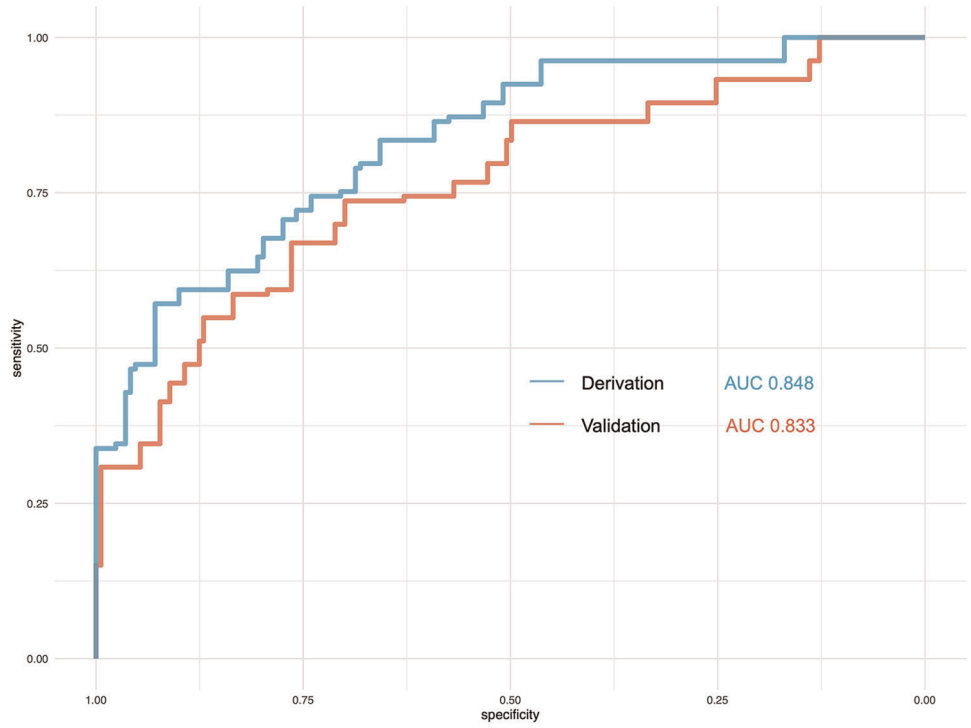

FIGURE 3
Comparison of the performance of the prediction model in the derivation and validation cohorts. AUC, area under the curve.

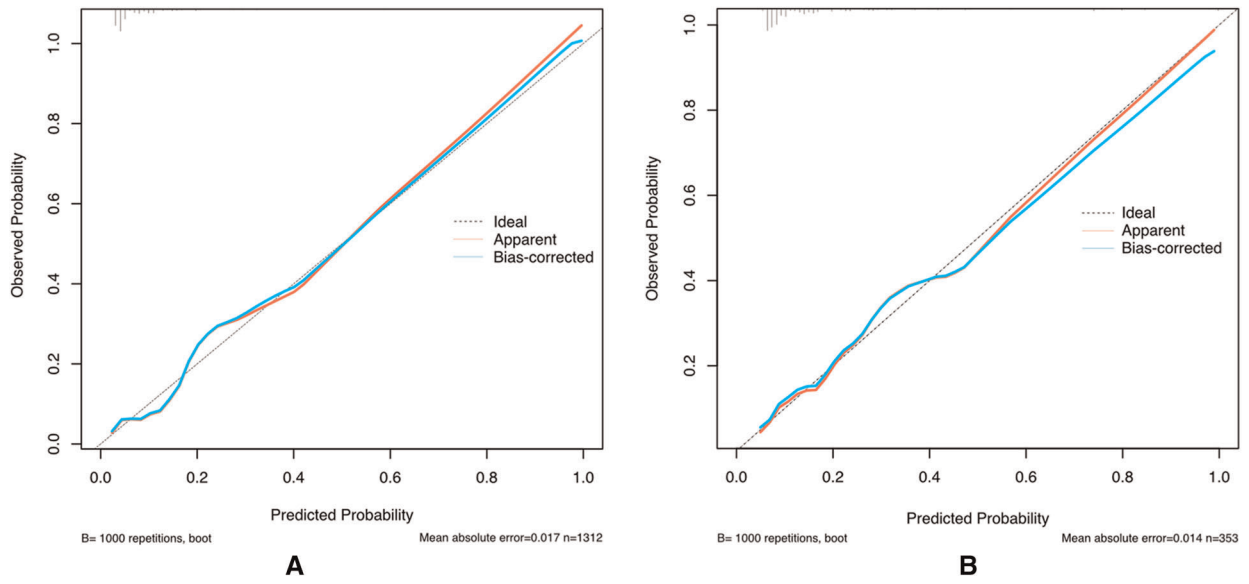

FIGURE 4
Calibration plot for the prediction model in the derivation and validation cohorts.

Although delirium may affect patients of various ages, geriatric patients suffer much more frequently and more severely from it. In an observational study that focused on preoperative and postoperative delirium, hip fracture patients older than 80 years were more likely to be complicated with delirium (25). The cause of the high incidence of delirium in

geriatric patients may be attributed to accumulated neuron injury accompanied by aging. At the same time, cerebrovascular accidents (CVA) can render geriatric patients more susceptible to delirium in stress states like trauma or surgery (26); moreover, impaired daily life function renders patients with a higher risk of delirium after stroke (27). In the present study, CVA with higher degrees of disability (evaluated with the modified Rankin scale) was also identified as a predictor of postoperative delirium, which indicates that the severity of neuroinjury brought by the CVA was associated with the risk of delirium.

Diabetes has been proved to be a predisposing factor for dementia (including vascular disease or Alzheimer's disease-related dementia) (28). Similarly, we observed an association between uncontrolled glucose levels and delirium episodes. It is rational to hypothesize that long-lasting vascular damage and inflammatory response in diabetes (29) will affect neuro functions.As supported by pathophysiological studies, elevated intracellular glucose levels will inhibit the mitochondrial function of neurons (30). The role of deregulated glucose metabolism in the cerebral spinal fluid has been reported to be related to cognitive dysfunction in mice and patients with delirium (31). Similarly, it has been reported that high variability of the serum glucose level was related to delirium in patients after aortic dissection surgery (15), which suggested a possible role of glucose management in delirium prevention for hip fracture patients.

High CCI has been proved (32) to be related to higher mortality and complications after hip fracture surgery. The CCI evaluated the number of comorbidities and the severity of the concomitant diseases, which was consistent with the result of Zhao et al. that the frailty of patients was a predictor of delirium after surgery (33). Another identified predictor in our study was active smoking. Physiological research has discovered that nicotine, the main component of tobacco, can affect the cerebral microvascular function and can prompt the process of atherosclerosis (34), which may further lead to delirium. Similarly, in our cohort, active smokers were liable to new-onset delirium, which may be attributed to the acetylcholine deficiency (35) caused by acute abstinence before surgery. In addition, disturbances of the internal environment caused by comorbidities or stress from the injury, presented with factors like high creatine levels, may also be interfering with the normal functioning of neurons and cause delirium (21, 33).

Medical interventions related to delirium

Benzodiazepines have been identified as a risk factor for delirium (36). When compared with other sedatives like propofol or dexmedetomidine, benzodiazepines are more efficient in affecting neurotransmitter concentrations and impairing the quality of sleep *via* slow-wave sleep suppression, which may finally lead to delirium (37). The fact that patients treated with benzodiazepines were more liable to delirium made the choice of sedatives even more critical in the surgery. On the contrary, opioids, which were reported as a risk factor for delirium in other studies (38, 39), were not included in the scoring system, which implies that the effect of sedatives can vary between different types of patients.

There is plenty of evidence that surgical delay is related to poor functional outcomes and mortality (40). The multivariable logistic regression in our study shows that surgical delay of >2 days was an independent risk factor for postoperative delirium, which indicates that, regardless of baseline conditions of patients, the delaying of the timely surgical intervention itself can affect cognitive function. A similar result was reported by Pioli et al. hat delay of surgery for hip fractures will increase the risk of delirium in patients with a history of cognitive impairments (41).

In view of the prevalence and prognosis of delirium after hip fracture surgery and arthroplasty, a validated scoring system will facilitate risk stratification for patients with identifiable risk factors of delirium at the time of hospital admission. In addition, timely intervention of risk factors will prevent about 30% of delirium episodes (42), making the search for risk factors and the development of prediction scores more reasonable. Based on the predictive variables identified in the present cohort, future studies can further explore the pathophysiological mechanisms of postoperative delirium in patients with hip fractures. What is more, interventional strategies can also be developed accordingly.

Currently, the treatment of delirium is mainly multidisciplinary, which focuses on interventions for various risk factors of delirium (43). Even though the multidisciplinary approach has not shown an overall significant improvement in mortality or hospitalization in random contrast trials, one of the studies suggested that this approach does reduce the time of recovery for cognitive functions (44). Given the lack of interventions that are supported by high-quality evidence, a clinician should direct more resources toward those with a higher risk of postoperative delirium and at least address correctable physiological variables in a timely manner.

Limitations

The present study is limited by several issues. First, as a result of the retrospective nature of this study, we used chart-based tools instead of a validated screening tool for delirium [e.g., Confusion Assessment Method (45)]. However, as evaluated by a previous study (18), this tool and Confusion Assessment Method had an overall good inter-rater agreement (with an agreement of 82%, kappa = 0.41). Second, for

benzodiazepines, we did not compare the difference between continuous infusion or boluses to the occurrence of postoperative delirium because only continuous infusion was related to delirium in one study (46). Finally, the score was derived from a single-center cohort; characteristics of the derivation cohort may not fit the whole population. The prediction score still needs to be validated in cohorts with more sufficient sample sizes in the future.

Conclusions

Based on retrospective data, a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty was derived and validated. The performance of the scoring system outperformed the models from previous studies. Although the generalization ability of the score needs to be tested in similar populations, the scoring system will enable delirium risk stratification for hip fracture patients and facilitate the development of strategies for delirium prevention.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University People's Hospital. Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JS. The first draft of the manuscript was written by JS, and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.919886/full#supplementary-material.

References

1. Curtis EM, Moon RJ, Harvey NC, Cooper C. The impact of fragility fracture and approaches to osteoporosis risk assessment worldwide. *Bone*. (2017) 104:29–38. doi: 10.1016/j.bone.2017.01.024

2. Cassell E, Clapperton A. A decreasing trend in fall-related hip fracture incidence in Victoria, Australia. *Osteoporos Int*. (2013) 24(1):99–109. doi: 10.1007/s00198-012-1937-6

3. Cooper C, Campion G, Melton 3rd LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int*. (1992) 2(6):285–9. doi: 10.1007/BF01623184

4. Investigators HA. Accelerated surgery versus standard care in hip fracture (hip attack): an international, randomised, controlled trial. *Lancet*. (2020) 395 (10225):698–708. doi: 10.1016/S0140-6736(20)30058-1

5. Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med*. (2017) 377(15):1456–66. doi: 10.1056/NEJMcp1605501

6. Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. (2021) 36(1):3–14. doi: 10.1002/gps.5408

7. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. (2010) 304 (4):443–51. doi: 10.1001/jama.2010.1013

8. Berian JR, Zhou L, Russell MM, Hornor MA, Cohen ME, Finlayson E, et al. Postoperative delirium as a target for surgical quality improvement. *Ann Surg*. (2018) 268(1):93–9. doi: 10.1097/SLA.0000000000002436

9. Kalisvaart KJ, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor

model. *J Am Geriatr Soc*. (2006) 54(5):817–22. doi: 10.1111/j.1532-5415.2006.00704.x

10. de Jong L, van Rijckevorsel V, Raats JW, Klem T, Kuijper TM, Roukema GR. Delirium after hip hemiarthroplasty for proximal femoral fractures in elderly patients: risk factors and clinical outcomes. *Clin Interv Aging*. (2019) 14:427–35. doi: 10.2147/CIA.S189760

11. Moerman S, Tuinebreijer WE, de Boo M, Pilot P, Nelissen RG, Vochteloo AJ. Validation of the risk model for delirium in hip fracture patients. *Gen Hosp Psychiatry*. (2012) 34(2):153–9. doi: 10.1016/j.genhosppsych.2011.11.011

12. Kim EM, Li G, Kim M. Development of a risk score to predict postoperative delirium in patients with hip fracture. *Anesth Analg*. (2020) 130(1):79–86. doi: 10.1213/ANE.0000000000004386

13. Xu W, Ma H, Li W, Zhang C. The risk factors of postoperative delirium in patients with hip fracture: implication for clinical management. *BMC Musculoskelet Disord*. (2021) 22(1):254. doi: 10.1186/s12891-021-04091-1

14. Wang LH, Xu DJ, Wei XJ, Chang HT, Xu GH. Electrolyte disorders and aging: risk factors for delirium in patients undergoing orthopedic surgeries. *BMC Psychiatry*. (2016) 16(1):418. doi: 10.1186/s12888-016-1130-0

15. Lin YJ, Lin LY, Peng YC, Zhang HR, Chen LW, Huang XZ, et al. Association between glucose variability and postoperative delirium in acute aortic dissection patients: an observational study. *J Cardiothorac Surg*. (2021) 16(1):82. doi: 10.1186/s13019-021-01456-4

16. Haggstrom LR, Nelson JA, Wegner EA, Caplan GA. 2-(18) F-fluoro-2-deoxyglucose positron emission tomography in delirium. *J Cereb Blood Flow Metab*. (2017) 37(11):3556–67. doi: 10.1177/0271678X17701764

17. Wassenaar A, van den Boogaard M, van Achterberg T, Slooter AJ, Kuiper MA, Hoogendoorn ME, et al. Multinational development and validation of an early prediction model for delirium in icu patients. *Intensive Care Med*. (2015) 41(6):1048–56. doi: 10.1007/s00134-015-3777-2

18. Inouye SK, Leo-Summers L, Zhang Y, Bogardus Jr ST., Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc*. (2005) 53(2):312–8. doi: 10.1111/j.1532-5415.2005.53120.x

19. Pisani MA, Araujo KL, Van Ness PH, Zhang Y, Ely EW, Inouye SK. A research algorithm to improve detection of delirium in the intensive care unit. *Crit Care*. (2006) 10(4):R121. doi: 10.1186/cc5027

20. Sullivan LM, Massaro JM, D'Agostino Sr RB. Presentation of multivariate data for clinical use: the framingham study risk score functions. *Stat Med*. (2004) 23(10):1631–60. doi: 10.1002/sim.1742

21. Malik AT, Quatman CE, Phieffer LS, Ly TV, Incidence KS. Risk factors and clinical impact of postoperative delirium following open reduction and internal fixation (ORIF) for hip fractures: an analysis of 7859 patients from the ACS-NSQIP hip fracture procedure targeted database. *Eur J Orthop Surg Traumatol*. (2019) 29(2):435–46. doi: 10.1007/s00590-018-2308-6

22. Wang CG, Qin YF, Wan X, Song LC, Li ZJ, Li H. Incidence and risk factors of postoperative delirium in the elderly patients with hip fracture. *J Orthop Surg Res*. (2018) 13(1):186. doi: 10.1186/s13018-018-0897-8

23. Gurunathan U, Marudhachalam K, Reynolds K. Preoperative delirium: not to be overlooked. *Anesth Analg*. (2016) 122(5):1727. doi: 10.1213/ANE.0000000000001202

24. Oh ES, Li M, Fafowora TM, Inouye SK, Chen CH, Rosman LM, et al. Preoperative risk factors for postoperative delirium following hip fracture repair: a systematic review. *Int J Geriatr Psychiatry*. (2015) 30(9):900–10. doi: 10.1002/gps.4233

25. Adunsky A, Levy R, Heim M, Mizrahi E, Arad M. The unfavorable nature of preoperative delirium in elderly hip fractured patients. *Arch Gerontol Geriatr*. (2003) 36(1):67–74. doi: 10.1016/s0167-4943(02)00058-4

26. Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry*. (2004) 12(1):7–21. doi: 10.1097/00019442-200401000-00002

27. Kotfis K, Bott-Olejnik M, Szylinska A, Listewnik M, Characteristics RI. Risk factors and outcome of early-onset delirium in elderly patients with first ever acute ischemic stroke—a prospective observational cohort study. *Clin Interv Aging*. (2019) 14:1771–82. doi: 10.2147/CIA.S227755

28. Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, et al. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology*. (2010) 75(13):1195–202. doi: 10.1212/WNL.0b013e3181f4d7f8

29. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol*. (2020) 8(4):325–36. doi: 10.1016/S2213-8587(19)30405-X

30. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. (2001) 414(6865):813–20. doi: 10.1038/414813a

31. Kealy J, Murray C, Griffin EW, Lopez-Rodriguez AB, Healy D, Tortorelli LS, et al. Acute inflammation alters brain energy metabolism in mice and humans: role in suppressed spontaneous activity, impaired cognition, and delirium. *J Neurosci*. (2020) 40(29):5681–96. doi: 10.1523/JNEUROSCI.2876-19.2020

32. Hasan O, Barkat R, Rabbani A, Rabbani U, Mahmood F, Noordin S. Charlson comorbidity index predicts postoperative complications in surgically treated hip fracture patients in a tertiary care hospital: retrospective cohort of 1045 patients. *Int J Surg*. (2020) 82:116–20. doi: 10.1016/j.ijsu.2020.08.017

33. Zhao H, You J, Peng Y, Feng Y. Machine learning algorithm using electronic chart-derived data to predict delirium after elderly hip fracture surgeries: a retrospective case-control study. *Front Surg*. (2021) 8:634629. doi: 10.3389/fsurg.2021.634629

34. Wu X, Zhang H, Qi W, Zhang Y, Li J, Li Z, et al. Nicotine promotes atherosclerosis via Ros-Nlrp3-mediated endothelial cell pyroptosis. *Cell Death Dis*. (2018) 9(2):171. doi: 10.1038/s41419-017-0257-3

35. Jasinska AJ, Zorick T, Brody AL, Stein EA. Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. *Neuropharmacology*. (2014) 84:111–22. doi: 10.1016/j.neuropharm.2013.02.015

36. Mody K, Kaur S, Mauer EA, Gerber LM, Greenwald BM, Silver G, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal effect. *Crit Care Med*. (2018) 46(9):1486–91. doi: 10.1097/CCM.0000000000003194

37. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the mends randomized controlled trial. *JAMA*. (2007) 298(22):2644–53. doi: 10.1001/jama.298.22.2644

38. Pun BT, Badenes R, La Calle G H, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. (2021) 9(3):239–50. doi: 10.1016/S2213-2600(20)30552-X

39. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The comparative risk of delirium with different opioids: a systematic review. *Drugs Aging*. (2017) 34(6):437–43. doi: 10.1007/s40266-017-0455-9

40. Tulic G, Dubljanin-Raspopovic E, Tomanovic-Vujadinovic S, Sopta J, Todorovic A, Manojlovic R. Prolonged Pre-operative hospital stay as a predictive factor for early outcomes and mortality after geriatric hip fracture surgery: a single institution open prospective cohort study. *Int Orthop*. (2018) 42(1):25–31. doi: 10.1007/s00264-017-3643-7

41. Pioli G, Bendini C, Giusti A, Pignedoli P, Cappa M, Iotti E, et al. Surgical delay is a risk factor of delirium in hip fracture patients with mild-moderate cognitive impairment. *Aging Clin Exp Res*. (2019) 31(1):41–7. doi: 10.1007/s40520-018-0985-y

42. Inouye SK, Bogardus Jr ST., Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. (1999) 340(9):669–76. doi: 10.1056/NEJM199903043400901

43. Soiza RL, Myint PK. The Scottish intercollegiate guidelines network (sign) 157: guidelines on risk reduction and management of delirium. *Medicina (Kaunas)* (2019) 55(8):491–6. doi: 10.3390/medicina55080491

44. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. *J Gerontol A Biol Sci Med Sci*. (2006) 61(2):176–81. doi: 10.1093/gerona/61.2.176

45. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. (1990) 113(12):941–8. doi: 10.7326/0003-4819-113-12-941

46. Zaal IJ, Devlin JW, Hazelbag M, Klein Klouwenberg PM, van der Kooi AW, Ong DS, et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med*. (2015) 41(12):2130–7. doi: 10.1007/s00134-015-4063-z

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EDITED BY
Carlos Suarez-Ahedo,
Hospital Médica Sur, Mexico

REVIEWED BY
Dejin Yang,
Beijing Jishuitan Hospital, China
Sebastian Walter,
University Hospital of Cologne, Germany
Paul Simon Unwin,
Independent Researcher, United Kingdom

*CORRESPONDENCE
Weiguo Wang
jointwwg@163.com
Wanshou Guo
zrgwsbucm@163.com

†These authors have contributed equally to this work and share first authorship

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Clinical and radiological outcomes of jumbo cup in revision total hip arthroplasty: A systematic review

Qiuyuan Wang[1,2†], Qi Wang[2,3†], Pei Liu[4], Juncheng Ge[2,3], Qidong Zhang[2], Wanshou Guo[1,2*] and Weiguo Wang[2*]

[1]Graduate School, Beijing University of Chinese Medicine, Beijing, China, [2]Department of Orthopaedic Surgery, China-Japan Friendship Hospital, Beijing, China, [3]Department of Orthopaedic Surgery, Peking University of China-Japan Friendship School of Clinical Medicine, Beijing, China, [4]Department of Adult Joint Reconstruction, Henan Luoyang Orthopedic Hospital (Henan Provincial Orthopedic Hospital), Zhengzhou, China

Introduction: Many studies have reported the clinical outcomes of a jumbo cup in revision total hip arthroplasty (rTHA) with acetabular bone defect. We conducted a systematic review to access the survivorship and clinical and radiological outcomes of a jumbo cup in rTHA.
Methods: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive literature search from PubMed, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews was performed with the keywords ("revision" OR "revision surgery" OR "revision arthroplasty") AND ("total hip arthroplasty" OR "total hip replacement" OR "THA" OR "THR") AND ("jumbo cup" OR "jumbo component" OR "extra-large cup" OR "extra-large component"). Studies reporting the clinical or radiological outcomes were included. The basic information and radiological and clinical results of these studies were extracted and summarized for analysis.
Results: A total of 19 articles were included in the systematic review. The analysis of clinical results included 953 hips in 14 studies. The re-revision-free survivorship of the jumbo cup was 95.0% at a mean follow-up of 9.3 years. Dislocation, aseptic loosening, and periprosthetic joint infection were the top three complications with an incidence of 5.9%, 3.0%, and 2.1%, respectively. The postrevision hip center was relatively elevated 10.3 mm on average; the mean postoperative leg-length discrepancy was 5.4 mm.
Conclusion: A jumbo cup is a favorable option for acetabular bone defect reconstruction in rTHA with satisfying survivorship and acceptable complication rates.

KEYWORDS
jumbo cup, acetabular bone defect, revision total hip arthroplasty, survivorship, rotation hip center

Introduction

Reconstruction of an acetabular bone defect is a difficult procedure in revision total hip arthroplasty (rTHA) (1). In rTHA, the primary goal of acetabular reconstruction is creating sufficient mechanical support and bone contact for the acetabular cup, thereby achieving bone ingrowth or ongrowth and attaining stability of the acetabular cup (2). In

addition, the position of the rotation hip center is also an important factor to consider. Due to the complexity and variety of the acetabular bone defect, it is highly possible for unexpected challenges to occur beyond the preoperative plan. Moreover, many patients who accept revision arthroplasty are at an advanced age with underlying diseases; therefore, there is need for enhancing surgical efficiency and limiting damage control. These factors all bring significant challenges to surgeons.

Before performing rTHA, an evaluation of the acetabular bone defect is necessary. The Paprosky classification, American Academy of Orthopaedic Surgeons (AAOS) classification, and Gross system are the most commonly used in preoperative planning (3, 4). Many new methods of evaluation have also been developed to help surgeons make better surgical strategy (5–9). Currently, the Paprosky type IIIA and IIIB and AAOS type III and IV are regarded as the most challenging conditions, which involve extensive bone loss of the acetabular rim and columns, and even pelvic discontinuity (10, 11). Several methods of reconstruction have been developed for severe acetabular bone loss in rTHA, such as structural allografts, impaction bone grafting, the jumbo cup, the highly porous metallic augments and hemispherical cup, the cup-cage system, custom monoflanged acetabular components, and the cup-on-cup technique (12–20). Many studies as well as systematic reviews have reported the clinical results of these reconstruction techniques (21–24), but the most effective solution remains controversial.

Using a jumbo cup is one of the most commonly recommended reconstruction methods for severe acetabular bone defect in rTHA. It was first reported by Jasty in 1998 (25). There is no strict definition for the jumbo cup. Most papers define the jumbo cup as a diameter of over 66 or 64 mm for males and over 62 or 60 mm for females. The advantages of the jumbo cup include the obvious simplified surgical procedure, more contact area with the host bone, and less requirement for bone graft (26). However, there are also some limitations in using the jumbo cup for reconstruction. For example, it may result in further bone loss (27), which may delay the full weight-bearing time and even cause a protrusion of the jumbo cup into the pelvic cavity. Therefore, the jumbo cup is usually applied in Paprosky type I–III acetabular bone defect and rarely used alone for pelvic discontinuity (11). In many cases, jumbo cups have to be set in a high position to provide sufficient contact with the host bone and mechanical support, which may lead to rotation center elevation, leg-length discrepancy (LLD), and soft tissue imbalance (28). Although many studies have reported the clinical results of the jumbo cup in rTHA, no systematic review has been conducted to date. In this context, the aim of this study is to systematically summarize the current evidence of the jumbo cup in rTHA, including survivorship and failure, radiological outcome, hip function, and complications.

Materials and methods

Literature search strategy

We conducted a comprehensive literature search from the electronic databases PubMed, EMBASE, Web of Science, and Cochrane Library. The last literature search was on 15 April 2022. The search project was based on the following keywords: ("revision" OR "revision surgery" OR "revision arthroplasty") AND ("total hip arthroplasty" OR "total hip replacement" OR "THA" OR "THR") AND ("jumbo cup" OR "jumbo component" OR "extra-large cup" OR "extra-large component"). The language was limited to English. If the abstract was not sufficient for us to include or exclude a study, we would download the full text. The literature search process was carried out on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (29).

Inclusion and exclusion criteria

Only those clinical studies that met the following criteria were included in this systematic review: (1) rTHA with acetabular bone defect; (2) using a jumbo cup for acetabular reconstruction; and (3) reporting clinical results or radiological data. Reviews, conference abstracts, non-English written articles, letters, case reports, experiment studies, and simulation studies were excluded from this systematic review.

Data extraction

Two researchers separately extracted all data according to the rules described above. We developed an extraction table for data extraction including the following: (1) basic information of each study; (2) radiological results evaluating the implant position; and (3) clinical results including studying the accuracy of the preoperative plan, intraoperative details, and postoperative function complications. All data were extracted by two investigators; any disagreement was solved by an expert surgeon and a third researcher to make a final decision.

Quality assessment

We used the Methodological Index for Non-Randomized Studies (MINORS) for quality assessment (30). This evaluation system involves 12 items for comparative studies and 8 items for noncomparative studies, with total scores of 24 and 16, respectively. The item was separately scored with 0, 1, and 2 corresponding to nonreported information,

inadequate information, and adequate information, respectively. Two authors independently filled the evaluation system. Studies that scored >75% of the total score were considered to have a low risk of bias.

Results

Literature selection

The literature search initially identified 101 articles and finally included 19 articles in this systematic review according to the inclusion and exclusion criteria (31–49) (**Figure 1**). Among the 19 articles, 2 articles were pure radiological studies (31, 40). There were three pairs of cognate articles (six articles) that were published in different years (38, 39, 41, 45, 48, 49). For these coupled cognate articles, the results of the more recent articles were adopted.

Quality assessment

Except for the two pure radiological studies, the remaining 17 clinical studies were included in the quality assessment (32–39, 41–49) (**Table 1**). Only one study was a comparative study and its quality was high (21/24) (33). The other 16 studies were noncomparative studies, with a mean MINORS score of 10.5, which indicated that the general quality of these studies was relatively low. Therefore, a further meta-analysis was not conducted.

Demographics and characteristics

A total of 1,406 hips were initially included in the review (**Table 2**). To analyze the clinical results, the two pure radiological studies were removed and the results of the cognate articles were merged and adjusted. As a result, 953 hips in 14 studies were included in the analysis of clinical results (32–39, 41–44, 46, 47) (**Tables 3–5**). The patients who underwent rTHA had a mean age of 62.5 years. The mean follow-up was 9.3 years. In the radiological result analysis part, 631 hips in 11 studies were included (31–34, 37, 40, 43, 44, 47–49). The data of the hip center position and leg-length discrepancy were extracted and analyzed (**Table 6**).

Definition of the jumbo cup

There were two main definitions of the jumbo cup among the studies. One was a diameter >66 mm for males and >62 mm for females and was usually adopted in European and American studies (35, 36, 39–42, 45, 46, 48). The other was a diameter >64 mm for males and >60 mm for females and was usually adopted in Asian studies (31–33, 44). Other definitions included diameter >60 mm (34, 47), >64 mm (43), >65 mm (38), >66 mm (49), and diameter >10 mm than templated contralateral hip (37).

Clinical analysis

Bone defect evaluation

All 14 studies reported the severity of acetabular bone defect. The Paprosky classification was adopted in 13 studies of 881 hips (32–37, 39, 41–44, 46, 47). Paprosky type IIB accounted for the largest proportion (26.6%, 234/881), followed by type IIA (22.5%, 198/881), type IIIA (21.6%, 190/881), type IIC (18.5%, 163/881), type IIIB (7.4%, 65/881), and type I (3.5%, 31/881). The AAOS classification was utilized in five studies with 372 hips (41, 43, 46, 48, 49). AAOS type III occupied the most (62.1%, 231/372), followed by type II (30.1%, 112/372), type I (7.3%, 27/372), and type IV (0.5%, 2/372). In most studies, additional procedures such as structural bone grafting and press-fit bone grafting were also performed to fill the severe acetabular bone defect.

Reoperation

All 14 clinical studies reported the rate of reoperation. The overall reoperation rate was 8.6% (82/953). The most common reasons for reoperation were aseptic loosening and dislocation with an incidence of 3.6% and 2.1%, respectively. Removal of the jumbo cup was defined as failure. The failure rate of the jumbo cups was 5.0% (48/953). Among the 48 failed jumbo cups, 22 were removed for aseptic loosening, 18 were removed for periprosthetic joint infection (PJI), and 8 were removed for dislocation. The survivorship of the jumbo cups was 95.0% in the mean follow-up of 9.3 years.

Complications

All 14 clinical studies reported complications. Due to the lack of a clear definition of complication, the overall complication rate was not calculated. Dislocation was the most common complication with a rate of 5.9%, followed by aseptic loosening (3.0% in acetabular and 2.4% in femoral) and PJI (2.1%).

Dislocation

Dislocation was the most frequent complication with a prevalence of 5.9% (56/953). Of the 56 dislocations, 20 (35.7%) accepted reoperation, with 7 re-revisions of the acetabular cup [five studies (36, 39, 41, 44, 46)], 7 femoral and liner re-revisions [three studies (39, 41, 42)], 4 femoral head and/or liners exchange [four studies (36, 39, 41, 42)], one femoral re-revision [one study (39)], and 1 resection arthroplasty [one study (41)].

