

Bone and Arthroscopy Science

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Bone and Arthroscopy Science

Focus and Scope

Bone and Arthroscopy Science is a peer-reviewed articles across a wide spectrum of clinical treatise, basic research, review, frontier of orthopedics, case analysis and comment. This journal is aimed at professionals at all levels engaged in the basic and clinical work of orthopedics. Each issue is guest-edited by an acknowledged expert and focuses on a single topic or controversy.

It mainly reports new viewpoints, new achievements and new technologies in basic and clinical research of bone and joint surgery. The covered topics include, but are not limited to: sports medicine and arthroscopy, prosthetic design, biomechanics, biomaterials, metallurgy, biologic response to arthroplasty materials *in vivo* and *in vitro*.

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Clinical Guideline for Perioperative Pain Management in Diabetic Foot Ulcers

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Abstract: This guideline outlines the pathophysiology and classification of neuropathic, ischemic, inflammatory, and procedural pain, and proposes a risk-stratified assessment using NRS/VAS combined with ulcer severity and comorbidities. Core recommendations emphasize preventive multimodal analgesia, prioritization of regional anesthesia, systematic management of neuropathic pain, protocolized procedural analgesia, and multidisciplinary collaboration.

Keywords: Diabetic foot ulcer; Perioperative pain; Procedural pain; Multimodal analgesia

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1. Introduction

Diabetic foot ulcer (DFU) is one of the most serious complications of diabetes, with high disability and amputation rates ^[1]. The mechanisms of DFU-related pain are complex and often coexist in the same patient, including burning or electric-shock neuropathic pain due to peripheral neuropathy, rest and nocturnal pain caused by limb ischemia, throbbing or tearing pain related to infection and inflammation, and procedure-related pain during dressing changes, debridement, toe amputation, and negative-pressure wound therapy (NPWT) ^[2]. Poor pain control reduces tolerance and adherence to dressing changes and debridement, impairs wound healing through stress responses, and exacerbates glycemic fluctuations and cardiovascular risk. It also markedly affects sleep and overall quality of life ^[3].

2. Scope and target population

This guideline applies to adult patients (≥ 18 years) with a confirmed diagnosis of DFU, including infection-predominant, ischemic, neuropathic, and mixed types, and focuses on perioperative and procedure-related pain

management ^[4]. The covered procedures include: Routine outpatient or ward dressing changes and bedside minor debridement; operative debridement and incision and drainage of abscesses; minor amputations such as toe or partial metatarsal resection; split-thickness skin graft harvesting and grafting, local flap reconstruction; application and change of NPWT and negative-pressure irrigation systems; management of foot wounds during and after revascularization procedures directly related to DFU ^[5].

The guideline does not primarily apply to: non-diabetic etiologies of foot ulcers; major amputations, where perioperative analgesia should follow anesthesia and surgical guidelines; or patients with chronic diabetic peripheral neuropathic pain without open wounds ^[6].

3. Pathophysiological basis and pain classification

Perioperative pain in DFU usually reflects the superimposition of chronic baseline pain and acute nociceptive pain from tissue injury ^[4]. Many patients have moderate-to-severe chronic pain before surgery; intraoperative and postoperative cutting, excision, and traction further increase pain intensity and complexity ^[7]. Conversely, excessive sedation or inappropriate drug use may increase the risk of falls, respiratory depression, and other complications. Effective management therefore requires a careful balance between analgesia and safety ^[7,8].

From the perspective of dominant mechanism, perioperative DFU pain can be classified as: Predominantly neuropathic pain; predominantly ischemic pain; predominantly infection- and inflammation-related pain; predominantly procedural pain; mixed-mechanism pain ^[9].

4. Preoperative assessment and risk stratification

Pain evaluation should include intensity, quality, duration, and precipitating or aggravating factors, with separate recording of rest pain and activity/procedural pain ^[10]. Medication history and previous analgesic use are equally important. Clinicians should clarify whether the patient has been receiving opioids, gabapentin/pregabalin, duloxetine, or other agents in order to judge tolerance, potential dependence, and the risk of cumulative adverse effects. Psychological state and cognitive function should also be assessed, as they significantly influence pain perception and cooperation ^[9].

5. Principles and clinical scenarios in perioperative pain management

Perioperative pain control in DFU should be based on multimodal analgesia while safeguarding hemodynamic stability and wound healing. In the absence of contraindications, paracetamol and NSAIDs may be combined, supplemented as necessary with agents for neuropathic pain and short-course, low-dose short-acting opioids, thereby minimizing the dose and adverse effects of any single drug ^[10].

