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ABOUT COVER

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EDITORIAL

Mortality rate after total knee arthroplasty or total hip arthroplasty in patients with a history of liver transplant

E Carlos Rodriguez-Merchan

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Abstract

In this editorial I comment on the article by Ahmed *et al* published in a recent issue of the *World J Orthop* 2023; 14: 784-790. It is well known that patients who have undergone a liver transplant (LT) may need to have a total hip arthroplasty (THA) or total knee arthroplasty (TKA) implanted. Ahmed *et al* stated that the mortality rate in these patients was similar to the one of the general population. However, there are three articles previously published that found higher mortality in LT patients who experienced THA/TKA than in the general population (individuals without LT). Therefore, in this Editorial I would like to point out that there is controversy in the literature regarding whether LT patients undergoing THA/TKA have higher mortality than the general population. Therefore, future research should attempt to resolve this controversy.

Key Words: Liver transplant; Total knee arthroplasty; Total hip arthroplasty; Results; Mortality

Core Tip: The existing publications are contradictory regarding mortality rates in liver transplant patients undergoing total hip arthroplasty and total knee arthroplasty. Therefore, this controversy should be duly analyzed in future studies.

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INTRODUCTION

Patients who have undergone a liver transplant (LT) may need to have a total hip arthroplasty (THA) or total knee arthroplasty (TKA) implanted. Considering the severity of the problem, several authors have analyzed the mortality of LT patients compared to the general population (patients without LT)[1-4].

THERE IS CONTROVERSY IN THE LITERATURE

In a recent article published by Ahmed *et al*[1] it was concluded that individuals with a history of LT experiencing TKA or THA had similar rates of mortality than individuals with no history of LT. However, there are three articles which contradict the conclusion of Ahmed *et al*[1].

In the systematic review and meta-analysis published in 2022 by Kim *et al*[2], individuals with a history of LT undergoing THA showed higher mortality rates than individuals with no history of LT.

In a retrospective review of total joint arthroplasty (TJA) after LT, Wu *et al*[3] stated that the mortality risk of patients with LT was considerable.

Ledford *et al*[4] also found higher mortality rates after TKA and THA in patients with a history of LT than in the general population.

CONCLUSION

The existing publications are contradictory regarding mortality rates in LT patients undergoing THA and TKA. Therefore, this controversy should be duly analyzed in future studies.

FOOTNOTES

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EDITORIAL

Expandable endoprostheses in skeletally immature patients: Where we are

Recep Öztürk

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Abstract

Approximately 45 percent of malignant bone tumors are seen under the age of 16 and one of the important results of growth plate sacrification in patients with immature skeletons is limb inequality. Until the early 1990s, the treatment options for these patients were rotationplasty or amputation. Multimodal approaches that combine imaging, chemotherapy, and surgical techniques have enabled the development of limb-preserving methods with satisfactory results. In order to overcome inequality problems, expandable prostheses have been developed in the 1980s. Extendable endoprosthesis replacements have been improved over the years and are now an established and safe alternative. Noninvasive prostheses appear to be advantageous compared to minimally invasive expandable prostheses that require multiple surgical procedures, but the complication rate remains high. Therefore, although expandable prostheses are not the definitive answer to the treatment of bone sarcomas in skeletally immature children, they are still a suitable interim choice until full adulthood is achieved. Due to reported high complication rates, the procedures require significant experience and are recommended for use only in specialized cancer centers.

Key Words: Bone sarcoma; Expandable endoprostheses; Limb salvage surgery; Non-invasive; Minimal-invasive; Invasive; Extendible endoprostheses

Core Tip: Extendable endoprosthesis replacements have been improved over the years and are now an established and safe alternative. Noninvasive prostheses appear to be advantageous compared to minimally invasive expandable prostheses that require multiple surgical procedures, but the complication rate remains high. Due to reported high complication rates, the procedures require significant experience and are recommended for use only in specialized cancer centers.

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INTRODUCTION

The most common malignant bone tumors are osteosarcoma and Ewing's Sarcoma, and these constitute 80% of all malignant bone tumors in children[1-3]. Approximately 45 percent of these tumors are seen under the age of 16[1]. An important consequence of growth plate resection in sarcoma surgery in patients with immature skeletons is limb inequality. Until the early 1990s, the treatment options for patients with a height difference of 4 cm or more after surgery were rotationplasty or amputation[4,5]. Although these two methods remain good options for selected patients today, technological advances, advances in prosthesis design, and multimodal approaches that combine imaging, chemotherapeutic modalities, and surgical techniques have enabled the development of limb-preserving methods with satisfactory results[1,6,]. In limb-sparing surgery, allografts, pedicled bone grafts, bone transfers and megaprostheses can be applied in approximately 85% of cases in children today[2]. Apart from this, Arthrodesis and allograft prosthesis composites are among the common options[6]. Arthrodesis is associated with poor function. Allografts are difficult to adapt to small anatomical structures, and problems such as lysis and nonunion are their limitations.

Approximately 60% of primary bone sarcomas in young patients occur in the distal femur or proximal tibia, and often require resection of the growth plate during surgery[1,2]. 35% and 30% of the growth of the lower extremity is attributed to the epiphyses of the distal femur and proximal tibia, respectively. This means that, unlike other regions, resections around the knee have a potential risk of discrepancy[1].

Extremity inequalities are accompanied by functional deficits, gait disorders, secondary obliquity in the pelvis and cosmetic problems[2,4]. In recent years, in order to overcome these problems, expandable prostheses have become an option in limb-sparing surgery for sarcoma patients with immature skeletons[1]. A growing prosthesis may potentially allow for final patient height as a result of preventing contralateral epiphysiodesis[7]. Although promising results are reported in the literature regarding these prostheses, there are also studies presenting high rates of complications and revisions[6].

The main indication for expandable prostheses is that the patient is expected to have a leg length difference of at least 3 cm in adulthood. A length difference of 3 cm or less can be compensated by making the operated side longer at the time of operation or by shoe modifications. Therefore, in these cases, it is more appropriate to use a classical adult type prosthesis[1]. After the age of 13 in boys and 11 in girls, It is accepted that an extension will not be expected to more than 3 cm. Therefore, there is no indication of expandable prosthesis in these patients[1,2].

The first expandable prostheses were reported in the 1980s[2]. In 1976, Scales *et al*[8] reported data on the first expandable prosthesis developed in Stanmore, England. In modular flexible prosthesis types, the middle part had to be changed for lengthening (a short module was replaced with a larger one)[9] and this required a large surgical exposure. In different models, extension was possible with a more minimal incision[2,9]. In 1992, minimally invasive expandable prostheses began to be reported[7]. Later, noninvasive prostheses were developed.

The two types of expandable prostheses currently widely used are minimally invasive and noninvasive types. An important advantage of minimally invasive type expandable prostheses seems to be that they are relatively cheap, but they require additional surgeries for lengthening with a screwdriver[1]. These open operations increase the risk of infection, and mechanical failure and aseptic loosening are among the other reported complications[10]. Noninvasive expandable prostheses do not require a surgical procedure for lengthening[11]. It is an advantage that there are no risks associated with anesthesia, and the risk of infection is considered to be less[10]. In minimally invasive prostheses, each lengthening procedure is an operation and is accompanied by pain, and intensive physiotherapy is required for a good functional result[13]. Stiffness and neurovascular injury are other problems and complications can sometimes result in amputation [14]. It is accepted that non-invasive magnetic system lengthening eliminates the risk of pain, stiffness and infection[13]. However, noninvasive expandable prostheses are relatively expensive and there is not enough literature with long-term results[1].

In 2001, there were published 7 cases of osteosarcoma in which they applied the Phenix (Phenix Medical, Paris, France) noninvasive expandable prosthesis. In 6 of the cases, they were used for revision of the previous operation[11]. They carried out a total of 21 extension transactions. Each lengthening took approximately 20 to 30 s and provided an average lengthening of 8 mm, accompanied by a slight feeling of discomfort during the procedure. Extension of the prosthesis was achieved by exposure to an external electromagnetic field. They stated that noninvasive expandable prostheses are a good alternative in difficult cases of limb-sparing surgery in children.

Gitelis *et al*[15] reported 18 cases of the Repiphysis system (originally known as the Phenix Prosthesis) in 2003. They performed a total of 58 lengthening procedures on 14 of the patients whom they followed for an average of 2 years. They

performed lengthenings between 1 and 7 cm. Each lengthening session was approximately 8 mm. They performed maximum lengthening in 3 patients and then switched to conventional prosthesis. As complications, they reported expandable component fractures in 2 patients, femoral component fracture in 1 patient, 2 stem fractures, 1 stem loosening and 1 deep infection. The Repiphysis prosthesis is known to use energy stored in a spring held compressed by a locking mechanism. Controlled release of the locking mechanism *via* an external electromagnetic field allows the device to be extended. The authors suggested that complications in these prostheses could be predicted and prevented. In the same year, Neel *et al*[16] reported the results of 18 Phenix noninvasive prostheses in malignant tumors around the knee. They performed extensions on 6 of the total patients. Lengthening between 1 and 30 mm was done in one session. Extensions were done in the outpatient clinic. At an average follow-up of 21 months, MSTS was 90% and revision of the prosthesis was required in 7 cases due to fracture or loosening. While there were cases where lengthening was not required, there were also cases where lengthening was done up to 6 cm. In addition, Belthur *et al*[17] applied proximal femur expandable prosthesis to 9 children. Three different generations of the Stenmore prosthesis (Mark III, IV, and V Stanmore Implants Worldwide, Stanmore, England) were used. Four patients died, and 5 patients were followed for an average of 7.6 years. A total of 63 operations were performed on five patients. Patients were lengthened by an average of 7 cm. The authors concluded that a lot of surgery was required for lengthening and revisions.

In 2006, Gupta *et al*[14] reported 7 cases in which they lengthened all patients by 4 or 5 cm using a Stanmore noninvasive prosthesis due to sarcoma located in the distal femur. The mean extension was 25 mm and mean knee flexion was 110 degrees. They calculated the average MSTS score as 68%. One patient died of disseminated disease. And they observed knee flexion deformity in one patient. By reversing the mechanism, they applied a 2 mm shortening and then full extension was achieved.

In 2010, Beebe *et al*[18] reported 12 cases in which they used repiphysis noninvasive expandable prosthesis in the upper and lower extremities and lengthened between 1 and 10 cm. They performed a total of 38 lengthening procedures on nine patients. In 3 patients, the tumor was in the proximal humerus. They reported that this noninvasive prosthesis provided acceptable functional results for both upper and lower extremity implantation. In the same year, Saghieh *et al*[19] reported the results of 17 custom-made Repiphysis prostheses, which they followed for an average of 61 months. 5-10 mm lengthening was applied at each session with an oral analgesic and the patient was discharged 30 min after the procedure. However, general anesthesia was required in 3 patients. One was due to pain during the procedure, one was due to anxiety, and one was due to extension mechanism malfunction. A total of 38 lengthening procedures between 2 and 15 mm were performed on 13 of the patients. The complications they reported were extension mechanism failure, femoral stem fracture, tibial fracture distal to the tibial stem, and infection. In this year, Dotan *et al*[20] reported the long-term results of 38 cases in which they applied 4 different expandable prostheses over the years. Model, which was elongated with sleeves in two cases, Lewis expandable adjustable prosthesis in five cases, and Kotz (minimally invasive) endoprosthesis in 29 cases and noninvasive prosthesis in 2 cases. They observed complications in 58% of the patients. The most common complication was infection, and they were diagnosed the infection 56 times. They detected early nerve damage in 8 patients and nerve damage after lengthening in 1 patient. All fully recovered with splints on follow up. They reported that approximately 3 cm of limb inequality was acceptable for good function. In these cases, planning a new operation to achieve equality brings the risk of complications. And, when skeletal growth is completed, replacement with a non-expanding prosthesis may be beneficial.

In 2010, Henderson *et al*[21] examined emotional acceptance by interviewing 15 patients who received expandable prostheses and their families. They reported that patients could have levels of happiness similar to people without the disease and that patients had good or excellent functional outcomes. In 2014, Ness *et al*[12] compared the functions of 13 patients, with an average age of 15 years, who received expandable prostheses, and 29 patients, with an average age of 19 years, who received modular prostheses. They found that there was no functional difference between the two groups. Also scores and revision rates were the same.

In 2013, Ruggieri *et al*[22] published 32 cases with noninvasive and minimal invasive prostheses in which they lengthened approximately half a cm to 16 cm and had an average MSTS of 79. They found that there was no functional difference in their study in which they used both types of expandable prostheses.

In 2015, Arteau *et al*[23] reported the results of 23 distal femoral expandable noninvasive prostheses. They used Repiphysis prosthesis in 14 patients, custom-made Biomet prosthesis in 8 patients, and Stanmore Juvenile Tumour System (JTS) in 1 patient. The tibial physis was preserved in all cases, except for the tibial stem entry point. In 15 of the cases, the growth of the tibia was less than the opposite side. Overgrowth was observed in the proximal tibia in 1 patient. In a total of 5 patients, an inequality of more than 2 cm was observed in the last follow-up, and epiphysiodesis was performed on the opposite side in 3 of these cases[24]. In 2015, Benevenia *et al*[25] published the results of 20 Repiphysis prostheses. They reported 15 complications at an average of 57 months. There was one dislocation, one contracture, 4 aseptic loosening, 5 structural failures, 3 deep infections and 1 relapse.

In 2016, Cipriano *et al*[26] reported on 10 patients with Repiphysis expandable prosthesis for distal femoral osteosarcoma whom they followed for an average of 6 years. They identified 37 implant-related complications and performed 15 revision surgeries. Six of these were aseptic loosening surgeries. Deterioration of the metadiaphyseal area surrounding the prosthesis stem was observed in all patients, deterioration in femoral length and cortical thinning were also common, which they thought would complicate potential future treatment with standard stem prostheses. Because there may be a problem with sufficient bone stock. As a result, the average MSTS score were 67.

In 2016, Torner *et al*[2] reported 7 cases between the ages of 8 and 12 in which Mutars Xpand noninvasive expandable prosthesis was applied. The average follow-up period was 65 months. The average MSTS score after rehabilitation was 26.3. They detected extension device malfunction in one patient and late infection in one patient. Extension intervals varied between 1 and 6 cm. In the knee megaprostheses used in these cases, the proximal physis of the tibia remained open and was allowed to grow naturally, thus minimizing limb inequality. In 2016, Schinhan *et al*[27] reported 71 cases in

which they applied invasive, minimally invasive or non-invasive prostheses and followed up for more than 2 years. The average MSTS was approximately 88%. They reported a total of 184 complications in 58 of the patients. 46% of these were soft tissue failures, 28% structural failures and 17% were infections. One of the structural failures mentioned in many series is stress shielding. It is more pronounced in children than in adults. It usually occurs in the first 2 years and no significant deterioration is observed afterward. In fact, it is not clear whether these findings lead to a risk of fracture.

Decilveo *et al*[1] published the results of 8 extremities of 7 patients in 2017. Four of the prostheses were noninvasive and 4 were minimally invasive. The mean functional outcome (MSTS scores) at the final follow-up was 93.3%. Functional outcomes for the noninvasive and minimally invasive expandable prostheses were 97% and 85%, respectively. Complications included temporary peroneal nerve palsy, infection, stiffness, and wound healing problems. Both appear to be safe and reliable means of reconstruction that permit limb salvage and provide good functional results considering the alternative is amputation. In 2018, Gilg *et al*[28] reported 21 cases in which primary arthroplasty was performed due to sarcoma and revision was performed with an expandable prosthesis due to complications. They followed all patients for at least one and a half years. They observed deep infection in 2 patients. The mean residual leg length difference was 15 mm. They stated that noninvasive growing prostheses are a successful option in eliminating leg length in revision surgery.

Gundavda *et al*[13] reported the results of 18 noninvasive prostheses in 2019. The mean MSTS score was 28.83. The number of lengthening procedures they performed on patients varied between 1 and 12. They followed patients for an average of 50 months. They stated that the high cost of noninvasive prostheses can be considered recovered because they do not require additional lengthening procedures. In addition, small lengthening at frequent intervals seems to be more physiological than the minimally invasive method. As a complication, revision was performed on 2 patients due to malfunction of the extension mechanism. Prosthesis infection was observed in one patient after release surgery due to flexion contracture. In addition, delayed infection requiring new surgical interventions and medical treatments was observed in 2 patients. In 2019, Ajit Singh *et al*[29] reported 20 cases in which they used minimally invasive expandable prostheses. They followed all cases for at least 2 years and 85% of cases for at least 5 years. During this period, they performed a total of 124 surgical interventions, 56 of which were extension surgeries.

Staals *et al*[30] reported a study containing data from 15 European reference centers in 2020. According to an average follow-up of 80 months in 299 cases, noninvasive prostheses had a lower risk of infection and there was no difference in aseptic loosening rates between cemented and cementless stems. In 2020, Portney *et al*[31] published a meta-analysis in which they examined 292 cases. There was an average follow-up period of 67 months. 89% of the cases were followed for at least 10 years. Limb inequality was present in 36% of the cases, and the rate increased as the follow-up period increased. Minimally invasive expandable prostheses had significantly lower complication rates than noninvasive prostheses, especially in terms of mechanical complications. Because there were many extension problems in noninvasive prostheses.

Lex *et al*[32] published their systematic review in 2021, in which they reviewed 19 articles reporting noninvasive expandable prostheses. They found the average implant revision rate to be 46%, and while this rate was zero in some studies, it was 100% in some studies. When the reasons for revision were examined starting from the most common, 10% of the revisions were caused by maximal lengthening, 8% were due to implant-related fractures, 6% were due to extension mechanism malfunctions, and 1% were due to wear. Approximately 20% of all patients had limb disparity of more than 2 cm at the time of last follow-up. The average MSTS score was approximately 85%. They stated that noninvasive Xpandible prostheses have a high risk of revision during follow-ups, but functional results are good in 5-year follow-ups, and it is a successful method in reducing limb inequality. Masrouha *et al*[33] reported the long-term results of 11 cases with the Repiphysis prosthesis in 2022. They followed all patients for at least approximately 12 years and reported failure of all implants at an average of 36 months. While the earliest failure was seen in the 3rd month, the latest was in the 72nd month. They reported 18 mechanical failures. They also described wound dehiscence, infection, implant collapse due to physeal damage, and periprosthetic fracture. They stated that there are high complication and revision rates in Repiphysis prostheses, similar to other expandable prostheses, and that all options should be carefully evaluated when determining the indication.

In 2022, Huang *et al*[6] published the results of an average of 9 years of follow-up of 29 cases in which they applied minimally invasive expandable prosthesis. All the patients were younger than 15 years of age, and they reconstructed the prosthesis on the resection side 2 cm longer than the resection length. When they detected a height difference of more than 3 cm in the follow-up radiographs, they planned an extension. To eliminate the incompatibility, they planned to lengthen it by 2 cm every 10 months. A total of 17 patients were lengthened by an average of 4 cm. The average MSTS score was 27. They reported a total of 2 revision surgeries, one due to infection and one due to aseptic loosening.

Shehadeh *et al*[34] reported the noninvasive results of 14 JTS Prostheses and 6 Mutars in 2022. They analyzed the cases for the presence of tibial multiplanar deformities. They found tibial deformity and/or growth abnormality in 14 of the patients (10 JTS, 4 Inplantcast) whom they followed for at least 2 years. They followed 11 of 14 cases with height inequality conservatively. They performed epiphysiodesis on the opposite side for two of them and replaced them with a long prosthesis for one. They found an average rotation of 13 degrees in the tibia in 11 of the patients. They also detected coronal angulation in 3 patients and sagittal angulation in 1 patient. No surgical intervention was required in any of the rotations and angulations. In the same year, Dukan *et al*[35] reported the results of 40 cases around the knee, which they followed for an average of 8.8 years. 28 Phenix and 12 Stanmore used prostheses. They found functional results to be significantly better in the Stanmore group. In addition, while implant survival was 100% in the Stanmore group, the prosthesis was explanted in all surviving patients in the Phenix group. The main reason for the revision operations was mechanical failure. At last follow-up, limb length equality was noted in 79% of Phenix-Repiphysis patients and 84% of Stanmore patients. The authors concluded that both prostheses were good and feasible. In addition, although long-term follow-up results of the prostheses are needed, it appears that Stanmore prostheses can be kept after skeletal maturity.

CONCLUSION

Extendable endoprosthesis replacements have been improved over the years and are now an established and safe alternative. Noninvasive prostheses appear to be advantageous compared to minimally invasive expandable prostheses that require multiple surgical procedures, but the complication rate remains high. There is an increased risk associated with the elongation and mechanical reliability of extendable implants compared to adult endoprostheses. Therefore, although expandable prostheses are not the definitive answer to the treatment of bone sarcomas in skeletally immature children, they are still a suitable interim choice until full adulthood is achieved. Due to reported high complication rates, the procedures require significant experience and are recommended for use only in specialized cancer centers.

FOOTNOTES

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EDITORIAL

Effect of weight-adjusted antimicrobial antibiotic prophylaxis on postoperative dosage and surgical site infection incidence in total joint arthroplasty

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Abstract

Surgical site infections (SSI) following total joint arthroplasty pose a significant concern for both providers and patients across the globe. Currently, administration of antimicrobial antibiotic prophylaxis is used throughout the world to reduce the incidence of SSI. However, the correct dosage and frequency of administration remains debatable. In this editorial, we emphasized the determination of the effect of administration of weight-adjusted antimicrobial antibiotic prophylaxis regime on the incidence of SSI and postoperative dosage reduction compared to the conventionally used regime during total joint arthroplasty. The results demonstrated similar efficacy between both regimes with respect to the incidence of SSI. In addition, weight-adjustment led to reduced postoperative dosage and has the potential to reduce chances of achieving lower therapeutic concentration, drug resistance, drug toxicity, and costs.

Key Words: Antibiotics; Antimicrobial prophylaxis; Weight-adjusted; Surgical site infections; Total joint arthroplasty; Knee arthroplasty; Hip arthroplasty

Core Tip: This editorial emphasized the evaluation of the efficacy of a weight-adjusted antimicrobial antibiotic prophylaxis regime on the incidence of surgical site infections and postoperative dosage reduction compared to a conventionally used regime during total joint arthroplasty. The results demonstrated similar efficacy between both regimes with respect to the incidence of surgical site infection. In addition, weight-adjustment led to reduced postoperative dosage and has the potential to reduce chances of achieving lower therapeutic concentration, drug resistance, drug toxicity, and costs.

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INTRODUCTION

Total joint arthroplasty (TJA), including total knee arthroplasty and total hip arthroplasty, is one of the most common elective orthopedic surgeries performed throughout the world[1]. Although good long-term results are reported in the majority of the patients, infections pose a considerable clinical challenge[1]. Surgical site infections (SSI), which frequently precedes periprosthetic joint infections, remains a significant source of morbidity, poor quality of life, and mortality in patients undergoing TJA[1]. As the number of TJA procedures continue to increase annually, so will the incidence of succeeding periprosthetic joint infections, instilling anxiety in both surgeons and patients[2]. Currently, prevention has been identified as the single most important strategy in combating SSI[1].

ANTIBIOTIC TREATMENT IN PRIMARY HIP AND KNEE ARTHROPLASTY

Administration of antimicrobial antibiotic prophylaxis (AMP) prior to the surgery to attain higher serum and tissue levels compared to the minimum inhibitory concentration of likely faced microorganisms that pose an elevated risk for infection have shown potential to reduce SSI after total knee arthroplasty or total hip arthroplasty[3]. It is also reported that SSI is lowest when AMP is administered preoperatively, followed by intraoperatively and during the immediate postoperative phases[4]. Its efficacy diminishes 24 h postoperatively[4]. In addition, AMP is presently administered globally in uniform dosages to all patients, irrespective of their weight. This approach may result in the delivery of either suboptimal or excessive therapeutic dosages in underweight or overweight patients, respectively. Suboptimal dosages may fail to achieve the minimum inhibitory concentration required to eliminate microorganisms, including bacteria, increasing the risk of drug resistance. On the other hand, prolonged and/or excessive dosages may lead to drug toxicity. Of note, obesity is identified as a major risk factor for SSI in TJA in various studies[5-8]. Moreover, it has been reported that a body mass index ≥ 35 or weight ≥ 100 kg may serve as a cutoff for a higher perioperative dosage of AMP[8]. Thus, an optimal dosage of systemic antibiotics adjusted by patient's body weight for prophylaxis is a significant protective factor for SSI [9]. Hence, a tailored AMP based on microorganisms likely to cause the infection, correct dosage, and frequency is essential to prevent SSI after TJA.

To some extent, an essential question regarding the best frequency and dosage of antibiotic treatment in primary hip and knee arthroplasty has been answered by Okoro *et al*[10]. They contrasted a weight-adjusted pre-operative dose [cefazolin 2 g intravenous (IV) for patients < 120 kg; cefazolin 3 g IV for patients > 120 kg] and a single postoperative dose at 2 h only (new regime) with a conventional (old regime) single preoperative dose (2 g cefazolin IV in all patients, regardless of the weight) and two postoperative antibiotic doses, 2 h and 8 h, respectively. No significant differences in the rate of deep and superficial infection between the groups 2 years after surgery were observed. Additionally, using an interrupted time series analysis and propensity score weighting, no statistically significant differences in the SSI rates between the two groups were observed. This study provided valuable insight to arthroplasty surgeons on benefits of using weight-adjusted dosage regime to prevent SSI, while reducing the postoperative dosage and chances of attaining lower therapeutic concentration, drug resistance, drug toxicity, and costs. The results from this study are in accordance with a recently published multicenter, prospective study that reported that administration of adequate, weight-adjusted dose and early, preoperative delivery of AMP can reduce SSI in TJA[11]. Furthermore, machine learning models, such as the neural network model, can be utilized to foretell patient-specific SSI following TJA to aid in clinical decision-making to improve results in at-risk patients[12].

CONCLUSION

The efficacy of a weight-adjusted AMP dosage regime is equivalent to a conventional AMP dosage regime in terms of SSI

incidence in TJA. In addition, weight-adjustment led to reduction in postoperative dosage, incidence for drug resistance and toxicity, and overall costs.

FOOTNOTES

Author contributions: Gupta A and Jain VK conceptualized the study and drafted, critically reviewed, and edited the manuscript. All authors approved the final version of the article for publication.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Investigation of contact behavior on a model of the dual-mobility artificial hip joint for Asians in different inner liner thicknesses

Taufiq Hidayat, Muhammad Imam Ammarullah, Rifky Ismail, Eko Saputra, M Danny Pratama Lamura, Chethan K N, Athanasius Priharyoto Bayuseno, J Jamari

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Abstract

BACKGROUND

The four components that make up the current dual-mobility artificial hip joint design are the femoral head, the inner liner, the outer liner as a metal cover to prevent wear, and the acetabular cup. The acetabular cup and the outer liner were constructed of 316L stainless steel. At the same time, the inner liner was made of ultra-high-molecular-weight polyethylene (UHMWPE). As this new dual-mobility artificial hip joint has not been researched extensively, more tribological research is needed to predict wear. The thickness of the inner liner is a significant component to consider when calculating the contact pressure.

AIM
To make use of finite element analysis to gain a better understanding of the contact behavior in various inner liner thicknesses on a new model of a dual-mobility artificial hip joint, with the ultimate objective of determining the inner liner thickness that was most suitable for this particular type of dual-mobility artificial hip joint.

METHODS
In this study, the size of the femoral head was compared between two diameters (28 mm and 36 mm) and eight inner liner thicknesses ranging from 5 mm to 12 mm. Using the finite element method, the contact parameters, including the maximum contact pressure and contact area, have been evaluated in light of the Hertzian contact theory. The simulation was performed statically with dissipated energy and asymmetric behavior. The types of interaction were surface-to-surface contact and normal contact behavior.

RESULTS
The maximum contact pressures in the inner liner (UHMWPE) at a head diameter of 28 mm and 36 mm are between 3.7-13.5 MPa and 2.7-10.4 MPa, respectively. The maximum von Mises of the inner liner, outer liner, and acetabular cup are 2.4–11.4 MPa, 15.7–44.3 MPa, and 3.7–12.6 MPa, respectively, for 28 mm head. Then the maximum von Mises stresses of the 36 mm head are 1.9-8.9 MPa for the inner liner, 9.9-32.8 MPa for the outer liner, and 2.6-9.9 MPa for the acetabular cup. A head with a diameter of 28 mm should have an inner liner with a thickness of 12 mm. Whereas the head diameter was 36 mm, an inner liner thickness of 8 mm was suitable.

CONCLUSION
The contact pressures and von Mises stresses generated during this research can potentially be exploited in estimating the wear of dual-mobility artificial hip joints in general. Contact pressure and von Mises stress reduce with an increasing head diameter and inner liner's thickness. Present findings would become one of the references for orthopedic surgery for choosing suitable bearing geometric parameter of hip implant.

Key Words: Contact behavior; Contact pressure; Finite element analysis; Dual-mobility; Artificial hip joint

Core Tip: The dual mobility hip system has the potential to be a great big bearing articulation if its technology is combined with highly cross-linked polyethylene. The modern artificial hip joint design has two free articulations between four parts: the femoral head, the inner liner, the outer liner as a metal cover to reduce wear, and the acetabular cup. Several studies show that prosthetic implant wear might be predicted partly by computing contact pressure distribution and contact area during everyday activities. A more reliable method of distinguishing between ideal and reality models may be incorporating activities with severe loading and boundary conditions.