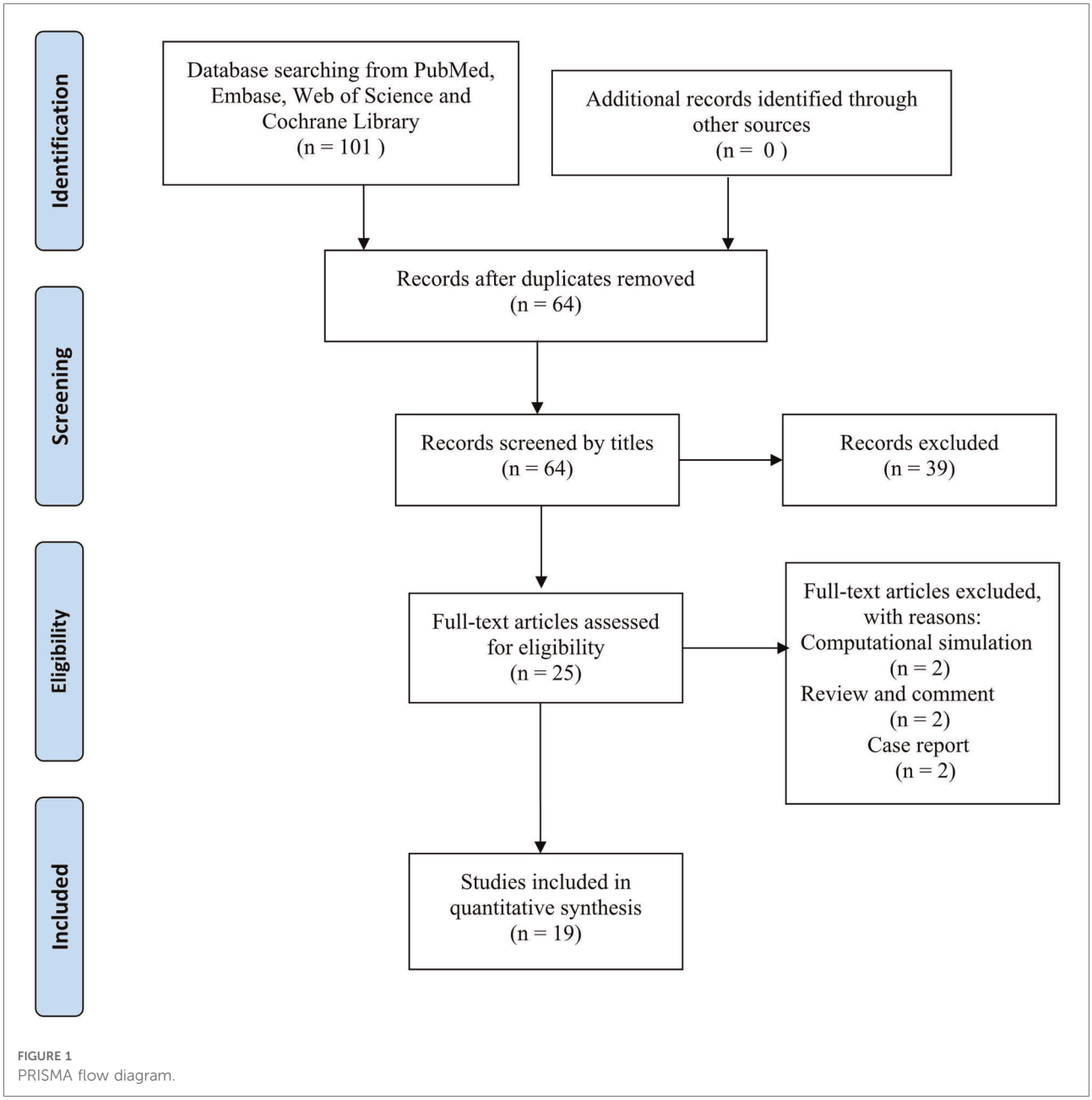

FIGURE 1
PRISMA flow diagram.

Aseptic loosening

The incidence of jumbo cup aseptic loosening was 3.0% [29 of 953 hips, 10 studies (33, 35–37, 39, 41–43, 46, 47)]. Among these cases, 22 were managed with acetabular re-revision, 5 refused reoperation, and 2 could not receive re-revision for medical problems.

Periprosthetic joint infection

PJI was the third most common complication after dislocation and aseptic loosening, with a rate of 2.1% [20 of 953 hips, 10 studies (32, 33, 36, 38, 39, 41–44, 47)]. Only one patient was treated with antibiotics only for his poor physical condition as he could not tolerate re-revision. The remaining 19 cases of PJI were treated with re-revision and the jumbo cups were removed.

Harris Hip Score

Eleven studies (687 hips) reported the pre- and postoperative Harris Hip Score (HHS) (32–36, 38, 39, 41, 43, 46, 47). The mean preoperative HHS was 49.4 (poor) and improved to 78.2 (fair) at the latest follow-up.

TABLE 1 MINORS scale.

Author/year	Clearly stated study aim	Inclusion of consecutive patients	Prospective collection of data	Appropriate endpoints	Unbiased assessment of endpoint	Appropriate follow-up period	Loss to follow-up less than 5%	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total score
Zhang 2019	2	2	2	2	1	2	0	0	NA	NA	NA	NA	9/16
Zhou 2018	2	2	2	2	1	2	2	0	2	2	2	2	21/24
Salem 2018	2	1	2	2	0	2	2	0	NA	NA	NA	NA	11/16
Moon 2018	2	1	2	2	0	2	2	0	NA	NA	NA	NA	11/16
McLaughlin 2018	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10/16
Jo 2016	2	1	2	2	0	2	2	0	NA	NA	NA	NA	11/16
von Roth 2015	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10/16
Gustke 2014	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12/16
Lachiewicz 2013	2	2	2	2	1	2	1	0	NA	NA	NA	NA	12/16
Wedemeyer 2008	2	1	2	2	0	2	2	0	NA	NA	NA	NA	11/16
Fan 2008	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12/16
Hendricks 2006	2	1	2	2	0	2	0	0	NA	NA	NA	NA	9/16
Gustke 2004	2	1	2	2	0	2	0	0	NA	NA	NA	NA	9/16
Patel 2003	2	1	2	1	0	2	2	0	NA	NA	NA	NA	10/16
Obenaus 2003	2	1	2	2	0	2	0	0	NA	NA	NA	NA	9/16
Whaley 2001	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12/16
Dearborn 2000	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10/16

MINORS, Methodological Index for Non-Randomized Studies.

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TABLE 2 Characteristics and patient demographics of included studies.

Author/ Year	Definition of jumbo cup	Study design	Hips of initial/ final cohort	Patients	Gender (M/F)	Age (y)	BMI	Follow-up	Acetabular bone defect classification	Revision reason
Peng 2021	Male: ≥64 mm; Female: ≥60 mm	Pure radiological	88/88	88	44/44	61 ± 11 (32–85)	NA	Postoperative 1 week	NA	NA
Zhang 2019	Male: ≥64 mm; Female: ≥60 mm	Retrospective	73/63	61	29/32	59.4 ± 11.4	24.9 ± 3.8	5.7 years (2–16)	Paprosky type IIA 16, IIB 9, IIC 24, IIIA 8, IIIB 6	Aseptic loosening 55, second stage of a two-stage revision for PJI 6, wear and osteolysis 2
Zhou 2018	Male: ≥64 mm; Female: ≥60 mm	Retrospective comparative study	80/77	77	43/34	60.6 ± 10.4	23.7 ± 3.4	52 months (24–104)	Paprosky type IIA 18, IIB 12, IIC 25, IIIA 14, IIIB 8	Aseptic loosening 61, PJI 6, fracture 1, dislocation 2, others 7
Salem 2018	>60 mm	Case series	17/17	17	9/8	52 (40–61)	NA	3.5 years (2–6)	Paprosky type IIB 4, IIIA 13	Aseptic loosening all
Moon 2018	Male: ≥66 mm; Female: ≥62 mm	Retrospective	85/80	80	47/33	57.7 (30–78)	24.3 (19.2–28.3)	10.4 years (5–16.1)	Paprosky type IIA 16, IIB 17, IIC 22, IIIA 19, IIIB 6	Aseptic all
McLaughlin 2018	Male: ≥66 mm; Female: ≥62 mm	Case series	61/30	28	14/14	71 (36–79)	33	13 years (10–16)	Paprosky type I 2, IIA 4, IIB 11, IIC 12, IIIA 1	Aseptic loosening 26, recurrent dislocation 3, severe osteolysis 1
Jo 2016	>10 mm than templated contralateral hip	Retrospective	60/51	51	22/29	60.7 (30–81)	23.2 (15.3–36.1)	51 months (12–154)	Paprosky type IIA 8, IIB 19, IIC 13, IIIA 11	Aseptic loosening 39, second stage of a two-stage revision for PJI 5, acetabular protrusion 5, recurrent dislocation 2
von Roth 2015	Male: ≥66 mm; Female: ≥62 mm	Retrospective	89/89	89	46/43	59 (30–83)	30 (19–37)	Clinical: 20 years (14–27); Radiographic; 19 years (10–25)	Paprosky type I 6, IIA 11, IIB 26, IIC 17, IIIA 25, IIIB 4	Acetabular loosening 38, aseptic acetabular and femoral loosening 42, aseptic acetabular loosening with femoral periprosthetic fracture 5, other indications 4
Nwankwo 2014	Male: ≥66 mm; Female: ≥62 mm	Pure radiological	98/98	98	57/41	62.4 ± 12.2	NA	Radiographic: 6 weeks	NA	NA
Gustke 2014	Male: ≥66 mm; Female: ≥62 mm	Retrospective	216/199	189	71/118	66	NA	10 years (2–19)	Paprosky type I 14, IIA 52, IIB 65, IIC 18, IIIA 34, IIIB 16 AAOS type I 8, II 74, III 115; pelvic discontinuity 2	Aseptic loosening of the acetabular component 148, septic loosening 21, recurrent dislocations 18, failed bipolar arthroplasties 4, persistent pain 2, excessive

(*continued*)

TABLE 2 Continued

Author/ Year	Definition of jumbo cup	Study design	Hips of initial/ final cohort	Patients	Gender (M/F)	Age (y)	BMI	Follow-up	Acetabular bone defect classification	Revision reason
										polyethylene wear patterns 3
Lachiewicz 2013	Male: ≥66 mm; Female: ≥62 mm	Retrospective	129/108	101	52/49	63 (33–88)	27 (16–41)	8.1 (2–22)	Paprosky type I 1, IIA 22, IIB 23, IIC 5, IIIA 40, IIIB 17	Painful aseptic loosening 89, PJI 10, periprosthetic femoral fracture 4, polyethylene wear 3, recurrent dislocation 1, chronic dislocation with periprosthetic femoral fracture 1
Wedemeyer 2008	≥64 mm	Retrospective	17/17	17	10/7	60 (44–78)	NA	82 months (33–149)	Paprosky type IIA 5, IIB 3, IIC 4, IIIA 5 AAOS type II 12, III 5	Aseptic prosthesis loosening all Primary hip revision surgery 9, second revision 7, third revision 1
Fan 2008	Male: ≥64 mm; Female: ≥60 mm	Retrospective	50/47	46	23/23	61.4 (23–79)	NA	65 months (48–84)	Paprosky type I 6, IIA 13, IIB 11, IIC 6, IIIA 5, IIIB 6	Loosening of the acetabular cups (septic 2 and aseptic 42), insert wear 3
Hendricks 2006	>65 mm	Retrospective	24/12	12	NA	NA	NA	13.9 years (12.3–16.2)	NA	NA
Gustke 2004	Male: ≥66 mm; Female: ≥62 mm	Case series	166/166	NA	NA	NA	NA	6.1 years	Paprosky type I 10, II 119, III 37; AAOS type II combined cavitary and segmental defects >105	NA
Patel 2003	Male: ≥66 mm; Female: ≥62 mm	Retrospective	43/43	42	NA	63 (25–86)	29 (21–42)	10 years (6–14)	Paprosky type IIA 21, IIB 6, IIC 10, IIIA 6 AAOS type I 9, II 11, III 23	Aseptic loosening 29, wear and osteolysis 7, part of a two-stage revision PJI 2, failed resurfacing procedures 5
Obenaus 2003	≥60 mm	Retrospective	99/60	59	NA	65.2 (39.8–79.5)	NA	5.6 years (4.1–7.1)	Paprosky type I 2, IIA 12, IIB 28, IIC 7, IIIA 9, IIIB 2	Aseptic cup loosening with enlargement of the acetabulum
Whaley 2001	Male: ≥66 mm; Female: ≥62 mm	Retrospective	89/89	89	46/43	59 (30–83)	30 (19–37)	7.2 years (5–11.3)	Paprosky type I 6, IIA 11, IIB 26, IIC 17, IIIA 25, IIIB 4; AAOS type I 3, II 10, III 76,	Acetabular loosening 38, aseptic acetabular and femoral loosening 42, aseptic acetabular loosening with femoral periprosthetic fracture 5, other indications 4

(*continued*)

TABLE 2 Continued

Author/ Year	Definition of jumbo cup	Study design	Hips of initial/ final cohort	Patients	Gender (M/F)	Age (y)	BMI	Follow-up	Acetabular bone defect classification	Revision reason
Dearborn 2000	≥66 mm	Case series	24/24	24	18/6	58 (21–81)	NA	7 years (5–10.3)	AAOS type I 7, II 5, III 12	NA

BMI, body mass index; AAOS, American Academy of Orthopaedic Surgeons; PJI, periprosthetic joint infection.

TABLE 3 Additional procedures, survival, and Harris Hip Score.

Study	No. of hips	Additional procedure	Survival	Harris Hip Score	
				Preoperative	Postoperative
Zhang 2019	63	Morselized allografting for acetabular protrusion	16 years: 96.8% (EP = reoperation)	46	83
Zhou 2018	77	Bulk allograft (2 hips) and impaction bone grafting (12 hips) was used in Paprosky type III acetabular bone loss	4 years: 94.2% (EP = radiological or clinical failure)	46.7 ± 13.2	83.1 ± 9.0
Salem 2018	17	Particulate bone grafting from the iliac crest	No re-revision at last follow-up (mean 3.5 years)	42 (24–59)	85 (72–92)
Moon 2018	80	Structural bone allograft (4 hips), morselized bone allograft (47 hips)	16 years: 85% (worst); 91% (best)	53	77
McLaughlin 2018	30	Packing acetabular deficiencies with allograft bone chips and local bone obtained from reaming	16 years: 92.6% (EP = re-revision); 97.4% (EP = cup aseptic loosening)	49 (37–59)	86 (64–94)
Jo 2016	51	Autogenic (ipsilateral iliac crest) or allogenic (fresh-frozen chip bone) morselized bone graft for medial cavitary bone defect	13 years: 86.3% (EP = implant failure)	NA	No rim fixation: 75 ± 7.6 Rim fixation: 85 ± 8.5
von Roth 2015 and Whaley 2001	89	Particulate bone grafting (54 hips), and bulk bone grafting (9 hips)	20 years: 83% (free from any acetabular revision), 88% (free from aseptic loosening of the metal acetabular component), and 85% (free from aseptic or radiographic definite loosening of the metal acetabular component)	56	71 (30–95)
Gustke 2014 and Gustke 2004	216	Particulate autografting (51 hips), particulate allografting (49 hips), bulk allografting (38 hips)	4 years: 98%; 16y:96% (acetabular component)	44	72
Lachiewicz 2013	108	Bone grafting (108 hips): crushed cancellous allograft only (98 hips), iliac crest autograft (4 hips), both allograft and autograft (5 hips)	10 years: 97.3%, 15 years: 82.8% (EP = either acetabular cup revision for aseptic loosening or definite radiographic evidence of loosening); 10 years: 93.8%, 15 years: 79.8% (EP = acetabular cup removal for any reason); 10 years: 88.5%, 15 years: 56.5% (EP = any reoperation involving the hip)	NA	
Wedemeyer 2008	17	Morselized bone graft (15 hips)	NA	62	83
Fan 2008	47	Allograft bone graft (25 patients)	5 years: 94.5% (EP = implant failure)	NA	
Hendricks 2006 and Dearborn 2000	24	Particulate autologous or allograft bone packing acetabular defects	NA	54 (31–82)	79 (46–98)
Patel 2003	43	Bulk allograft (8 hips), morselized allograft alone (27 hips)	Acetabular shell: 14 years: 92%; acetabular shell: 13 years: 83%	48 ± 15	81 ± 18
Obenaus 2003	60	Press-fit structural allografting (7 hips), mixture of autologous slurry and allogenic bone chips (10 hips)	NA	58.7 (28–97.7)	90.6 (61.1–100)

EP, ending point.

TABLE 4 Summary of complications.

Study	No. of hips	Dislocation	PJI	Aseptic loosening		Osteolysis	Superficial infection	Nerve injury	Fracture	DVT	Medical complications
				Acetabular	Femoral						
Zhang 2019	63	1	1	0	0	0	0	NA	1	NA	NA
Zhou 2018	77	4	2	1	NA	0	0	0	0	0	0
Salem 2018	17	0	0	0	0	0	1	0	0	0	NA
Moon 2018	80	3	0	7	NA	7	1	1	NA	NA	3
McLaughlin 2018	61	3	2	1	NA	0	0	NA	NA	1	NA
Jo 2016	51	0	0	4	0	3	1	NA	1	NA	NA
von Roth 2015 and Whaley 2001	89	11	1	5	5	1	0	5	1	NA	1
Gustke 2014	216	9	1	3	NA	NA	NA	NA	NA	NA	NA
Lachiewicz 2013	108	12	4	4	5	2	0	0	3	NA	NA
Wedemeyer 2008	17	1	1	1	NA	0	2	NA	NA	NA	NA
Fan 2008	47	5	1	0	0	0	1	NA	NA	NA	NA
Hendricks 2006 and Dearborn 2000	24	5	5	0	1	1	0	2	3	NA	1
Patel 2003	43	2	0	2	1	0	0	0	0	0	NA
Obenaus 2003	60	0	2	1	0	0	0	NA	NA	NA	NA
Total	953	5.9% 56/953	2.1% 20/953	3.0% 29/953	2.4% 12/502	1.9% 14/720	0.8% 6/720	1.8% 8/438	1.9% 9/472	0.5% 1/196	1.8% 5/270

PJI, periprosthetic joint infection; DVT, deep vein thrombosis.