Analgesia should be pre-emptive rather than purely reactive. For procedures expected to cause moderate-to-severe procedural pain, medications should be given 30–60 minutes before the intervention to avoid exacerbating pain during or after the procedure ^[11]. Whenever possible, local or regional anesthesia—such as ankle block, popliteal sciatic block, or dorsal/plantar foot nerve blocks—should be prioritized, with careful monitoring of limb perfusion, to reduce systemic opioid requirements. All analgesic decisions must balance pain relief against perfusion and healing, avoiding deep sedation or hypotension that may cause falls and cardiovascular events, while also preventing sympathetic overactivation from uncontrolled pain ^[12].

For outpatient or bedside dressing changes and small-area debridement, a graded approach based on risk stratification is recommended. In low-risk patients, oral paracetamol with short-term NSAIDs is often sufficient^[3]. For patients who are pain-sensitive or have had poor previous dressing-change experiences, local measures such as topical lidocaine gel or spray, or small-field infiltration anesthesia before the procedure, can reduce procedural pain. In moderate-risk patients, procedural analgesia should be emphasized: control irrigant temperature and irrigation pressure, avoid vigorous wiping and prolonged exposure, and break long procedures into stages with brief rest intervals as needed^[12].

For operative large-area debridement and minor amputations, regional nerve block combined with light sedation should be considered a first-line option^[9]. Scheduled dosing or patient-controlled analgesia is preferred over purely as-needed dosing, and existing neuropathic-pain regimens should be continued or adjusted to prevent rebound pain and disruptive nocturnal pain that may impair sleep and glycemic control^[13].

For NPWT application and changes, negative-pressure irrigation, and skin grafting, these procedures should be assumed to cause at least moderate procedural pain^[14]. Standard practice should include pre-procedure oral analgesics combined with local anesthesia; for patients with high baseline pain or prior poor tolerance, a short-acting opioid may be added briefly. During NPWT, attention must be paid to pain at both donor and recipient sites^[15]. If patients report intolerable traction-type pain under suction, negative pressure can be reduced, interface layers can be thickened, or intermittent rather than continuous suction can be used^[16].

6. Non-pharmacological interventions and patient education

Non-pharmacological strategies are an important adjunct in perioperative pain management. Clear, explanatory communication about procedural steps, expected pain intensity, and planned analgesic measures can markedly reduce fear, catastrophic thinking, and anticipatory anxiety related to dressing changes and debridement^[17].

7. Special populations and high-risk situations

Elderly patients and those with renal impairment or heart failure have reduced tolerance to NSAIDs and opioids. In such cases, doses and duration should be strictly limited, with a greater reliance on paracetamol, local anesthetics, and regional blocks^[18].

8. Summary of recommendations (OCEBM and Delphi)

Evidence levels are assigned according to the OCEBM framework, integrating data from systematic reviews, cohort studies, and case series (see **Table 1**).

Table 1. Recommendations for procedural pain management in diabetic foot ulcers (DFU)

No.	Summary of recommendations	Level of evidence (OCEBM)	Strength of recommendation	Delphi Consensus (%)
R1	All DFU patients scheduled for procedures should undergo standardized pain assessment and classification (by source and intensity).	3B	A	94
R2	For procedures expected to cause at least moderate procedural pain, preventive multimodal analgesia should be used rather than single-agent, rescue-only analgesia.	2B	A	91
R3	For moderate-to-severe debridement and minor amputations, regional nerve blocks should be prioritized and, where appropriate, combined with light sedation to reduce systemic opioid exposure.	2C	A	90
R4	Ongoing neuropathic pain should be managed according to pathways for painful diabetic peripheral neuropathy (PDPN) and integrated with perioperative analgesic planning.	2C	B	88
R5	Procedural pain should be routinely assessed before dressing changes and debridement, and managed with oral analgesics and/or local anesthesia as procedural analgesia.	3B	A	92
R6	For high-risk patients (elderly, multimorbid, or long-term opioid users), individualized analgesic plans should be developed with participation from anesthesia/pain services.	3C	B	89
R7	NPWT application and changes should be regarded as procedures causing at least moderate pain; preventive analgesia and local anesthesia should be provided, and negative-pressure settings adjusted according to tolerance.	3B	B	86
R8	A system for NRS-based pain recording and follow-up should be established, and pain control incorporated into the comprehensive outcome assessment of DFU management.	3C	B	90

9. Future directions and updating plan

High-quality evidence specifically addressing perioperative pain management in DFU remains limited. Existing studies focus mainly on neuropathic pain or general perioperative analgesia, with very few prospective data on dressing changes, debridement, NPWT, and minor amputations in DFU. Future research should include multicenter prospective cohorts or randomized controlled trials comparing different multimodal analgesic combinations, regional anesthesia techniques, and non-pharmacological interventions, and their impact on pain control, glycemic stability, and wound healing.