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INTRODUCTION

Bousquet pioneered the idea of a dual-mobility (DM) artificial hip joint (AHJ) in the 1970s[1]. The polyethylene liner of the dual mobility system is concave on the inside for internal movement and convex on the outside for external motion. The design uses efficient large bearings to replicate metal-on-metal (MoM) articulation[2,3]. The use of highly cross-linked polyethylene bearings has grown, and preliminary findings have been shared[4,5]. They have low initial wear rates, meaning less osteolysis and a longer implant lifespan[4-6]. The dual mobility hip system has the potential to be a great big bearing articulation if its technology is combined with highly cross-linked polyethylene[7]. Having two options for movement should keep things stable and retain most of the range of motion[8-10].

The modern artificial hip joint design has two free articulations between four parts: the femoral head, the inner liner, the outer liner as a metal cover to reduce wear, and the acetabular cup (Figure 1). This geometric shape was introduced by the Center for Biomechanics Biomaterials Biomechatronics and Biosignal Processing (CBIOM3S), Department of Mechanical Engineering, Universitas Diponegoro, Semarang, Indonesia, and has received a patent from the Ministry of Law and Human Rights of the Republic of Indonesia with patent number S00201703018. The range of motion (RoM) of this design is projected to be greater than that of single-mobility (SM) devices with a similar-sized head[9]. This wider RoM is needed by Asians to carry out their daily activities, especially worship activities[11-14]. Additionally, it may shield the convex ultra-high-molecular-weight polyethylene (UHMWPE) liner's surface from wear. The DM's metal cover

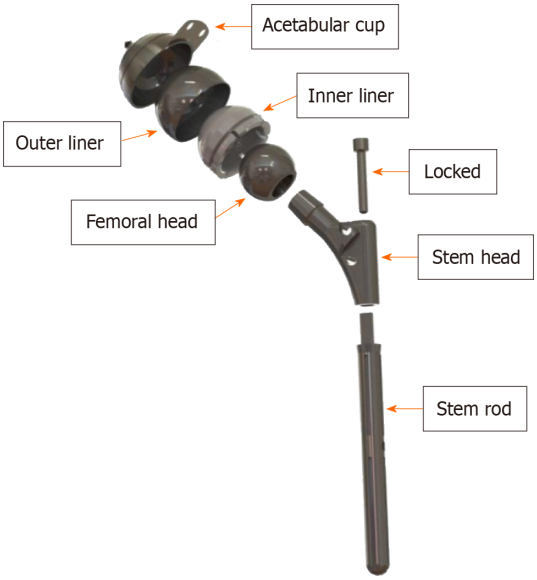


Figure 1 New dual-mobility artificial hip joint concept for Asians.

(namely the outer liner) shields the inner liner from damage as it slides into the cup. Several research projects have been carried out on this novel DM AHJ[15-18]. Despite this, further study is still required, particularly on the tribological traits that might be used to quantify wear. Obviously, it helps to verify the findings and develop the method based on the work of others.

Although conducting experiments on contact mechanics using hip joint simulators is a common method, finite element analysis (FEA) is also a good choice for predicting contact pressure in hip joints[19]. Several studies[20-22] show that prosthetic implant wear might be predicted partly by computing contact pressure distribution and contact area during everyday activities. Using the finite element method, the contact parameters, including the maximum contact pressure and contact area, have been evaluated in light of the Hertzian contact theory[20,21].

The stresses encountered at the contact surfaces may dictate the wear processes and hence may be connected to the wear volume and particle size, making knowledge of the contact mechanics of a prosthetic bearing crucial. In order to evaluate the bearing's structural integrity and prevent undesirable outcomes such as equatorial contacts and the femoral head being gripped by the acetabular cup, it is essential to compare the contact stresses to the strength of the bearing materials[23].

Due to the novelty of the DM AHJ model, limited study has been conducted on it. An investigation is required to identify the inner liner thickness of this DM AHJ in the most optimal manner. This study aims to utilize finite element analysis to learn more about the contact behavior of varying inner liner thicknesses on a novel model of DM AHJ, with the end goal of determining the optimal inner liner thickness for this particular DM AHJ. The femoral head is measured and compared between two sizes in this study: small head (28 mm) and big head (36 mm). Eight inner liner thicknesses range from 5 mm to 12 mm. Contact pressures and von Mises stresses, determined in this work, may be utilized to estimate the wear and the failure of DM AHJ in general.

MATERIALS AND METHODS

The outer liner and the acetabular cup were stainless steel 316L (SS316L) in this investigation. The inner liner was made of UHMWPE. Finite element software, Abaqus, was used for static analysis. The elastic modulus of SS316L was 200000 MPa [24], whereas that of UHMWPE was just 1000 MPa[25]. SS316L and UHMWPE had Poisson's ratios of 0.3[24] and 0.4[25], respectively. The following were the technical specs of the rig used for this FEA: Processor (Intel Xeon E5 2698 v3), Memory (64 GB), and Graphics Adapter (VGA): Quadro P2000 from Nvidia.

Finite element model

The femoral head had a diameter of 28 mm, representing the "small head" , and 36 mm representing the "big head" . In AHJ, these are the typical sizes utilized. The thickness of the inner liner varied from 5 mm to 12 mm over a total of eight distinct options. Dubin's research on dual-mobility sizes accommodates the inner liner thicknesses of this order[26]. Radial clearance adopted from Hidayat *et al*[18], where inner liner and the head was 150 μm, while the clearance between the outer liner and the cup was 50 μm. One millimeter thick described the outer liner, and two millimeters described the acetabular cup[18].

The materials were thought to be isotropic, homogenous, and linear elastic[27]. In order to speed up the FEA while maintaining the same level of precision, the femoral head was modeled as an analytical rigid body[28]. With a butterfly mesh model based on an open cube box concept[29], the inner liner was meshed using eight-node structural hexahedron

elements (C3D8R), which eliminated the need for a combination of tetrahedral and hexahedral elements and the resulting potential for irregular stress concentrations[30]. The outer liner and acetabular cup used the quadratic tetrahedral (C3D10H) mesh model to avoid errors in visualizing contact pressure. Distinguishing the mesh model on the outer liner and inner liner is also done by Wegrzyn *et al*[31]. The FEA model for DM AHJ used in this work is shown in Figure 2.

The output of quadratic shape functions is less impacted by mesh refinement, thus offering a better approximation of the underlying geometry. They are also more stable. These advantages are because quadratic shape functions have a higher degree of quadraticity[32]. With fewer elements, quadratic elements may morph more convincingly and accurately depict geometric curvature. Quadratic elements can also deform more correctly and realistically than linear ones[33].

The mesh convergence test yielded the proper mesh size for the simulation, which was 0.8 mm for hexahedral and 1.5 mm for tetrahedral (Figure 3). On the head of 28 mm and 36 mm, the inner liner's elements were between 19596–68430 and 28800–100800, respectively. The number of elements often used in finite element (FE) simulations are 8352[34], 6912 [35], 6800–15500[36], and 3864[37]. Therefore, the number of elements in this study is sufficient and valid for FE simulation to be carried out. Table 1 displays the materials, element types, number of elements, and nodes used to create each part.

Loading and boundary conditions

The cup and the liner began in their anatomically optimal positions at an inclination angle of 45 degrees and an anteversion angle of zero[38]. The head and the cup had the same inclination and anteversion angle, making them concentric. The epicenter of the head served as the origin of a fixed Cartesian coordinate system (x, y, z). During the creation of the rigid body for the head, its center was set as a reference point. All degree of freedom was restricted on the acetabular cup's outer surface.

Figure 4 depicts the DM hip joint reference frame, which allows for three relative rotations between the linked components (the pelvis and the femur). The letter FE represents flexion and extension in the sagittal plane, AA represents adduction and abduction in the frontal plane, and IER represents an internal and external rotation in the horizontal plane. Medial-lateral (ML), anterior-posterior (AP), and proximal-distal (PD) are the three orthogonal axes around which these motions occur[39].

Under normal gait cycle conditions, the load occurred on the XYZ axis, which was centered on the femoral head reference point[40]. This load used in the study refer previous study from Jamari *et al*[41]. The stance phase of the gait cycle begins at 0 percent when the right heel makes contact with the floor and continues until approximately 60 percent when the toes lift off the floor. The swing phase of the gait cycle begins at 60 percent and continues until 100 percent when the heel makes contact with the floor again. During the swing phase, there is no contact between the foot and the floor. Figure 5 uses and reproduces the hip joint internal forces encountered during gait cycles.

The simulation was performed statically with dissipated energy and asymmetric behavior. The types of interaction were surface-to-surface contact and normal contact behavior. There were three interaction statuses: the head-inner liner used finite sliding, the inner liner-outer liner used small sliding (because both were bonded), and the outer liner-acetabular cup used finite sliding as well. All interactions were stabilized using contact control with automatic stabilization and augmented Lagrange. Stabilization effects were only implemented in the first step in which this control was addressed. These characteristics would only affect contact interactions specified by contact surface behavior.

Dry contact mechanics

Hertz's contact theory is also used to determine the dry contact mechanics of DM AHJ. This contact mechanic is achieved with the help of a ball-on-plane model with the same level of accuracy. The radius of equivalent ball, R, is determined from the inner liner and head radii, R_i and R_h, and the diametral clearance, c, as derived in equation 1[21]:

$$R = \frac{R_i R_h}{c} \quad (1)$$

The interaction of a rigid indenter with a flat, large specimen is highly relevant in many situations. Hertz discovered that the radius of the contact, a, is linked to the indenter force F, the radius of the equivalent ball, R, and the elastic modulus of the materials by equation 2:

$$a^3 = \frac{3FR}{4E^*} \quad (2)$$

Which describes the most common case of contact between a rigid sphere and a flat surface. Where $E*$ is the combined modulus of the inner liner and the head given by equation 3:

$$\frac{1}{E^*} = \frac{1}{2}\left(\frac{(1-v_i^2)}{E_i} + \frac{(1-v_h^2)}{E_h}\right) \quad (3)$$

E_i and v_i define the inner liner's elastic modulus and Poisson's ratio, whereas E_h and v_h characterize the head's elastic modulus and Poisson's ratio, respectively. The maximum contact pressure, P_m, is calculated by dividing the indenter load by the predicted contact area and serves as a helpful normalizing parameter with real-world relevance. The maximum contact pressure formula is shown in equation 4:

$$P_m = \frac{4F}{3\pi a^2} \quad (4)$$

RESULTS

Verification of the FE model

Valid data can only be obtained from the simulation if the FE model has been verified. The simulation findings were

Table 1 Materials and mesh specification

Components	Materials	Element types	Number of elements (range)[1]	Number of nodes (range)[1]
28 mm femoral head				
Femoral head	analytical rigid body			
Inner liner	UHMWPE	Hexahedral (C3D8R)	19596–68430	23331–74256
Outer liner	SS316L	Tetrahedral (C3D10H)	6552–12147	13317–24557
Acetabular cup	SS316L	Tetrahedral (C3D10H)	13942–23839	23918–40901
36 mm femoral head				
Femoral head	analytical rigid body			
Inner liner	UHMWPE	Hexahedral (C3D8R)	28800–100800	34167–109040
Outer liner	SS316L	Tetrahedral (C3D10H)	9512–16189	19249–32654
Acetabular cup	SS316L	Tetrahedral (C3D10H)	19425–32320	33354–55278

[1]Left value for 5 mm thickness, and right value for 12 mm inner liner thickness. UHMWPE: Ultra-high-molecular-weight polyethylene.

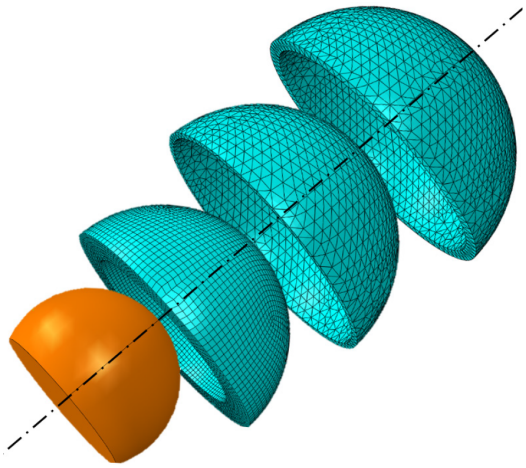


Figure 2 Mesh model.

checked by comparing them with the results found by Ruggiero and Silica[42]. The maximum contact pressure during typical walking cycles is compared in Figure 6 between the present simulation findings and the results of Ruggiero and Silica[42]. Ruggiero used a 28 mm head diameter, and the thickness of the liner was 9.5 mm. Therefore, the simulation in the current study also used a head diameter of 28 mm and the inner liner thickness of 9 mm and 10 mm for comparison.

The comparison graph demonstrates that the average difference between the current study (9 mm and 10 mm thickness) with those predicted by Ruggiero and Silica[42] is not significant, coming in at 4% and 2%, respectively that in acceptable range[27]. Variations in input quantities or parameter settings in the FEA program likely account for the discrepancy[43-45]. However, this is not an issue if the trend line agrees well with previous study as validation. Afterward, a complete simulation was run to determine the contact pressure and von Mises stress for two different head diameters (28 mm and 36 mm) and eight inner liner thicknesses (from 5 mm to 12 mm). The findings of contact pressure and von Mises stress for both head diameters and eight thicknesses of inner liner are discussed in the following subsection.

Contact pressure

The initial output of the simulation was contact pressure. Contact pressure is the ratio between the typical load and the actual contact area, which is the total of the front and rear contact areas. There were contacts between two sets of surfaces. First, hard-on-soft contact[46] occurred at the head surface, paired with the inner liner's concave surface. The second was hard-on-hard contact[47] between the acetabular cup's concave surface and the outer liner's convex surface.

Figure 7 depicts the maximum contact pressure on the inner liner, outer liner, and acetabular cup surfaces. The maximum contact pressure at a head diameter of 28 mm and 36 mm is shown in Figure 6, respectively. The highest load occurs when the gait cycle reaches 20%. At 28 mm head diameter, the maximum contact pressure is 13.5 MPa, on the inner liner thickness of 5 mm. While the head diameter is 36 mm, the maximum contact pressure is 10.4 MPa, on the inner liner thickness of 5 mm. There is a decrease in the highest contact pressure by 23%.

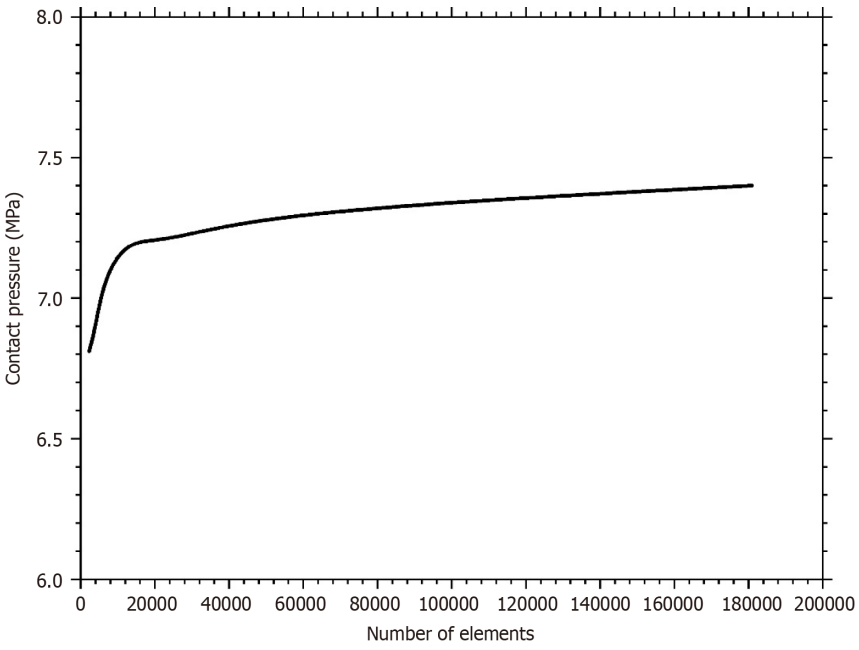


Figure 3 Convergence test.

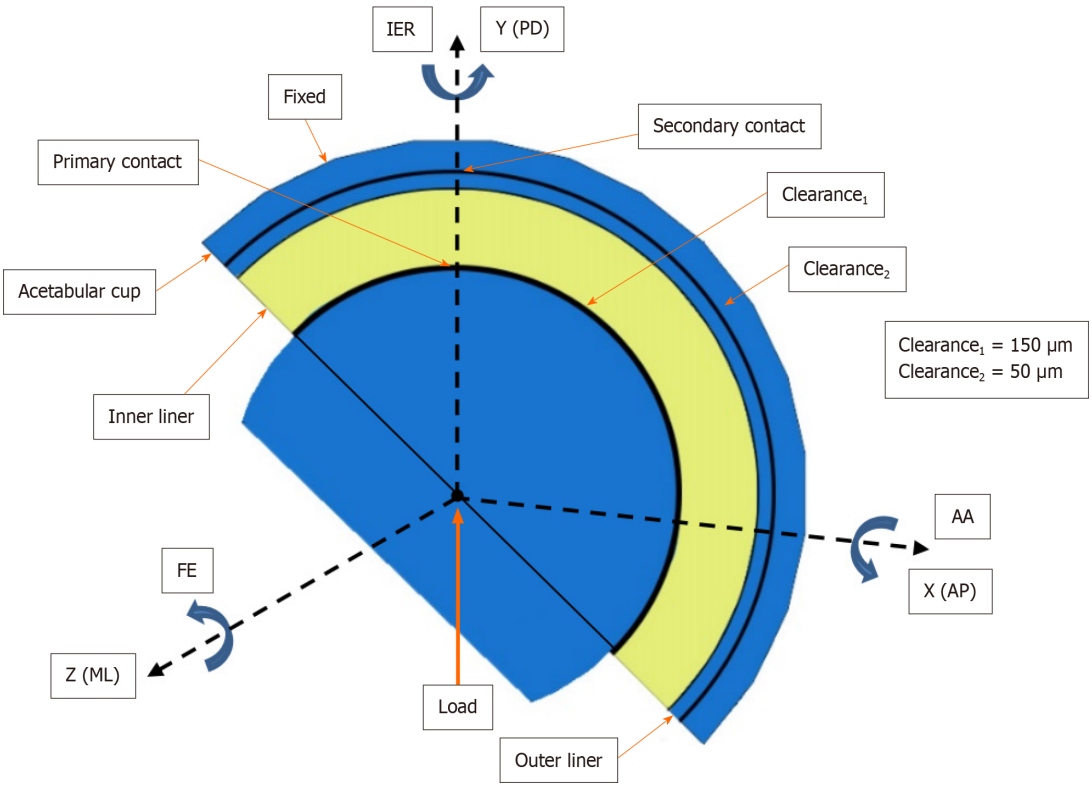


Figure 4 The DM hip joint reference frame. AP: Anterior-Posterior; IER: Internal-External Rotation; PD: Proximal-Distal; FE: Flexion-Extension; ML: Medial-Lateral; AA: Adduction- Abduction.

Then the lowest load occurs when the gait cycle is between 80%-90%. At 28 mm head diameter, the maximum contact pressure is 3.7 MPa, on the inner liner thickness of 12 mm. While the head diameter is 36 mm, the maximum contact pressure is 2.7 MPa, on the inner liner thickness of 8 mm. There is a decrease in the lowest contact pressure by 26%. The maximum contact pressure is lower with a head diameter of 36 mm than a head diameter of 28 mm. This finding demonstrates that as head diameter increases, contact pressure decreases. However, additional study is still required to determine how much larger the maximum head diameter may be made.

Figure 8 shows the percentage increase in contact pressure value on the outer liner and acetabular cup compared to the inner liner. The inner liner with a thickness of 12 mm has the smallest increase in contact pressure of the 28 mm head,

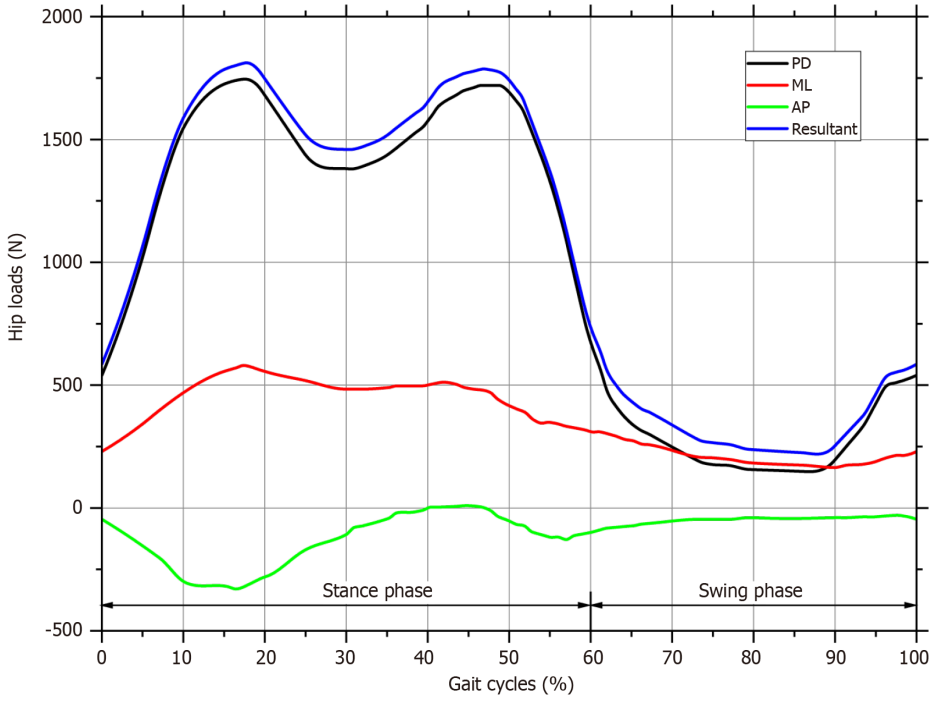


Figure 5 Hip loads during normal walking cycles, reproduced from[42]. AP: Anterior-Posterior; PD: Proximal-Distal; ML: Medial-Lateral.

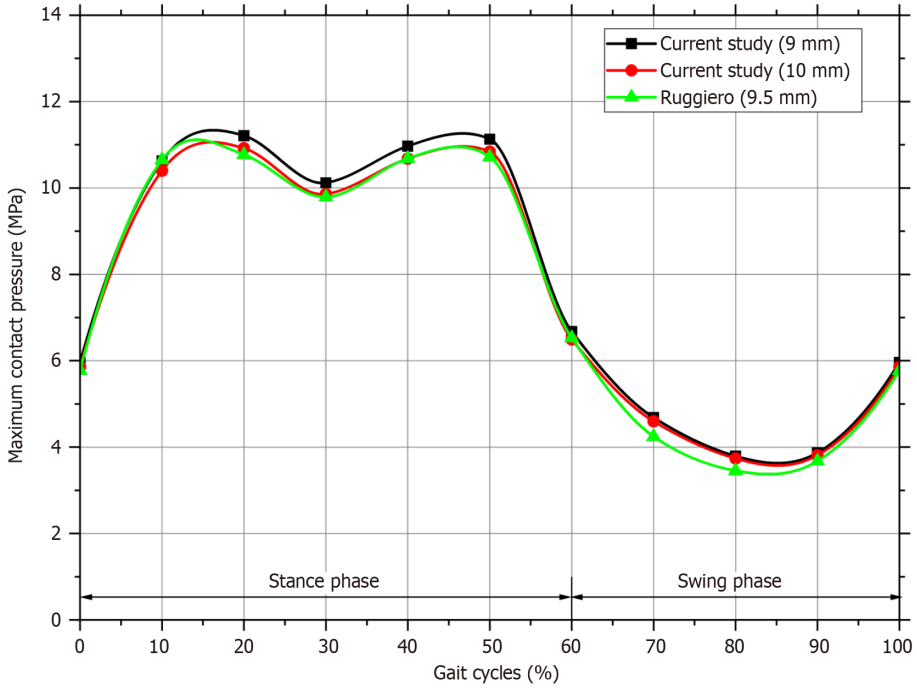


Figure 6 Finite element model verification.

which is 3% on the outer liner and 11% on the acetabular cup. It indicates that the contact pressure in the outer liner and acetabular cup is low and relatively just above the contact pressure in the inner liner. Additionally, with a head diameter of 36 mm, an increase in contact pressure of 7% on the outer liner and 8% on the acetabular cup takes place when the thickness is 8 mm. The lower the column, the better the thickness of the inner liner. The most proper inner liner thickness is depicted with the lowest column.

In SM AHJ, the ideal thickness of the inner liner is determined only by the liner. In distinction to SM AHJ, DM AHJ requires simultaneous and related consideration of contact pressure values on the inner liner, outer liner, and acetabular cup to determine the ideal thickness of the inner liner. Considering the proximity of the contact pressure values between the inner liner, outer liner, and acetabular cup, the suitable inner liner for a 28 mm head is 12 mm. In contrast, an 8-millimeter-thick inner liner is ideal for a 36-millimeter-diameter head. Figure 9 provides a visual representation of the results of the contact pressure distribution during gait cycles at 20% (maximum load) and at 80% (minimum load).

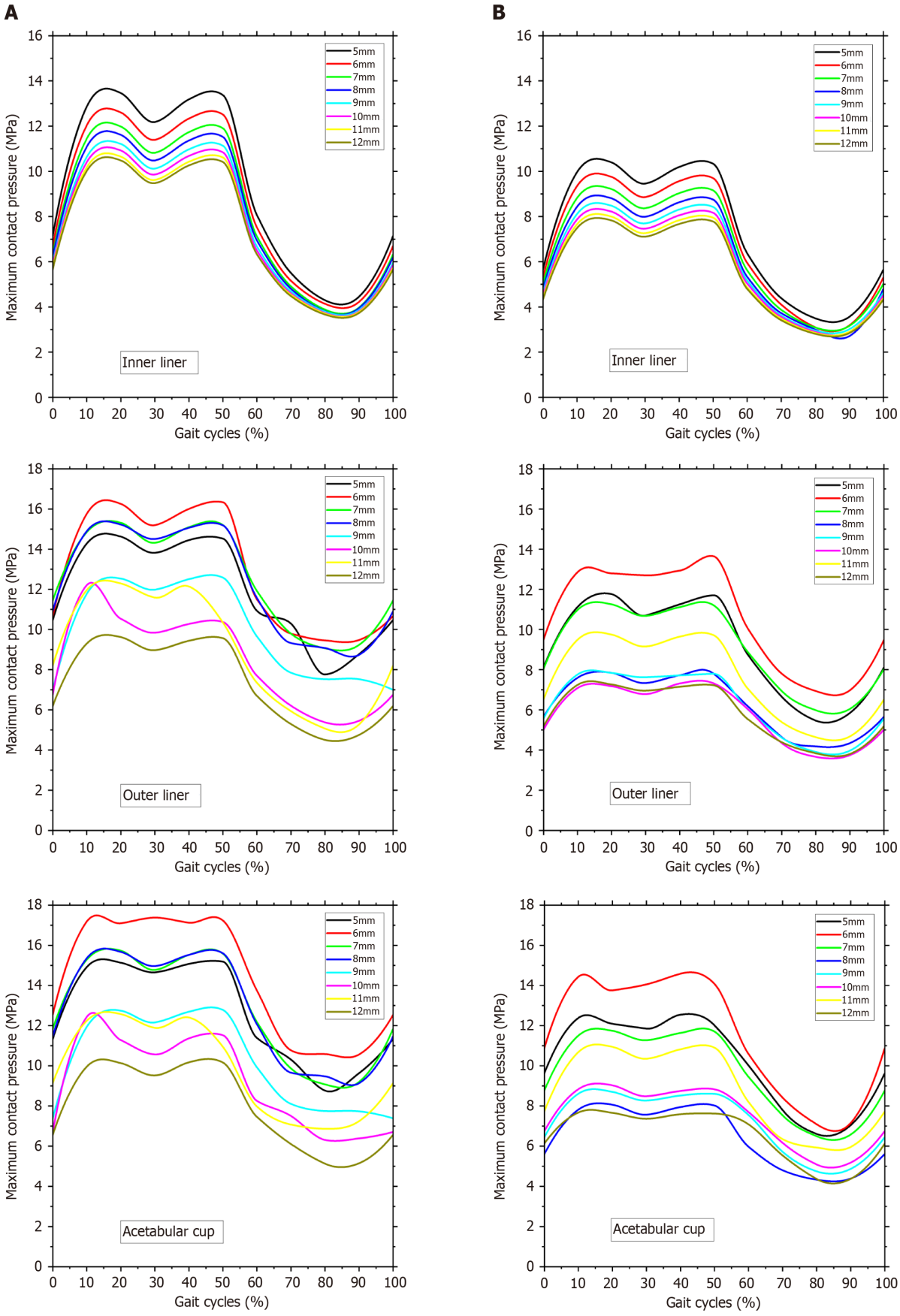


Figure 7 Maximum contact pressures based on gait cycles. A: 28 mm head diameter; B: 36 mm head diameter.