Radiological measurements

Vertical position of the hip center

Seven studies (461 hips) reported the postoperative vertical distance of hip center elevation relative to the contralateral hip center (31–33, 37, 40, 47, 49). The postrevision hip center was elevated 10.3 mm on average. Five studies (293 hips) compared the pre- and postoperative vertical positions of the hip center (32, 33, 43, 44, 48). Compared with the preoperative condition, the postrevision hip center dropped 6.2 mm on average in the vertical position.

Horizontal position of the hip center

Four studies (279 hips) reported the postoperative lateral migration of the hip center relative to the contralateral hip center (31–33, 37). The revision hip center moved 0.4 mm laterally on average. Four studies compared the pre- and postoperative horizontal positions of the hip center (32, 33, 43, 48). The postoperative hip center migrated 1.4 mm laterally on average compared with the preoperative position.

Leg-length discrepancy

Three studies reported an improvement of LLD (32–34). The mean LLD was corrected from a preoperative 18.8 mm to a postoperative 5.4 mm.

Discussion

The jumbo cup has been used for acetabular bone defect reconstruction in rTHA for a long time. To the best of our knowledge, this is the first systematic review to evaluate the evidence of a jumbo cup in rTHA. In general, the results indicated that the jumbo cup was a favorable option for acetabular reconstruction in rTHA for satisfying survivorship and acceptable complication rates.

As was summarized previously, there was no unified definition for the jumbo cup. The definition differed between the studies and could be influenced by the factors of time, race, and surgeon preference. Therefore, to a greater extent, the jumbo cup represents a special idea for acetabular reconstruction. By using a “very large” cup in this study, the

TABLE 5 Terms of reoperation and revision.

Study	No. of hips	Overall reoperation	Reasons for reoperation						Cup re-revision
			Dislocation	Aseptic loosening	PJI	Osteolysis	Fracture	Others	
Zhang 2019	63	2	0	0	1	0	1	0	1 (1 PJI)
Zhou 2018	77	2	0	1	1 (1.3%)	0	0	0	2 (1 PJI, 1 aseptic loosening)
Salem 2018	17	0	0	0	0	0	0	0	0
Moon 2018	80	2	0	1	0	2	0	0	1 (1 aseptic loosening due to osteolysis)
McLaughlin 2018	61	5	2	1	2	0	0	0	4 (2 PJI, 1 aseptic loosening, 1dislocation)
Jo 2016	51	4	0	4	0	0	0	0	4 (4 aseptic loosening)
von Roth 2015 and Whaley 2001	89	18	4	10 (5 A, 5 F)	1	1	1	1	7 (5 aseptic loosening, 1 PJI, 1 dislocation)
Gustke 2014 and Gustke 2004	216	8	7	3	1	0	0	0	7 (3 aseptic loosening, 3 dislocation, 1 PJI)
Lachiewicz 2013	108	20	3	8 (3 A, 5 F)	4	2 (F)	3	0	7 (3 aseptic loosening, 4 PJI)
Wedemeyer 2008	17	2	0	1	1	0	0	0	2 (1 aseptic loosening, 1 PJI)
Fan 2008	47	3	2	0	1	0	0	0	3 (2 dislocation, 1 PJI)
Hendricks 2006 and Dearborn 2000	24	8	1	0	5	1 (F)	0	1 (nonunion)	5 (5 PJI)
Patel 2003	43	5	1	3 (2 A, 1 F)	0	0	0	1	3 (2 aseptic loosening, 1 dislocation)
Obenaus 2003	60	3	0	1	2	0	0	0	2 (1 aseptic loosening, 1 PJI)
Total	953	82/953 8.6%	20/953 2.1%	34/953 3.6%	19/953 2.0%	6/953 0.6%	5/953 0.5%	3/953 0.3%	48/953 (18 PJIs, 22 aseptic loosenings, 8 dislocations) 5.0%

PJI, periprosthetic joint infection.

contact area with the host bone increased; thereby, the goal of three-point stability and bone ingrowth was achieved.

With respect to postoperative complications, dislocation occupied the first position, with the highest rate of 5.9%. Therefore, we should lay emphasis on this complication and try to place the large diameter femoral head component to reduce the rate of dislocation. We should also identify the patients with high risk of dislocation in advance according to the reported risk factors related to dislocation after rTHA, such as advanced age, history of instability, and prior revision history (50). However, this rate of dislocation (5.9%) is also acceptable because the rate of dislocation is naturally high after rTHA, with 5%–35% in various studies (51–54). In a meta-analysis by Guo et al. that included 4,656 rTHAs, the accumulated incidence of postoperative dislocation was 9.04% (55). Many factors contribute to the high rate of dislocation after rTHA. Due to the extensive exposure in revision arthroplasty, the soft tissue deconstruction process is more severe, especially in revision for PJI because of the thorough debridement procedure. In addition, the posterolateral approach is commonly applied in rTHA, which also leads to injuries of the abduction muscles and an increased risk of dislocation (56, 57). Moreover, the rotation center may not restore in its original position and the offset may also be unsatisfying after rTHA. All these factors may lead to soft tissue imbalance and further postoperative dislocation. However, most dislocations can be addressed by conservative therapy; dislocation is just the second cause for reoperation. Therefore, it is also unnecessary to harbor too much fear for dislocation.

The rate of reoperation was 8.6% and the re-revision of the jumbo cups was 5.0%. Aseptic loosening was the primary mode of failure leading to reoperation and re-revision of the jumbo cups. This may be related to the fixation mechanism of the

TABLE 6 Radiological outcome.

Study	Hips	Vertical position of hip center (mm)			Horizontal position of hip center (mm)			Leg-length discrepancy (mm)	
		Preoperative	Postoperative	Contralateral	Preoperative	Postoperative	Contralateral	Preoperative	Postoperative
Peng 2021	88	NA	23.0 ± 6.1	15.4 ± 3.4	NA	36.4 ± 4.6	35.9 ± 4.4	NA	
Zhang 2019	63	29.7 ± 10.4	22.3 ± 7.6	14.0 ± 3.7	30.8 ± 6.6	29.5 ± 3.7	30.3 ± 3.3	−16.8 ± 17.1	−5.6 ± 11.8
Zhou 2018	77	30.3 ± 10.4	24.1 ± 8.4, +9.6 ± 8.7 relative to the contralateral		30.5 ± 6.9	31.1 ± 4.8, −0.5 ± 8.2 relative to the contralateral		−18.8 ± 16.1	−6.2 ± 15.5
Salem 2018	17	NA			NA			−26 (−20 to 30)	−1 (−5 to 0)
Jo 2016	51	Superior migration of 12.1 ± 4.5 mm in rim fixation group, 11.3 ± 5.6 mm in no rim fixation group			Lateral migration of 3.0 ± 1.3 mm in rim fixation group, 2.3 ± 1.5 mm in no rim fixation group			NA	
Nwankwo 2014	98	NA	32.6 ± 9.6	21.7 ± 8	NA			NA	
Wedemeyer 2008	17	35 ± 8	31 ± 9	NA	34.5 ± 7.2	36.2 ± 6.8	NA	NA	
Fan 2008	47	31	27	NA	NA			NA	
Obenaus 2003	60	NA	11.4 mm (0–41) above anatomic rotation center	NA	NA			NA	
Whaley 2001	89	40 (17–67)	33 (10–58)	NA	39	43	NA	NA	
Dearborn 2000	24	NA	Elevated averagely 4 mm	NA	NA			NA	

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jumbo cup, which increases the contact area with the host bone to achieve bone ingrowth. Nevertheless, the local host bone may become severely ossified and the bioactivity of the implanted bone is also unreliable. In addition, there is some bone loss in the filing process. These elements can impede bone ingrowth and further lead to a failure of fixation. Hence, if the intraoperative findings indicate that the condition of the local host bone is poor for bone ingrowth, the rotation center elevation technique should be adopted to provide more contact area as well as better bioactivity of the host bone, which is beneficial for bone ingrowth and biomechanical instability.

The radiological outcome indicated that the rotation center position was elevated postoperatively compared with the original anatomical position. This is quite understandable for the combination of the rotation center elevation technique to achieve successful bone ingrowth as mentioned before. Another finding is that the elevation of the rotation center position has already existed preoperatively due to the acetabular bone defect, which also attained a certain degree of correction through the rTHA. The mean postoperative LLD was only 5.4 mm, which is quite acceptable and has no adverse influence on the patient's feeling and limb function. The Harris Hip Score also improved significantly, which indicated that the general condition (pain, activity, deformity, and range of motion) of the hip improved after rTHA. The revised hip could be regarded as meeting the need for daily life, as the mean postoperative HHS was up to the fair level. Thus, although *in situ* reconstruction of the rotation center is the gold standard in rTHA, good clinical results can also be received in the condition of rotation center elevation.

PJI is a disastrous complication that keeps troubling arthroplasty surgeons. For rTHA, the risk of PJI is higher than in primary THA. The rate of PJI in postrevision THA was in the range of 1.3%–17.3% from different registers (58–60). Fröschen et al. retrospectively analyzed 68 rTHAs using custom-made acetabular implants for Paprosky IIIA or IIIB acetabular bone defect reconstruction; the rate of postoperative PJI was unexpectedly up to 22% (61). In systematic reviews of other reconstruction methods for acetabular bone defect, the PJI rates of the custom triflange acetabular component and cup-cage technique were 6.2% and 3.3%, respectively (21, 22). In our systematic review of the jumbo cup for rTHA, the rate of PJI was only 2.1%, which can be regarded as relatively low. We speculate that this reduced rate of PJI may be due to the simplified procedure in acetabular reconstruction of jumbo cups, which may save surgical time and lower the risk of PJI. Another reason is that the jumbo cup method requires a smaller amount of implant compared with other methods, such as porous metallic augments, cup-cage, and monoflanged acetabular component. However, many factors can affect the rate of PJI, such as femoral revision or no revision, use of antibiotics, type of material, and implant coating design. Therefore, we still recommend that this relatively low rate of PJI should be treated with caution because of some existing bias and the relatively simple statistical method.

There are also some controversies on using the jumbo cup for rTHA. In 2016, Lachiewicz and Watters pointed out that although the jumbo cup had shown excellent 10-year survivorship, the late loosening of "first-generation" porous surfaces and wear with periprosthetic osteolysis of traditional polyethylene liners had also been reported and needed more attention (27). They also recommended the use of enhanced porous coatings, highly cross-linked polyethylene liners, and large femoral heads in jumbo cup reconstruction. Zhou et al. retrospectively compared 74 consecutive rTHAs using metal augments with a cementless hemispherical cup and 77 consecutive rTHAs using the jumbo cup (33). The biomechanical parameters of the metal augment group, such as rotator center position, leg-length discrepancy, head-cup difference, and femoral offset, are all superior to those of the jumbo cup group. In recent years, many advanced reconstruction techniques such as 3D printing, custom prosthesis, and robot-assisted arthroplasty have been developed and seem to stand for the future direction of rTHA (62–64). Even so, the results of our systematic review have already supported the jumbo cup as a successful method for acetabular reconstruction in rTHA. The development of advanced biomaterials will further improve the performance of the jumbo cup.

Our study also has several limitations, some of which are listed here. First, the quality of the included studies is relatively low, and most of these are of a single-arm design. Second, the sample size is also relatively limited. In addition, the acetabular bone defects of many included cases are mild-to-moderate and relatively easy to reconstruct. In fact, the reconstruction for severe acetabular bone defect is the real hot spot and core problem in rTHA. Therefore, if only the performance of the jumbo cup for severe acetabular defect is discussed, the results may not be presented as well as those in our study. Unfortunately, most papers report the overall survivorship and failure and do not report the relation with the extent of bone defect. Therefore, this relation was not explored in this systematic review. Certainly, on the other hand, the results can also indicate that the jumbo cup is a good option for mild-to-moderate acetabular bone defect at least.

Conclusion

In summary, according to this systematic review, the jumbo cup is a recommended method for acetabular reconstruction in

rTHA. The clinical outcomes and survivorship of the jumbo cup are satisfying. However, in most cases, the acetabular bone defects are mild to moderate. Further research is still required to review its performance for severe or extreme acetabular bone defect reconstruction.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

WG and WW set the topic and designed the protocol. QZ and JG conducted the literature search and quality assessment. QyW, QW, and PL extracted and analyzed the data and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Volpin A, Konan S, Biz C, Tansey RJ, Haddad FS. Reconstruction of failed acetabular component in the presence of severe acetabular bone loss: a systematic review. *Musculoskelet Surg.* (2019) 103:1–13. doi: 10.1007/s12306-018-0539-7

2. Sheth NP, Nelson CL, Springer BD, Fehring TK, Paprosky WG. Acetabular bone loss in revision total hip arthroplasty: evaluation and management. *J Am Acad Orthop Surg.* (2013) 21:128–39. doi: 10.5435/JAAOS-21-03-128

3. D'Antonio JA, Capello WN, Borden LS, Bargar WL, Bierbaum BF, Boettcher WG, et al. Classification and management of acetabular abnormalities in total hip arthroplasty. *Clin Orthop Relat Res.* (1989) 243:126–37. doi: 10.1097/00003086-198906000-00019

4. Paprosky WG, Perona PG, Lawrence JM. Acetabular defect classification and surgical reconstruction in revision arthroplasty. A 6-year follow-up evaluation. *J Arthroplasty.* (1994) 9:33–44. doi: 10.1016/0883-5403(94)90135-x

5. Jaenisch M, Wirtz DC, Kohlhof H, Gathen M, Kabir K, Koob S, et al. APP-guided assessment of acetabular defects in hip revision arthroplasty: a structured approach to a complex situation. *Arch Orthop Trauma Surg.* (2021):1–10. doi: 10.1007/s00402-021-04270-8

6. Wirtz DC, Jaenisch M, Osterhaus TA, Gathen M, Wimmer M, Randau TM, et al. Acetabular defects in revision hip arthroplasty: a therapy-oriented classification. *Arch Orthop Trauma Surg.* (2020) 140:815–25. doi: 10.1007/s00402-020-03379-6

7. Walter SG, Thomas TS, Kenndoff D, Thomas W. Mid-term follow-up after all-size acetabular revision and proposal for a stability classification system. *Hip Int.* (2020) 30:431–7. doi: 10.1177/1120700019839698

8. Zhang JW, Liu XL, Zeng YM, Zhai ZJ, Mao YQ, Yu DG, et al. Comparison of 3D printing rapid prototyping technology with traditional radiographs in evaluating acetabular defects in revision hip arthroplasty: a prospective and consecutive study. *Orthop Surg.* (2021) 13:1773–80. doi: 10.1111/os.13108

9. Meynen A, Vles G, Zadpoor AA, Mulier M, Scheys L. The morphological variation of acetabular defects in revision total hip arthroplasty—a statistical shape modeling approach. *J Orthop Res.* (2021) 39:2419–27. doi: 10.1002/jor.24995

10. Hasenauer MD, Paprosky WG, Sheth NP. Treatment options for chronic pelvic discontinuity. *J Clin Orthop Trauma.* (2018) 9:58–62. doi: 10.1016/j.jcot.2017.09.009

11. Babis GC, Nikolaou VS. Pelvic discontinuity: a challenge to overcome. *EFORT Open Rev.* (2021) 6:459–71. doi: 10.1302/2058-5241.6.210022

12. Cassar-Gheiti AJ, Mei XY, Afenu EA, Safir OA, Gross AE, Kuzyk P. Midterm outcomes after reconstruction of superolateral acetabular defects using flying buttress porous tantalum augments during revision total hip arthroplasty. *J Arthroplasty.* (2021) 36:2936–41. doi: 10.1016/j.arth.2021.03.040

13. Li GY, Zhang XQ, Chen M, Luo ZL, Ji XF, Shang XF. Modular revision strategy with bispherical augments in severe acetabular deficiency reconstruction. *Int Orthop.* (2022) 46:215–22. doi: 10.1007/s00264-021-05195-y