Disclosure statement

The authors declare no conflict of interest.

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Trends in the Burden of Osteoarthritis in China Compared with G20 Countries, 1990–2023: An Analysis of the Global Burden of Disease Study

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Abstract: *Background:* Osteoarthritis (OA) is a leading cause of disability worldwide. China is undergoing rapid population ageing, yet how its OA burden compares with that of other G20 countries over time has not been fully quantified. *Methods:* Using data from the Global Burden of Disease 1990–2023 study, we described OA incidence, prevalence, and disability-adjusted life years (DALYs) for China and the aggregated G20. We analyzed age-standardized rates (ASRs) and absolute numbers for adults ≥ 30 years by year, age group, and anatomical site (knee, hip, hand, other). Temporal trends were summarized by estimated annual percentage change. We visualized overall time trends in incidence, age-specific rates, and case numbers in 2023, and the distribution of OA subtypes in China versus the G20. *Results:* From 1990 to 2023, China's age-standardized incidence rate (ASIR) increased from 487.1 to 550.2 per 100,000, while annual incident cases rose from 4.68 to 11.90 million. Age-standardized prevalence and DALY rates also rose modestly, but absolute numbers of prevalent cases and DALYs more than doubled. Compared with the G20 aggregate, China showed steeper increases in both incidence and case numbers. In 2023, incidence, prevalence, and DALY rates climbed steadily with age in both China and the G20, with incidence peaking at 55–64 years, prevalence at 85–94 years, and DALY rates at 70–79 years; the bulk of cases occurred between 50 and 74 years. Across anatomical sites, knee OA contributed the largest share of burden, followed by hand, other sites, and hip OA, with a broadly similar ranking in China and the G20. *Conclusion:* From 1990 to 2023, China experienced a marked rise in OA burden, driven mainly by population growth and ageing. Older adults, especially those with knee and hand OA, carry the greatest share of the disease. Healthcare planning should prioritize age-friendly prevention, early diagnosis, and long-term rehabilitation.

Keywords: Osteoarthritis; Global Burden of Disease; G20 countries; Incidence and prevalence

Online publication: December 31, 2025

1. Introduction

Osteoarthritis (OA) is the most common joint disease and a major cause of pain, functional limitation, and

reduced quality of life among older adults. Clinically, OA is characterized by progressive cartilage degeneration, subchondral bone remodeling, and synovial inflammation, leading to chronic pain, stiffness, and disability. With no curative pharmacological treatment available, management focuses on symptom control, maintenance of function, and, in advanced cases, joint replacement surgery. As life expectancy increases and lifestyles become more sedentary, OA is emerging as one of the dominant chronic conditions in ageing societies.

China, with the largest population in the world, is undergoing a rapid demographic transition with a growing proportion of older adults. This change is expected to substantially increase the number of people living with OA and to place heavy demand on orthopedic, rehabilitation, and long-term care services ^[1]. G20 countries share similar challenges but are at different stages of economic development, demographic transition, and health-system capacity. Comparing China with the broader G20 context can therefore provide insights into how population structure and development level shape the OA burden, and where prevention and service planning should be prioritized ^[2].

The Global Burden of Disease (GBD) study provides a consistent framework for quantifying and comparing the burden of diseases and injuries across countries, time, and demographic groups. Using the most recent GBD 1990–2023 estimates, we aimed to describe long-term trends in OA incidence, prevalence, and disability-adjusted life years (DALYs) in China in comparison with the G20 aggregate. We focused on overall temporal patterns, age-specific profiles, and the contribution of different anatomical sites, illustrated in three key figures.

2. Methods

2.1. Data source and case definition

We used publicly available estimates from the GBD 1990–2023 study. OA was defined according to standard GBD case definitions based on clinical and radiographic criteria and mapped to relevant ICD codes. GBD distinguishes OA of the knee, hip, hand, and other sites; these four subtypes were analyzed separately and combined as total OA.

2.2. Measures

For China and the aggregated G20, we extracted incident cases, prevalent cases, and DALYs for OA among adults aged 30 years and older from 1990 to 2023. Age-standardized incidence, prevalence, and DALY rates per 100,000 population were calculated using the GBD standard population. We further obtained age-specific rates and case numbers for 2023 by 5-year age group, and site-specific ASRs for knee, hip, hand, and other OA.