Von mises stress

The second simulation outcome is von Mises stress. The von Mises stress is frequently employed to determine whether an isotropic and ductile metal will yield under complicated loading conditions[48]. In this DM AHJ, von Mises stress was measured on the inner liner, outer liner, and acetabular cup components. The inner liner was fabricated from UHMWPE, while the outer liner and acetabular cup were fabricated from 316L stainless steel. The maximal von Mises stresses on the inner liner, outer liner, and acetabular cup are shown in Figure 10. Figure 10A depicts the maximum von Mises stress at a head diameter of 28 mm, whereas Figure 10B depicts the maximum von Mises stress with a head diameter of 36 mm.

The outer liner has the highest von Mises value, in contrast to the contact pressure value found in the acetabular cup. The high von Mises is due to the outer liner being the thinnest DM AHJ component. Accordingly, descending von Mises values are as follows: outer liner, acetabular cup, and inner liner. At the same head diameter of 28 mm, the von Mises stress on the outer liner is about 79% more than on the inner liner. The incidence of von Mises in the acetabular cup rises by 19%. On the head with a 36 mm diameter, von Mises stress increases by 78% on the outer liner and 14% on the acetabular cup.

DISCUSSION

Regarding the outer liner and acetabular cup, the contact pressures occur on the convex and concave surfaces. The outer liner and acetabular cup trend lines are identical to the inner liner trend line, but the value is greater than that. Therefore, the sequence of the contact pressure values, going from the lowest to the highest, is as follows: Inner liner, outer liner, and acetabular cup.

The components of DM AHJ have well-defined maximum contact pressure values, and it is simple to determine such values. The maximum contact pressures in the outer liner at a head diameter of 28 mm and 36 mm are between the range of 4.5-16.3 MPa and 3.7-13.6 MPa, respectively. In contrast, the maximum contact pressures in the acetabular cup at a head diameter of 28 mm and 36 mm are between the range of 5.1-17.4 MPa and 4.3-14.6 MPa, respectively. In other words, the contact pressure is proportional to the applied load. When the load is increased, so is the contact pressure.

Several salient features characterize the contact issue in MoP prosthetic joints[49]. It should be noted that the metal component of a prosthetic joint has an elastic modulus that is 200 times or more than that of polyethylene. The elastic modulus of SS316L is 200000 MPa, whereas that of UHMWPE is just 1000 MPa. Therefore, the metal prosthetic component behaves identically to that of a rigid body, causing significant deformations in the polyethylene. The second characteristic is that the initial contact on the MoP is non-conformal due to a clearance between the head and the liner. The wider the clearance, the more non-conformal it will be[50]. Then once it is given a high load, the polyethylene will be severely deformed, while the head remains unaltered, resulting in conformal contact. The third key feature is that the polyethylene layer is restricted to a maximum thickness at a certain point.

These three characteristics render Hertzian theory inappropriate for problem-solving involving MoP prosthetic joints [51]. The reason is that the Hertzian theory is used when the deformation occurs on both contact surfaces. However, in MoP AHJ, the deformation takes place solely on the surface of the UHMWPE. The Hertzian theory is based on the non-conformal surface hypothesis. Nevertheless, if the polyethylene is substantially deformed, the Hertzian concept is no longer applicable since the contact has become conformal. The Hertzian theory is more appropriate for MoM AHJ[50]. Another issue is that the Hertzian theory only applies to thicknesses of a semi-infinite range; it cannot be used for thicknesses of a limited range, such as the UHMWPE layer on AHJ[52].

This study's predicted contact pressure is consistent with earlier FE studies. The maximum contact pressures in the inner liner (UHMWPE) at a head diameter of 28 mm and 36 mm are between 3.7-13.5 MPa and 2.7-10.4 MPa, respectively. Wang *et al*[53] suggested that the contact pressure on the inner cup surface varies from 3.2 to 11.5 MPa. According to Wu *et al*[54], the contact pressure is between 1.5 and 15 MPa. Hua *et al*[55] reported that the contact pressure varies between 4 and 11 MPa. According to other researchers, the contact pressure values range between 6 and 19 MPa[56-58].

Maximum contact pressure diminishes as the thickness of the inner liner increases. Keep in mind, however, that there is a maximum thickness for the inner liner since it will also affect the diameter of the acetabular cup, given the greatest diameter of the acetabular cup that the acetabulum socket can still tolerate. Dubin *et al*[26] reported the maximum cup diameter to be 74-80 mm, but Chan *et al*[59] reported the maximum acetabular cup diameter to be 58 mm. In their study, Hua *et al*[55] used 56 mm for the outer diameter of the acetabular shell. In this current research, the outside diameter of the acetabular cup is 58.4 mm for a 12 mm inner liner thickness and 28 mm head diameter. While the head is 36 mm with an inner liner thickness of 12 mm, the acetabular cup has an outer diameter of 66.4 mm. Therefore, the thickness of the inner liner in this investigation remains within the permissible dimensions.

The maximum von Mises of the inner liner, outer liner, and acetabular cup are 2.4–11.4 MPa, 15.7–44.3 MPa, and 3.7–12.6 MPa, respectively, for 28 mm head. Then the maximum von Mises stresses of the 36 mm head are 1.9-8.9 MPa for the inner liner, 9.9-32.8 MPa for the outer liner, and 2.6-9.9 MPa for the acetabular cup. It should be noted that UHMWPE has a range of yield strengths. According to Malito *et al*[60], the engineering yield stress in UHMWPE formulations varies from 21.7 to 26.2 MPa. UHMWPE has a tensile strength of 35 MPa[61]. The maximum von Mises of the inner liner is lower than the yield strength of UHMWPE.

The predicted stresses matched those found in the FE works of literature used in this investigation. According to the subject-specific hip model, Anderson *et al*[62] presented that the von Mises stresses are between 0 and 44 MPa. Harris *et al* [63] found that, for healthy volunteers, peak stress while walking is 7.5 MPa, which is within the expected range under physiological stresses. Ravera *et al*[64] demonstrated that the von Mises stress varies between 0 and 12 MPa. According to Wu *et al*[54], the acetabular cartilage undergoes peak von Mises stresses of 7.5 MPa for a normal hip, 14.9 MPa for a

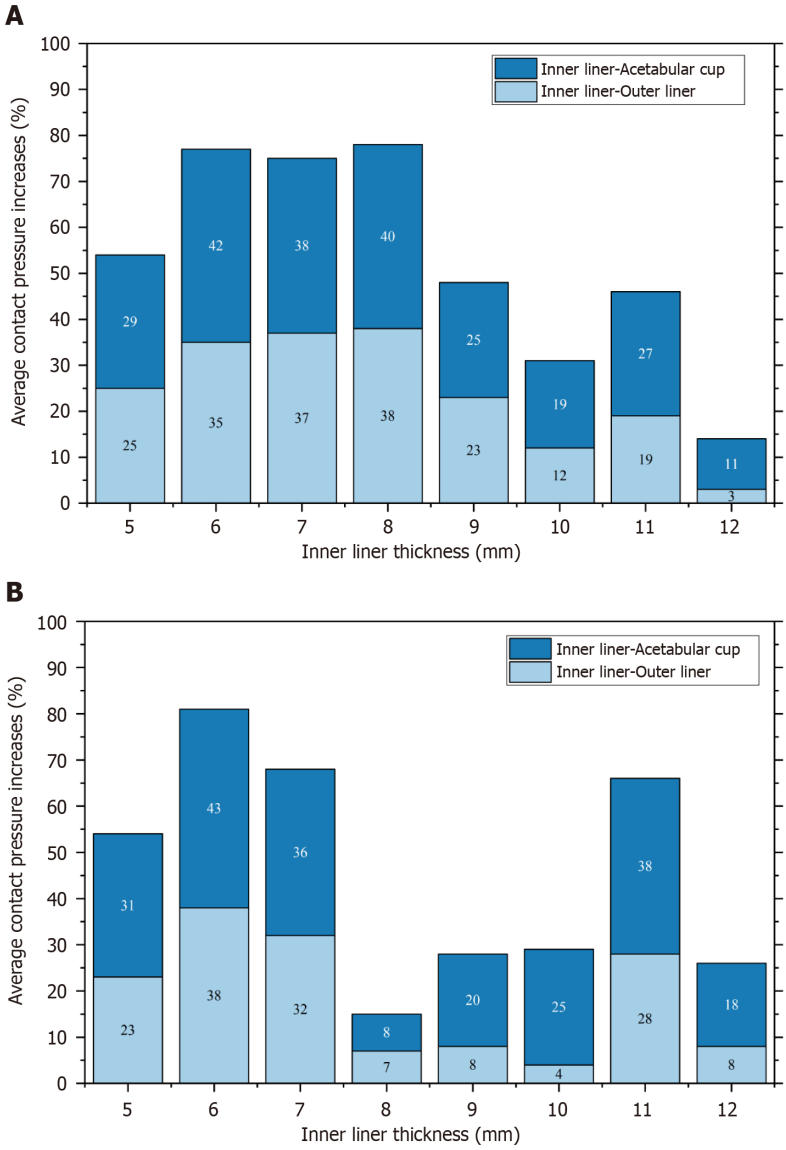


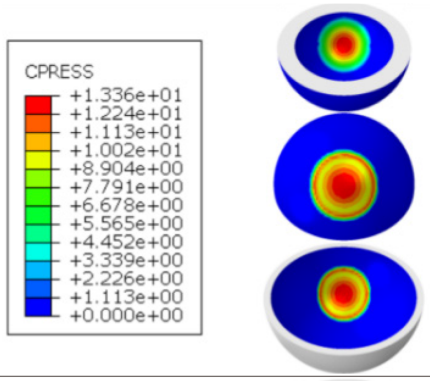
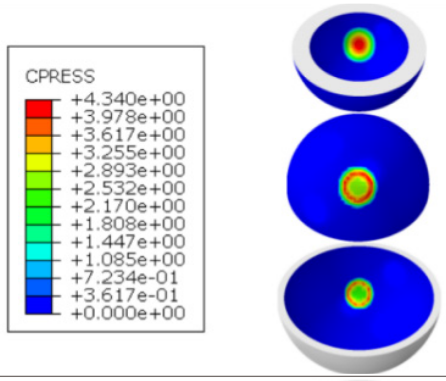
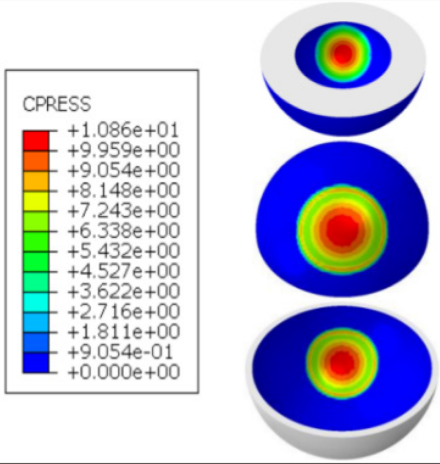
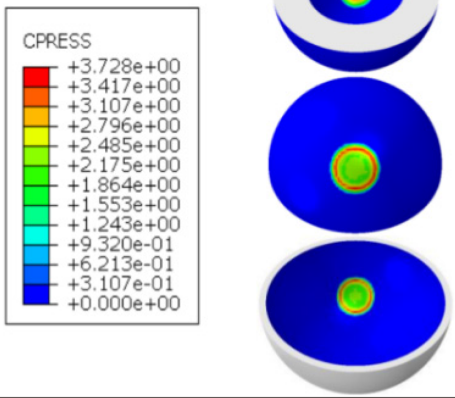
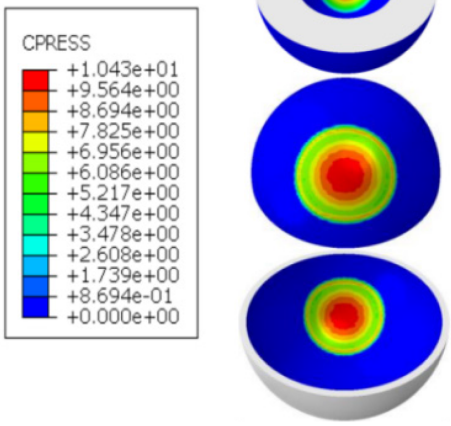
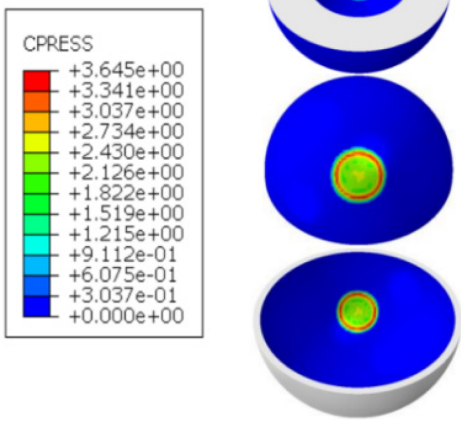
Figure 8 The average increase in contact pressures. A: 28 mm head diameter; B: 36 mm head diameter.

sphere-replaced hip, and 13.1 MPa for a rotating ellipsoid-replaced hip. Dalli *et al*[56] stated that the maximum von Mises is 13.5 MPa. All of the simulated results presented illustrates contact behavior in DM AHJ that would bring beneficial to choosing suitable geometry for implant patient.

CONCLUSION

It is possible to conclude that the inner liner's maximum von-Mises and contact pressure values are much less than the UHMWPE material's yield strength (21-27 MPa). As the inner liner's thickness rises, maximum contact pressure decreases. The maximum contact pressure is lower, with a head diameter of 36 mm compared to a head diameter of 28 mm. As a result, contact pressure and von Mises stress reduce with an increasing head diameter and inner liner's thickness. The results of this study indicate that for a head with a diameter of 28 mm, an inner liner thickness of 12 mm is optimal. As for the 36 mm diameter head, the appropriate inner liner thickness is 8 mm. In this investigation, regular cycles of normal walking were the only activity examined. A more reliable method of distinguishing between ideal and reality models may be incorporating activities with severe loading and boundary conditions. Another drawback is that static analysis was used instead of dynamic analysis. In contrast, a more noticeable impact may be predicted if the investigation is conducted dynamically with continuous loading and more realistic boundary conditions. Then, more studies are required for the various head diameter and research about the wear and lubrication of this DM AHJ component. The findings in the present computational simulation would become orthopedic surgeon referral for choosing suitable geometry of DM AHJ for their patient.

A

Inner liner thickness (mm)	Component	Gait cycles (%)	
		20% (maximum load)	80% (minimum load)
5	Inner liner Outer liner Acetabular cup		
10	Inner liner Outer liner Acetabular cup		
12	Inner liner Outer liner Acetabular cup		

B

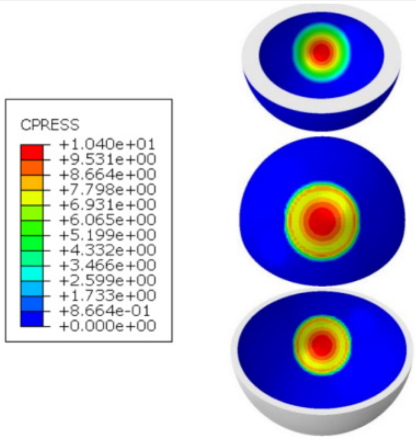
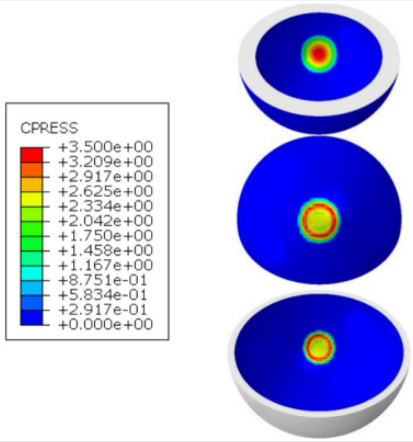
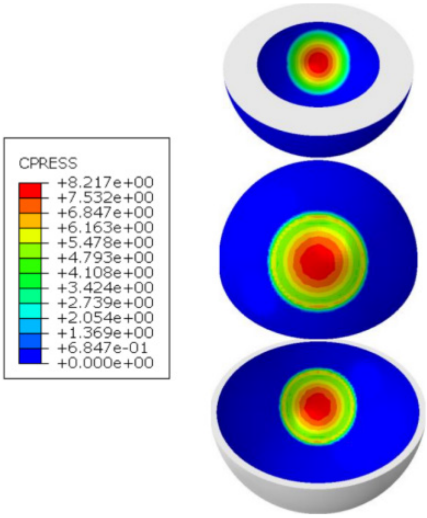
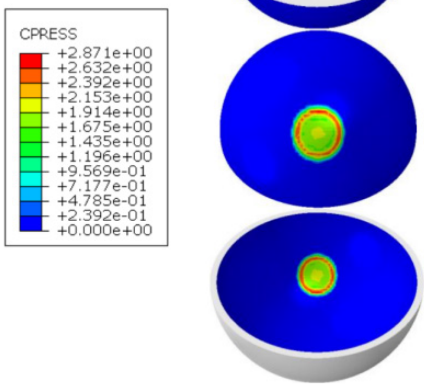
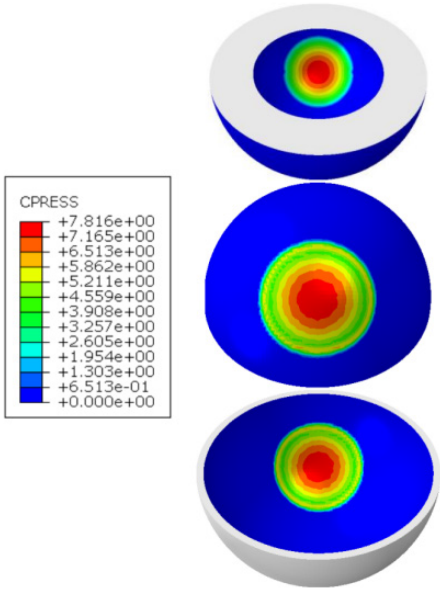
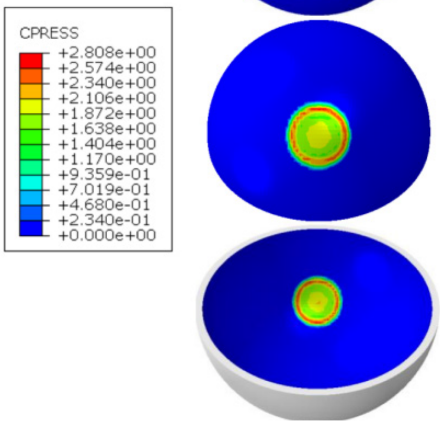
Inner liner thickness (mm)	Component	Gait cycles (%)	
		20% (maximum load)	80% (minimum load)
5	Inner liner Outer liner Acetabular cup		
10	Inner liner Outer liner Acetabular cup		
12	Inner liner Outer liner Acetabular cup		

Figure 9 Visualization of contact pressures. A: 28 mm head; B: 36 mm head.

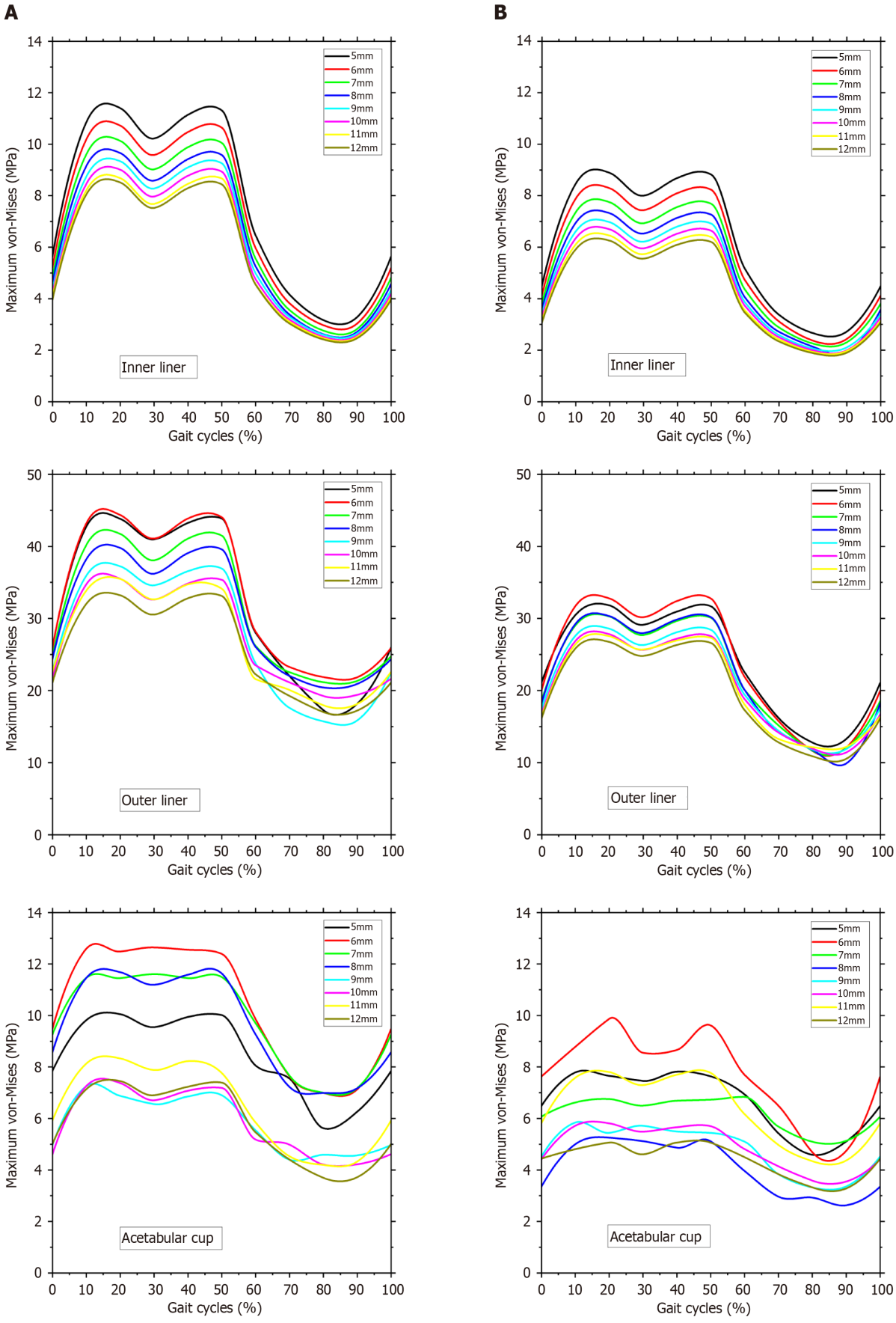


Figure 10 Von mises stress. A: 28 mm head diameter; B: 36 mm head diameter.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effect of inflammatory response on joint function after hip fracture in elderly patients: A clinical study

Jia-Ming Wang, Yu-Tao Pan, Chen-Song Yang, Ming-Chong Liu, Sheng-Chao Ji, Ning Han, Fang Liu, Gui-Xin Sun

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Abstract

BACKGROUND

Excellent hip joint function facilitates limb recovery and improves the quality of survival. This study aimed to investigate the potential risk factors affecting postoperative joint functional activity and outcomes in elderly hip fractures patients and to provide evidence for patient rehabilitation and clinical management.

AIM

To explore the relationship between inflammatory factors and hip function and the interaction between inflammation and health after hip fracture in elderly patients.

METHODS

The elderly patients who had hip fracture surgery at our hospital between January 1, 2021, and December 31, 2022 were chosen for this retrospective clinical investigation. Patients with excellent and fair postoperative hip function had their clinical information and characteristics gathered and compared. Age, gender, fracture site, surgical technique, laboratory indices, and other variables that could have an impact on postoperative joint function were all included in a univariate study. To further identify independent risk factors affecting postoperative joint function in hip fractures, risk factors that showed statistical significance in the univariate analysis were then included in a multiple logistic regression analysis. In addition to this, we also compared other outcome variables such as visual analogue scale and length of hospital stay between the two groups.

RESULTS

A total of 119 elderly patients with hip fractures were included in this study, of

whom 37 were male and 82 were female. The results of univariate logistic regression analysis after excluding the interaction of various factors showed that there was a statistically significant difference in interleukin (IL)-6, IL-8, IL-10, C-reactive protein (CRP), and complement C1q (C1q) between the fair and excellent joint function groups ($P < 0.05$). The results of multiple logistic regression analysis showed that IL-6 > 20 pg/mL [(Odds ratio (OR) 3.070, 95%CI: 1.243-7.579], IL-8 > 21.4 pg/ mL (OR 3.827, 95%CI: 1.498-9.773), CRP > 10 mg/L (OR 2.142, 95%CI: 1.020-4.498) and C1q > 233 mg/L (OR 2.339, 95%CI: 1.094-5.004) were independent risk factors for poor joint function after hip fracture surgery (all $P < 0.05$).

CONCLUSION

After hip fractures in older patients, inflammatory variables are risk factors for fair joint function; therefore, early intervention to address these markers is essential to enhance joint function and avoid consequences.

Key Words: Hip function; Fracture; Inflammatory factors; Risk factors; Prevention

Core Tip: Interleukin (IL)-6 > 20 pg/mL, IL-8 > 21.4 pg/mL, C-reactive protein > 10 mg/L, and complement C1q (C1q) > 233 mg/L may be independent risk factors for fair postoperative joint function in patients with hip fracture. In addition, C1q represented a specific risk factor for fair joint function after hip fracture surgery in elderly patients, these predictors may provide a new strategy for the treatment of hip fracture.

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INTRODUCTION

Hip fractures are a serious and prevalent public health issue[1,2]. The high rates of sickness, mortality, and disability that are associated with ageing populations in particular pose a serious concern[3,4]. Also, as an osteoporotic fracture, it is highly susceptible to re-fracture[5], which will affect the patient's mobility and quality of life[6,7]. The number of hip fractures is expected to increase to 4.5 million worldwide by 2050 as the population ages[8], and China will account for a significant proportion[9,10], thus the resulting physical and psychological problems, increased hospitalization costs and the social burden will pose a huge challenge in the future[11,12].

There are many risk factors for hip fracture, such as age, gender, smoking, osteoporosis, nutrition and medication[12,13]. However, few studies have explored the relevance of inflammatory factors to the prognosis of surgery in elderly hip fracture patients. Immunoinflammatory responses and oxidative stress have been shown to affect post-operative hip fracture outcomes[14]. There are several inflammatory factors associated with fracture trauma and bone healing, for example, interleukin (IL)-6 is increased in osteoporotic human bone and promotes the development and persistence of the inflammatory response that affects fracture healing[15]; elevated concentrations of IL-8 and IL-10 in the synovial fluid of patients with acute tibial plateau fractures[16]; C-reactive protein (CRP) is associated with mortality at one year after hip fracture surgery[17]; complement C1q (C1q) is also involved in the process of innate and acquired immunity and is important in maintaining the balance of the immune response[18].

The establishment and modification of patients' rehabilitation exercises and treatment programmes depends in large part on the post-operative joint function, degree of pain perception, and duration of hospital stay following the hip fracture. The choices made about useful serum markers, prompt adjustments to treatment plans for better prognosis, and more efficient use of medical resources have a significant impact on families and society as a whole. Therefore, it is particularly necessary to explore the risk factors associated with older individuals after hip fracture surgery. This study aimed to analyze which inflammatory factors might be associated with joint mobility and prognostic outcomes after hip fracture surgery, and to establish direction for further study.

MATERIALS AND METHODS

Ethics

This study was a retrospective design. All procedures and methods of our study were carried out under the procedures and regulations of Shanghai East Hospital. Meanwhile, our hospital ethics committee reviewed and approved this research under the approval number: [2022] Research Audit No. 278. Written informed consent was obtained from all participants in this study, and all data related to the patients were complete and detailed and handled confidentially.

General information

A total of 119 patients diagnosed with hip fractures were selected from the electronic case database of Shanghai East Hospital from January 1, 2021 to December 31, 2022, who met the diagnostic criteria for hip fracture and had completed elective surgery in our hospital. Then, all patients were divided into a postoperative fair hip function group (Score < 80) and a postoperative excellent hip function group (Score ≥ 90) according to the Harris hip function scale[19], with 37 males and 82 females, aged 56-100 years, with a mean age of (76.4 ± 12.29) years (Table 1). All included hip fracture patients in this study underwent proximal femoral nail antirotation (PFNA) and total hip arthroplasty (THA), including 61 patients who underwent PFNA and 58 patients who underwent THA (Table 1).

Inclusion and exclusion criteria

The inclusion criteria for our study were: (1) Age ≥ 50 years; (2) Diagnosis of disease met the criteria for hip fracture; and (3) Patients received surgical treatment in our hospital. Exclusion criteria: (1) No surgical treatment; (2) Hip fracture due to high energy injury; (3) Open fracture; (4) Fracture occurred with excessive blood loss; (5) Associated with bone metabolic or inflammatory diseases; (6) Received medications affecting bone metabolism and inflammatory factors such as glucocorticoids, antibiotics, calcitonin, bisphosphonates, etc. prior to admission to the hospital; (7) Pathological fracture; and (8) Patients with severe liver and kidney disease and malignancy.