14. Loppini M, Schiavi P, Rocca AD, Traverso F, Rocca FD, Mazziotta G, et al. Double-trabecular metal cup technique for the management of Paprosky type III defects without pelvic discontinuity. *Hip Int.* (2018) 28:66–72. doi: 10.1177/1120700018813208

15. Chang CH, Hu CC, Chen CC, Mahajan J, Chang Y, Shih HN, et al. Revision total hip arthroplasty for Paprosky type III acetabular defect with structural allograft and tantalum trabecular metal acetabular cup. *Orthopedics.* (2018) 41:e861–7. doi: 10.3928/01477447-20181023-02

16. Brown NM, Morrison J, Sporer SM, Paprosky WG. The use of structural distal femoral allograft for acetabular reconstruction of Paprosky type IIIA defects at a mean 21 years of follow-up. *J Arthroplasty.* (2016) 31:680–3. doi: 10.1016/j.arth.2015.10.020

17. Hipfl C, Janz V, Löchel J, Perka C, Wassilew GI. Cup-cage reconstruction for severe acetabular bone loss and pelvic discontinuity: mid-term results of a consecutive series of 35 cases. *Bone Joint J.* (2018) 100-B:1442–8. doi: 10.1302/0301-620X.100B11.BJJ-2018-0481.R1

18. Webb JE, McGill RJ, Palumbo BT, Moschetti WE, Estok DM. The double-cup construct: a novel treatment strategy for the management of Paprosky IIIA and IIIB acetabular defects. *J Arthroplasty.* (2017) 32:S225–31. doi: 10.1016/j.arth.2017.04.017

19. Barlow BT, Oi KK, Lee YY, Carli AV, Choi DS, Bostrom MP. Outcomes of custom flange acetabular components in revision total hip arthroplasty and predictors of failure. *J Arthroplasty.* (2016) 31:1057–64. doi: 10.1016/j.arth.2015.11.016

20. Li H, Qu X, Mao Y, Dai K, Zhu Z. Custom acetabular cages offer stable fixation and improved hip scores for revision THA with severe bone defects. *Clin Orthop Relat Res.* (2016) 474:731–40. doi: 10.1007/s11999-015-4587-0

21. De Martino I, Strigelli V, Cacciola G, Gu A, Bostrom MP, Sculco PK. Survivorship and clinical outcomes of custom triflange acetabular components in revision total hip arthroplasty: a systematic review. *J Arthroplasty*. (2019) 34:2511–8. doi: 10.1016/j.arth.2019.05.032

22. Changjun C, Xin Z, Mohammed A, Liyile C, Yue L, Pengde K. Survivorship and clinical outcomes of "cup-cage" reconstruction in revision of hip arthroplasty for chronic pelvic discontinuity: a systematic review. *Surgeon*. (2021) 19:e475–84. doi: 10.1016/j.surge.2020.11.007

23. Wang CX, Huang ZD, Wu BJ, Li WB, Fang XY, Zhang WM. Cup-cage solution for massive acetabular defects: a systematic review and meta-analysis. *Orthop Surg*. (2020) 12:701–7. doi: 10.1111/os.12710

24. Walter SG, Randau TM, Gravius N, Gravius S, Fröschen FS. Monoflanged custom-made acetabular components promote biomechanical restoration of severe acetabular bone defects by metallic defect reconstruction. *J Arthroplasty*. (2020) 35:831–5. doi: 10.1016/j.arth.2019.10.040

25. Jasty M. Jumbo cups and morsalized graft. *Orthop Clin North Am*. (1998) 29:249–54. doi: 10.1016/s0030-5898(05)70323-0

26. Emerson Jr RH, Head WC. Dealing with the deficient acetabulum in revision hip arthroplasty: the importance of implant migration and use of the jumbo cup. *Semin Arthroplasty*. (1993) 4:2–8.

27. Lachiewicz PF, Watters TS. The jumbo acetabular component for acetabular revision: curtain calls and caveats. *Bone Joint J*. (2016) 98-B:64–7. doi: 10.1302/0301-620X.98B1.36139

28. Nwankwo C, Dong NN, Heffernan CD, Ries MD. Do jumbo cups cause hip center elevation in revision THA? A computer simulation. *Clin Orthop Relat Res*. (2014) 472:572–6. doi: 10.1007/s11999-013-3169-2

29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Br Med J*. (2009) 339:b2535. doi: 10.1136/bmj.b2535

30. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological Index for Non-Randomized Studies (MINORS): development and validation of a new instrument. *ANZ J Surg*. (2003) 73:712–6. doi: 10.1046/j.1445-2197.2003.02748.x

31. Peng YW, Shen JM, Zhang YC, Sun JY, Du YQ, Zhou YG. Jumbo cup in hip joint renovation may cause the center of rotation to increase. *World J Clin Cases*. (2021) 9:6300–7. doi: 10.12998/wjcc.v9.i22.6300

32. Zhang J, Huang Y, Zhou B, Zhou Y. Mid-term follow-up of acetabular revision arthroplasty using jumbo cups. *Orthop Surg*. (2019) 11:811–8. doi: 10.1111/os.12522

33. Zhou B, Zhou Y, Yang D, Tang H, Shao H, Huang Y. The utilization of metal augments allows better biomechanical reconstruction of the hip in revision total hip arthroplasty with severe acetabular defects: a comparative study. *J Arthroplasty*. (2018) 33:3724–33. doi: 10.1016/j.arth.2018.08.027

34. Salem Eid A, Kotb A, Elshabrawy W. Cementless jumbo cups for revision of failed Furlong prosthesis. A case series. *J Clin Orthop Trauma*. (2020) 11:56–61. doi: 10.1016/j.jcot.2018.08.009

35. Moon JK, Ryu J, Kim Y, Yang JH, Hwang KT, Kim YH. Acetabular revision arthroplasty using press-fitted jumbo cups: an average 10-year follow-up study. *Arch Orthop Trauma Surg*. (2019) 139:1149–60. doi: 10.1007/s00402-019-03214-7

36. McLaughlin JR, Lee KR. Acetabular revision arthroplasty using an uncemented deep profile jumbo component: a ten to sixteen year follow-up study. *J Arthroplasty*. (2018) 33:496–9. doi: 10.1016/j.arth.2017.09.002

37. Jo WL, Lim YW, Im JH, Kim SC, Kwon SY, Kim YS. Comparative study of peripheral rim fixation using jumbo cup in revisional hip arthroplasty. *Hip Pelvis*. (2017) 29:24–9. doi: 10.5371/hp.2017.29.1.24

38. Hendricks KJ, Harris WH. Revision of failed acetabular components with use of so-called jumbo noncemented components. A concise follow-up of a previous report. *J Bone Joint Surg Am*. (2006) 88:559–63. doi: 10.2106/JBJS.E.00389

39. von Roth P, Abdel MP, Harmsen WS, Berry DJ. Uncemented jumbo cups for revision total hip arthroplasty: a concise follow-up, at a mean of twenty years, of a previous report. *J Bone Joint Surg Am*. (2015) 97:284–7. doi: 10.2106/JBJS.N.00798

40. Nwankwo CD, Ries MD. Do jumbo cups cause hip center elevation in revision THA? A radiographic evaluation. *Clin Orthop Relat Res*. (2014) 472:2793–8. doi: 10.1007/s11999-014-3632-8

41. Gustke KA, Levering MF, Miranda MA. Use of jumbo cups for revision of acetabulae with large bony defects. *J Arthroplasty*. (2014) 29:199–203. doi: 10.1016/j.arth.2012.11.010

42. Lachiewicz PF, Soileau ES. Fixation, survival, and dislocation of jumbo acetabular components in revision hip arthroplasty. *J Bone Joint Surg Am*. (2013) 95:543–8. doi: 10.2106/JBJS.L.00758

43. Wedemeyer C, Neuerburg C, Heep H, von Knoch F, von Knoch M, Löer F, et al. Jumbo cups for revision of acetabular defects after total hip arthroplasty: a retrospective review of a case series. *Arch Orthop Trauma Surg*. (2008) 128:545–50. doi: 10.1007/s00402-007-0501-x

44. Fan CY, Chen WM, Lee OK, Huang CK, Chiang CC, Chen TH. Acetabular revision arthroplasty using jumbo cups: an experience in Asia. *Arch Orthop Trauma Surg*. (2008) 128:809–13. doi: 10.1007/s00402-007-0492-7

45. Gustke KA. Jumbo cup or high hip center: is bigger better. *J Arthroplasty*. (2004) 19:120–3. doi: 10.1016/j.arth.2004.02.012

46. Patel JV, Masonis JL, Bourne RB, Rorabeck CH. The fate of cementless jumbo cups in revision hip arthroplasty. *J Arthroplasty*. (2003) 18:129–33. doi: 10.1054/arth.2003.50038

47. Obenaus C, Winkler H, Girtler R, Huber M, Schwägerl W. Extra-large press-fit cups without screws for acetabular revision. *J Arthroplasty*. (2003) 18:271–7. doi: 10.1054/arth.2003.50049

48. Whaley AL, Berry DJ, Harmsen WS. Extra-large uncemented hemispherical acetabular components for revision total hip arthroplasty. *J Bone Joint Surg Am*. (2001) 83:1352–7. doi: 10.2106/00004623-200109000-00010

49. Dearborn JT, Harris WH. Acetabular revision arthroplasty using so-called jumbo cementless components: an average 7-year follow-up study. *J Arthroplasty*. (2000) 15:8–15. doi: 10.1016/s0883-5403(00)90999-9

50. Faldini C, Stefanini N, Fenga D, Neonakis EM, Perna F, Mazzotti A, et al. How to prevent dislocation after revision total hip arthroplasty: a systematic review of the risk factors and a focus on treatment options. *J Orthop Traumatol*. (2018) 19:17. doi: 10.1186/s10195-018-0510-2

51. Khatod M, Barber T, Paxton E, Namba R, Fithian D. An analysis of the risk of hip dislocation with a contemporary total joint registry. *Clin Orthop Relat Res*. (2006) 447:19–23. doi: 10.1097/01.blo.0000218752.22613.78

52. Wetters NG, Murray TG, Moric M, Sporer SM, Paprosky WG, Della Valle CJ. Risk factors for dislocation after revision total hip arthroplasty. *Clin Orthop Relat Res*. (2013) 471:410–6. doi: 10.1007/s11999-012-2561-7

53. Jo S, Jimenez Almonte JH, Sierra RJ. The cumulative risk of re-dislocation after revision THA performed for instability increases close to 35% at 15years. *J Arthroplasty*. (2015) 30:1177–82. doi: 10.1016/j.arth.2015.02.001

54. Alberton GM, High WA, Morrey BF. Dislocation after revision total hip arthroplasty: an analysis of risk factors and treatment options. *J Bone Joint Surg Am*. (2002) 84:1788–92. doi: 10.2106/00004623-200210000-00008

55. Guo L, Yang Y, An B, Yang Y, Shi L, Han X, et al. Risk factors for dislocation after revision total hip arthroplasty: a systematic review and meta-analysis. *Int J Surg*. (2017) 38:123–9. doi: 10.1016/j.ijsu.2016.12.122

56. Kurkis GM, Chihab S, Farley KX, Anastasio AT, Bradbury TL, Guild GN. Anterior revision hip arthroplasty is associated with higher wound complications but fewer dislocations compared to posterior revision hip surgery. *J Arthroplasty*. (2021) 36:250–4. doi: 10.1016/j.arth.2020.07.030

57. Robertson RN, Parks NL, Ho H, Hopper Jr RH, Hamilton WG. Does approach influence the dislocation rate following head and liner exchange in revision hip arthroplasty. *J Arthroplasty*. (2022) 37:336–41. doi: 10.1016/j.arth.2021.10.005

58. Badarudeen S, Shu AC, Ong KL, Baykal D, Lau E, Malkani AL. Complications after revision total hip arthroplasty in the Medicare population. *J Arthroplasty*. (2017) 32:1954–8. doi: 10.1016/j.arth.2017.01.037

59. Gold PA, Garbarino LJ, Sodhi N, Anis HK, Ehiorobo JO, Kurtz SM, et al. A 6-year trends analysis of infections after revision total hip arthroplasty. *Ann Transl Med*. (2019) 7:76. doi: 10.21037/atm.2019.01.48

60. Goldman AH, Sierra RJ, Trousdale RT, Lewallen DG, Berry DJ, Abdel MP. The Lawrence D. Dorr surgical techniques & technologies award: why are contemporary revision total hip arthroplasties failing? An analysis of 2500 cases. *J Arthroplasty*. (2019) 34:S11–11S16. doi: 10.1016/j.arth.2019.01.031

61. Fröschen FS, Randau TM, Hischebeth G, Gravius N, Gravius S, Walter SG. Mid-term results after revision total hip arthroplasty with custom-made acetabular implants in patients with Paprosky III acetabular bone loss. *Arch Orthop Trauma Surg*. (2020) 140:263–73. doi: 10.1007/s00402-019-03318-0

62. Hao Y, Luo D, Wu J, Wang L, Xie K, Yan M, et al. A novel revision system for complex pelvic defects utilizing 3D-printed custom prosthesis. *J Orthop Translat*. (2021) 31:102–9. doi: 10.1016/j.jot.2021.09.006

63. von Hertzberg-Boelch SP, Wagenbrenner M, Arnholdt J, Frenzel S, Holzapfel BM, Rudert M. Custom made monoflange acetabular components for the treatment of Paprosky type III defects. *J Pers Med*. (2021) 11(4):283. doi: 10.3390/jpm11040283

64. Sefati S, Hegeman R, Alambeigi F, Iordachita I, Kazanzides P, Khanuja H, et al. A surgical robotic system for treatment of pelvic osteolysis using an FBG-equipped continuum manipulator and flexible instruments. *IEEE ASME Trans Mechatron*. (2021) 26:369–80. doi: 10.1109/tmech.2020.3020504

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EDITED BY
Carlos Suarez-Ahedo,
Hospital Médica Sur, Mexico

REVIEWED BY
Shane J. Nho,
Rush University, United States
Ryogo Furuhata,
Ashikaga Red Cross Hospital, Japan

*CORRESPONDENCE
Wang Gangliang
wgliang@zju.edu.cn

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Endoscopic treatment for calcific tendinitis of the gluteus medius: A case report and review

Chen Jian[1], Wang Dan[2] and Wang Gangliang[1]*

[1]Department of Orthopedics, Sir Run Run Shaw Hospital, Hangzhou, Zhejiang, China, [2]Department of Orthopedics, Tonglu First People's Hospital, Hangzhou, China

Tendon calcification is a common disease, with the shoulder rotator cuff being the most common site. However, calcific tendinitis of the gluteus medius has rarely been reported. This study reports the case of a 64-year-old woman diagnosed with calcific tendinitis of the gluteus medius and experiencing right lateral hip pain with no apparent trigger. After unsuccessful conservative treatment, hip endoscopy was performed on this patient, allowing for a clear view of a "toothpaste-like" lesion in the gluteus medius tendon. A shaver was used to remove the lesion. After 8 weeks and 14 months of follow-up, the patient could return to regular daily and social activities. This study shows that endoscopic surgery can lead to effective, rapid recovery and minimally invasive clinical outcomes in patients with tendon calcification near the hip joint.

KEYWORDS

calcific tendinitis, gluteus medius, hip pain, minimally invasive (MI), endoscopic treatment

Introduction

Calcific tendinitis is the deposition of calcium hydroxyapatite crystals in periarticular muscular attachments (1). The etiology of calcific tendinitis is unclear, and the suggested causes include hereditary, metabolic, post-traumatic, and postoperative conditions (2).

Several tendons can become calcified, including those in the shoulder rotator cuffs, near the hip joints, and in hands and wrists (1, 2). However, calcific tendinitis of the gluteus medius, first described by Goldenberg and Leventhal in 1936 (3), is relatively uncommon and sporadically reported (4–8).

Generally, conservative methods for calcific tendinitis are satisfactory, including physiotherapy, non-steroidal anti-inflammatory drugs, local glucocorticoid injection, extracorporeal shock wave therapy, and small needle scalpel therapy (7). However, surgical treatment is usually performed in refractory cases.

Hip endoscopy is minimally invasive and entirely extra-articular, which can help avoid incising the hip capsule fibers, which causes hip joint instability. However, this procedure has been reported only in a few calcific tendinitis cases (2, 6, 9–11). Herein, we report the case of a patient with rare calcific tendinitis of the gluteus medius.