Evaluation method

The hip function is classified according to the Harris hip function scale, which is used to assess the outcome of various hip disorders, including: (1) Pain; (2) Function; (3) Deformity; and (4) Joint mobility. The score greater than or equal to 80 was classified as excellent group, and the score less than 80 was classified as fair group. The visual analogue scale (VAS) [20], is a visual analogue of the severity of pain. The scale is divided into 10 equal parts using a ruler, starting at 0 for no pain, 1-3 for mild pain, 4-6 for moderate pain, and 7-10 for severe pain, allowing the patient to subjectively state where they are on the scale and thus express the level of pain.

Data collection

The following clinical characteristics were collected and reviewed by two experts: Age, sex, hypertension, diabetes, fracture laterality, type of fracture site, surgical approach, time from injury to surgery, VAS score, and length of hospital stay.

In addition, laboratory tests that may affect the prognosis of patients with hip fractures were also collected and analyzed, specifically. Neutrophil count, lymphocyte count, IL-6, IL-8, IL-10, CRP, serum C1q. Finally, all clinical information collected was independently reviewed and confirmed by another specialist.

Statistical analysis

The measurement data were expressed as mean ± SD, and the count data were expressed as the number of cases and percentage; the *t*-test for independent samples was used for measurement data between groups, and the chi-square test was used for count data. The covariates that were statistically significant after one-way logistic analysis were further analyzed using multiple logistic regression to determine the risk factors affecting functional limitation of the hip joint after hip fracture surgery, with $P < 0.05$ being considered statistically significant. IBM SPSS Statistics 25 software was used for statistical analysis of the relevant data and GraphPad Prism 9 software was used for the graphical interpretation of the findings.

RESULTS

Patient characteristics and single-factor logistic regression analysis

A total of 119 elderly patients with hip fractures from Shanghai East Hospital affiliated with Tongji University were included in this study. 67 patients had fair hip function after surgery and 52 patients had excellent hip function after surgery. As shown in Table 1, there were significant differences in IL-6, IL-8, IL-10, CRP, and C1q ($P < 0.05$). However, there were no significant differences in age, gender, hypertensive disease, diabetes, fracture location, surgical approach, time from injury to surgery, serum neutrophil count, and lymphocyte count ($P > 0.05$).

Comparison of outcomes

The differences between the two groups were statistically significant ($P < 0.05$) in terms of length of hospital stay (Figure 1), while the differences in VAS scores were not statistically significant ($P > 0.05$). Table 2 shows outcomes for both groups of patients during the observation period

Multivariate logistic regression analysis

The risk factors from the univariate regression analysis were included in the multivariate logistic regression analysis, and as shown in Table 3 and Figure 2, IL-6 > 20 pg/mL [(Odds ratio (OR) 3.070, 95%CI: 1.243-7.579], IL-8 > 21.4 pg/ mL (OR 3.827, 95%CI: 1.498-9.773), CRP > 10 mg/L (OR 2.142, 95%CI: 1.020-4.498) and C1q > 233 mg/L (OR 2.339, 95%CI: 1.094-5.004) were independent risk factors for limited hip mobility after hip fracture surgery (all $P < 0.05$).

Table 1 Patient characteristics of included patients, *n* (%)/mean ± SD

	Fair hip function after surgery (*n* = 67)	Excellent hip function after surgery (*n* = 52)	Total (*n* = 119)	t/χ^2	*P* value
Age (yr)	76.88 ± 12.54	75.79 ± 12.05	76.4 ± 12.29	0.538	0.660
Sex				0.005	0.946
Female	46 (68.7)	36 (69.2)	82 (68.9)		
Male	21 (31.3)	16 (30.8)	37 (31.1)		
Hypertension				0.149	0.699
Yes	41 (61.2)	30 (57.7)	71 (59.7)		
No	26 (38.8)	22 (42.3)	48 (40.3)		
Diabetes				0.008	0.929
Yes	15 (22.4)	12 (23.1)	27 (22.7)		
No	52 (77.6)	40 (76.9)	92 (77.3)		
Types				0.030	0.862
Femoral neck	32 (47.8)	24 (46.2)	56 (47.1)		
Trochanteric	35 (52.2)	28 (53.8)	63 (52.9)		
Surgical method				0.016	0.899
PFNA	34 (50.7)	27 (51.9)	61 (51.3)		
THA	33 (49.3)	25 (48.1)	58 (48.7)		
Time from injury to					
Surgery	4.69 ± 2.85	5.15 ± 2.82	4.89 ± 2.84	0.876	0.425
Neut	6.09 ± 2.38	6.49 ± 2.36	6.29 ± 2.36	0.643	0.806
Lymph	1.20 ± 0.61	1.14 ± 0.44	1.17 ± 0.53	0.455	0.152
IL-6	53.08 ± 28.24	24.58 ± 9.57	37.03 ± 24.43	2.54	0.012
IL-8	47.99 ± 23.39	24.06 ± 10.48	34.52 ± 20.98	7.47	< 0.01
IL-10	11.43 ± 4.83	9.44 ± 3.89	10.31 ± 4.42	2.49	0.014
CRP	21.76 ± 18.12	10.00 ± 5.55	15.14 ± 13.91	5.022	< 0.01
C1q	207.44 ± 49.24	174.84 ± 66.86	189.08 ± 61.75	2.949	0.004

PFNA: Proximal femoral nail antirotation; THA: Total hip arthroplasty; IL: Interleukin; CRP: C-reactive protein; C1q: Complement C1q.

Table 2 Outcomes

	Fair hip function after surgery (*n* = 67)	Excellent hip function after surgery (*n* = 52)	F. group *vs* E. group	
Outcome	mean ± SD	mean ± SD	Mean diff. (95%CI)	*P* value
VAS	2.03 ± 0.82	1.85 ± 0.78	0.18 (-0.11-0.48)	0.827
Length of hospital-ization	14.31 ± 7.85	13.72 ± 3.98	0.59 (1.60-2.78)	0.036

VAS: The visual analogue scale; SD: Standard deviation.

DISCUSSION

The years 2020 to 2030 are known as the decade of healthy ageing[21]. As the population ages, hip fractures are becoming more common in the elderly population, and in those over 65 years of age, hip fractures can lead to serious complications and reduce life expectancy[22,23]. The current treatment is still mainly surgical, but due to advanced age, weak organ

Table 3 Logistic regression analysis on the risk factors of postoperative fair joint function in patients with hip fracture

Items	β	SE	OR	95%CI	*P*
IL-6 > 20 pg/mL	1.122	0.461	3.070	1.243-7.579	0.015
IL-8 > 21.4 pg/mL	1.342	0.478	3.827	1.498-9.773	0.005
IL-10 > 5.90 pg/mL	0.719	0.438	2.053	0.871-4.841	0.10
CRP > 10 mg/L	0.762	0.379	2.142	1.020-4.498	0.044
C1q > 233 mg/L	0.850	0.388	2.339	1.094-5.004	0.028

IL: Interleukin; CRP: C-reactive protein; C1q: Complement C1q; OR: Odds ratio; SE: System error.

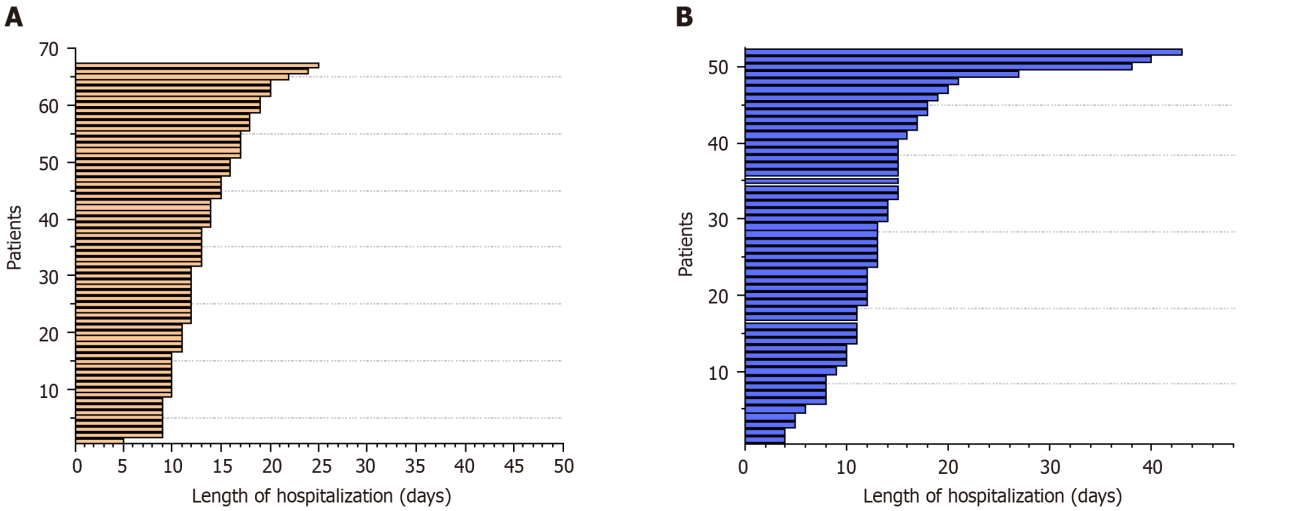

Figure 1 Swimming plot. A: Length of hospitalization for patients with excellent joint function after hip fracture; B: Length of hospitalization for patients with fair joint function after hip fracture.

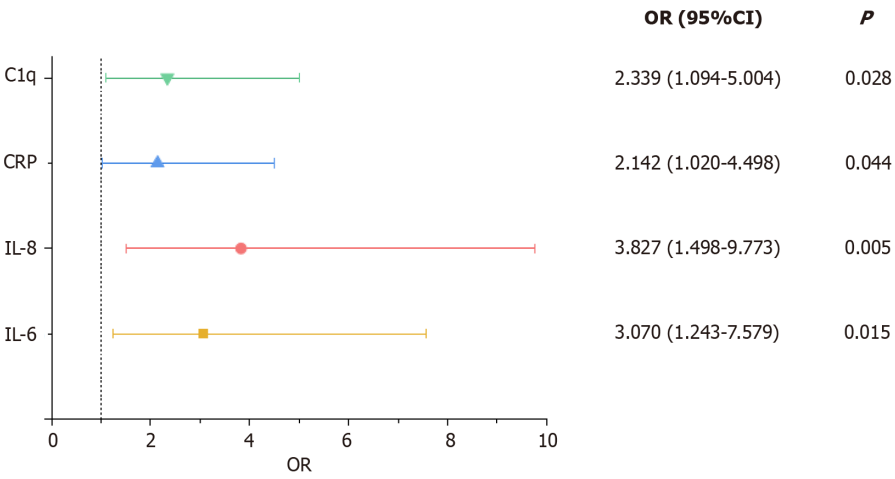

Figure 2 Multifactorial logistic regression analysis of postoperative fair hip functional in elderly hip fractures patients. CRP: C-reactive protein; IL: Interleukin; C1q: Complement C1q; OR: Odds ratio.

function, and already existing comorbidities, often patients undergo surgery with a high mortality rate and multiple complication outcomes[3,12], therefore the identification of risk factors, as well as stratification of inpatients and precise and personalized treatment, is beneficial to improve the prognosis of elderly hip fracture patients. However, there is a lack of accurate clinical indicators for prognosticating hip function after hip fracture surgery in the elderly. This study focuses on analysing the possible association between inflammatory factor levels and hip function after hip fracture surgery in the elderly. Our findings suggest that IL-6 > 20 pg/mL, IL-8 > 21.4 pg/mL, CRP > 10 mg/L, and C1q > 233 mg/L are independent risk factors for poorer postoperative joint function in hip fracture patients, and that there are

significant differences in length of hospital stay in these study subjects ($P < 0.05$). Thus, these suggest that physicians may need to take clinical measures to address these risk factors to prevent the occurrence and development of postoperative complications.

Numerous investigations have examined the evaluation of patients' mortality, morbidity, and voluntary mobility following hip fractures. According to Xu *et al*[24] elderly hip fracture patients' grip strength and weakness may be predictive of unfavorable outcomes. Thomas *et al*[25] compared the effects of the various surgical schedules on health outcomes in hip fracture patients and showed that delaying the timing of surgery in patients with poor health status did not have a beneficial effect. Furthermore, there is some disagreement over the risk factors reported in various nations and areas. For instance, one study found that women are more likely than men to suffer hip fractures that result in poor outcomes[26], while another study found that male patients are more likely to experience complications from hip fractures[27]. This could be due to their coexistence with multiple underlying conditions and poor habits. The development of databases and predictive indicators is essential to improving poor patient outcomes and boosting public health efficiency and well-being due to the world's and China's growing aging populations. Our study was based on a Shanghai population with a mean age of 76.4 ± 12.29 years, with the highest age of patients being 100 years. In addition to normal blood tests and CRP, our study focused more on lymphokines and complement, which have received less research attention, as we believe these factors play an irreplaceable role in fracture occurrence and bone healing throughout.

When a hip fracture occurs, immune cells around the fracture site secrete cytokines such as pro-inflammatory IL-6, IL-8, and anti-inflammatory IL-10[28,29], which stimulate mesenchymal stem cells (MSCs) to migrate to the fracture site and promote fracture repair, these lymphokines and CRP were also found to be significantly elevated in the serum of elderly hip fracture patients with coexisting complications[30]. Some studies have reported CRP as a major risk factor for death after hip fracture[17,31], this is consistent with our study that CRP is a risk factor for poor joint function. In addition, our finding that gender and fracture type did not correlate with hip fracture was also consistent with the finding of Yu *et al* [32].

We also looked at cytokines and complements, which are less common in other Chinese hospitals, in addition to CRP. Furthermore, although the Harris score is frequently employed to measure hip function in patients both before and after surgery, it is important to investigate how it correlates with other variables because there aren't many studies emphasizing the importance of inflammatory factors on joint function. C1q levels are associated with inflammation-related and metabolic diseases[33], and hip fracture in the elderly as a fragility fracture, therefore C1q was also included in the study protocol, and the results showed that C1q is an independent risk factor for fair joint function after hip fracture surgery. In contrast, IL-10 was not found to be a risk factor for fair hip function in this study, probably because the timing of the appearance of each cytokine after trauma varies and IL-10 as an anti-inflammatory factor was not elevated to the concentration level it should be during the hospital stay.

There are some limitations to this study. Firstly, this is a single-center retrospective study with small sample size, potential confounding factors that may affect the clarity of the results, and the ability to detect differences between groups may be inadequate. However, from the beginning of the study, we set uniform standards, with two specialist physicians independently collecting data and checking by a senior physician to reduce study bias, although we would need multi-center institutions and hospitals and larger sample sizes to eliminate bias. Secondly, we only observed and analyzed functional activity and tests during hospitalization in elderly hip fracture patients. To better reflect the prognosis of the patients, we also added additional outcome factors like VAS and length of stay. However, because the patients' circumstances varied and their privacy was protected, we did not investigate complications or mortality after discharge. It is planned that additional prospective research would be carried out in the future to examine the risk variables influencing hip function following surgery.

CONCLUSION

In conclusion, this study indicates several risk factors for less favourable prognosis of joint function in hip fracture patients, and these predictors may help alert physicians to develop rehabilitation protocols and early intervention.

ARTICLE HIGHLIGHTS

Research background

The incidence of hip fractures and postoperative complications in the elderly is increasing. With the advent of the aging society, addressing this public health problem is becoming a non-negligible issue. At present, while the risk factors of hip function recovery after hip fracture in elderly patients are subjects of recent investigation, their specific impact on populations with hip fractures remains relatively not investigated.

Research motivation

In elderly people with hip fractures, the relationship between various inflammatory markers and joint function remains to be further studied.

Research objectives
This study aims to reveal the potential impact of inflammation on joint function in elderly patients with hip fractures, which may provide new approaches for the treatment and rehabilitation of hip fractures.

Research methods
Of 119 patients with hip fractures who underwent elective surgery at Shanghai East Hospital between January 1, 2021, and December 31, 2022 were included in this retrospective analysis. Participants' comprehensive clinical data, including: Age, sex, hypertension, diabetes, type of fracture site, surgical approach, time from injury to surgery, visual analogue scale score, and length of hospital stay, were collected and analyzed using statistical software. For the measurement data between groups, the independent samples *t*-test was employed, and for the count data, the chi-square test was utilised. To ascertain the risk factors influencing the functional limitation of the hip joint following a hip fracture, additional multivariate logistic regression analyses were carried out on the covariates that were statistically significant by one-way logistic analysis, with $P < 0.05$ being deemed statistically significant.

Research results
In this study involving 119 participants with an average age ≥ 75 years, there were no significant differences in age, sex, hypertensive disease, diabetes, fracture types, surgical approach, injury to surgery time, serum neutrophil count, and lymphocyte count. There were significant differences in interleukin (IL)-6, IL-8, IL-10, C-reactive protein (CRP), and complement C1q (C1q) between the two groups. Notably, we also looked at cytokines and complement, which have received relatively less attention in other hospitals in China, and these findings suggest several inflammation-related risk factors for fair joint function in patients with hip fractures.

Research conclusions
To sum up, CRP, IL-6, IL-8 and C1q in patients with fair hip function after surgery were significantly higher than those in patients with excellent hip function in our study.

Research perspectives
These results suggest that there is a certain correlation between inflammatory factors and the postoperative function of hip fracture, and provide a fresh approach for future research of the relationship between inflammation and joint function.

FOOTNOTES

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Author contributions: Wang JM and Pan YT carried out the studies and drafted the manuscript; Sun GX and Liu F participated in the design of the study and conceived of the study; Yang CS and Liu MC contributed materials/analysis tools; Ji SC and Ning H performed the statistical analysis. All authors participated in the preparation of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Safety of tranexamic acid in surgically treated isolated spine trauma

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Abstract

BACKGROUND

Tranexamic acid (TXA), a synthetic antifibrinolytic drug, effectively reduces blood loss by inhibiting plasmin-induced fibrin breakdown. This is the first study in the United Kingdom to investigate the effectiveness of TXA in the surgical management of isolated spine trauma.

AIM

To assess the safety of TXA in isolated spine trauma. The primary and secondary outcomes are to assess the rate of thromboembolic events and to evaluate blood loss and the incidence of blood transfusion, respectively.

METHODS

This prospective observational study included patients aged ≥ 17 years with isolated spine trauma requiring surgical intervention over a 6-month period at two major trauma centers in the United Kingdom.

RESULTS

We identified 67 patients: 26 (39%) and 41 (61%) received and did not receive TXA, respectively. Both groups were matched in terms of age, gender, American Society of Anesthesiologists grade, and mechanism of injury. A higher proportion of patients who received TXA had a subaxial cervical spine injury classification or thoracolumbar injury classification score > 4 (74% *vs* 56%). All patients in the TXA group underwent an open approach with a mean of 5 spinal levels involved and an average operative time of 203 min, compared with 24 patients (58%) in the non-

TXA group who underwent an open approach with an average of 3 spinal levels involved and a mean operative time of 159 min. Among patients who received TXA, blood loss was < 150 and 150–300 mL in 8 (31%) and 15 (58%) patients, respectively. There were no cases of thromboembolic events in any patient who received TXA.

CONCLUSION

Our study demonstrated that TXA is safe for isolated spine trauma. It is challenging to determine whether TXA effectively reduces blood loss because most surgeons prefer TXA for open or multilevel cases. Further, larger studies are necessary to explore the rate, dosage, and mode of administration of TXA.

Key Words: Tranexamic acid; Infection; Trauma; Thromboembolic disease; Minimally invasive; Percutaneous

Core Tip: Since the introduction of tranexamic acid (TXA), it has been used for reducing blood loss in various surgical specialties such as Urology, general surgery, trauma and orthopedics. TXA use for elective spine surgery is well documented but there is scarce literature to explain the safety of TXA in isolated whole spine trauma. This study looks at the clinical practice of spine surgeons in two major United Kingdom trauma centres and explore the safety of TXA. The study sets the foundation for future research with larger number of patients and to improve the clinical practice.

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INTRODUCTION

Trauma is the foremost cause of mortality globally among individuals under the age of 45 years[1]. On a worldwide scale, traumatic spine injuries (TSI) are estimated to occur at a rate of 10.5 cases per 100000 people, leading to 768473 new TSI cases each year. Almost half of them (48.8%) require surgical intervention[2]. In the United Kingdom, traumatic spinal cord injuries manifest in 16 new cases per million people[3,4], with an annual report of over 1200 new cases[5].

Tranexamic acid (TXA), a synthetic antifibrinolytic drug, effectively reduces blood loss by inhibiting the plasmin-induced breakdown of fibrin[6]. Its initial application dates back to the early 1960s for managing postpartum hemorrhage [7]. Extensive randomized controlled trials (RCTs) and meta-analyses have consistently validated the safety and efficacy of TXA in various medical domains, including cardiac surgery, obstetrics, urology, orthopedics, and trauma[8-14].

Although there exists supporting evidence for the safety of TXA in elective spine procedures and complex deformity operations[15-18], the literature on the use of TXA in spinal operations due to trauma remains limited[19]. Furthermore, there is no consensus on the use and dosage of TXA in isolated spine trauma[10,9,20]. Hence, this prospective observational study marks a pioneering effort in the United Kingdom to investigate the efficacy of TXA in treating isolated spine trauma.

The primary objective of this study was to establish whether TXA administration increases the risk of thromboembolic events in patients with isolated spine trauma who underwent surgical intervention. The secondary objective was to assess the safety of TXA by evaluating blood loss and the incidence of perioperative blood transfusions.

MATERIALS AND METHODS

Study design

This was a prospective observational investigation conducted at two major trauma centers in United Kingdom. This study was registered with the local audit and quality improvement teams as a service evaluation and adhered to the principles of the Declaration of Helsinki, revised in 2013. The need for formal ethical review was determined using the National Health Service Research Ethics Committee decision tool.

Patient selection

We included patients aged ≥ 17 years who had isolated spine trauma at any level requiring surgical intervention between January 1 and June 31, 2022, across the two sites. Patients < 16 years of age and those with polytrauma and isolated spine trauma managed nonoperatively were excluded.

The sample size was calculated for two independent groups TXA and Non-TXA by using G*power software. The estimated sample size obtained from the power analysis was at least 50 respondents for group 1 and 50 respondents for group 2 respectively.

Data collection

Data collection was prospectively conducted using Google Forms with a standardized proforma divided into three sections. Section 1 captured baseline characteristics, including demographic data, comorbidities, preoperative hemoglobin (Hb) levels, mechanism of injury, level of spine involvement, subaxial cervical spine injury classification (SLIC) or thoracolumbar injury classification (TLIC) scores, and regular medications, including antithrombotic (antiplatelet or anticoagulant). Section 2 focused on surgical specifics, including the type of surgery, approach, technique (open *vs* minimally invasive), administration, dosage and regimen of TXA, intraoperative blood loss, use of cell salvage, use of a drain, and the number of units of blood transfused intraoperatively. Section 3 assessed postoperative factors, such as postoperative Hb levels, length of hospital stays, and complications such as wound breakdown, venous thromboembolism (VTE), acute kidney injury, and mortality.

Preoperative Hb levels were recorded on the basis of the most recent preoperative laboratory full blood count, whereas postoperative Hb levels were documented from the first laboratory full blood count measured postoperatively. Intraoperative blood loss (IBL) was defined as the total blood collected through suction, surgical sponges, and drapes at the end of the operation. It was categorized into four groups: < 150, 150–300, 300–500, and < 500 mL.

Statistical analysis

Quantitative data are presented as mean and standard deviation, whereas qualitative data are summarized as frequencies and percentages. Group comparisons used chi-squared or Fisher's exact test and Student's *t*-test, with statistical significance set at *P* value < 0.05.

RESULTS

Baseline characteristics

Between January 1 and June 31, 2022, 67 patients with isolated spine injuries underwent surgical intervention across both sites. These patients were categorized into two groups: those who received TXA were placed in the TXA group (n = 26, 39%), and the remaining patients were assigned to the non-TXA group (n = 41, 61%). The average age of patients in the TXA and non-TXA groups was 57 and 56 years, respectively. Both groups were similar in terms of age (P = 0.9), gender (P = 0.2), antithrombotic usage (P = 0.6), spine pathology (P = 0.45), SLIC or TLIC score (P = 0.7), and American Society of Anesthesiologists grade (P = 0.48) (Table 1).

Mechanical falls were the most frequent cause of injury in both groups. Two individuals in the non-TXA group were hospitalized because of epileptic episodes resulting in spinal fractures. Spinal fractures were the primary underlying pathology in both groups. In the TXA group, four patients were regularly taking anticoagulants (apixaban), one was on clopidogrel, and one was on aspirin. Among the patients in the non-TXA group, three were using regular aspirin. An SLIC or TLIC score of > 4 was prevalent in both groups, with a higher proportion observed in the TXA group (74% *vs* 56%, P = 0.7) (Table 1).

Surgical characteristics

Operative details for both groups are compared in Table 2. TXA use was relatively common (22%) during stabilization and fusion procedures. In the TXA group, all patients underwent open surgery, with a posterior approach used in 17 cases (65%). Meanwhile, 17 patients (41%) in the non-TXA group underwent minimally invasive surgery. Regarding the number of spine levels involved, the TXA group ranged from 2 to 9 levels, with an average of 5, whereas the non-TXA group averaged 3.4 levels (P = 0.04). When comparing the TXA and non-TXA groups, the TXA group had significantly longer operation times (P = 0.03).

Outcomes

In the TXA group, 15 patients (58%) experienced blood loss between 150 and 300 mL, compared with only four patients (10%) in the non-TXA group (Table 3). The administration of TXA was based on the surgeons' preferences. In the non-TXA group, the majority (88%) of patients had blood loss of <150 mL. Cell salvage was performed twice in the TXA group and only once in the non-TXA group. Two patients in the non-TXA group and one in the TXA group received two units of platelet transfusion during surgery, following consultations with the hematology team. These patients were on aspirin and had low platelet counts upon admission. Regarding drain placement, 21 patients (81%) in the TXA group had drains inserted postoperatively, compared with 19 patients (46%) in the non-TXA group. Drains were removed within 24 h for most patients because of minimal blood loss.

The average hospital stay was 10 d, with no significant difference between the two groups (3 d in the non-TXA group *vs* 10 d in the TXA group, P = 0.7). This variation was primarily attributed to patients with spinal cord injuries who required extended hospitalization while awaiting a bed in the spine injury units (Table 3). Preoperative Hb levels showed no significant differences between the TXA and non-TXA groups (127.5 mL *vs* 136.7 mL; range 8–15.9 g/dL *vs* 9–18 g/dL, P = 0.5) (Figure 1).

Table 4 shows regression model investigating the association between the dependent variable and three predictors: Estimated intraoperative blood loss, blood loss in drain, and TXA. The total model has a modest positive correlation (R = 0.338) and accounts for roughly 11.4% of the variability in the dependent variable, as shown by R square. The adjusted R square, accounting for the number of predictors, is 0.072. The estimate's standard error is 1.337, indicating the model's forecast precision.

Table 1 Baseline characteristics, *n* (%)

Groups	TXA group (*n* = 26)	Non-TXA group (*n* = 41)	*P* value
Demographics			
Number of patients	26	41	
Mean age (yr)	57	56	0.9
Male	15 (58)	26 (63)	0.2
Female	11 (42)	15 (36)	
Regular use of antithrombotic			
Yes	6 (23)	3 (7)	0.6
No	20 (77)	38 (93)	
Mechanism of injury			
RTA	5 (19)	4 (10)	0.45
Fall	18 (69)	34 (83)	
Other (eizures, trauma)	3 (7)	3 (7)	
Spine pathology			
Spinal fracture	23 (88)	37 (90)	0.45
Spinal cord injury	3 (11)	3 (10)	
SLIC/TLIC score			
0-3	2 (7.6)	3 (7)	0.7
4	3 (11)	14 (34)	
> 4	19 (74)	23 (56)	
Not applicable	2 (7.6)	1 (2)	
ASA grades			
Grade 4	1 (4)	3 (7)	0.48
Grade 3	9 (35)	8 (19)	
Grade 2	8 (30.6)	21 (51)	
Grade 1	8 (30.6)	9 (22)	

ASA: American Society of Anesthesiologists; RTA: Road traffic accidents; SLIC: Subaxial cervical spine injury classification; TLIC: Thoracolumbar injury classification; TXA: Tranexamic acid.

Only one patient in the TXA group received a postoperative blood transfusion because of a substantial drop in Hb from 112 to 76. This patient underwent a three-level decompression and stabilization procedure, received TXA on induction, and was not on any antithrombotic medication. In the non-TXA group, one patient experienced a postoperative drop in Hb from 110 to 95 and was managed with an iron transfusion.

Postoperative complications

In the TXA group, 14 patients (53.8%) did not experience any complications. The most common complication in this group was chest infection. Two patients tested positive for coronavirus disease 2019 (COVID-19) during their hospital stay. One patient later developed hospital-acquired pneumonia (HAP). Four other patients developed HAP, one of whom required intensive care support for noninvasive ventilation. Additionally, one patient developed type 2 respiratory failure but was deemed unfit for further interventions. Wound infections were observed in three patients, two of whom were managed using antibiotics and regular monitoring, whereas one required further wound washout in the operating theater. One patient experienced unstable liver function tests postoperatively, and the cause remained unidentified. No thromboembolic events were reported in the TXA group. However, one patient with an incomplete spine injury passed away postoperatively because of cardiovascular complications.

In the non-TXA group, two patients were diagnosed with pulmonary embolisms confirmed by computed tomography pulmonary angiograms, and one patient experienced non-ST segment elevation myocardial infarction during their hospital stay. Two patients in this group tested positive for COVID-19, and three developed pneumonia during admission. Three patients had renal complications, one of whom required an high-dependency unit stay. Additionally, two patients experienced postoperative electrolyte imbalances, necessitating medical intervention. Three patients underwent a

Table 2 Surgery characteristics, *n* (%)

Surgery characteristics	TXA group (*n* = 26)	Non-TXA group (*n* = 41)	*P* value
Type of operation			
Corpectomy + fusion	2 (7.6)	1 (2)	
Stabilization	6 (23)	24 (58)	
Decompression	1 (4)	0	
Fusion	1 (4)	1 (2)	
Stabilization + fusion	6 (23)	0	
Decompression + fusion	7 (27)	9 (22)	
Decompression + stabilization	3 (11)	6 (14)	
Approach			
Open	26 (100)	24 (58)	0.04
Minimally invasive	0	17 (41)	
Type of approach			
Anterior	8 (31)	8 (19)	0.4
Posterior	17 (65)	32 (78)	
Both	1 (4)	1 (2)	
Levels involved	4.6 (2-9)	1.4 (1–7)	0.02
Duration of surgery (min)	203 (120–428)	159 (48–540)	0.03

TXA: Tranexamic acid.

Table 3 Comparison of outcomes between the tranexamic acid and non-tranexamic acid groups, *n* (%)

Outcomes	TXA group (*n* = 26)	Non-TXA group (*n* = 41)	*P* value
Intraoperative blood loss			
< 150 mL	8 (31)	36 (88)	0.03
150-300 mL	15 (58)	4 (10)	
300-500 mL	3 (11)	1 (2)	
Intraoperative cell salvage	2 (7.6)	1 (2)	
Intra-operative transfusion	1 (4)	2 (5)	
Drain inserted	21 (81)	19 (46)	
Time of drain removal			
24 h	11 (42)	14 (34)	0.002
48 h	9 (35)	5 (12)	
> 48 h	1 (4)	0	
Admittance to discharge (d)	10	3	0.7

TXA: Tranexamic acid.

second operation: two for revision of screws on postoperative day 1 because both patients experienced altered neurology due to screws in the spinal cord. Another patient had wound dehiscence, necessitating further debridement and closure. On postoperative day 3, one patient in the non-TXA group developed headaches, photophobia, dizziness, and tinnitus after a suspected cerebrospinal fluid leak. This patient was thoroughly evaluated by the neurology team and conservatively managed. Another patient had a localized hematoma that was conservatively treated following anterior cervical decompression and fusion. There was no reported mortality in the non-TXA group.

Table 4 Regression analysis

Model	R	R square	Adjusted R square	Std. Error of the estimate
1	0.338[1]	0.114	0.072	1.337

[1]Predictors: Constant, estimated intraoperative blood loss, blood loss in drain, tranexamic acid.

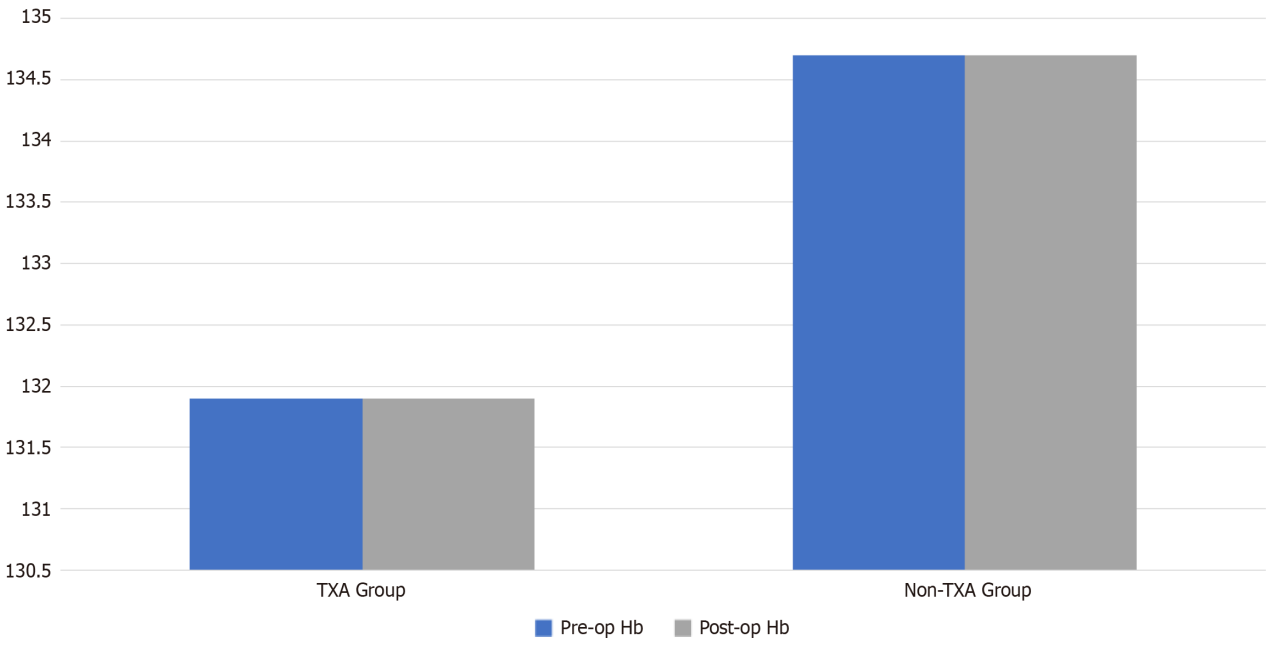

Figure 1 Comparison of pre- and day 1 post-op hemoglobin in both groups. Hb: Hemoglobin; TXA: Tranexamic acid.

DISCUSSION

This study represents the first reported investigation into the effectiveness of TXA in cases of isolated whole-spine trauma. The administration of TXA was based on surgeons' preferences, with a tendency toward open surgical approaches associated with higher anticipated intraoperative blood loss, particularly in cases of severe injuries, multilevel involvement, and in patients on regular antithrombotic medications. Notably, no thrombotic complications were reported intraoperatively in the TXA group, indicating the safety of TXA use in isolated spine trauma cases. Furthermore, only one patient required postoperative blood transfusion. In our study, we did not find any significant difference in the patients' groups in terms of gender or ethnicity.

This study serves as a preliminary exploration of the potential use of TXA in isolated spine injuries. Multiple RCTs have previously demonstrated the efficacy of TXA in elective spine surgery[9] and thoracolumbar burst fractures[21]. These trials have shown a reduction in intraoperative and total blood loss in patients with TXA. However, there remains a lack of consensus in the literature regarding the optimal TXA administration regimen[15]. The literature indicates that TXA can be administered in various forms, including intravenously and topically or as an infusion. A meta-analysis by Xiong *et al*[16] reported no significant difference in outcomes between intravenous and topical TXA administration. In this study, the choice of TXA administration regimen was left to the surgeons' preferences, with 1 g of intravenous TXA administered upon induction in the TXA group.

Interestingly, in our study, we observed that surgeons did not use TXA for two-level cervical decompressions and fusions, which could be due to the expectation of lower blood loss in cervical procedures and aligns with the findings of an RCT by Elwatidy *et al*[22], who found no significant difference in blood loss with TXA use in cervical operations. However, in our study, the TXA group included cases involving multiple cervical spine levels (3–6) for fusion and decompression, where TXA was deemed necessary because of a higher risk of bleeding when multiple levels were involved. There are limited available data on the use of TXA in isolated cervical spine trauma. A prospective, randomized study on three cervical spine levels reported a significant reduction in blood loss during cervical laminoplasty surgery using TXA[23]. Our study found no significant difference in the number of levels operated on between the two groups, which contradicts the findings of Colomina *et al*[9] in elective settings. Individual data indicate that surgeons tend to prefer an open technique for decompression and stabilization surgeries involving more than three levels. There is also limited literature available regarding the use of TXA in open *vs* minimally invasive spine surgery approaches. In our study, TXA was administered for cases performed *via* an open approach but not for minimally invasive surgery, consistent with cases where blood loss was < 150 mL in two-level fracture fixations, and patients did not require a drain or experience postoperative issues. Despite the variability in levels involved in the TXA group, our investigation

identified a significant difference (P = 0.03) in the duration of surgery between the two groups, aligning with the findings of Shen *et al*[21] for thoracolumbar burst fractures and elective spine operations[9].

An increasing number of meta-analyses of RCTs have emphasized the blood-saving effects of TXA in spine surgery [24]. Shen *et al*[21] demonstrated a significant reduction in blood loss in the TXA group of 39 patients undergoing surgery for thoracolumbar burst fractures compared with the placebo group. They reported reductions in total blood loss, IBL, and postoperative blood loss in the TXA group (P = 0.001), whereas hidden blood loss (HBL) remained similar between the TXA and placebo groups (P = 0.08). HBL was calculated using a formula rather than a direct measurement[21]. These findings contrast with an earlier study by Sudprasert *et al*[19], who found no significant difference (P = 0.8) in a cohort of 29 patients with thoracolumbar trauma undergoing posterior fusion and receiving topical TXA. Our findings align with the results of Sudprasert *et al*[19] because we found no significant reduction in IBL in the two groups. Zhang *et al*[25] conducted a meta-analysis of 11 studies involving multilevel elective spine surgery in 2019 and reported that intravenous TXA effectively reduced IBL. In contrast, Elmose *et al*[26] found that intravenous TXA had no statistically significant impact on IBL, operative time, or complications during minor lumbar spine surgery. We understand that all these studies show variation in results and lack consensus on the usage of TXA in spinal patients. Additional research is warranted to better understand the use of TXA in spine trauma cases.

In our study, two patients in the TXA group received cell salvage, and platelets were transfused intraoperatively. One patient also required a blood transfusion during surgery. These findings are consistent with a meta-analysis of seven studies conducted by Yang *et al*[15] and the results reported by Sudprasert *et al*[19] for thoracolumbar trauma. Multiple studies[15,19,21,27] have shown a significant decrease in drain blood loss and the average time to drain removal. However, our study did not identify any difference in the time for drain removal, which may be attributed to the fact that patients in the TXA group underwent multilevel spine surgery, leading to the surgeon's preference for keeping the drain. To date, there has been limited research on postoperative Hb levels. Our study found no significant difference in Hb levels before the operation and on day 1 Hb level postoperative.

Limitations

This study has subject to several limitations. Data were collected over 6 months, resulting in a sample size of 67 patients. The exclusion of patients with missing data introduced some heterogeneity into the study, including variations in spine levels and diverse surgical techniques performed by approximately 15 different surgeons across two distinct centers. As an observational study, it carries inherent confounding risks when patients who received TXA are compared with those who did not, given the absence of randomization. Factors such as the type of surgery, surgical approach, levels, preoperative Hb levels, and the operating surgeon could introduce confounding effects. The use of TXA was at the discretion of the surgeons, typically for patients at a high risk of bleeding or undergoing multilevel surgery.

There could be a potential for inaccuracy of the first postoperative Hb value; the results may be affected by intravenous crystalloid-induced hemodilution during the intraoperative period. Instead of precise IBL values, we categorized the data into four distinct ranges, accounting for blood loss through surgical sponges and drapes. Data on blood loss in the drain were not collected for all patients, which contributed to the limitation.

When assessing the postoperative risks of VTE during the hospital stay, we considered the intraoperative administration of both mechanical and chemical thromboprophylaxis. This study included patients who regularly used antithrombotic medications but did not provide information regarding the duration of medication use or whether it was discontinued before surgery.

CONCLUSION

Our study indicates that TXA can be safely used in cases of isolated spine trauma, with no evidence of an elevated risk of blood transfusion or VTE in either group. However, it is challenging to definitively conclude from this study whether TXA effectively reduces blood loss because TXA was predominantly used in open or multilevel surgical cases. To establish the full extent of the efficacy of TXA in isolated spine trauma, further research is warranted to compare its effectiveness across open *vs* minimally invasive techniques and in cases involving single *vs* multilevel procedures.

ARTICLE HIGHLIGHTS

Research background

There is no data looking at safety of the tranexamic acid (TXA) in the surgical management of isolated whole spine trauma. This study sets the foundation for the future research work.

Research motivation

This is the only study looking at the safety of TXA in surgically treated isolated whole spine trauma. There is no consensus on the administration, dosage and route of TXA delivered for these injuries.

Research objectives

The overall objective of this study is to look at the safety of the TXA in surgically treated isolated whole spine trauma.

Research methods
This prospective observational study included patients aged ≥ 17 years with isolated spine trauma requiring surgical intervention over a 6-month period at two major trauma centers in the United Kingdom. We used SPSS for statistical analysis.

Research results
We identified 67 patients: 26 (39%) and 41 (61%) received and did not receive TXA, respectively. Both groups were matched in terms of age, gender, American Society of Anesthesiologists grade, and mechanism of injury. A higher proportion of patients who received TXA had a subaxial cervical spine injury classification or thoracolumbar injury classification score > 4 (74% *vs* 56%). All patients in the TXA group underwent an open approach with a mean of 5 spinal levels involved and an average operative time of 203 min, compared with 24 patients (58%) in the non-TXA group who underwent an open approach with an average of 3 spinal levels involved and a mean operative time of 159 min. Among patients who received TXA, blood loss was < 150 and 150–300 mL in 8 (31%) and 15 (58%) patients, respectively. There were no cases of thromboembolic events in any patient who received TXA.

Research conclusions
We concluded that TXA is safe for isolated spine trauma. It is challenging to determine whether TXA effectively reduces blood loss because most surgeons prefer TXA for open or multilevel cases.

Research perspectives
This study sets the foundation for further research trials in patients with isolated spine trauma managed with surgical intervention.

FOOTNOTES

Author contributions: Zahra W, Nayar SK, and Bhadresha A contributed to data collection; Zahra W and Nayar SK contributed to data analysis; Jasani V and Aftab S contributed to supervision; Zahra W, Jasani V and Aftab S contributed to project idea; Zahra W contributed to writing the manuscript and literature review; Nayar SK contributed to review the manuscript; Jasani V and Aftab S contributed to overall supervision.

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ORIGINAL ARTICLE

Prospective Study

Long-term assessment of collagenase treatment for Dupuytren's contracture: A 10-year follow-up study

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Abstract

BACKGROUND

Enzymatic fasciotomy with collagenase clostridium histolyticum (CCH) has revolutionized the treatment for Dupuytren's contracture (DC). Despite its benefits, the long-term outcomes remain unclear. This study presented a comprehensive 10-year follow-up assessment of the enduring effects of CCH on patients with DC.

AIM

To compare the short-term (12 wk) and long-term (10 years) outcomes on CCH treatment in patients with DC.

METHODS

A cohort of 45 patients was treated with CCH at the metacarpophalangeal (MCP) joint and the proximal interphalangeal (PIP) joint and underwent systematic re-evaluation. The study adhered to multicenter trial protocols, and assessments were conducted at 12 wk, 7 years, and 10 years post-surgery.

RESULTS

Thirty-seven patients completed the 10-year follow-up. At 10 years, patients treated at the PIP joint exhibited a 100% recurrence. However, patients treated at the MCP joint only showed a 50% recurrence. Patient satisfaction varied, with a

lower satisfaction reported in PIP joint cases. Recurrence exceeding 20 degrees on the total passive extension deficit was observed, indicating a challenge for sustained efficacy. Significant differences were noted between outcomes at the 7-year and 10-year intervals.

CONCLUSION

CCH demonstrated sustained efficacy when applied to the MCP joint. However, caution is warranted for CCH treatment at the PIP joint due to a high level of recurrence and low patient satisfaction. Re-intervention is needed within a decade of treatment.

Key Words: Collagenase; Xiapex; Dupuytren disease; Dupuytren recurrence; Long term follow-up

Core Tip: Collagenase has shown efficacy in the treatment of Dupuytren's contracture (DC). While its short-term effectiveness is well-documented in the existing literature, there is an absence of studies addressing the long-term outcomes of collagenase treatment of DC. The objectives of this study were to compare the short-term and long-term (10 years) outcomes and to assess the satisfaction with the treatment in 45 subjects enrolled in a phase 3 study in 2012.

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INTRODUCTION

Patients with Dupuytren's contracture (DC), also known as palmar fibromatosis, experienced a significant breakthrough for treatment in the early 21st century. This advancement was marked by the introduction of the enzymatic fasciotomy technique, which is a novel approach involving the infiltration of the fibrous cord with collagenase derived from collagenase clostridium histolyticum (CCH)[1-5]. In contrast to traditional surgical procedures, enzymatic fasciotomy is a less invasive alternative[5-11]. However, the long-term outcomes of this innovative technique are unknown due to its recent introduction and the scarcity of studies with extended follow-up periods[6-9,12-18].

There is a growing trend of re-assessing patients who underwent enzyme fasciotomy[5]. Notably, it has been observed that some individuals treated with this technique have not experienced sustained long-term benefits. In 2012, our institution enrolled 45 patients into a phase 3 study to receive CCH for the treatment of DC with palpable cord manifestations. A comprehensive 7-year follow-up revealed a recurrence of the disease, particularly among patients who were treated at the proximal interphalangeal (PIP) joint. Additionally, there was evidence of recurrence in patients who were treated at the metacarpophalangeal (MCP) joint[6]. The aim of this study was to compare the outcomes observed at 12 wk post-treatment with those documented over a 10-year follow-up period.

MATERIALS AND METHODS

This study was part of a multicenter trial aligned with the Ministry of Health Decree of May 8, 2003 and was carried out at the Unit of Orthopaedics and Surgery of the Hand at the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome (Ethics Committee Protocol P/488-857-872-1041-1113/CE/2012)[3]. Initiated in January 2012, the study involved 45 patients receiving CCH injection for the treatment of DC with palpable cord manifestations. The primary focus was to evaluate the long-term (10 years) clinical outcomes following CCH treatment in individuals diagnosed with DC.

Inclusion and exclusion criteria

The inclusion and exclusion criteria of the prospective study are listed in Table 1. Within the framework of the present investigation, all individuals who had been previously subjected to a comprehensive review during the 7-year follow-up were systematically contacted. Those re-examined at 10 years after treatment underwent assessments encompassing both goniometric and clinical parameters.

Treatment

The surgery procedure was conducted by experienced hand surgeons injecting the appropriate drug quantity into the affected cords. A sterile dressing was applied, and patients were told to refrain from finger extension. The following day, a forced extension disrupted the pathologic cord, and a thermoplastic splint was applied for 7 d continuously followed by 12 h each day for an additional 7 d. Evaluations were conducted before treatment and 7 d after the procedure by the

Table 1 Inclusion and exclusion criteria of the prospective study

Inclusion criteria	Exclusion criteria
DC with a PED of at least 20° at MCPJ and any degree at PIPJ	Breastfeeding or pregnant (or planning to be) during the treatment phase
No oral anticoagulant therapy; patient in therapy with anti-platelet drugs (discontinued for at least 7 d before treatment)	Undergoing any treatment of the affected hand up to 90 d prior to commencement of the trial
Positive table-top test (a patient fails to lay the palm of the hand and the fingers flat on a table surface)	Known systemic hypersensitivity to collagenase or any of the other components of the product
TPED ≥ 45° (that is greater than or equal to the second stage according to the Tubiana-Michon classification)	Presence of other psychiatric or organic conditions that could jeopardize the patient's compliance
Palpable cord	
Informed consent from the patient	
Consent for examination according to the plan	

DC: Dupuytren's contracture; PED: Passive extension deficit; MCPJ: Metacarpophalangeal joint; PIPJ: Proximal interphalangeal joint; TPED: Total passive extension deficit.

surgeon and a physiotherapist. The 10-year follow-up was conducted by the same treating surgeon.

Data collection and follow-up

Passive extension deficit (PED) and total PED (TPED) measurements were recorded before treatment and 12 wk, 7 years, and 10 years after treatment. Additionally, the recurrence rate of the disease at 7 years after treatment was assessed. Recurrence was characterized as a postoperative angular deformity exceeding 20° in at least one of the treated joints accompanied by the presence of a detectable cord[10,11]. Recurrence could be accompanied by a loss of hand function necessitating further intervention. The overall satisfaction of participants was appraised using a 10-point scale known as the general satisfaction index administered during the 10-year follow-up visit.

In light of recent advancements in patient-reported outcome measures, our patients underwent evaluation utilizing the Michigan Hand Questionnaire (MHQ) and the Unité Rhumatologique des Affections de la Main Scale (URAM Scale)[19,20].

End points

The primary endpoint of the study was assessment of the long-term efficacy and the occurrence of significant disease recurrence at the 10-year follow-up. The secondary outcomes included evaluating sustained functionality at the 7-year follow-up and assessing general satisfaction with the received treatment.

Statistical analysis

The presented data encompassed mean values and standard deviations, with precision limited to a single decimal digit. Parametric data were subjected to comparative analysis using the Student's *t* test, while non-parametric data underwent analysis *via* the Mann-Whitney test or Wilcoxon test. Significance levels were set at $P < 0.05$. The statistical analyses were conducted using GraphPad Software Prism 8 for Mac (La Jolla, CA, United States).

RESULTS

For the initial study, 45 patients (38 males and 7 females) were enrolled. At the 7-year follow-up, 3 patients required surgical treatment before completing the established follow-up due to an unsatisfactory clinical result. Two patients died and did not complete the 7-year follow-up assessment. At the 10-year follow-up, an additional 2 patients did not complete the assessment. Therefore, 37 patients were included in the current study. Patients were categorized by treatment in the MCP joint or in the PIP joint.

Patients treated at the MCP joint

There were 31 patients treated at the MCP joint (10-year PED: 11.5 ± 11.4; range: 0-30). Nine patients (29.0%) had a recurrence on the treated joint (Figure 1 and Table 2). Seventeen patients (54.8%) had a worse TPED due to recurrence of disease by PIP joint involvement (10-year TPED: 25.8 ± 10.9; range: 0-50). Overall patient satisfaction was 6.7 ± 1.7. The mean MHQ score was 80 ± 21. The mean URAM score was 59 ± 19. A statistically significant difference was observed when comparing the outcomes at the 7-year follow-up and at the 10-year follow-up for PED ($P = 0.00222$) and TPED ($P < 0.00001$).

Table 2 Results for patients injected at the metacarpophalangeal joint

Patient	MCPJ PED in degrees				MCPJ TPED in degrees				10-yr recurrence
	Before	12 wk	7 yr	10 yr	Before	12 wk	7 yr	10 yr	
1	60	0	0	5	70	10	10	25	Yes
2	75	0	5	5	75	10	10	25	Yes
3	50	0	5	5	50	5	10	15	No
4	45	0	0	0	60	10	10	20	No
5	45	0	5	5	55	10	10	15	No
6	90	0	5	30	100	10	10	40	Yes
7	50	0	5	5	50	5	10	15	No
8	50	0	5	5	50	5	10	15	No
9	45	0	5	10	95	10	10	20	No
10	70	0	5	35	75	10	10	40	Yes
11	70	0	0	0	70	10	10	10	No
12	45	5	5	5	50	5	10	15	No
13	45	5	5	10	45	10	10	20	No
14	50	5	5	5	50	10	15	40	Yes
15	50	0	5	5	50	5	5	15	No
16	45	5	10	10	45	10	10	20	No
17	45	0	5	5	45	5	10	25	Yes
18	70	5	0	0	80	10	10	30	Yes
19	50	0	5	25	50	10	15	40	Yes
20	45	0	5	25	45	10	10	40	Yes
21	80	0	5	5	95	10	10	30	Yes
22	45	5	5	25	45	10	20	50	Yes
23	50	0	0	0	45	10	10	30	Yes
24	45	5	5	5	45	15	10	15	No
25	45	0	5	5	45	5	10	35	Yes
26	45	0	5	25	45	10	10	40	Yes
27	65	5	10	30	65	10	25	30	Yes
28	45	5	15	30	45	10	10	30	Yes
29	50	0	0	0	50	5	10	10	No
30	45	5	5	5	55	10	10	15	No
31	45	0	15	30	55	10	10	30	Yes
mean ± SD	60	0	0	5	70	10	10	25	N/A
	75	0	5	5	75	10	10	25	N/A

MCPJ: Metacarpophalangeal joint; PED: Passive extension deficit; TPED: Total passive extension deficit; N/A: Not applicable; SD: Standard deviation.

Patients treated at the PIP joint

There were 6 patients treated at the PIP joint (10-year PED: 41.7 ± 5.2; range: 35-50). All patients experienced recurrence at the treated joint (Figure 2 and Table 3). All patients had a worse TPED due to recurrence of the disease by PIP joint involvement (10-year TPED: 56.7 ± 8.2; range: 50-70). Overall patient satisfaction was 5.0 ± 0.6. The mean MHQ score was 70 ± 15. The mean URAM score was 63 ± 16. The sample size (n = 6) did not meet the criteria for the Wilcoxon test to approximate normality. Therefore, accurate computation of a P value was not feasible.

Table 3 Results for patients injected at the proximal interphalangeal joint

Patient	PIPJ PED in degrees				PIPJ TPED in degrees				10-yr recurrence
	Before	12 wk	7 yr	10 yr	Before	12 wk	7 yr	10 yr	
32	50	10	30	40	50	10	15	50	Yes
33	65	10	20	40	70	10	15	50	Yes
34	70	20	25	50	70	20	25	60	Yes
35	65	10	20	40	65	10	20	50	Yes
36	60	15	20	45	70	10	15	70	Yes
37	90	15	20	35	95	15	15	60	Yes
mean ± SD	66.7	13.3	22.5	41.7	70.0	12.5	17.5	56.7	N/A
	13.3	4.1	4.2	5.2	14.5	4.2	4.2	8.2	N/A

PIPJ: Proximal interphalangeal joint; PED: Passive extension deficit; TPED: Total passive extension deficit; N/A: Not applicable; SD: Standard deviation.

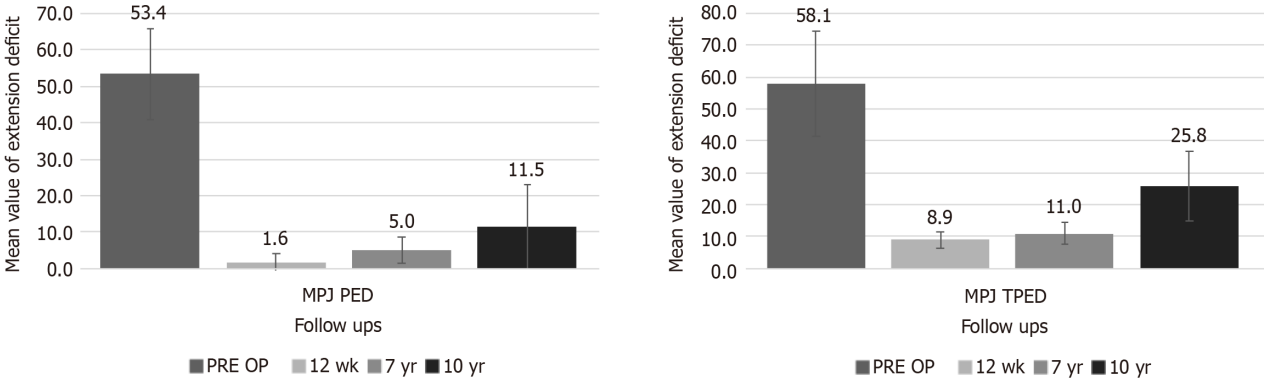

Figure 1 Results for patients injected at metacarpal-phalangeal joints level reported in Table 2. All numerical data are reported in degrees. Standard deviations are reported as interval. MPJ: Metacarpal-phalangeal joints; PED: Passive extension deficit; TPED: Total passive extension deficit; PRE OP: Pre operative.

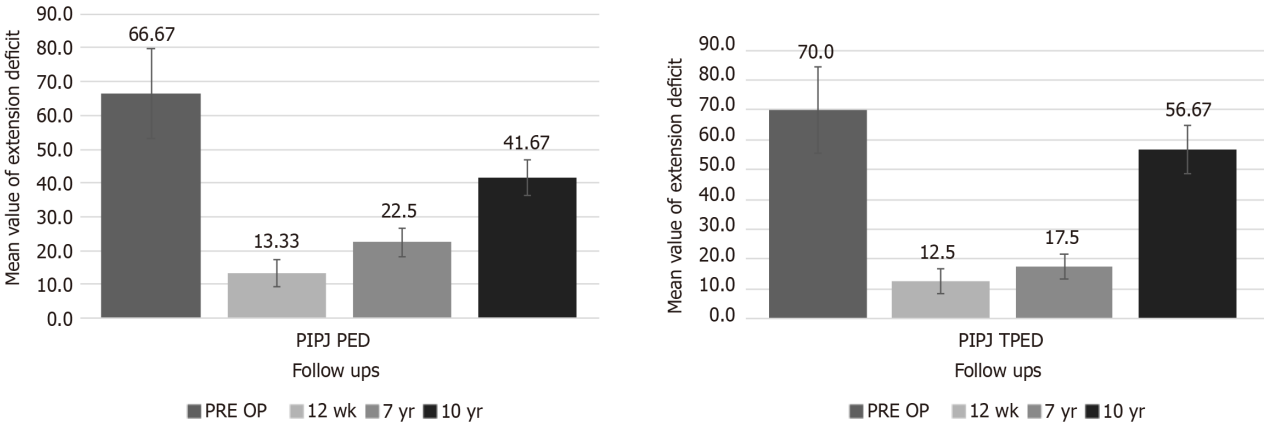

Figure 2 Results for patients injected at proximal inter-phalangeal joints level reported in Table 3. All numerical data are reported in degrees. Standard deviations are reported as interval. PIPJ: Proximal inter-phalangeal joints; PED: Passive extension deficit; TPED: Total passive extension deficit; PRE OP: Pre operative.