Case report

The case of a 64-year-old woman with a history of diabetes mellitus and hypertension is reported here. The patient presented with a 2-year history of right lateral hip pain with no apparent trigger. The pain was aggravated after 10 min of walking and relieved after a break. The pain was predominantly located in the greater trochanter and did not radiate to the lower back or lower extremities. The patient did not experience fever, chills, or limb weakness. However, hip pain was increasingly severe over the past year, hindering hip motion and interfering with sleep. The patient unsuccessfully attempted conservative treatment with oral non-steroidal anti-inflammatory drugs (NSAIDs) and traditional Chinese medicine.

The physical examination revealed an antalgic gait. The Trendelenburg and FABER (flexion abduction external rotation) tests were positive. Moderate tenderness upon palpation of the greater trochanter was experienced. The range of motion was limited compared with the left side. The range of flexion was 90°, extension was 10°, abduction was 25°, and adduction was 20°. The legs were lengthened equally, and neurological examination showed no abnormalities. The initial Harris hip score was 57.45, and the visual analog scale (VAS) score for hip pain in the resting state was 4.

Plain radiography showed a 1.0 × 2.0 cm diameter calcific deposit superomedial to the greater trochanter; this corresponded to the tendinous insertion of the gluteus medius (**Figure 1A**). Magnetic resonance imaging (MRI) showed evidence of calcific tendinitis (**Figure 1B–D**); calcific deposits were hypointense on T1- and T2-weighted images. The sedimentation rate and white blood cell count were within normal ranges.

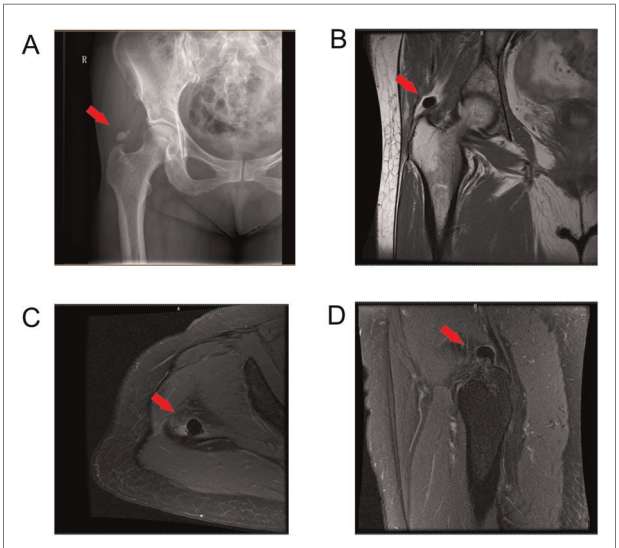

FIGURE 1
(A) Preoperative plain radiograph, (B) T2 coronal, (C) T1 horizontal, and (D) T1 coronal. View of MRI showing the calcification around the tip of the right greater trochanter (marked with arrows).

As conservative treatment was unsuccessful, hip endoscopy was performed (6, 9, 12). The patient was placed supine on a traction table. A sufficient amount of traction was applied to the operative hip to provide a 10–12 mm distraction of the hip joint. Standard anterolateral, mid-anterior, and distal anterolateral portals were used. An anterolateral approach (ALA) was first performed under fluoroscopic control, which was approximately 1 cm superior and anterior to the anterior edge of the greater trochanter. Next, an anteromedial approach (AMA) was established under endoscopy surveillance (**Figure 2A**). A 30° hip scope was inserted to visualize the gluteus medius tendon and the tip of the greater trochanter (**Figure 2B**).

Endoscopic imaging confirmed the radio-opacity on plain radiography. A soft white toothpaste-like material was observed when the degenerated gluteus medius tendon was debrided (**Figure 3A,B**). A motorized shaver was used to remove the material and debride the degenerated tendons. Postoperative radiography revealed that no calcification remained (**Figure 3C**). The specimen was sent for pathologic examination, which confirmed that the calcified tendon consisted of hydroxyapatite crystals and proliferative tendon fibrous tissue (**Figure 3D**).

The patient was mobilized and allowed to bear weight as tolerated. In addition, straight-leg raise exercises were started on postoperative day one and resisted knee extension strengthening exercises continued for 6 weeks. The Trendelenburg test and Patrick sign were negative at 8 weeks, and no restrictions were imposed on activities due to symptoms. The last recorded Harris hip score was 92.45, and the VAS score was 1 at 14 months after surgery.

Discussion

In the present case, the patient was diagnosed with calcific tendinitis of the gluteus medius. Deposing focal apatite crystals in the tendon can result in acute or chronic hip pain during daily activities; joint movements may aggravate these symptoms (13). The presenting symptoms, in this case, were chronic pain in the posterolateral region of the right hip and right hip movement limitations.

The most common site of calcific tendinitis is the shoulder, occurring in approximately 3% of adults (1); other sites include the joint tendons such as wrists (14) or knees (15–17). In addition, calcific tendinitis has been reported in tendons near the hip joint, such as the gluteus minimus (6), gluteus medius (18), gluteus maximus (12, 19), gemellus superior, gemellus inferior (2), and rectus femoris (9).

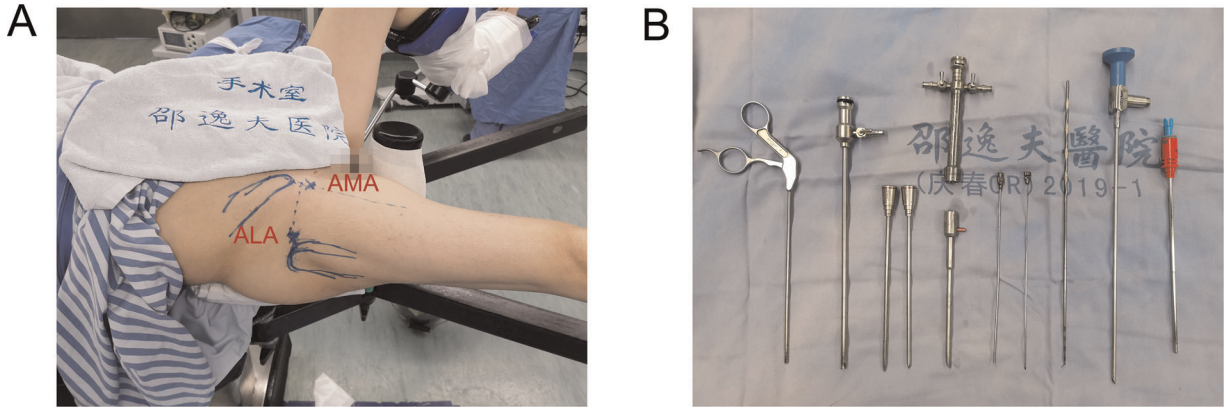

FIGURE 2
(A) The patient was placed supine on a traction table; an anterolateral approach (ALA) was approximately 1 cm superior and anterior to the anterior edge of the greater trochanter; an anteromedial approach (AMA) was performed at the junction of a sagittal line drawn from the anterior superior iliac spine and a horizontal line drawn from ALA (B) surgical instruments used in hip endoscopic surgery.

The gluteus medius is located on the lateral side of the iliac wing; it is the main abductor muscle in the hip joint. It plays an important role in both standing and walking. Degeneration and strain of the tendon, in this case, are possible causes of the patient's calcific tendinitis.

The calcium around the greater trochanter can cause mild to severe pain according to different calcific stages as described in the Uhthoff HK (20). Stage 1: Precalcific phase, fibrocartilaginous transformation within tendon fibers, which is asymptomatic. Stage 2: Formative phase, calcifications formed, usually causing subacute mild pain. Stage 3: Resorptive phase, the tendon develops increased vasculature and calcium deposits are removed by phagocytes; severe acute pain that can be highly disabling and unresponsive to common analgesics is experienced. Stage 4: Postcalcific phase, self-healing, and repair of the tendon fibers over several months, associated with pain and restricted function. Thus, different degrees of pain exist in stages 2–4, which explains why, in some cases, calcium around the greater trochanter can be found incidentally but is not clinically symptomatic.

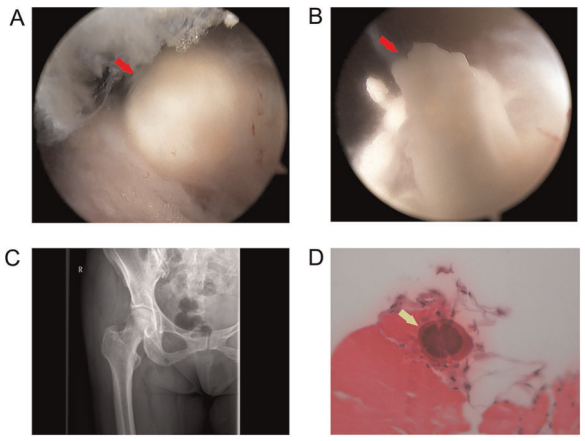

FIGURE 3
(A) Endoscopic view of a calcified deposit, (B) Endoscopic view showing a soft white toothpaste-like material in the deposit, (C) postoperative plain radiograph view showing complete removal of the calcific deposit, and (D) hydroxyapatite crystals in the specimen confirmed by a pathologic examination (marked with arrows).

The treatment for calcific tendinitis of the gluteus medius is summarized in **Table 1**. Surgical treatment can be adopted in patients with failed conservative treatments or severe symptoms. However, the use of endoscopy to treat the disease is not widespread, as tendon calcification of the hip joint is rare and sporadic, and endoscopic treatment has been reported only in a few cases (2, 6, 9–11). Comba et al. (10). described the surgical technique of endoscopic surgical removal in patients with calcific tendinitis of the rectus femoris. Kandemir et al. (6). and Su et al. (12). described the endoscopic treatment of the gluteus medius and maximus calcified tendinitis and considered it an effective treatment.

In our case, endoscopic surgery was used to treat the patient, which led to effective, rapid recovery and a minimally invasive clinical outcome. Therefore, given the patient's outcome to date, endoscopic treatment of calcific tendinitis of the gluteus medius may be an appropriate treatment option.

Clinically, tendon calcification of the hip joint usually presents pain and tenderness around the hip with movement limitations. These atypical symptoms make it possible to misdiagnose the disease as osteochondroma, gout, ossifying myositis, heterotopic calcification, or lumbar spinal disease.

A thorough medical history and physical examination are essential for diagnosis. For example, patients with heterotopic calcification and myositis ossificans often have a history of trauma (11), while those with gout often have a high uric acid

TABLE 1 Review of articles regarding the treatment of calcific tendinitis of the gluteus medius.

No.	First author	Patient No.	Treatment	Follow-up	Outcomes	Reference
1	Yang I (4)	1	Direct injection with local anesthetic and steroids at the gluteus lesion and anti-inflammatory agents	24 months	Symptom-free	*Skeletal Radiol* 2002
2	Kandemir U (6)	1	Endoscopic treatment	Three months	symptom-free	*Arthroscopy* 2003
3	Sakai T (5)	1	Non-steroidal anti-inflammatory drugs (NSAIDs)	Two years	Clinical symptoms had not recurred	*J Orthop Sci* 2004
4	Lin W (18)	1	Acupuncture and small needle scalpel therapy	Six months	Satisfied with the condition	*Acupunct Med* 2012
5	Almedghio S (8)	2	Analgesia and NSAIDs	Three weeks; N/A	Pain-free; symptom complete resolution	*J Orthop Case Rep* 2014
6	Vereecke E (21)	1	Ultrasound-guided needle lavage and injection of anesthetic/corticosteroid	Within a few days	Symptoms resolved	*J Belg Soc Radiol* 2015
7	Jo H (7)	1	Ultrasound-guided barbotage of the calcification	Six months	Remained pain-free	*Ann Rehabil Med* 2016

level. Imaging techniques, such as ultrasound, computed tomography (CT) (19, 22), or MRI (5), should be used in cases of diagnostic uncertainty. CT may help evaluate osseous involvement, while MRI can demonstrate tissue edema and rule out bone tumors. In addition, the typical presenting symptoms of lateral hip pain may occasionally mimic lumbar radiculopathy and vice versa. Therefore, obtaining a lumbar MRI may be warranted in select patients (2, 7).

Conclusion

We report a well-documented case of rare calcific tendinitis of the gluteus medius. Endoscopic surgery is considered a feasible and effective option for patients with hip calcific tendinitis who do not respond to conservative treatment, with few risks, rapid recovery, and satisfactory outcomes. However, a longer follow-up time and a large patient sample size are needed to draw reliable conclusions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Sir Run Shaw Hospital. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CJ and WD wrote the draft and revised it. WG collected the data. All authors contributed to the article and approved the submitted version. All authors read and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Holt PD, Keats TE. Calcific tendinitis: a review of the usual and unusual. *Skeletal Radiol*. (1993) 22(1):1–9. doi: 10.1007/BF00191518

2. Yang WB, Xu QK, Liu XH, Bakhshi P, Wang H, Shao ZW, et al. Arthroscopic treatment of calcific tendinitis of gemellus superior and gemellus inferior: a case report and literature review. *Orthop Surg*. (2022) 14(3):621–7. doi: 10.1111/os.13186

3. Goldenberg RR, Leventhal GS. Supratrochanteric calcification. *Journal of Bone and Joint Surgery*. (1936) 18:205–11.

4. Yang I, Hayes CW, Biermann JS. Calcific tendinitis of the gluteus medius tendon with bone marrow edema mimicking metastatic disease. *Skeletal Radiol*. (2002) 31(6):359–61. doi: 10.1007/s00256-002-0516-x

5. Sakai T, Shimaoka Y, Sugimoto M, Koizumi T. Acute calcific tendinitis of the gluteus medius: a case report with serial magnetic resonance imaging findings. *J Orthop Sci*. (2004) 9(4):404–7. doi: 10.1007/s00776-004-0799-y

6. Kandemir U, Bharam S, Philippon MJ, Fu FH. Endoscopic treatment of calcific tendinitis of gluteus medius and minimus. *Arthroscopy*. (2003) 19(1):E4. doi: 10.1053/jars.2003.50021

7. Jo H, Kim G, Baek S, Park HW. Calcific tendinopathy of the gluteus medius mimicking lumbar radicular pain successfully treated with barbotage: a case report. *Ann Rehabil Med*. (2016) 40(2):368–72. doi: 10.5535/arm.2016.40.2.368

8. Almedghio S, Garneti N. The acute and chronic presentation of gluteus medius calcific tendinitis: a case report of two. *J Orthop Case Rep*. (2014) 4(4):48–50. doi: 10.13107/jocr.2250-0685.225

9. Peng X, Feng Y, Chen G, Yang L. Arthroscopic treatment of chronically painful calcific tendinitis of the rectus femoris. *Eur J Med Res*. (2013) 18(1):49. doi: 10.1186/2047-783X-18-49

10. Comba F, Piuzzi NS, Zanotti G, Buttaro M, Piccaluga F. Endoscopic surgical removal of calcific tendinitis of the rectus femoris: surgical technique. *Arthrosc Tech*. (2015) 4(4):e365–369. doi: 10.1016/j.eats.2015.03.022

11. Zini R, Panascì M, Papalia R, Franceschi F, Vasta S, Denaro V. Rectus femoris tendon calcification: arthroscopic excision in 6 top amateur athletes. *Orthop J Sports Med*. (2014) 2(12):2325967114561585. doi: 10.1177/2325967114561585

12. Su CA, Ina JG, Raji Y, Strony J, Philippon MJ, Salata MJ. Endoscopic treatment of calcific tendinitis of the gluteus maximus: a case report. *JBJS Case Connect*. (2021) 11:e20.00974-6. doi: 10.2106/JBJS.CC.20.00974

13. Jr MD, Gatter RA. Recurrent acute inflammation associated with focal apatite crystal deposition. *Arthritis Rheum*. (1966) 9(6):804–19. doi: 10.1002/art.1780090608

14. Torbati SS, Bral D, Geiderman JM. Acute calcific tendinitis of the wrist. *J Emerg Med*. (2013) 44(2):352–4. doi: 10.1016/j.jemermed.2012.08.028

15. Tennent TD, Goradia VK. Arthroscopic management of calcific tendinitis of the popliteus tendon. *Arthroscopy*. (2003) 19(4):E35. doi: 10.1053/jars.2003.50124

16. Song K, Dong J, Zhang Y, Chen B, Wang F, Zhao J, et al. Arthroscopic management of calcific tendonitis of the medial collateral ligament. *Knee*. (2013) 20(1):63–5. doi: 10.1016/j.knee.2012.05.004