DISCUSSION

This investigation represents one of the longest follow-up studies demonstrating the efficacy of enzymatic fasciotomy. It should be noted that during this follow-up study, collagenase was removed from the European market, but not due to safety or efficacy issues. The data from this 10-year follow-up, along with data from the 7-year follow-up[6], has revealed novel findings for the use of collagenase in the treatment of DC. Our results mostly align with trends observed in other studies with shorter follow-up periods[6,12-18].

Previous studies with extended follow-ups have already reported instances of disease recurrence. Zhang *et al*[12] documented a recurrence rate of 80% and the necessity for re-intervention in 53% of cases after a minimum of 5 years of follow-up. Similarly, Göransson *et al*[14] reported a 5-year recurrence rate of 50% that was accompanied by high patient satisfaction. Our previous study, evaluating the population 7 years after treatment[6], revealed that 86.7% of PIP joint-treated patients and 65.6% of MCP joint-treated patients experienced recurrence of the contracture. Notably, 86.7% of patients concluded treatment after a single collagenase injection despite subsequent recurrences[6].

Our analysis adhered to the international consensus definition of recurrence[11], which revealed that 54.8% of patients exhibited a deterioration of more than 20 degrees of TPED in the MCP joints. According to this criterion, 100% of patients treated at the PIP joint experienced a recurrence. Additionally, if we included patients with 20 degrees of TPED (the lower limit of recurrence definition), the recurrence rate would reach 67.7%. Notably, no patient exhibited a TPED of zero at the 10-year follow-up. In addition, our evaluation did not account for the potential activation of the disease in untreated fingers.

The recurrence is likely due to DC pathophysiology and the nature of CCH treatment. While CCH enables cord lysis, it does not eliminate a substantial portion of pathological aponeurosis, which allows the persistence of pathological collagen. There is limited evidence suggesting that CCH induces inflammatory stimulation, potentially activating the generation of further pathological collagen.

Despite these challenges, patients generally express satisfaction with the treatment, particularly when applied to the MCP joint. Conversely, patients treated at the PIP joint exhibited lower satisfaction levels, necessitating further treatment in most cases.

Given our findings, we would recommend collagenase treatment for palpable cords at the MCP joint if it were currently available. We also recommend cautioning patients about the potential for recurrence. Conversely, we do not recommend CCH application at the PIP joint due to low patient satisfaction, the high recurrence rate, and the need for re-intervention within 10 years.

Our study had some limitations, including result disparities between the MCP joint and PIP joint, and a 17.6% loss to follow-up from the initial sample of 45 patients. The deterioration observed in this case series underscores the importance of re-evaluating cases beyond the typical 5-year follow-up.

CONCLUSION

The use of CCH in treating DC is recommended when applied to palpable cords at the MCP joint. The benefits of the treatment are the non-invasiveness and the rapid postoperative recovery. However, patients should be informed of the risk of recurrence.

ARTICLE HIGHLIGHTS

Research background

Dupuytren's contracture (DC), also known as palmar fibromatosis, has been shown to be successfully treated with enzymatic fasciotomy. This novel approach involves the injection of collagenase derived from collagenase clostridium histolyticum (CCH) into a fibrous cord causing DC.

Research motivation

In contrast to traditional surgical procedures, enzymatic fasciotomy is a less invasive alternative. However, the long-term outcomes of this innovative technique remain largely unexplored. Recently, there has been a growing trend of re-assessing patients who underwent enzymatic fasciotomy. Notably, it has been observed that not all individuals treated with this technique have experience long-term efficacy.

Research objectives

This study compared the short-term (12 wk) and long-term (10 years) outcomes of CCH treatment of DC.

Research methods

This was a prospective study that was part of a multicenter trial conducted in a university hospital beginning in 2012. Our institution conducted 45 injections of CCH for the treatment of DC with palpable cord manifestations. A comprehensive 7-year follow-up revealed a recurrence of the disease, particularly among patients injected at the proximal interphalangeal (PIP) joint. Additionally, there was evidence of disease recurrence in patients injected at the metacarpo-

phalangeal (MCP) joint.

Research results

When CCH was injected at the PIP joint, 100% of patients experienced recurrence at 10 years. When CCH was injected at the MCP joint, over 50% of patients experienced recurrence after 10 years. There was a statistically significant difference in passive extension deficit (PED) and total PED when comparing the outcomes at the 7-year follow-up and the 10-year follow-up.

Research conclusions

The use of CCH for the treatment of DC is recommended when applied to palpable cords at the MCP joint. However, patients should be informed of the risk of recurrence. We do not recommend CCH for the treatment of DC at the PIP joint due to low patient satisfaction, the high rate of recurrence, and the need for re-intervention within 10 years.

Research perspectives

The deterioration observed in our case series underscores the importance of re-evaluating cases beyond the typical 5-year follow-up. Further long-term studies are required to completely evaluate the long-term efficacy of CCH for the treatment of DC.

FOOTNOTES

Author contributions: Passiatore M wrote the manuscript; Cilli V, Cannella A, Caruso L, and Sassara GM participated in acquisition, analysis, and interpretation of the data; Taccardo G was the guarantor, designed the study, and performed the surgical treatments; De Vitis R designed the study and performed the surgical treatments; Taccardo G and De Vitis R critically revised the article for important intellectual content; All authors read and approved the final manuscript.

Institutional review board statement: This prospective study was approved by the local ethics committee (Ethics Committee Protocol P/488-857-872-1041-1113/CE/2012).

Clinical trial registration statement: This study is registered at ClinicalTrial.Gov. The registration identification number is NCT01229436.

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ORIGINAL ARTICLE

Basic Study

Exercise promotes osteogenic differentiation by activating the long non-coding RNA H19/microRNA-149 axis

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Abstract

BACKGROUND

Regular physical activity during childhood and adolescence is beneficial to bone development, as evidenced by the ability to increase bone density and peak bone mass by promoting bone formation.

AIM

To investigate the effects of exercise on bone formation in growing mice and to investigate the underlying mechanisms.

METHODS

20 growing mice were randomly divided into two groups: Con group (control group, $n = 10$) and Ex group (treadmill exercise group, $n = 10$). Hematoxylin-eosin staining, immunohistochemistry, and micro-CT scanning were used to assess the bone formation-related indexes of the mouse femur. Bioinformatics analysis was used to find potential miRNAs targets of long non-coding RNA H19 (lncRNA H19). RT-qPCR and Western Blot were used to confirm potential miRNA target genes of lncRNA H19 and the role of lncRNA H19 in promoting osteogenic differentiation.

RESULTS

Compared with the Con group, the expression of bone morphogenetic protein 2 was also significantly increased. The micro-CT results showed that 8 wk moderate-intensity treadmill exercise significantly increased bone mineral density, bone volume fraction, and the number of trabeculae, and decreased trabecular segregation in the femur of mice. Inhibition of lncRNA H19 significantly upregulated the expression of miR-149 and suppressed the expression of markers of osteogenic differentiation. In addition, knockdown of lncRNA H19 significantly downregulated the expression of autophagy markers, which is consistent with the results of autophagy-related protein changes detected in mouse femurs by immunofluorescence.

CONCLUSION

Appropriate treadmill exercise can effectively stimulate bone formation and promote the increase of bone density and bone volume in growing mice, thus enhancing the peak bone mass of mice. The lncRNA H19/miR-149 axis plays an important regulatory role in osteogenic differentiation.

Key Words: Exercise; Osteogenic differentiation; Bone formation; Bone mesenchymal stem cells; Autophagy

Core Tip: Adolescence is a critical period for laying the foundation for optimal peak bone mass in adulthood. Studies have shown that pre-puberty and early puberty are the periods when bones are most responsive to mechanical loading. It is essential to explore the effect of exercise on promoting bone formation in adolescence and its underlying mechanisms. In this paper, we explored the promotional effects of treadmill exercise on bone formation in growing mice and further explored the underlying mechanisms. Our results validate that moderate intensity running exercise is effective in stimulating bone formation and promoting increases in bone mineral density and bone mass, thereby enhancing peak bone mass in growing mice. Notably, the long non-coding RNA H19 (lncRNA H19)/microRNA-149 (miR-149) axis plays an important regulatory role in the osteogenic differentiation of bone mesenchymal stem cells. Overall, this paper emphasizes that exercise may promote bone formation in mice through the lncRNA H19/miR-149 axis, which may be closely related to the activation of autophagy.

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INTRODUCTION

Bone tissue is a dense connective tissue that is part of the endoskeleton of vertebrates. Physiologically, bone is subjected to a dynamic mechanical environment of continuous remodeling through two coordinated and synchronized processes, including osteoblast-driven bone formation and osteoclast-driven bone resorption, which help the bone to develop an optimized morphological structure to adapt to changing loads and maintain homeostasis[1]. As a typically mechanically responsive tissue, bone can respond to stimuli of mechanical loading: physiological loading induces bone formation, whereas lack of loading or overloading can lead to bone resorption[2,3]. Mechanical loading is a major regulator of bone formation and resorption, playing a crucial role in the metabolic homeostasis of bone[4,5].

Osteoporosis is one of the most serious health problems in older women. Current strategies to prevent osteoporosis in women focus on increasing peak bone mass at skeletal maturity and reducing bone loss in midlife and late menopause[6,7]. Previous studies have demonstrated that 25%-40% of adult bone mass is gained during puberty, a critical period for laying the foundation for optimal peak bone mass in adulthood[8], which helps to reduce the chances of osteoporosis in old age[9,10]. Regular physical activity during childhood and adolescence is beneficial for musculoskeletal development, and its beneficial effects can continue into adulthood and even old age[11,12]. Therefore, exercising at an appropriate intensity during adolescence is crucial for increasing peak bone mass. Currently, however, there is a lack of clarity regarding the underlying mechanisms by which exercise promotes bone formation during puberty.

Long non-coding RNAs (lncRNAs) are by-products of RNA polymerase II transcription, a group of non-coding transcripts ≥ 200 nucleotides in length, which do not have the function of coding proteins[13,14]. Unlike microRNAs (miRNAs), which are non-coding RNAs that do not encode proteins, lncRNAs can fold into complex secondary or higher spatial structures, allowing for better target recognition[15]. Accumulating studies have shown that lncRNAs can regulate the expression of protein-coding genes epigenetically, transcriptionally, and post-transcriptionally, thereby affecting a range of biological processes, including the regulation of bone metabolism[16,17]. Studies have shown that lncRNAs exhibit the following three functions during osteogenic differentiation: (1) Regulating osteogenic differentiation by mediating epigenetic modifications; (2) Regulating osteogenic differentiation through signaling pathways; and (3) Regulating osteogenic differentiation by acting as miRNA sponges or precursor structures[18,19]. Some of the lncRNAs

were found to be mechanosensitive and regulated by mechanical stress, including lncRNA H19[20-22]. LncRNA H19, located on human chromosome 11p15.5, is one of the best-known imprinted genes[23,24]. LncRNA H19 was found to be highly expressed in adult muscle tissues and upregulated during differentiation and regeneration of adult myoblasts[25]. In addition, lncRNA H19 may be involved in the regulation of atherosclerosis[26], myocardial injury[27], and osteogenic differentiation[28]. It has been shown that inhibition of lncRNA H19 promotes osteogenic differentiation of human adipogenic stem cells[29]. However, another study found that lncRNA H19 deficiency could inhibit osteogenic differentiation of bone mesenchymal stem cells (BMSCs)[30,31]. The possible reason for this is the difference in stem cell types. In addition, simple *ex vivo* experiments cannot adequately reflect the complex biological response processes in organisms. Therefore, the potential regulatory role of lncRNA H19 in osteogenic differentiation needs to be further elucidated.

Our previous study found that exercise protects against cartilage damage in mice by upregulating lncRNA H19[22]. Since bone is also a major effector organ of mechanical exercise, we hypothesized that exercise may promote osteogenic differentiation by modulating lncRNA H19 expression. Based on the clinical experience of exercise therapy to promote peak bone mass and the foundation of our team's previous research, this study aimed to observe the effect of moderate-intensity treadmill exercise to promote bone formation in growing-age mice and to further investigate the regulatory role of lncRNA H19 in this process, which is of great significance for bone health in the general population and for the development of new strategies for the treatment of bone-related diseases.

MATERIALS AND METHODS

Animal experiments

All procedures of this study were reviewed and approved by the Ethics Committee of Exercise Science Experiment of Beijing Sport University (Approval No. 2023026A). Twenty 3-wk-old female C57BL/6 mice were purchased from Beijing Huafukang Bio-technology Co. Ltd. and housed in an SPF-class animal laboratory environment with temperature and relative humidity at (22 ± 2) °C and 55%-75%. Normal circadian rhythms were administered. All mice are allowed to move freely within the cage. Adaptive feeding of mice for one week is required before the formal experiment begins.

After the end of adaptive feeding, twenty mice were randomly divided into two groups: Con group (control group, n = 10) and Ex group (treadmill exercise group, n = 10). Mice in the Con group were free to move around the cage, while mice in the Ex group were forced to perform treadmill exercises. The treadmill exercise program was developed based on the experience of our group's previous research[22,32,33]. The protocol during the formal treadmill exercise experiment was one hour per day, five days per week, for a total of eight weeks. It should be noted that during the formal experiment, the speed was gradually increased from 5 m/min to 15 m/min in the first five minutes at the beginning of each running exercise, followed by running at a constant speed of 15 m/min for 50 min, and the speed was gradually reduced from 15 m/min to 0 m/min in the last five minutes at the end of the running exercise. The specific treadmill running program is shown in Table 1. After eight weeks of treadmill running training, all mice were anesthetized by inhalation of isoflurane and subjected to neck transection. Before sacrifice, all mice were fed water without feeding for 24 h. No mice showed abnormal mortality in this experiment.

Hematoxylin-eosin staining

After PFA fixation, the mouse femur was placed in EDTA decalcification solution for 2-3 wk for decalcification. The decalcification solution was changed every other day. The standard for complete decalcification is that the needle tip of the syringe can easily penetrate the cortical bone. The samples were then dehydrated, transparent, waxed, embedded in a tissue wax block, and finally sectioned (4 μm per section). Subsequently, routine hematoxylin-eosin (HE) staining was performed according to the instructions. After staining, the sections were observed and photographed under an inverted optical microscope.

Immunohistochemical staining

Mouse femur paraffin sections were placed in a 60 °C oven for 30 min and then subjected to treatment with xylene, xylene, xylene, 100% ethanol, 95% ethanol, and 80% ethanol. After dewaxing, antigen repair, blocking, primary antibody incu-bation, secondary antibody incubation, and DAB staining were performed. The staining process was terminated after positive expression was observed under the microscope. Subsequently, the nucleus was stained using hematoxylin staining. Conventional dehydration and xylene transparency were performed. Finally, neutral resin adhesive was used for sealing. The sections were observed and photographed under an inverted optical microscope.

Immunofluorescence staining

Similar to the immunohistochemical staining steps, the mouse femur paraffin sections were sequentially subjected to dewaxing, antigen repair (microwave repair can reduce bone tissue loss), blocking, primary antibody incubation (anti-Beclin1, abmart, T55092), secondary antibody incubation, re-antigen repair, addition of primary antibody (anti-P62, abmart, T55546), secondary antibody incubation, DAPI re-staining of the cell nucleus, and blocking. Finally, images were taken under the SP8 Leica laser confocal microscope. The nucleus was stained blue (excitation wavelength 330-380 nm, emission wavelength 420 nm), Beclin1 protein was stained red (excitation wavelength 510-560 nm, emission wavelength 590 nm), and P62 protein was stained green (excitation wavelength 465-495 nm, emission wavelength 515-555 nm).

Table 1 Treadmill exercise program

Stages	Time	Speed	Duration
Acclimatization treadmill exercise	Day 1	6 m/min	30 min
	Day 2	9 m/min	40 min
	Day 3	12 m/min	50 min
Formal treadmill exercise	Days 4 to 7	15 m/min	60 min
	Weeks 2 to 8	15 m/min	60 min

micro-CT

The mouse knee joints were carefully isolated, and the intact femur were placed in PFA fixative for 48 h for fixation before micro-CT scanning. The Skyscan1276 scanning device was used to scan the rat knee joint. The knee was placed in the Skyscan1276 *ex vivo* sample scanning bed. The scanning parameters were as follows: Camera pixel size (μm) = 9.01; source voltage (kV) = 69; source current (μA) = 100; image pixel size (μm) = 9.92. After scanning, NRecon and DataViewer software were used to adjust all samples to the same position in the 3D axes to facilitate subsequent more precise selection of the region of interest for reconstruction. CTan software was used for further analysis of bone microstructural parameters, including bone mineral density (BMD), bone volume fraction (BV/TV), the number of trabeculae (Tb.N), and trabecular segregation (Tb.Sp). The place where the growth plate disappeared was chosen as the starting point of the region of interest, and 100 Layers were selected upwards as the region of interest for 3D reconstruction. Finally, CTvox was used for 3D reconstruction of regions of interest. After the micro-CT scan was completed, the femur was placed in an EDTA decalcification solution for decalcification for subsequent paraffin embedding and pathological sectioning.

Extraction of primary bone marrow mesenchymal stem cells

The lower limb of the mouse was severed at the hip joint (pay attention to preserving the intact femoral trochanter). The muscles and other soft tissues of the lower limbs were carefully peeled off. Subsequently, the femur and tibia were carefully separated at the knee joint (the fibula can be detached). Sterile ophthalmic scissors were used to cut both ends of the femur and tibia to expose the bone marrow cavity. Then, a 1 mL syringe was used to draw a complete culture medium containing 10% FBS and rinse the bone marrow cavity until all the tissue in the bone marrow cavity was washed down and appeared white. Finally, a pipette was used to repeatedly blow the culture medium containing bone marrow tissue and inoculate it into a 10cm culture dish. After 4-6 d, the cells can adhere to the culture dish.

Alkaline phosphatase staining

After the osteogenic induction and differentiation of primary BMSCs, the PBS solution was washed three times, followed by PFA to fix the BMSCs for 10-15 min. PBS solution was used to wash the cells three times again. Finally, an alkaline phase (ALP) staining solution (Sigma, B5655) was used to stain the cells. BMSCs were incubated at room temperature and in a dark environment, and the staining of cells was observed in real time. After a significant blue color appeared, the staining was terminated.

Alizarin red staining

After the osteogenic induction and differentiation of primary BMSCs, the PBS solution was washed three times, followed by PFA to fix the BMSCs for 10-15 min. PBS solution was used to wash the cells three times again. Finally, an alizarin red staining solution (Servicebio, G1038) was used to stain the cells. BMSCs were incubated at room temperature, and the staining of cells was observed in real-time. After a significant red color appeared, the staining was terminated.

Bioinformatics analysis

The sequence and annotation information of lncRNA-H19 was queried through the NCBI database to understand the biological function, expression pattern, and regulatory mechanism of this gene. The sequence of lncRNA-H19 was predicted to clarify the structure of its miRNAs containing target sites. Four websites, ENCORI, mricode, DINATOOLS, and LncACTdb, were used for predictive analysis of miRNA target genes for lncRNA H19 (ENCORI: https://rnasysu.com/encori/index.php; mricode: http://www.mircode.org; DINATOOLS: http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=site/index; LncACTdb: http://www.bio-bigdata.net/LncACTdb/index.htm). The intersection of the four sites identified four potential target miRNAs (miR-148a, miR-185, miR-212, and miR-149).

Cell transfection experiment in vitro

Primary BMSCs were washed three times using PBS when they grew to 30%-50% fusion. Specialized media for cell transfection with low serum was used. The si-lncRNA H19 and NC with Lipofectamine® 3000 Liposome transfection reagent (Invitrogen, L3000015) were added to low-serum cell transfection-specific medium, respectively. After 8 h, a 10% FBS complete culture medium was used to replace the low serum culture medium for subsequent experiments.

RT-qPCR

The total RNA of the cells was extracted using the Trizol method to detect the expression of target genes. Briefly, cells were washed three times with PBS. Six-well plates were prepared by adding 1 mL of Trizol to each well and transferring to 1.5 mL EP tubes. Subsequently, 200 μL of chloroform was added to each well, shaken vigorously, and centrifuged at 12000 rpm, 4 °C for 15 min. An equal amount of isopropanol was added to the supernatant, mixed upside down, and then centrifuged at 12000 rpm, 4 °C for 15 min. 1 mL of 75% ethanol was added to the supernatant and centrifuged at 7500 rpm, 4 °C for 5 min. The supernatant was discarded and air-dried so that the alcohol could be completely evaporated. Add 20 μL of DPEC water to dissolve the RNA. RNA concentration was measured using a spectrophotometer. The Takara SYBRGreen kit (Takara, RR820A) was used for real-time fluorescent quantitative amplification of target genes. β-actin was used as an internal reference. The $2^{-\Delta\Delta CT}$ method was used to analyze the data. As shown in Table 2, all primers involved were designed using Primer Premier 5.0 software.

Western blot

RIPA lysate was used to extract total protein from BMSCs for the detection of target protein expression. Briefly, BMSCs were washed three times with PBS, and 100 μL of Ripa lysate containing 1% protein phosphatase inhibitor was added to a six-well plate. The adherent primary BMSCs were scraped off using a cell scraper and transferred to 1.5 mL EP tubes, which were shaken on ice for 20 min and then sonicated. After centrifugation at 12000 rpm for 20 min, the supernatant was taken and transferred to a 1.5 mL EP tube. Then, after measuring the protein concentration with the BCA kit to homogenize the protein concentration, the protein loading buffer was added and cooked at 100 °C for 8 min. The proteins were separated using SDS-PAGE gel electrophoresis and then transferred to PVDF membranes. Subsequently, the protein-containing PVDF membrane was subjected to blocking, primary antibody incubation, and secondary antibody incubation. Finally, the chemiluminescent solution was used to develop the protein image. Anti-ALP (Invitrogen, PA5-106391), anti-bone morphogenetic protein 2 (BMP2) (Invitrogen, PA5-85956), anti-SP7 (Invitrogen, PA5-115697), anti-Beclin1 (abmart, T55092), Anti-microtubule-associated protein 1 light chain 3 beta (LC3B) (abmart, T55992), anti-β-actin (abmart, TP70573), anti-GAPDH (abmart, MG212519S), and anti-β-tubulin (abclonal, A12289) were used as primary antibody. The interest protein grayscale values were counted using Image J software.

Data analysis

The data from each group were analyzed using SPSS 20.0 software. GraphPad Prism 8 was used to graph statistical data. Results are expressed as mean ± SD. Independent samples *t*-test was used to compare the differences between two groups, while one-way ANOVA and the LSD method were used to compare the differences between multiple groups. $P < 0.05$ indicates a significant difference.

RESULTS

Exercise promotes bone formation in growing mice

Growth-phase mice were selected to undergo mandatory 8 wk of moderate-intensity treadmill exercise to stimulate bone formation, thereby enhancing peak bone mass. As shown in Figure 1A, compared with the Con group, the femoral growth plate of mice in the Exercise group was significantly thickened, accompanied by distinct chondrocyte stratification: resting-zone chondrocytes, proliferating chondrocytes, and hypertrophic chondrocytes, which is suggestive of an active osteogenic function. Immunohistochemical staining showed that the expression of BMP2, a marker of osteogenic differentiation, was also significantly increased in the Ex group of mice (Figure 1B). A recent study found that exercise may alleviate bone loss in aging mice by modulating autophagy[34]. Therefore, we preliminarily examined the expression of markers of autophagy in the femur and found that the level of autophagy was significantly increased in the femur of mice in the Ex group (Figure 1C). Consistently, micro-CT results showed that 8 wk of moderate-intensity treadmill exercise significantly increased BMD, BV/TV, and Tb.N) and decreased Tb.Sp in the femur of mice (Figure 1D and E). Thus, we found that 8 wk of moderate-intensity treadmill exercise significantly promoted femoral bone formation and increased peak bone mass in growing mice, which may be related to the activation of autophagy.

Exercise promotes osteogenic differentiation of mouse BMSCs

BMSCs from the femur and tibia of Con and Ex group mice were extracted for osteogenic differentiation induction using an osteogenic differentiation medium to verify whether exercise increased peak bone mass in growing mice by promoting osteogenic differentiation of BMSCs. First, we performed stem cell characterization of primary cells extracted from mouse bone marrow. As shown in Figure 2A and B, primary mouse BMSCs subjected to ALP staining and alizarin red staining showed good stem cell properties 7 and 14 d after osteogenic induction of differentiation, respectively. Subsequently, we explored the possible mechanisms by which exercise promotes osteogenic differentiation by bioinformatics analysis to find potential miRNA targets of lncRNA H19. As shown in Figure 2C and D, bioinformatics analysis suggested four potential miRNAs (miR-148a, miR-185, miR-212, and miR-149). Further, RT-qPCR results showed that the expression of miR-149 was significantly down-regulated in Ex-group BMSCs, which was opposite to the expression trend of lncRNA H19 (Figure 2E and F), suggesting that miR-149 may be a direct target gene of lncRNA H19 during the osteogenic differentiation of BMSCs. In addition, we found that compared to the Con group, the mRNA and protein expression levels of osteogenic differentiation markers of BMSCs in the Ex group were significantly higher, including ALP and BMP2 (Figure 2E-H). Notably, autophagy-related protein markers such as Beclin1 and LC3B were also significantly up-

Table 2 Primer sequences

Genes	Primer sequence (5'-3')
lncRNA H19	Forward: 5'- GCTCCACTGACCTTCTAAAC -3' Reverse: 5'- ACGATGTCTCCTTTGCTAAC -3'
miR-149	Forward: 5'- TGGCTCCGTATCTTCACTCC -3'
β-actin	Forward: 5'-CTGTCCCTGTATGCCTCTG-3' Reverse: 5'-ATGTCACGCACGATTTCC-3'
ALP	Forward: 5'-CCAACTCTTTTGTGCCAGAGA-3' Reverse: 5'-GGCTACATTGGTGTTGAGCTTTT-3'
Runx2	Forward: 5'-AGAGTCAGATTACAGATCCCAGG-3' Reverse: 5'-TGGCTCTTCTTACTGAGAGAGG-3'
BMP2	Forward: 5'- GTGCAGATCCTAGGTTTCTCTG-3' Reverse: 5′- CAGGATCTCATTCTCTTGGATC-3′
Osterix	Forward: 5'-TGGTACAAGGCAGGCATCCA-3' Reverse: 5'-GGAGCAAAGTCAGATGGGTAAGT-3'

regulated in BMSCs from the Ex group (Figure 2G and H). Thus, exercise significantly promotes osteogenic differentiation of BMSCs in growth-phase mice, which may be associated with activation of the lncRNA H19/miR-149 axis and autophagy.

Exercise promotes osteogenic differentiation of BMSCs through upregulation of lncRNA H19/miR-149

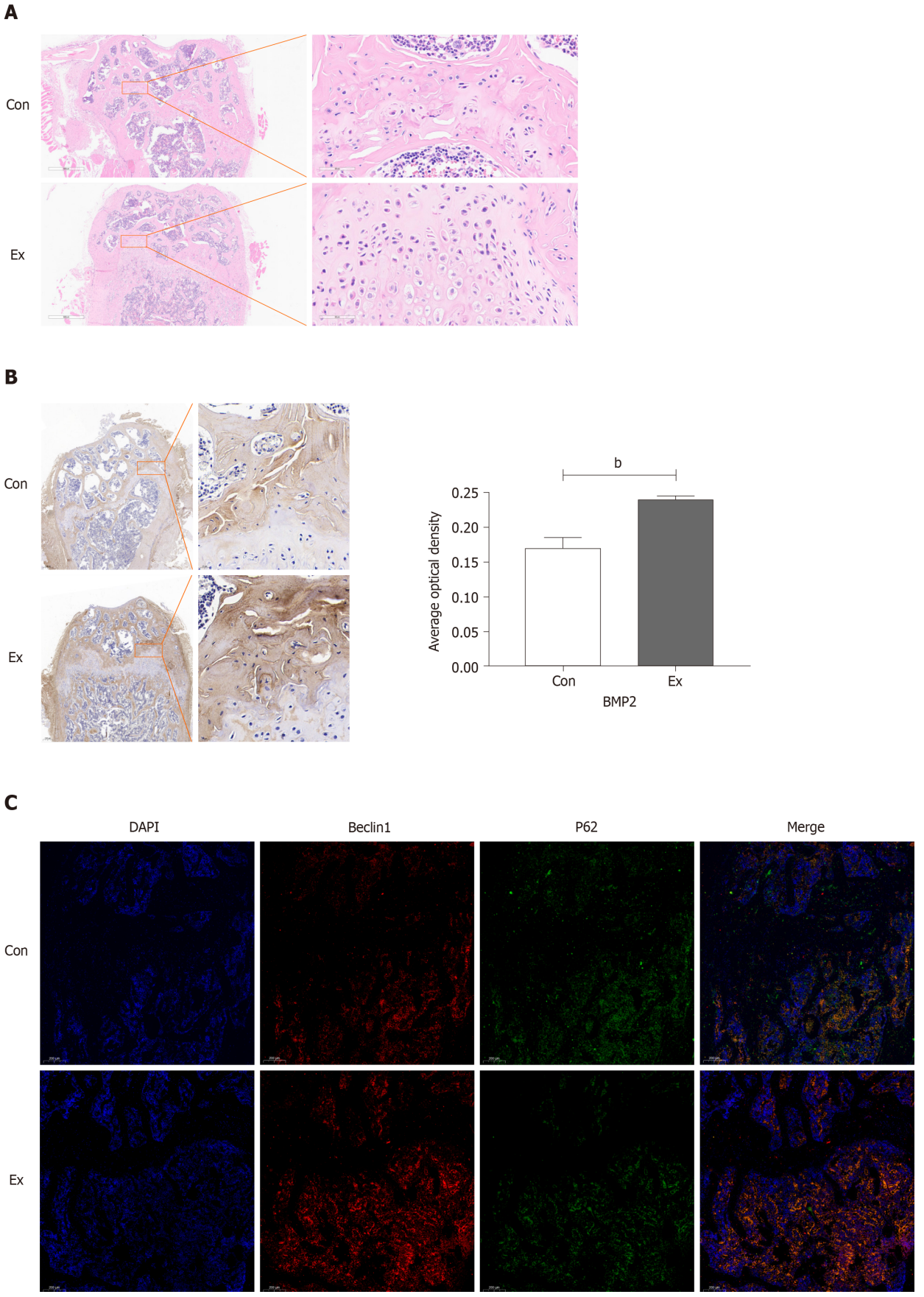
Cell transfection techniques were used to inhibit the expression of lncRNA H19 to verify that the lncRNA H19/miR-149 axis can mediate the process of exercise-promoting osteogenic differentiation in BMSCs. Wild-type mouse BMSCs were extracted for 3 d for osteogenic differentiation induction, as the effective time for si-RNA transfection was 48-72 h. It was found that ALP staining was hampered after lncRNA H19 was knocked down (Figure 3A). However, there was no significant difference in the results of alizarin red staining due to the short time of osteogenic induction of differentiation (Figure 3B). Subsequently, we examined the expression of genes and protein markers related to osteogenic differentiation after the knockdown of lncRNA H19. As shown in Figure 3C-E, inhibition of lncRNA H19 significantly suppressed osteogenic differentiation of BMSCs, characterized by a significant decrease in the expression of markers of osteogenic differentiation such as ALP, Runx2, and BMP2. Meanwhile, the knockdown of lncRNA H19 can significantly upregulate miR-149 expression, which further demonstrates that the lncRNA H19/miR-149 axis may play an important regulatory role in the osteogenic differentiation of BMSCs. In addition, we found that inhibition of lncRNA H19 significantly abolished the activation of Beclin1 and LC3B, resulting in reduced levels of autophagy (Figure 3D and E). The above results suggest that exercise can promote osteogenic differentiation of BMSCs by upregulating the lncRNA H19/miR-149 axis, which may be related to the activation of autophagy.

DISCUSSION

Peak bone mass acquired during adolescence is essential for bone health. The gradual loss of bone mass in adulthood is irreversible[9]. However, exercise is effective in increasing peak bone mass during puberty. More peak bone mass means an increase in relative bone mass in adulthood, which can effectively reduce the risk of osteoporotic fractures[10]. Therefore, it is valuable to explore in depth the potential role of exercise in promoting bone formation during adolescence. In this study, the promotional effect of treadmill exercise on bone formation in growing mice and its underlying mechanisms were explored (Figure 4).

Since mice reach sexual maturity at 6-8 wk and can be defined as adult mice at 12 wk[35]. 4-wk-old growing mice were selected to perform treadmill exercises. Previous studies have shown that short-term programs and/or low-intensity exercise programs are not effective in stimulating bone formation, regardless of gender or age, while high-intensity exercise imposes excessive loads on the bone, causing damage to the bone tissue[35]. Hamann *et al*[36] suggested that there may be a critical strain threshold to stimulate bone formation. For example, Maurel *et al*[37] observed no increase in whole-body BMD after exercise, which could be attributed to insufficient intensity of the exercise program. Furthermore, another study demonstrated that a population-based moderate-intensity physical activity intervention program during childhood appears to exert beneficial effects on several musculoskeletal characteristics[38]. In addition, most studies have shown that moderate-intensity exercise with a mean duration of 8 wk or more can promote improvements in bone microarchitecture[39-42]. Therefore, for the present study, moderate-intensity treadmill exercise was chosen as the intervention for growing mice for 8 wk.

Our results showed a significant increase in BMD, BV/TV, and Tb. N and a decrease in trabecular separation in the femur of mice in the Ex group compared to the Con group, suggesting that 8 wk of moderate-intensity treadmill exercise is effective in stimulating bone formation and significantly increasing BMD in growing mice, which contributes to the enhancement of the peak bone mass in adulthood. Notably, in HE staining, we found that the thickness of the growth plate of mice in the Ex group was significantly increased, and the proliferation and differentiation of cells in all layers of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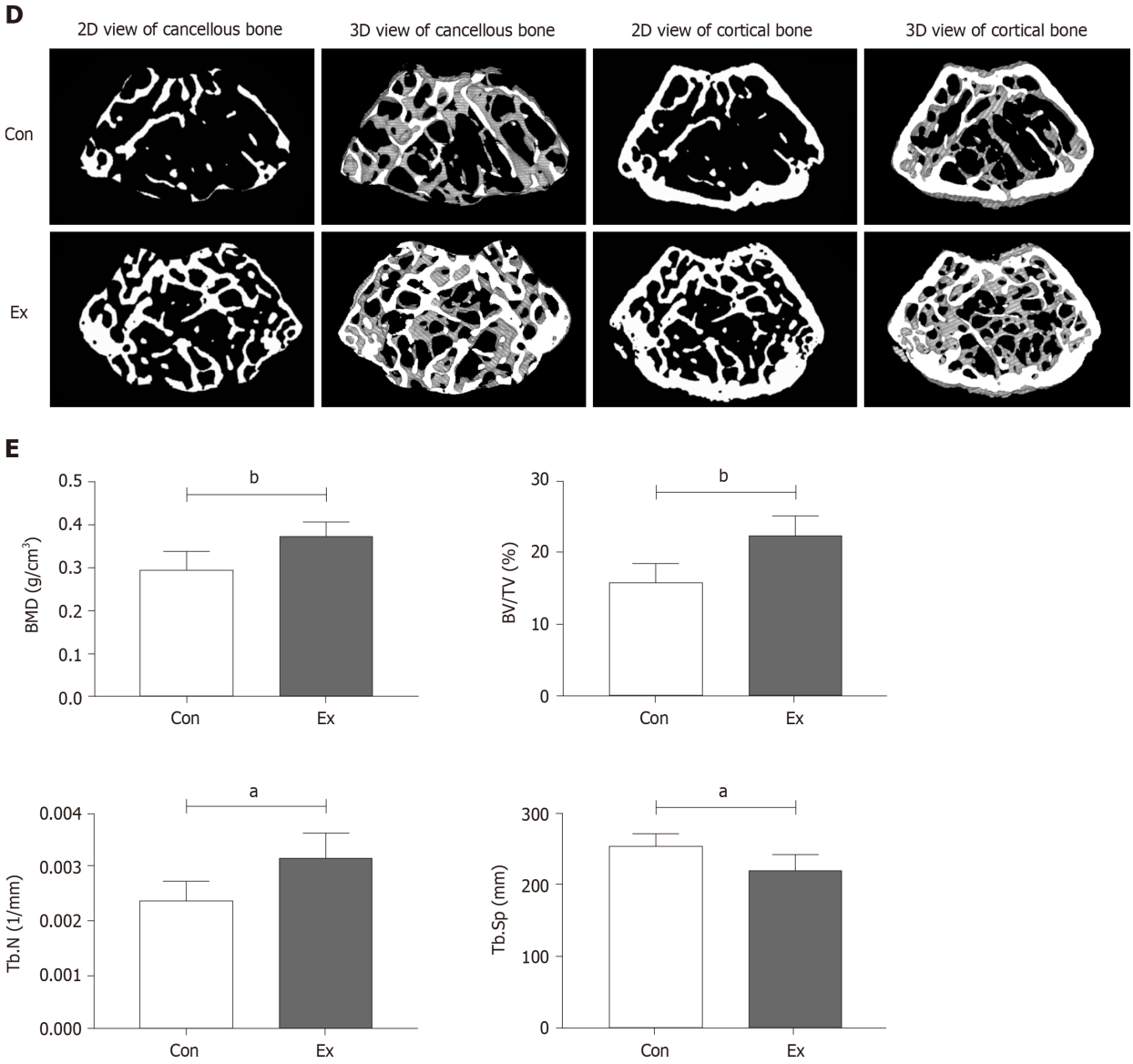
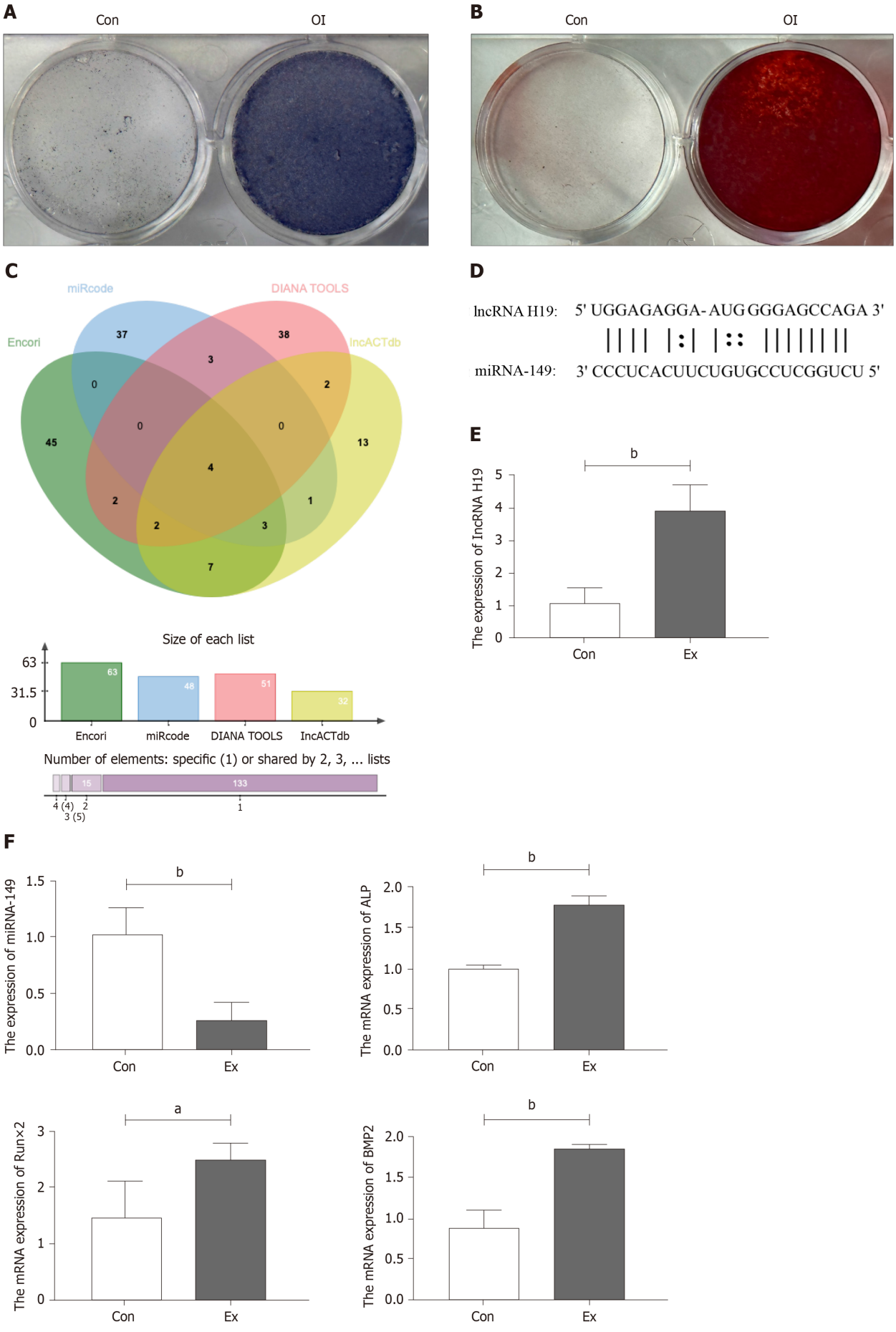


Figure 1 Exercise promotes bone formation in growing mice. A: Hematoxylin-eosin staining of mouse femur; B: Changes in bone morphogenetic protein 2 protein expression in mouse femur by immunohistochemical staining; C: Changes in protein expression of Beclin1 and P62 in mouse femur by immunofluorescence staining; D and E: Reconstruction images and bone morphometric indices of changes in the distal femur in mice by micro-CT scanning. n = 6, $^{a}P < 0.05$, $^{b}P < 0.01$. Con: Control group; Ex: Treadmill exercise group.

the bone growth plate were active. The growth plate, a cartilaginous tissue located between the epiphysis and the diaphysis, is the main differentiation region for longitudinal bone growth and consists mainly of chondrocytes and extracellular matrix[43,44]. During the juvenile period, the proliferation and differentiation of cartilage are balanced with the rate of new bone production, thus ensuring that the growth plate can maintain a certain thickness while the length of the diaphysis increases. With age, the proliferative potential of chondrocytes in the growth plate of adolescent children is gradually exhausted. When the proliferative and osteogenic activity of cartilage ceases, the growth plate is completely ossified and fused, accompanied by a reduction in the width of the growth plate. Simultaneously, the longitudinal growth of the long bones stops[45]. Impaired or premature closure of the bone growth plate function can lead to short stature, limb length incongruity, and abnormal skeletal development in children since continued maturation of bone growth plate cartilage can provide a scaffold for bone deposition[46]. It was found that the proliferation and hypertrophy of chondrocytes in the epiphyseal plate were more pronounced in joints subjected to weight-bearing stress. The stress-affected cell proliferation and differentiation were closely related to the elevated expression level of parathyroid hormone-related protein (PTHrP)[47]. Another study found that short-term cyclic stress can upregulate the expression of PTHrP in growth plate chondrocytes, which in turn affects growth plate development[48]. In the present study, the improvement in the thickness of the distal femoral growth plate by exercise may be an important reason for promoting bone formation and bone growth in growing mice. In addition, the growth plates are more susceptible to injury since they are composed of cartilage, which is weaker than solid bone[44]. It has been shown that shock loading inhibits bone growth throughout adolescence in young rats. This may be due to excessive shock loading, causing damage to the bone growth plate, which in turn inhibits normal bone formation[49]. Therefore, we have to emphasize the necessity of controlling the intensity of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miRNA-149: 3' CCCUCACUUCUGUGCCUCGGUCU 5'
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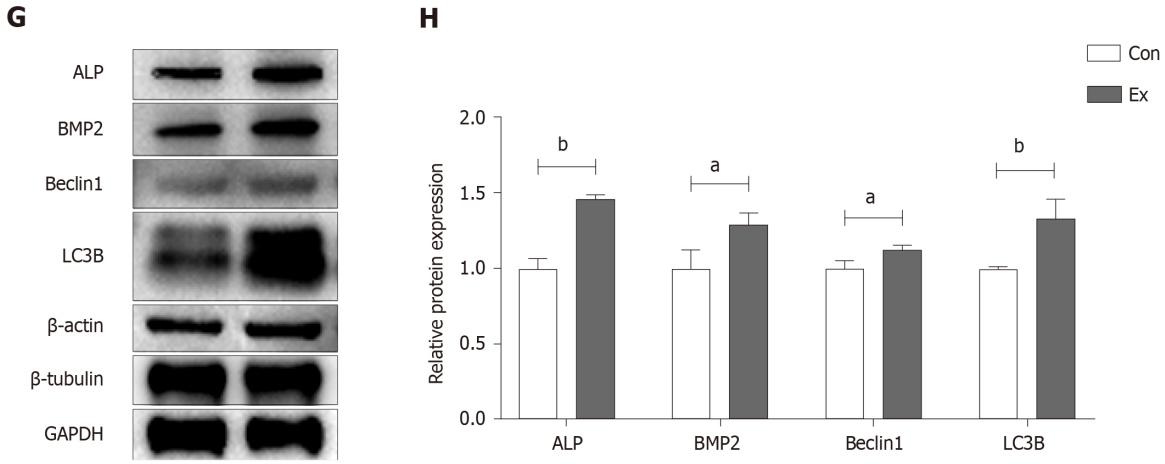

Figure 2 Exercise promotes osteogenic differentiation of mouse bone mesenchymal stem cells. A: Alkaline phase staining of mouse bone mesenchymal stem cells (BMSCs) at 7 d of osteogenic differentiation induction; B: Alizarin red staining of mouse BMSCs at 14 d of osteogenic differentiation induction; C and D: Identification of potential miRNAs targets of lncRNA H19 by bioinformatics analysis; E and F: Changes in mRNA levels of lncRNA H19, miR-149, and osteogenic differentiation-associated markers after induction of osteogenic differentiation in mouse primary BMSCs by RT-qPCR; G and H: Changes in protein level of osteogenic differentiation-related marker and autophagy-related marker after induction of osteogenic differentiation in mouse primary BMSCs. n = 3, ^{a}P < 0.05, ^{b}P < 0.01. Con: Control group; OI: Osteogenic differentiation induction; Ex: Treadmill exercise group.

exercise when performing exercise interventions in mice during the growth period. Moreover, the timing of growth plate development is the limiting factor in determining height[50,51]. Therefore, we propose the hypothesis that exercise may also promote an increase in BMD and peak bone mass by prolonging the development time/delaying the healing time of the growth plate in mice.

To investigate the effects and potential mechanisms of exercise to promote osteogenesis in growing mice, BMSCs from the femur and tibia of Con and Ex group mice were extracted for further experiments. We found that the expression of lncRNA H19 was significantly higher in BMSCs in the Ex group compared to the Con group, while the mRNA and protein expression levels of ALP and BMP2 were significantly higher, suggesting that exercise significantly promotes the osteogenic differentiation of BMSCs in growth-phase mice, which may be related to the upregulation of lncRNA H19. Subsequently, small interfering RNA was used to inhibit lncRNA H19 expression in BMSCs to verify whether exercise promotes osteogenic differentiation *via* lncRNA H19. The results showed that si-H19 significantly inhibited osteogenic differentiation of BMSCs by ALP staining, although alizarin red staining showed no significant difference due to the too-short time of osteogenic differentiation. RT-qPCR with WB analysis also further demonstrated that si-H19 significantly inhibited osteogenic differentiation of BMSCs. Therefore, exercise may promote osteogenesis by upregulating lncRNA H19. Since lncRNA H19 can act as a miRNAs sponge to regulate bone formation during osteogenic differentiation[18], we further identified five potential miRNAs targets of lncRNA H19 by bioinformatics analysis. Combined with bioinformatics analysis, we preliminarily found that the expression of miR-149 was decreased during osteogenic differentiation of BMSCs by RT-qPCR, which was opposite to the expression trend of lncRNA H19, suggesting that miR-149 may be a direct target gene of lncRNA H19 during the osteogenic differentiation of BMSCs. It has been reported that miR-149 is involved in the regulation of calcium ions, bone matrix mineralization, and bone resorption, as well as the differentiation and maintenance of bone tissue by targeting multiple pathways and genes[52]. Furthermore, miR-149 was found to be associated with osteosarcoma. miR-149 can target the expression of BMP9 to promote osteosarcoma progression [53]. In the present study, we found that the expression of miR-149 was significantly upregulated after knockdown of lncRNA H19, which further demonstrated that the lncRNA H19/miR-149 axis may play an important regulatory role in the osteogenic differentiation of BMSCs.

It is worth mentioning that in our study, compared with the Con group, the expression level of Beclin1 protein in the femur of mice in the Ex group was significantly increased while the expression of P62 protein was significantly decreased. Furthermore, the expression levels of Beclin1 and LC3B were also significantly up-regulated in the BMSCs of mice in the Ex group. It indicates that exercise may promote bone formation in mice by activating autophagy. Beclin1, p62, and LC3B are regulators of autophagy. High expression of Beclin1 accompanied by a decrease in p62 protein suggests that autophagy is activated, and vice versa[54]. Autophagy is a self-degradation process that balances energy sources in response to cellular stress[55]. Autophagy plays an important role in bone homeostasis. Studies have shown that estradiol can rescue osteoblasts from apoptosis by promoting autophagy through the Er-Erk-mTOR pathway[56]. Additionally, autophagy is closely related to osteoblast differentiation and mineralization. Mineral needle-like structures within the cytoplasm are mainly located in autophagy-like vesicles. Inhibition of autophagy leads to a decrease in the mineralization capacity of osteoblasts, whereas inhibition of autophagic flow prevents the outward transport of minerals from osteoblasts[57,58]. Previous studies have found that under mechanical stress, osteoblasts can promote osteoclastogenesis through autophagy-mediated receptor activator of nuclear factor κB ligand (RANKL) secretion[59]. Recent studies have reported that miRNAs play an important role in autophagy regulation. Wang *et al*[60] found that miR-140-5p and miR-149 can enhance chondrocyte autophagic activity by regulating the number of autophagic vesicles in human primary chondrocytes. In our study, we found that inhibition of lncRNA H19 significantly down-regulated the expression of

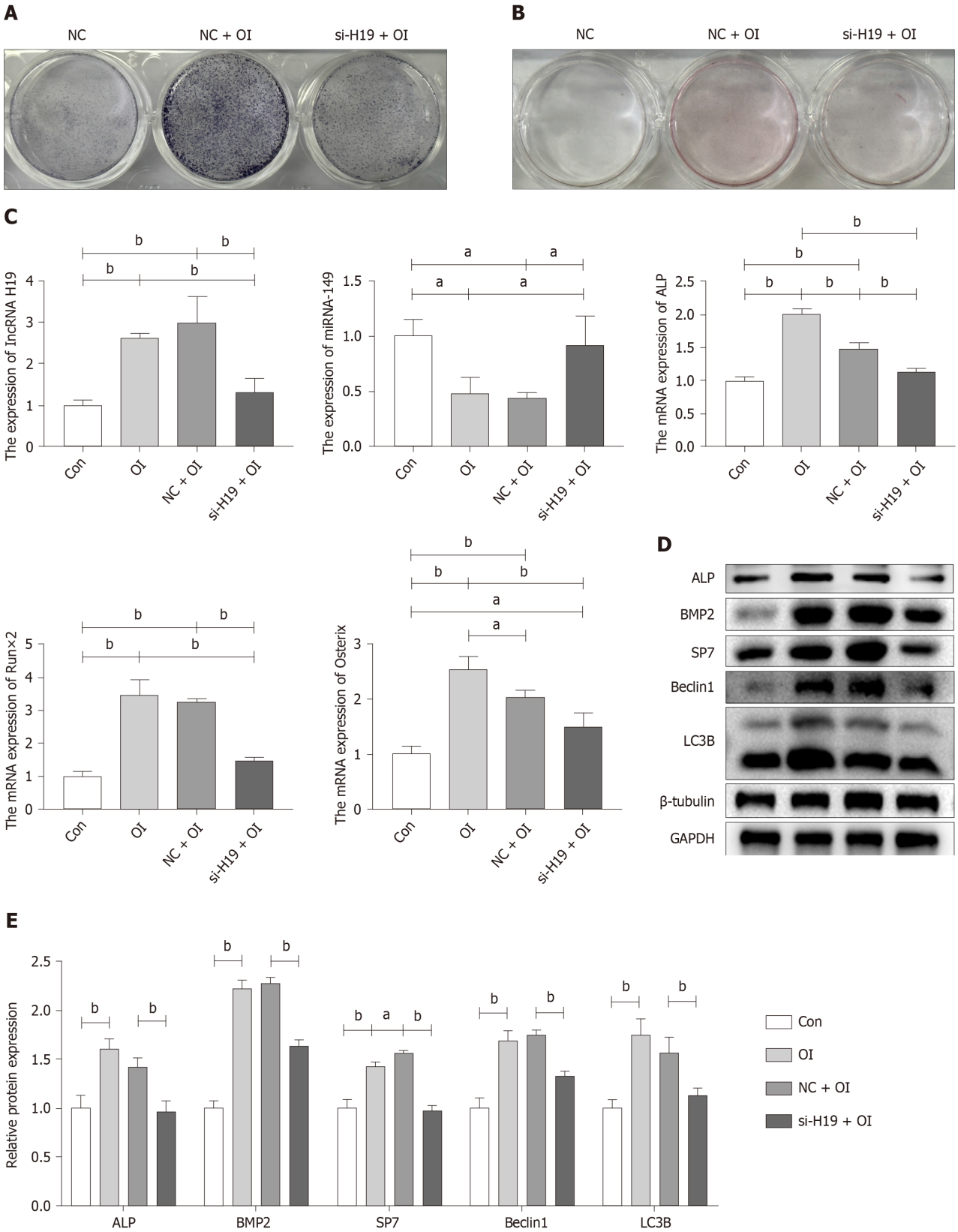

Figure 3 Exercise promotes osteogenic differentiation of bone mesenchymal stem cells through upregulation of lncRNA H19/miR-149. A: Alkaline phase staining of bone mesenchymal stem cells (BMSCs) 3 d after osteogenic induction of differentiation; B: Alizarin red staining of BMSCs 3 d after osteogenic induction of differentiation; C: Gene expression changes of lncRNA H19, miR-149 and osteogenic differentiation-related markers in BMSCs after osteogenic differentiation induction and si-lncRNA H19 interference by RT-qPCR; D and E: Protein expression changes of osteogenic differentiation-associated markers and autophagy-associated markers in BMSCs after osteogenic differentiation induction and si-lncRNA H19 interference by WB technique. $n = 3$, $^{a}P < 0.05$, $^{b}P < 0.01$. Con: Control group; NC: Negative control group; OI: Osteogenic differentiation induction group.

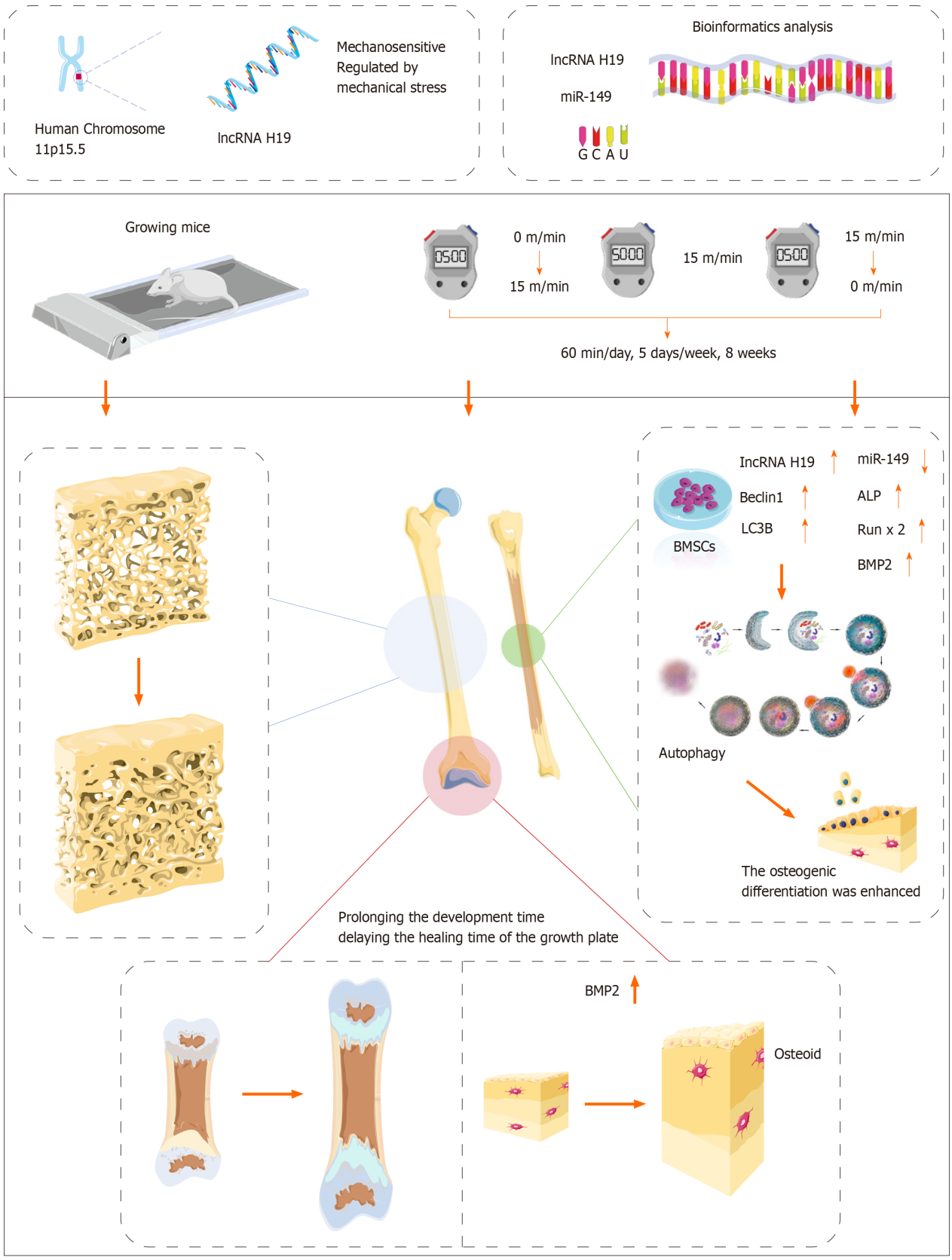

Figure 4 Summary diagram of this study.