17. Tsujii A, Tanaka Y, Yonetani Y, Iuchi R, Shiozaki Y, Horibe S. Symptomatic calcification of the anterior cruciate ligament: a case report. *Knee*. (2012) 19(3):223–5. doi: 10.1016/j.knee.2011.05.008

18. Lin W, Liu CY, Tang CL, Hsu CH. Acupuncture and small needle scalpel therapy in the treatment of calcifying tendonitis of the gluteus medius: a case report. *Acupunct Med*. (2012) 30(2):142–3. doi: 10.1136/acupmed-2012-010149

19. Mizutani H, Ohba S, Mizutani M, Otake S, Otsuka T, Nakamura T. Calcific tendinitis of the gluteus maximus tendon with cortical bone erosion: CT findings. *J Comput Assist Tomogr*. (1994) 18(2):310–2. doi: 10.1097/00004728-199403000-00030

20. Uhthoff HK, Sarkar K. Calcifying tendinitis. *Baillieres Clin Rheumatol*. (1989) 3:567–81. doi: 10.1016/s0950-3579(89)8000m9-3

21. Vereecke E, Mermuys K, Casselman J. A case of bilateral acute calcific tendinitis of the gluteus medius. Treated by ultrasound-guided needle lavage and corticosteroid injection. *J Belg Soc Radiol*. (2015) 99(2):16–9. doi: 10.5334/jbr-btr.810

22. Hottat N, Fumière E, Delcour C. Calcific tendinitis of the gluteus maximus tendon: CT findings. *Eur Radiol*. (1999) 9(6):1104–6. doi: 10.1007/s003300050799

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EDITED BY
Carlos Suarez-Ahedo,
Hospital Médica Sur, Mexico

REVIEWED BY
Carlos Abilio Sanchez Mojica,
National Autonomous University of Mexico, Mexico
Xinhua Qu,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Min Dai
daimin@medmail.com.cn

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Relationship of idiopathic femoral head necrosis with blood lipid metabolism and coagulation function: A propensity score-based analysis

Xiaolong Yu, Shengtao Zhang, Bin Zhang and Min Dai*

Department of Orthopedics, Artificial Joints Engineering and Technology Research Center, The First Affiliated Hospital of Nanchang University, Nanchang, China

Background: Nontraumatic osteonecrosis of the femoral head (ONFH) can be corticosteroid-induced, alcohol-induced, and idiopathic ONFH (IONFH). Although corticosteroid- and alcohol-induced ONFH has been investigated extensively regarding its relationship with blood lipids and coagulation factor levels. However, the effect of blood lipid metabolism and coagulation function on IONFH has rarely been studied. Therefore, this study aimed to analyse the relationship of IONFH with blood lipid and coagulation indicators.

Methods: Total 680 patients diagnosed with IONFH in our institution during January 2011–June 2019 who met the inclusion criteria composed the case group; 613 healthy persons who underwent physical examination at our institution during the same period composed the control group. Propensity scores were used for baseline feature matching, and two matching groups each with 450 patients were established. After the matching, blood lipid and coagulation factor levels of both groups were comparatively analysed.

Results: The case group showed significantly higher total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) levels, low-density/high-density lipoprotein (LDL/HDL) ratio, and apolipoprotein B (Apo-B) levels than the control group ($p < 0.05$). Conversely, the HDL and apolipoprotein A (Apo-AI) levels in the case group were significantly lower than those in the control group ($p < 0.05$). Regarding coagulation indicators, the activated partial thromboplastin time and prothrombin time were lower in the case group than in the control group; however, the differences were insignificant ($p > 0.05$). Furthermore, fibrinogen (FIB) levels and thrombin time (TT) in the case group were higher than those in the control group. There were significant differences between the two groups only in terms of FIB levels ($p < 0.05$), while TT was not significantly different ($p > 0.05$).

Abbreviations
HDL, high-density lipoprotein; IONFH, idiopathic osteonecrosis of the femoral head; LDL, low-density lipoprotein; ONFH, osteonecrosis of the femoral head; TG, triglyceride; TC, total cholesterol; Apo-AI, apolipoprotein A; Apo-B, apolipoprotein B; APTT, activated partial thromboplastin time; PT, prothrombin time; FIB, fibrinogen; TT, thrombin time.

Conclusions: IONFH has strong associations with blood lipid metabolism and coagulation function, which provide an avenue for exploring the mechanism of IONFH.

KEYWORDS

femur head necrosis, lipid metabolism, coagulation function, propensity score matching, idiopathic necrosis of the femoral head

Background

Osteonecrosis of the femoral head (ONFH) leads to the death of osteocytes and other bone marrow components due to interruption of blood supply to the femoral head that induces structural changes and collapse of the subchondral bone internally, which manifests as joint pain and dysfunction (1–3). Epidemiological data show that in the year 2000, the incidence of ONFH in the general population of the United States ranged from 300,000 to 600,000, with approximately 10,000 to 20,000 stable new cases each year (4, 5). Another study reported that the total number of patients with ONFH among the general population aged ≥15 years in China was about 8.12 million (6). Femoral head ischaemia can be divided into two categories: traumatic and nontraumatic ONFH. The aetiology of traumatic ONFH is direct vascular injury, blocking the blood flow to the femoral head, caused by a femoral neck fracture or dislocation of the hip joint (7). Currently, the aetiology of nontraumatic ONFH is not completely clear, which makes early diagnosis and treatment difficult.

Nontraumatic ONFH can be divided into three main aetiologic associations: corticosteroid-induced, alcohol-induced, and idiopathic ONFH (IONFH) (8). Corticosteroid use and alcohol intake are two of the most common causes of nontraumatic ONFH (9), accounting for about 40% of nontraumatic cases (10). Therefore, patients with these two factors can consciously take preventive measures and be examined timely for early diagnosis. However, some studies have shown that patients without corticosteroid- or alcohol-induced ONFH are regarded as patients with IONFH due to the unknown aetiology, such as spondylolisthesis of femoral head epiphysis, systemic lupus erythematosus, HIV infection, and hyperlipidaemia (8, 11, 12), indicating that IONFH is also an important cause of nontraumatic ONFH.

Corticosteroid- and alcohol-induced ONFH related to blood lipid metabolism and coagulation function has been investigated thoroughly (13–16). However, only a few reports probed on how lipid metabolism and coagulation function associate with IONFH. The aetiology of nontraumatic ONFH is mainly based on abnormal lipid metabolism and coagulation function (17, 18). Disorders of lipid metabolism may cause ischemia by increasing intraosseous pressure and decreasing blood flow ultimately leading to nontraumatic ONFH. In addition, insufficient fibrinolysis and thrombotic tendency also seem to play an essential role in nontraumatic ONFH. Given that IONFH is categorized as nontraumatic ONFH, it is necessary to elucidate the relationship between IONFH and lipid metabolism and coagulation function.

In this retrospective study, we hypothesised that most patients with IONFH had strong associations with blood lipid and coagulation factor levels. Therefore, the purpose of this study was to investigate the relationship between IONFH and endogenous lipid metabolism as well as coagulation.

Methods

Patient selection

Between January 2011 to June 2019, 1,293 patients who met the eligibility criteria were enrolled, of whom, 680 were diagnosed with IONFH (case group). In parallel, 613 healthy persons were selected by computerised randomisation from our institution's database who had been physically examined during the same period (control group). The inclusion criteria were as follows: (1) without any corticosteroid nor alcohol use and (2) with complete clinical medical records. The exclusion criteria were as follows: (1) with chronic kidney disease, chronic obstructive pulmonary disease, or cancer; (2) with incomplete or indeterminate clinical characteristics; (3) with corticosteroid-induced ONFH (the patient had a medication history of prednisolone or equivalent hormone >2 g for 3 months, with a steroid history of more than 3 months, and was diagnosed as ONFH within 2 years) and alcohol-induced ONFH (the average weekly drinking of pure alcohol >320 g, with a drinking history of more than 6 months, and diagnosed as ONFH within 1 year); (4) with hyperlipidaemia or taking lipid-lowering drugs and (5) taken heparin, oral anticoagulants, aspirin, or other platelet antiaggregants. To minimise possible confounding factors, propensity scores were matched at 1:1 with the calliper set at 0.2. The matched variables included the following demographic data: age, sex, body mass index (BMI), and a basic medical history of smoking, hypertension, and diabetes. After matching, 450 patients with IONFH comprised the case group and 450 healthy patients comprised the control group. A clear and intuitive flow chart of the patient selection process is shown in **Figure 1**.

Data collection

IONFH patients are diagnosed at our institution in the outpatient clinic by an experienced clinician with a

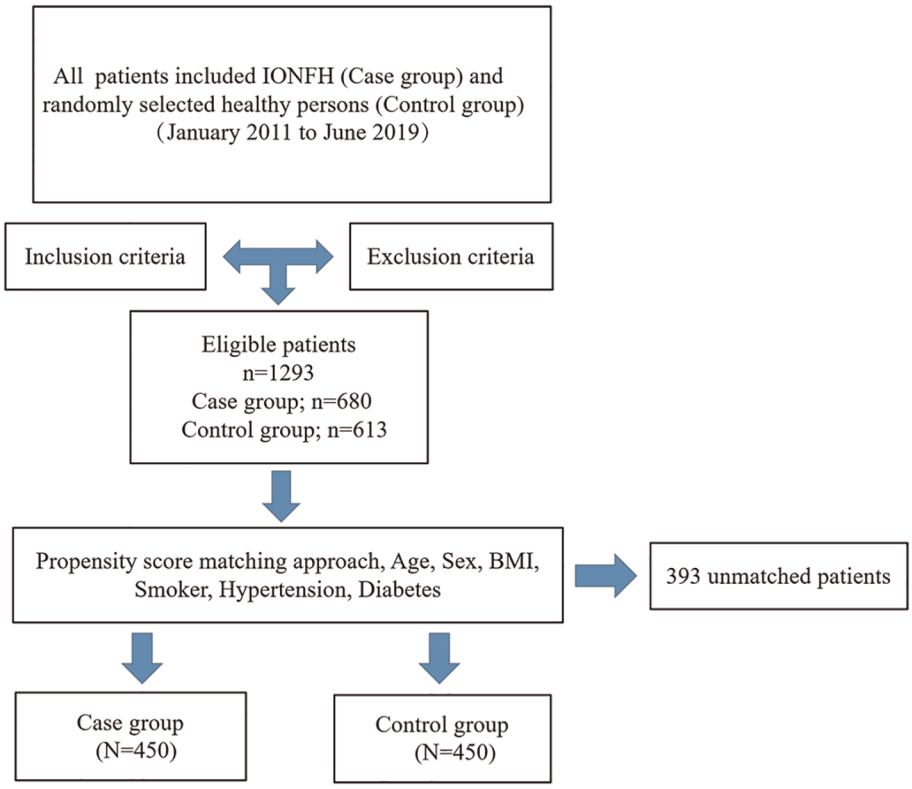

FIGURE 1
Patient selection flow chart. IONFH: idiopathic osteonecrosis of the femoral head.

comprehensive analysis of the patient's clinical symptoms, physical signs and imaging ancillary examinations. After the diagnosis was confirmed, blood lipids and coagulation indicators were examined in the ward the next morning after admission. The following data were obtained retrospectively from medical records: age, sex, body mass index (BMI), diagnosis, smoking history, hypertension, and diabetes. Furthermore, data on total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein A (apo-AI), apolipoprotein B (apo-B), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB) levels, and thrombin time (TT) were collected. An automatic biochemical analyser (OLYMPUS 5421, Olym-pus Corporation, Tokyo, Japan and Hitachi-7600, Hitachi Corporation, Tokyo, Japan) was used.

Statistical analysis

SPSS (version 26.0 SPSS, Chicago, IL, USA) was used for propensity score matching and subsequent statistical analysis. Continuous variables are shown as mean ± standard deviation, and group variables are shown as numbers and percentages. Continuous variables were analysed using the two-tailed Student's independent t-test, and the Pearson chi-square test was applied to compare the percentages for binary data. $p < 0.05$ was considered as statistically significant.

Results

Propensity score matching results

Data of patients before and after the propensity score matching are presented in **Tables 1**, **2**, respectively. The average age of patients was 61.5 ± 15.9 years in the initial cohort, 58.7 ± 12.7 years in the case group, and 64.5 ± 18.3 years in the control group. The average BMI in the initial cohort was 24.0 ± 2.0 and that in the case and control group was 23.6 ± 1.8 and 24.6 ± 2.1, respectively. In addition, a majority of patients in the control group were female (61.7%), whereas the gender distribution of females (46.2%) in the case group was lower. Before matching, except for smokers, we found statistical differences in other parameters. However, after matching the patients, both groups of 450 patients were created, and we found no significant difference in any of the parameters considered.

TABLE 1 Baseline characteristics of 1,293 patients in the case group and control group.

Variables	Total	Case gruop	Control group	*p* value
Number of patients	1293	680 (52.6%)	613 (47.4%)	
Age (years)	61.5 ± 15.9	58.7 ± 12.7	64.5 ± 18.3	<0.001
BMI (kg/m^2)	24.1 ± 2.0	23.6 ± 1.8	24.6 ± 2.1	<0.001
Female (%)	692 (53.5%)	314 (46.2%)	378 (61.7%)	<0.001
Smoking (%)	162 (12.5%)	95 (14.0%)	67 (10.9%)	0.099
Hypertension (%)	308 (23.8%)	136 (20%)	172 (28.1%)	0.001
Diabetes (%)	120 (9.3%)	41 (6%)	79 (12.9%)	<0.001

TABLE 2 Baseline characteristics of case group and control group by 1:1 matching on propensity score.

Variables	Total	Case gruop	Control group	*p* value
Number of patients	900	450 (50%)	450 (50%)	
Age (years)	60.9 ± 15.4	60.3 ± 13.4	61.6 ± 17.1	0.215
BMI (kg/m^2)	24.0 ± 2.0	23.9 ± 1.7	24.1 ± 2.3	0.138
Female (%)	513 (57%)	256 (56.9%)	257 (57.1%)	0.946
Smoking (%)	91 (10.1%)	49 (10.9%)	42 (9.3%)	0.439
Hypertension (%)	205 (22.8%)	105 (23.3%)	100 (22.2%)	0.691
Diabetes (%)	69 (7.7%)	39 (8.7%)	30 (6.7%)	0.260

Comparison of blood lipid levels between the two groups

Based on propensity score matching of the whole cohort, we identified blood lipid levels associated with IONFH. As shown in Table 3, levels of TC, TG, LDL, apo-B, and the LDL/HDL ratio in the case group were 4.39 ± 0.87 mmol/L, 1.22 ± 0.59 mmol/L, 2.67 ± 0.75 mmol/L, 0.91 ± 0.23 g/L and 2.27 ± 0.88, respectively, which were significantly higher than those in the control group. Conversely, the HDL and apo-AI levels were 1.25 ± 0.34 mmol/L and 1.17 ± 0.24 g/L, respectively, which were significantly lower than those in the control group. All differences in blood lipid levels were statistically significant.

TABLE 3 Comparison of serum lipid indicators between groups.

Variables	Case gruop	Control group	*p* value
Number of patients	450	450	
TC (mmol/L)	4.39 ± 0.87	4.21 ± 0.87	0.002
TG (mmol/L)	1.22 ± 0.59	0.91 ± 0.37	<0.001
LDL (mmol/L)	2.67 ± 0.75	2.43 ± 0.71	<0.001
HDL (mmol/L)	1.25 ± 0.34	1.34 ± 0.35	<0.001
LDL/HDL	2.27 ± 0.88	1.93 ± 0.76	<0.001
Apo-AI (g/L)	1.17 ± 0.24	1.43 ± 0.30	<0.001
Apo-B (g/L)	0.91 ± 0.23	0.78 ± 0.22	<0.001

TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo-AI, apolipoprotein A; Apo-B, apolipoprotein B.

Comparison of coagulation levels between the two groups

Given that the pathogenesis of IONFH is associated with interruption of blood supply by the hypercoagulable state, we analysed the effect of four blood coagulation factors on IONFH. The APTT and PT levels in the case group were lower than those in the control group, though the differences were statistically insignificant (Table 4). In addition, the FIB levels and TT of the case group were higher than those of the control group. However, only the difference in FIB levels of both groups was significant, while the difference in TT was insignificant.