Beclin1 and LC3B, leading to a decrease in autophagy levels. This suggests that exercise can promote osteogenic differentiation of BMSCs through up-regulation of the lncRNA H19/miR-149 axis, which may be related to the activation of autophagy. That is, exercise may promote osteogenic differentiation through lncRNA H19/miR-149/autophagy in growth-stage mice. Unfortunately, in this study, we did not provide sufficient evidence to support this hypothesis. In addition, it is well known that exercise inhibits adipogenesis. In HE staining, we found that there was no significant change in adipocytes in the bone marrow cavity of mouse femurs after 8 wk of exercise, which may be because we used

mice that were not disease models, such as the osteoporosis model. Therefore, osteoporosis model mice can be selected to further explore whether exercise can inhibit lipogenic differentiation through the lncRNA H19/miR-149 axis while promoting osteogenic differentiation. And, it can also be deeply explored whether this process is similarly related to the regulation of autophagy.

CONCLUSION

In summary, our study demonstrated that moderate intensity running exercise can effectively stimulate bone formation and promote the increase of bone density and bone volume in growing mice, thus enhancing the peak bone mass of mice. Notably, the lncRNA H19/miR-149 axis plays an important regulatory role in the osteogenic differentiation of BMSCs, and this process may be related to the activation of autophagy.

ARTICLE HIGHLIGHTS

Research background

It is well known that exercise promotes bone growth and development. However, the underlying mechanisms by which exercise promotes bone formation are not fully understood.

Research motivation

Our previous findings suggest that the mechanosensitive lncRNA H19 is involved in the regulation of cartilage homeostasis. Therefore, we propose the hypothesis that mechanosensitive lncRNA H19 may be involved in mediating the process of exercise-promoted bone formation. This study will provide more theoretical basis for exercise promoting bone health.

Research objectives

The aim of this study was to investigate whether mechanosensitive lncRNA H19 could promote bone formation by targeting miR-149. This study reveals for the first time the potential regulatory role of the lncRNA H19/miR-149 axis in exercise-promoted bone formation, providing a scientific basis for the promotion of bone health by exercise.

Research methods

The potential role of lncRNA H19/miR-149 axis in exercise-promoted bone formation was fully validated *in vivo* and *in vitro* by RT-qPCR, WB, IF, IHC, and micro-CT combined with bioinformatics analysis.

Research results

In vivo, exercise could activate autophagy by promoting the expression of lncRNA H19 and inhibiting the expression of miR-149, thereby promoting bone formation. *In vitro*, knockdown of lncRNA H19 was able to inhibit autophagy by upregulating miR-149 expression, thereby inhibiting osteogenic differentiation of bone mesenchymal stem cells.

Research conclusions

Exercise can promote autophagy and bone formation through activation of the lncRNA H19/miR-149 axis.

Research perspectives

The potential role of the lncRNA H19/miR-149/autophagy axis in exercise-promoted bone formation was further validated by gain of function and loss of function in animal experiments.

FOOTNOTES

Co-first authors: Xu-Chang Zhou and Dong-Xue Wang.

Author contributions: Ni GX and Zhou XC designed and coordinated the study; Wang DX and Yang YJ performed the experiments, acquired and analyzed data; Zhao RB interpreted the data; Zhou XC and Liu SY acquired the Fund; Zhou XC and Wang DX wrote the manuscript; all authors approved the final version of the article.

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Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Beijing Sport University (Approval Number: 2023026A).

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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ORIGINAL ARTICLE

Basic Study

Anatomic location of the first dorsal extensor compartment for surgical De-Quervain's tenosynovitis release: A cadaveric study

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Abstract

BACKGROUND

De-Quervain's tenosynovitis is a disorder arising from the compression and irritation of the first dorsal extensor compartment of the wrist. Patients who fail conservative treatment modalities are candidates for surgical release. However, risks with surgery include damage to the superficial radial nerve and an incomplete release due to inadequate dissection. Currently, there is a paucity of literature demonstrating the exact anatomic location of the first dorsal extensor compartment in reference to surface anatomy. Thus, this cadaveric study was performed to determine the exact location of the first extensor compartment and to devise a reliable surgical incision to prevent complications.

AIM

To describe the location of the first dorsal compartment in relation to bony surface landmarks to create replicable surgical incisions.

METHODS

Six cadaveric forearms, including four left and two right forearm specimens were dissected. Dissections were performed by a single fellowship trained upper extremity orthopaedic surgeon. Distance of the first dorsal compartment from landmarks such as Lister's tubercle, the wrist crease, and the radial styloid were calculated. Other variables studied included the presence of the superficial radial nerve overlying the first dorsal compartment, additional compartment subsheaths, number of abductor pollicis longus (APL) tendon slips, and the presence of a pseudo-retinaculum.

RESULTS

Distance from the radial most aspect of the wrist crease to the extensor retinaculum was 5.14 mm ± 0.80 mm. The distance from Lister's tubercle to the distal aspect of the extensor retinaculum was 13.37 mm ± 2.94 mm. Lister's tubercle to the start of the first dorsal compartment was 18.43 mm ± 2.01 mm. The radial

styloid to the initial aspect of the extensor retinaculum measured 2.98 mm ± 0.99 mm. The retinaculum length longitudinally on average was 26.82 mm ± 3.34 mm. Four cadaveric forearms had separate extensor pollicis brevis compartments. The average number of APL tendon slips was three. A pseudo-retinaculum was present in four cadavers. Two cadavers had a superficial radial nerve that crossed over the first dorsal compartment and retinaculum proximally (7.03 mm and 13.36 mm).

CONCLUSION

An incision that measures 3 mm proximal from the radial styloid, 2 cm radial from Lister's tubercle, and 5 mm proximal from the radial wrist crease will safely place surgeons at the first dorsal compartment.

Key Words: De-Quervain's tenosynovitis; First extensor compartment; Cadaveric study; Superficial radial nerve; Radial styloid; Lister's tubercle

Core Tip: Surgical release of the first extensor compartment at the level of the wrist has been well documented with multiple different techniques. Injury to the superficial radial nerve, decompressing the incorrect compartment, tendon injury, and incomplete release of the compartment leads to patient morbidity. We describe the precise anatomic location of the first dorsal compartment in relation to bony surface landmarks to create replicable surgical incisions. We demonstrate the location of the superficial radial nerve and document the variances in the first compartment sub-sheaths. In doing so, we have created a surgical protocol that will ensure a complete first compartment release.

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INTRODUCTION

De-Quervain's tenosynovitis is a common pathology of the wrist resulting in thickening of the synovial sheath and extensor retinaculum containing the first dorsal extensor compartment[1]. Subsequent irritation of the first dorsal compartment, containing the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons, leads to radial sided wrist pain and inflammation[2]. Repetitive grasping and twisting motions of the hand and wrist leads to increased inflammation along with decreased functional use of the wrist. Initial non-operative management of De-Quervain's tenosynovitis includes the use of over-the-counter anti-inflammatory medications, supportive thumb spica bracing, and corticosteroid injections[3,4]. Failure of these conservative measures warrants surgical intervention[2-4].

Surgical release of the first extensor compartment is the standard of care following failure of conservative treatment modalities. Various surgical techniques have been described in the literature to ensure a complete release of the compartment. Prior studies have compared the efficacy of transverse *vs* longitudinal incisions to achieve a safe release of the compartment, with both techniques having their own risks and benefit profiles[5-8]. Novel techniques including ultrasound guided and percutaneous release of the first dorsal compartment have also been studied to ensure efficacy and safety[9,10]. However, surgical intervention does pose risk, mainly to the superficial radial nerve which courses in close proximity to the surgical incision. The literature has closely documented the course and associated branches of the superficial radial nerve, which can arise 1.5 cm-2 cm proximal to Lister's tubercle and 5 cm-8 cm from the radial styloid, placing great emphasis on meticulous care to avoid iatrogenic nerve injury during release of the tendon sheath[11-15].

Interestingly, multiple anatomic variants and sub-sheaths within the compartment itself can hinder a complete surgical release and resolution of clinical symptoms. Cadaveric studies have documented varying numbers of tendons and tendon slips of the APL in the first dorsal compartment[16-18]. Differing numbers of subsheaths and septi between tendons were found once the compartment was exposed, requiring further dissection to ensure a complete release of all constricting factors on the tendon sheath[18-20].

However, there is currently a paucity of literature that accurately demonstrates the exact anatomic location of the first dorsal compartment at the level of the wrist[21,22]. The inability to accurately replicate a reliable surgical incision into the first compartment places the superficial radial nerve at risk and may lead to inadequate releases based on sub-sheath vari-ability. Therefore, the inability to create reproducible incisions intra-operatively can lead to unnecessary dissection into other extensor compartments, damage to surrounding neurovascular structures, increased operative time, and wound complications.

The aim of this study is to determine the precise anatomic location of the first dorsal compartment in relation to bony surface landmarks in order to create reliable and replicable surgical incisions. Secondary aims of this project are to document the location of the superficial radial nerve and to document the variances in the first compartment sub-sheaths. In doing so, our aim is to create a surgical protocol that will ensure a complete first compartment release without injury to

the surrounding neurovascular structures when treating De-Quervain's tenosynovitis.

MATERIALS AND METHODS

Six cadaveric forearms were obtained to perform this study including four left and two right forearm specimens. All specimens included the entire forearm and hand from the proximal ulna to the fingertips. In total, four cadavers were male and two were female. All cadaver specimens were obtained from different individuals. Cadaver specifications included age ranges from thirty to sixty years of age. The two right forearm specimens were from a sixty-year-old male and a thirty-seven-year-old female specimen. Of the four left forearm specimens, three were from male cadavers while one forearm was from a female cadaver. The age ranges for the left forearm cadavers included a fifty-five-year-old male, fifty-eight-year-old male, thirty-three-year-old male, and a thirty-two-year-old female.

Inclusion criteria for our study included cadaver models within age ranges of 30-60 with no prior trauma history or surgical intervention to the wrist and hand region that would otherwise confound results from a soft tissue standpoint. Exclusion criteria included cadavers with prior history of wrist or hand surgical intervention. Cadavers with a history of surgical history including retained hardware, prior fractures, history of skin grafting, or soft tissue or bony trauma were excluded. All specimens included the entire forearm and hand from the proximal ulna to the fingertips. Any specimens with evidence of prior amputations related to trauma or vascular disease were excluded. Fresh frozen cadaveric forearms were thawed only once at which time all surgical dissections were undertaken (Figure 1). The cadaveric forearms were purchased using institutional research funding.

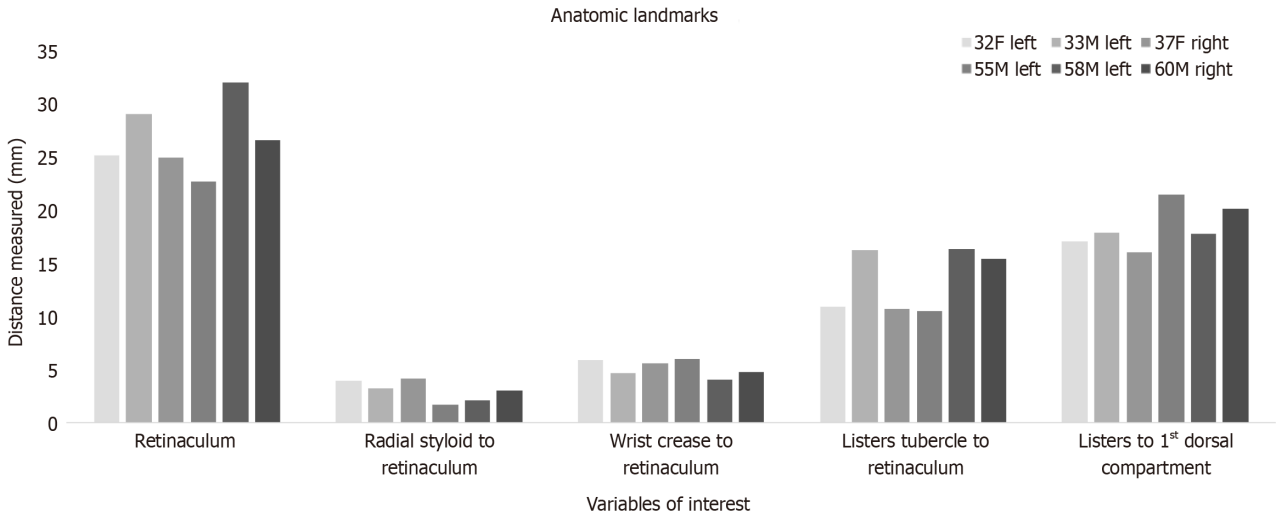

Figure 1 Histogram demonstrating superficial landmark data points for six cadaveric specimens. Each data bar demonstrates the value obtained for the cadaveric forearm specified in the legend provided. Notably, all variables do not demonstrate a significant outlier and maintain a close distribution of variables independent of laterality, age, and sex of the specimen. This demonstrates that the radial styloid, wrist crease, and Lister's tubercle are all reliable markers to use to determine the location of the first dorsal compartment.

Surgical technique

All cadaveric dissections and data measurements were performed by a single fellowship trained hand and upper extremity orthopaedic attending surgeon under loupe magnification. Dissection was performed in one sitting with all cadaveric arms having undergone the same timeframe of thawing. A longitudinal incision was used for all specimens centered dorsally over the radial styloid and extended proximally to ensure full exposure of all structures. Dissection was performed using a #15 scalpel to incise skin and dermis. Metzenbaum scissors were subsequently used to dissect subcutaneous tissues in order to identify structures such as the superficial radial nerve, the first dorsal compartment, and all associated sub-sheaths. The entire first dorsal compartment, extensor retinaculum, and available branches of the superficial radial nerve were identified and marked. After appropriate exposure was achieved, the pre-determined variables were measured using caliper instruments (Figure 2A-D).

Variables of interest

Various data points were obtained to maximize a reproducible surgical site incision over the first dorsal compartment. The length of the distal phalanx of the thumb and the distance from the thumb distal interphalangeal joint to the tip of the digit were two topographical data points that were collected. Creating an incision centered over the first dorsal compartment based on those two measurements was analyzed to determine the proximity of those values to the extensor retinaculum. The overall length of the extensor retinaculum was obtained and served as a key measurement that allowed comparison measurements from other landmarks (Figure 2A). Other landmarks of interest included Lister's tubercle, the

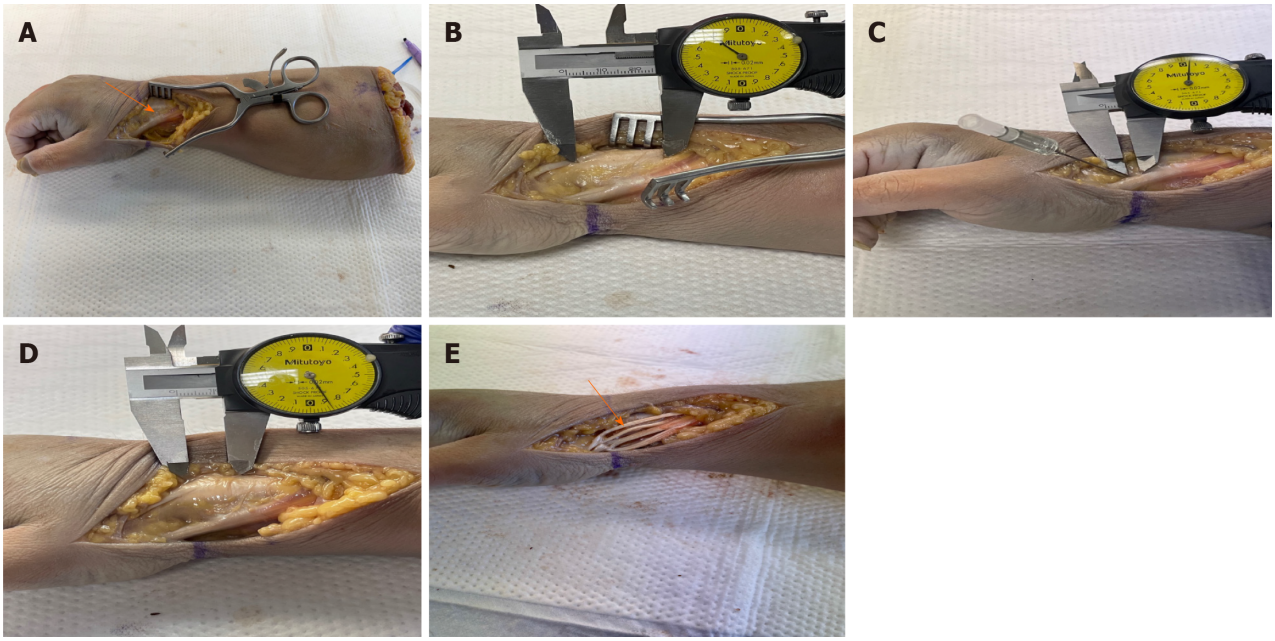

Figure 2 Cadaveric dissection. A: Initial cadaveric dissection of the first dorsal compartment. Right forearm cadaver model with a longitudinal incision centered over the first dorsal extensor compartment. Superficial dissection through the subcutaneous fat was performed with a scalpel blade and Metzenbaum scissors. Deep dissection and retraction of the soft tissues demonstrates the underlying musculature and extensor retinaculum as shown by the black arrow; B: Full length view of the extensor retinaculum. Cadaveric dissection demonstrating the full extent of the extensor retinaculum. Caliper measurements were performed as demonstrated in this graphic. The average length of the extensor retinaculum from its proximal to its distal length was 26.82 mm ± 3.34 mm; C: Deep dissection of the radial styloid and extensor retinaculum. Dissection demonstrating the most distal aspect of the radial styloid to the most distal aspect of the extensor retinaculum. An 18-gauge needle is used to mark the radial styloid process. The length from the radial styloid to the initial aspect of the extensor retinaculum measured 2.98 mm ± 0.99 mm; D: Anatomic relationship shown between Lister's tubercle to the first dorsal extensor compartment. Lister's tubercle is seen marked by the most distal aspect of the caliper, while the first extensor compartment shown by the proximal caliper marker. The distance from Lister's tubercle to the proximal aspect of the retinaculum measured 13.37 mm ± 2.94 mm while distance from Lister's tubercle to the start of the first dorsal compartment was 18.43 mm ± 2.01 mm; E: Multiple abductor pollicis longus (APL) tendon slips and sub-sheaths. Deep dissection into the first extensor compartment demonstrates multiple tendon slips of the APL tendon as shown by the black arrow. Four separate tendon slips are shown by the arrow, ultimately resulting in incomplete compartment release if not thoroughly dissected. The average number of APL tendon slips was three. A pseudo-retinaculum was also present in four out of six cadavers.

wrist crease, and the radial styloid. Obtaining distances from each of these landmarks to the extensor retinaculum were obtained to determine which data points reliably placed our incision over the first dorsal compartment (Figure 2B-D). Important other parameters that were documented included the presence or absence of the superficial radial nerve overlying the first dorsal compartment, additional compartment sub-sheaths, number of APL tendon slips, and the presence of a pseudoretinaculum (Figure 2E). All measurements were obtained using the same methodology in each cadaveric forearm.

Statistical analysis

Cadaveric measurement data were analyzed using descriptive statistics. The mean, standard deviation and standard error values were calculated manually using standard equations. Confidence intervals were then computed manually using standard formulas prior to the creation of the data figures and tables. Statistical review of the study was performed by a biomedical statistical team at our home institution.

RESULTS

Data points from all six cadavers were analyzed to determine the overall distribution of each variable of interest (Figure 1). Data gathered remained in proximity within each variable analyzed as no significant outliers were seen after histogram analysis (Figure 1). All measurements from the six cadavers were also averaged prior to comparison amongst the other data points. The average length of the thumb distal phalanx was 30.11 mm ± 3.39 mm while the average length of the distal phalanx crease to the tip of the digit was 30.70 mm ± 3.74 mm. The average length of the extensor retinaculum from its proximal to its distal length was 26.82 mm ± 3.34 mm. Therefore, the length from the thumb interphalangeal joint to the thumb tip gives a reasonable estimate of about 3 mm and can be used as a measurement to determine the overall length of the extensor retinaculum. The distance from the radial most aspect of the wrist crease to the retinaculum was 5.14 mm ± 0.80 mm. The distance from Lister's tubercle to the proximal aspect of the retinaculum measured 13.37 mm ± 2.94 mm while distance from Lister's tubercle to the start of the first dorsal compartment was 18.43 mm ± 2.01 mm. The length from the radial styloid to the initial aspect of the extensor retinaculum measured 2.98 mm ± 0.99 mm (Table 1).

Table 1 Superficial landmarks and associated distance from the first dorsal compartment

Anatomic landmarks	Mean (mm)	SD	*N*	SE	95%CI
Distal phalanx	30.11	3.39	6	1.38	(27.40-32.82)
Distal phalanx crease to tip of finger	30.70	3.74	6	1.52	(27.71-33.68)
Retinaculum	26.82	3.34	6	1.37	(24.14-29.49)
Radial styloid to retinaculum	2.98	0.99	6	0.40	(2.18-3.77)
Superficial radial nerve crossing proximal to retinaculum	10.20	4.48	2	3.17	(3.99-16.40)
Wrist crease to retinaculum	5.14	0.80	6	0.33	(4.50-5.78)
Listers tubercle to retinaculum	13.37	2.94	6	1.20	(11.02-15.73)
Listers tubercle to 1st dorsal compartment	18.43	2.01	6	0.82	(16.82-20.04)
Separate EPB compartment	0.66	N/A	6	N/A	
Number of APL slips	3.00	0.63	6	0.26	(2.49-3.51)
Pseudo-retinaculum	N/A	N/A	4	N/A	

Various data points and anatomic landmarks obtained from the cadaveric dissection presented as averages for all specimens included in the study. The average length of the extensor retinaculum was 26.82 mm ± 3.34 mm. The distance from the radial most aspect of the wrist crease to the retinaculum was 5.14 mm ± 0.80 mm. The distance from Lister's tubercle to the proximal aspect of the retinaculum measured 13.37 mm ± 2.94 mm while distance from Lister's tubercle to the start of the first dorsal compartment was 18.43 mm ± 2.01 mm. The presence of a pseudo-retinaculum and separate extensor pollicis brevis compartments were only seen in 4 out 6 cadavers. Average abductor pollicis longus slips in all cadavers was 3. Of note, the superficial radial nerve was only seen in two cadaver dissections. SD: Standard deviation; N: Sample size; SE: Standard error; CI: Confidence interval; EPB: Extensor pollicis brevis; APL: Abductor pollicis longus; N/A: Not available.

Only two cadavers had a superficial radial nerve that crossed over the first dorsal compartment. In two cadaver specimens, the superficial radial nerve was initially encountered at 7.03 mm and 13.36 mm proximal to the most proximal aspect of the extensor retinaculum. In both of those dissections, the superficial radial nerve was seen continuing its course directly dorsal over the extensor retinaculum and radial to the radial styloid. The superficial radial nerve was not encountered even with thorough dissection in the remaining four cadavers. Four out of six cadaveric forearms had a separate EPB compartments and sub-sheaths. The average number of APL tendon slips was three. A pseudo-retinaculum was also present in four out of six cadavers. A pseudo-retinaculum was not appreciated in cadavers that did not have a separate EPB sub-sheath (Table 1).

DISCUSSION

De-Quervain's tenosynovitis warrants surgical intervention in patients who continue to suffer from significant wrist pain and decreased function after failing conservative modalities including physical therapy, anti-inflammatory medications, and corticosteroid injections. Surgical release of the first extensor compartment at the level of the wrist has been well documented with multiple different techniques implementing either longitudinal or transverse incisions. Risk of iatrogenic injury to the superficial radial nerve, decompressing the incorrect compartment, tendon injury, and incomplete release of the compartment can lead to significant patient morbidity. Currently, there has not been a documented reproducible incision that reliably places surgeons in the first dorsal compartment that ensures a safe and complete surgery.

Wilhelmi *et al*[23] demonstrated that the distance from the palmar digital crease to the proximal interphalangeal crease (mean, 2.42 cm ± 0.03 cm) correlated to the distance of the proximal edge of the A1 pulley from the digital palmar crease (mean, 2.45 cm ± 0.03 cm). They determined that surface landmark ratios can be a reliable and reproducible tool that can lead to successful A1 pulley release without complication in trigger finger surgery[23]. Hazani *et al*[21] performed a bony landmark cadaveric study that mapped out and demonstrated that the radial styloid is 0.32 cm ± 0.57 cm from the distal edge of the extensor retinaculum.

Our study demonstrated that the radial styloid was similarly only 2.98 mm ± 0.99 mm from the distal aspect of the retinaculum. Notably, we also noted that Lister's tubercle is only 13.37 mm ± 2.94 mm from the proximal aspect of the retinaculum and 18.43 mm ± 2.01 mm from the first compartment itself. The most radial aspect of the wrist crease is only about 5 mm distal to the retinaculum as well. The length from the thumb interphalangeal joint to the thumb tip provides an estimate of about 3 mm for the entire distance from the radial styloid to the end of the retinaculum. Thus, any incision extending 3 cm distal to the radial styloid will place the surgeon at end of the retinaculum, establishing a complete release. Ultimately, placing an incision 3 mm from the radial styloid, 2 cm from Lister's tubercle, and 5 mm from the radial wrist crease can be used to safely place the incision at the level of the first dorsal compartment.

Matzon *et al*[24] demonstrated the common presence of multiple APL slips in 78% of patients and found that 55% of patients had two subsheaths while 8% had three subsheaths. Kulthanan and Chareonwat[25] re-affirmed those results and demonstrated in contrast that the EPB had a single tendon in 98% of cases. Their study demonstrated that the APL had multiple slips in 89% of cases ($P < 0.001$)[25]. Our cadaver forearms had a mean of 3 separate APL slips, with multiple slips being present in each case. EPB sub-sheaths were present in 67% of our cadaveric cases. Therefore, we recommend a thorough evaluation intra-operatively to document and subsequently release all noted APL slips and to also release all EPB sub-sheaths as they will be present in the majority of cases. Being cognizant of this anatomic variant intra-operatively will allow for a full surgical release that can be accomplished during each case.

Importantly, Samarakoon *et al*[12] found that the superficial radial nerve branches 5.1 cm proximal to the radial styloid. They also found that the superficial radial nerve can branch 0.4 cm from the center of the first dorsal compartment and 1.6 cm from Lister's tubercle[12]. Gurses *et al*[11] found that the lateral dorsal digital branch to the thumb, off of the superficial radial nerve, coursed directly over the first dorsal compartment in 8 out of 20 cadavers. In our study, we found the superficial radial nerve present in close proximity in only 2 out of the 6 cadavers (7.03 mm and 13.36 mm proximal to the retinaculum). The other four dissections did not demonstrate a clear superficial radial nerve nearby our surgical site. However, if the superficial bony landmark measurements stated above are followed, we anticipate that the superficial radial nerve will not be encountered as unnecessary dissection will not be undertaken.

The main limitation of our study includes the small sample size. We were only able to perform six cadaveric dissections which limits the overall data points available for comparison to other studies and diminishes the overall generatability to the general population. Ultimately, a higher sample size of cadaveric forearms could be dissected in the future to obtain a larger data set.

CONCLUSION

Superficial landmarks are a reliable way to create a reproducible incision over the first dorsal compartment in order to obtain a complete release and protect the superficial radial nerve. Creating an incision that measures 3 mm proximal from the radial styloid, 2 cm proximal from Lister's tubercle, and 5 mm radial from the radial wrist crease will safely place surgeons at the level of the first dorsal compartment. Extending the incision 3 cm proximal to the radial styloid will fully encompass the extensor retinaculum and allow for a complete release. The APL tendon does reliably have multiple slips and the EPB does contain multiple sub-sheaths in the majority of cases, which are important anatomic variants to be cognizant of intra-operatively.

FOOTNOTES

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