Discussion

This study was based on propensity score matching to compare differences in blood lipid levels and coagulation factors between patients with IONFH (case group) and healthy adults (control group). The results showed that TC, TG, LDL, Apo-B, and FIB levels and the LDL/HDL ratio in the case group were higher than those in the control group, whereas HDL and Apo-AI levels were significantly lower in the case group than in the control group. Our results emphasise upon the relationship between blood lipid and coagulation function in patients with IONFH and provide an avenue for exploring the mechanism of IONFH. From our results, we ascertain that in these IONFH patients, disease progression would be effectively delayed and patients would be prevented from requiring total hip arthroplasty (19–21).

TABLE 4 Comparison of four coagulation indicators between groups.

Variables	Case gruop	Control group	*p* value
Number of patients	450	450	
APTT (s)	26.89 ± 4.68	27.41 ± 4.07	0.076
PT (s)	10.82 ± 1.64	11.03 ± 1.96	0.082
FIB (g/L)	2.97 ± 0.78	2.53 ± 0.72	<0.001
TT (s)	20.17 ± 2.38	19.93 ± 2.13	0.111

APTT, activated partial thromboplastin time; PT, prothrombin time; FIB, fibrinogen; TT, thrombin time.

Although the pathophysiological mechanism of IONFH remains unclarified, previous studies have shown that imbalances in blood lipid metabolism are indispensably associated with ONFH (22–24). In an animal experimental model of ONFH (25), an increase in blood lipid levels was the first change observed, which supports the notion that lipid levels may be related to osteonecrosis occurrence. Furthermore, in a related study, the cholesterol-lowering drug lovastatin could prevent the development of osteonecrosis in chickens *in vivo* by inhibiting the effects on chicken fat-specific gene expression (26). This is consistent with our findings that an increase in TC levels in peripheral blood is associated with an increased risk of IONFH. Some studies concluded that TG and LDL are independent risk factors and diagnostic criteria for ONFH (27, 28). Interestingly, our data are also consistent with previously published results described above; that is, TG and LDL levels in the case group were significantly higher than those in the control group. Additionally, Miyanishi et al. (29) reported that in a rabbit osteonecrosis model, the LDL/HDL cholesterol ratios of the osteonecrosis group were higher. Our novel findings are noteworthy as they support the hypothesis that higher LDL/HDL cholesterol ratios may also contribute to the pathogenesis of IONFH. On the other hand, apolipoproteins bind to lipids, they are present in plasma as lipoproteins, and mediate lipid transport through interactions with cellular receptors (30). Particularly, Apo-AI and Apo-B are two key proteins of lipid metabolism involved in ONFH (14), but their role in IONFH remains unclear. Our results suggest that both decreased Apo-AI and elevated Apo-B are risk factors for IONFH, which supports Hao's apolipoprotein gene polymorphism report that has a susceptibility to IONFH (31). Taken together, IONFH was highly associated with blood lipid metabolism.

There is considerable evidence to conclude that coagulation function affects the pathogenesis of ONFH (15, 16). In this study, the levels of coagulation factors affecting IONFH were evaluated and the results showed that only FIB levels were significantly higher in the IONFH population than in the control group ($p < 0.05$), while other indicators such as APTT, PT, TT were statistically insignificant ($p > 0.05$), which is consistent with the results of previous studies that described the association between coagulation function and IONFH (16, 32). For example, Glueck et al. (13) stated that genetic propensity to thrombosis and fibrinolysis are risk factors for IONFH. Moreover, Gagala et al. (33) also highlighted that inherited hypofibrinolysis is a risk factor for IONFH in the Polish population. Since IONFH has a close association with the coagulation level of FIB, intravascular coagulation function might be affecting its occurrence and development, which needs further evaluation.

Regarding the pathogenesis of IONFH caused by lipid metabolism and coagulation function, the findings of this study are consistent with the theory that injury of vascular endothelial cells and fat embolism increase pressure on the femoral head, which ultimately reduces the blood supply. First, due to damage to the vascular endothelial cells by hyperlipidaemia and the formation of a prethrombotic state, the ability of vascular endothelial cells to synthesise nitric oxide is decreased, which disrupts vasoconstriction and vasodilation (34). Second, hypercholesterolaemia with elevated serum cholesterol levels, fatty deformities in the liver, and systemic fat embolism, may cause an increased intraosseous pressure that destroys the microcirculation in the femoral head (35, 36). Third, high triglyceride levels are a risk factor for ischaemic heart disease and stroke (37, 38), which can partly or totally block the blood flow to the femoral head, while patients with IONFH tend to develop asymptomatic IONFH through similar mechanisms (28). Finally, the commonality in IONFH cases is the compromised blood flow to the affected area. All the above mechanisms can ultimately result in reduced blood flow to the femoral head, which can lead to bone ischaemia and death (9, 39, 40).

Corticosteroid-induced ONFH, alcohol-induced ONFH, and IONFH are the three main etiologies of nontraumatic ONFH. Corticosteroid- and alcohol-induced ONFH with lipid metabolism and coagulation have been reported extensively in the previous literature. However, only a few reports have explored the relationship between lipid metabolism and coagulation with IONFH. In this study, we performed statistical analysis based on a large sample of data collected at our institution and demonstrated that IONFH is closely associated with lipid metabolism and coagulation function. It provides a channnel to be able to explore the mechanism of action of nontraumatic ONFH as a whole in the future, and also provides potential ideas for the prevention of ONFH.

Despite these findings, this study has some limitations. First, this study was a single-centre retrospective case-control trial, not a randomised controlled trial. Although the sample size is relatively large, it had some limitations. Second, although propensity score matching was used to control certain confounding factors, uncontrolled selection and recall bias was possible; therefore, a prospective randomised study would better analyse the relationship of IONFH with blood lipid metabolism and coagulation function.

Conclusion

From our results, we suggest that the occurrence of IONFH is highly associated with blood lipid levels and coagulation factors; thus, it provides an avenue of thought for exploring the mechanism of IONFH. Moreover, the specific effects of blood lipid metabolism and coagulation function on IONFH need further analysis.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was undertaken in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated hospital of Nanchang University. A waiver of informed consent was obtained from ethics committee of the First Affiliated hospital of Nanchang University, since the data were analyzed from the electronic medical record and reported without personal identifiers.

Author contributions

YXL and ZST collected the data. YXL, ZST and ZB wrote the manuscript and did the statistical analysis. DM supervised the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.938565/full#supplementary-material.

References

1. Mont MA, Cherian JJ, Sierra RJ, Jones LC, Lieberman JR. Nontraumatic osteonecrosis of the femoral head: where do we stand today? A ten-year update. *J Bone Joint Surg Am*. (2015) 97(19):1604–27. doi: 10.2106/JBJS.O.00071

2. Choi HR, Steinberg ME, Edward YC. Osteonecrosis of the femoral head: diagnosis and classification systems. *Curr Rev Musculoskelet Med*. (2015) 8 (3):210–20. doi: 10.1007/s12178-015-9278-7

3. Zalavras CG, Lieberman JR. Osteonecrosis of the femoral head: evaluation and treatment. *J Am Acad Orthop Surg*. (2014) 22(7):455–64. doi: 10.5435/JAAOS-22-07-455

4. Lieberman JR, Berry DJ, Mont MA, Aaron RK, Callaghan JJ, Rajadhyaksha AD, et al. Osteonecrosis of the hip: management in the 21st century. *Instr Course Lect*. (2003) 52:337–55. PMID: 12690862

5. Aldridge 3rd JM, Urbaniak JR. Avascular necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. *Am J Orthop*. (2004) 33(7):327–32. PMID: 15344574

6. Zhao DW, Yu M, Hu K, Wang W, Yang L, Wang BJ, et al. Prevalence of Nontraumatic osteonecrosis of the femoral head and its associated risk factors in the Chinese population: results from a nationally representative survey. *Chin Med J*. (2015) 128(21):2843–50. doi: 10.4103/0366-6999.168017

7. Zhang Y, Sun R, Zhang L, Feng L, Liu Y. Effect of blood biochemical factors on nontraumatic necrosis of the femoral head: logistic regression analysis. *Orthopade*. (2017) 46(9):737–43. doi: 10.1007/s00132-017-3408-4

8. Liu F, Wang W, Yang L, Wang B, Wang J, Chai W, et al. An epidemiological study of etiology and clinical characteristics in patients with nontraumatic osteonecrosis of the femoral head. *J Res Med Sci*. (2017) 22:15. doi: 10.4103/1735-1995.200273

9. Cohen-Rosenblum A, Cui Q. Osteonecrosis of the femoral head. *Orthop Clin North Am*. (2019) 50(2):139–49. doi: 10.1016/j.ocl.2018.10.001

10. Tan G, Kang PD, Pei FX. Glucocorticoids affect the metabolism of bone marrow stromal cells and lead to osteonecrosis of the femoral head: a review. *Chin Med J*. (2012) 125(1):134–9. doi: 10.3901/JME.2012.14.134

11. Larson AN, McIntosh AL, Trousdale RT, Lewallen DG. Avascular necrosis most common indication for hip arthroplasty in patients with slipped capital femoral epiphysis. *J Pediatr Orthop*. (2010) 30(8):767–73. doi: 10.1097/BPO.0b013e3181fbe912

12. Morse CG, Mican JM, Jones EC, Joe GO, Rick ME, Formentini E, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. *Clin Infect Dis*. (2007) 44(5):739–48. doi: 10.1086/511683

13. Glueck CJ, Freiberg RA, Tracy T, Stroop D, Wang P. Thrombophilia and hypofibrinolysis: pathophysiologies of osteonecrosis. *Clin Orthop Relat Res*. (1997) 334:43–56. doi: 10.1097/00003086-199701000-00007

14. Wang Y, Cao Y, Li Y, Guo Y, Wang Q, Yang M, et al. Genetic association of the ApoB and ApoA1 gene polymorphisms with the risk for alcohol-induced osteonecrosis of femoral head. *Int J Clin Exp Pathol*. (2015) 8(9):11332–9. PMID: 26617857

15. Jones LC, Mont MA, Le TB, Petri M, Hungerford DS, Wang P, et al. Procoagulants and osteonecrosis. *J Rheumatol*. (2003) 30:783–91. PMID: 12672200

16. Fukui K, Kominami R, Shinohara H, Matsumoto T. Glucocorticoid induces micro-fat embolism in the rabbit: a scanning electron microscopic study. *J Orthop Res*. (2006) 24(4):675–83. doi: 10.1002/jor.20091

17. Seamon J, Keller T, Saleh J, Cui Q. The pathogenesis of nontraumatic osteonecrosis. *Arthritis*. (2012) 2012:601763. doi: 10.1155/2012/601763

18. Sekiya F, Yamaji K, Yang K, Tsuda H, Takasaki Y. Investigation of occurrence of osteonecrosis of the femoral head after increasing corticosteroids

in patients with recurring systemic lupus erythematosus. *Rheumatol Int*. (2010) 30 (12):1587–93. doi: 10.1007/s00296-009-1194-y

19. Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone*. (2012) 50 (1):325–30. doi: 10.1016/j.bone.2011.11.002

20. Zhao D, Zhang Y, Wang W, Liu Y, Li Z, Wang B, et al. Tantalum rod implantation and vascularized iliac grafting for osteonecrosis of the femoral head. *Orthopedics*. (2013) 36(6):789–95. doi: 10.3928/01477447-20130523-26

21. Zhao D, Cui D, Lu F, Wang B, Wang W, Tian F, et al. Combined vascularized iliac and greater trochanter graftings for reconstruction of the osteonecrosis femoral head with collapse: reports of three cases with 20 years follow-up. *Microsurgery*. (2012) 32(7):546–51. doi: 10.1002/micr.21995

22. Wang GJ, Sweet DE, Reger SI, Thompson RC. Fat-cell changes as a mechanism of avascular necrosis of the femoral head in cortisone-treated rabbits. *J Bone Joint Surg Am*. (1977) 59(6):729–35. doi: 10.2106/00004623-197759060-00003

23. Moskal JT, Topping RE, Franklin LL. Hypercholesterolemia: an association with osteonecrosis of the femoral head. *Am J Orthop*. (1997) 26(9):609–12. PMID: 9316722

24. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. *Semin Arthritis Rheum*. (2002) 32(2):94–124. doi: 10.1053/sarh.2002.33724b

25. Nishida K, Yamamoto T, Motomura G, Jingushi S, Iwamoto Y. Pitavastatin may reduce risk of steroid-induced osteonecrosis in rabbits: a preliminary histological study. *Clin Orthop Relat Res*. (2008) 466(5):1054–8. doi: 10.1007/s11999-008-0189-4

26. Wang GJ, Cui Q, Balian G. The nicolas andry award. The pathogenesis and prevention of steroid-induced osteonecrosis. *Clin Orthop Relat Res*. (2000) (370):295–310. doi: 10.1097/00003086-200001000-00030

27. Zeng X, Zhan K, Zhang L, Zeng D, Yu W, Zhang X, et al. The impact of high total cholesterol and high low-density lipoprotein on avascular necrosis of the femoral head in low-energy femoral neck fractures. *J Orthop Surg Res*. (2017) 12(1):30. doi: 10.1186/s13018-017-0532-0

28. Kuroda T, Tanabe N, Wakamatsu A, Takai C, Sato H, Nakatsue T, et al. High triglyceride is a risk factor for silent osteonecrosis of the femoral head in systemic lupus erythematosus. *Clin Rheumatol*. (2015) 34(12):2071–7. doi: 10.1007/s10067-015-3075-y

29. Miyanishi K, Yamamoto T, Irisa T, Yamashita A, Jingushi S, Noguchi Y, et al. A high low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a potential risk factor for corticosteroid-induced osteonecrosis in rabbits. *Rheumatology*. (2001) 40(2):196–201. doi: 10.1093/rheumatology/40.2.196

30. Marcel YL, Mcpherson R, Hogue M, Czarnecka H, Zawadzki Z, Weech PK, et al. Distribution and concentration of cholesteryl ester transfer protein in plasma of normolipemic subjects. *J Clin Investig*. (1990) 85:10–7. doi: 10.1172/JCI114397

31. Hao Y, Guo H, Xu Z, Qi H, Wang Y, Lu C, et al. The relationship between apolipoprotein genes polymorphisms and susceptibility to osteonecrosis of the femoral head: a meta-analysis. *Lipids Health Dis*. (2018) 17(1):192. doi: 10.1186/s12944-018-0827-0

32. Zalavras C, Dailiana Z, Elisaf M, Bairaktari E, Vlachogiannopoulos P, Katsaraki A, et al. Potential aetiological factors concerning the development of osteonecrosis of the femoral head. *Eur J Clin Invest*. (2000) 30:215–21. doi: 10.1046/j.1365-2362.2000.00621.x

33. Gagala J, Buraczynska M, Mazurkiewicz T, Ksiazek A. Prevalence of genetic risk factors related with thrombophilia and hypofibrinolysis in patients with osteonecrosis of the femoral head in Poland. *BMC Musculoskelet Disord*. (2013) 14:264. doi: 10.1186/1471-2474-14-264

34. Feng Y, Yang SH, Xiao BJ, Xu WH, Ye SN, Xia T, et al. Decreased in the number and function of circulation endothelial progenitor cells in patients with avascular necrosis of the femoral head. *Bone*. (2010) 46(1):32–40. doi: 10.1016/j.bone.2009.09.001

35. Hungerford DS, Lennox DW. The importance of increased intraosseous pressure in the development of osteonecrosis of the femoral head: implications for treatment. *Orthop Clin North Am*. (1985) 16(4):635–54. doi: 10.1016/S0030-5898(20)30432-6

36. Tian L, Yu X. Lipid metabolism disorders and bone dysfunction–interrelated and mutually regulated. *Mol Med Rep*. (2015) 12(1):783–94. doi: 10.3892/mmr.2015.3472

37. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, et al. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-pacific region. *Circulation*. (2004) 110(17):2678–86. doi: 10.1161/01.CIR.0000145542.24347.18

38. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation*. (2007) 115(4):450–8. doi: 10.1161/CIRCULATIONAHA.106.637793

39. Cenni E, Fotia C, Rustemi E, Yuasa K, Caltavuturo G, Giunti A, et al. Idiopathic and secondary osteonecrosis of the femoral head show different thrombophilic changes and normal or higher levels of platelet growth factors. *Acta Orthop*. (2011) 82(1):42–9. doi: 10.3109/17453674.2011.555368

40. Kim H, Cho C, Cho Y, Cho S, Yoon K, Kim K. Significant associations of PAI-1 genetic polymorphisms with osteonecrosis of the femoral head. *BMC Musculoskelet Disord*. (2011) 12:160. doi: 10.1186/1471-2474-12-160

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