2.3. Statistical analysis and visualization

Temporal trends in ASRs were summarized using estimated annual percentage change. For descriptive purposes, we highlighted the trajectory of OA incidence from 1990 to 2023 and contrasted China with the G20 aggregate ^[3]. To explore age patterns, we compared age-specific rates and case numbers of incidence, prevalence, and DALYs in 2023 between China and the G20. Finally, we summarized the relative contribution of knee, hip, hand, and other OA to the total age-standardized burden in 2023. Analyses were descriptive and based on standard GBD summary statistics.

3. Results

3.1. Overall temporal trends

Between 1990 and 2023, China's age-standardized incidence rate (ASIR) of OA increased modestly from 487.1 to 550.2 per 100,000, corresponding to a small but persistent positive annual change. Over the same period, the number of new OA cases more than doubled, rising from about 4.7 million to nearly 12 million per year. Age-standardized prevalence and DALY rates also showed mild upward trends, whereas the absolute numbers of people living with OA and the DALY burden increased sharply, reflecting the combined effects of population growth and ageing. As shown in **Figure 1**, similar qualitative patterns were observed in the G20 aggregate, but the slope of increase in both ASIR and case numbers was generally steeper in China, particularly after the early 2000s.

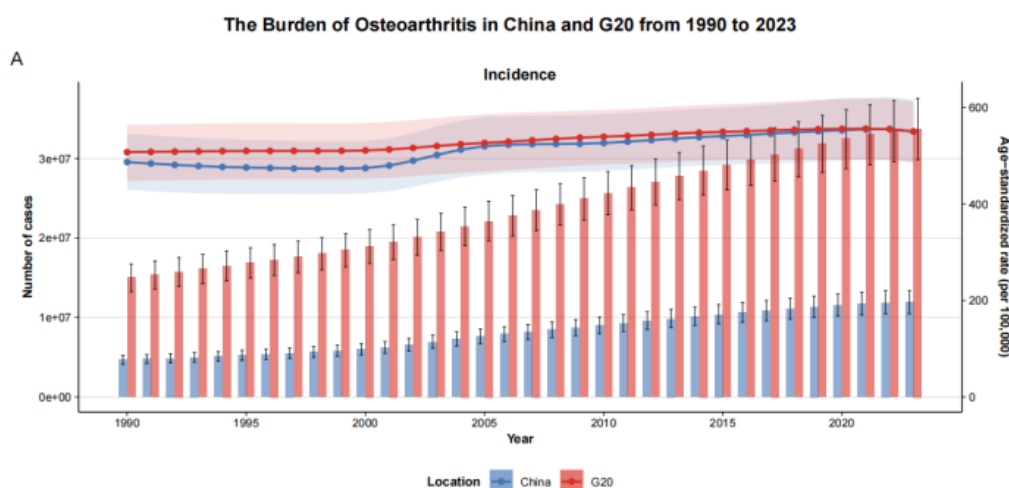


Figure 1. Temporal trends in osteoarthritis incidence in China and the G20, 1990–2023. Bars display the annual number of incident osteoarthritis cases, and overlying lines show the age-standardized incidence rate (per 100,000) for China (blue) and the G20 (red). Shaded bands around the lines indicate 95% uncertainty intervals.

3.2. Age-specific patterns in 2023

Age-specific analyses showed a strong gradient of OA burden with advancing age in both China and the G20 (**Figure 2**). In 2023, incidence rates rose steadily from the 30–34-year group, peaked at 55–64 years, and then declined slightly at the oldest ages. In contrast, prevalence rates increased almost monotonically with age, reaching their maximum in the 85–94-year group, consistent with the chronic and accumulative nature of OA. DALY rates peaked somewhat earlier, around 70–79 years, indicating that functional limitation and health loss are most pronounced in late-elderly adults.

When absolute numbers of cases were considered, the bulk of the burden was concentrated in middle-to-older adults. For both China and the G20, the highest numbers of incidents and prevalent cases, as well as DALYs, occurred between 50 and 74 years. China contributed a substantial share of global cases in these age bands. Although patterns of age-specific rates were broadly similar between China and the G20, age-specific prevalence and DALY rates tended to be slightly higher in the G20 at most ages, whereas China showed particularly rapid growth in case numbers due to its large and ageing population.



Figure 2. Age-specific burden of osteoarthritis in China and the G20 in 2023. The upper panels present age-specific incidence, prevalence, and DALY rates (per 100,000) for adults aged ≥ 30 years, while the lower panels show the corresponding numbers of incident cases, prevalent cases, and DALYs. Blue bars represent China and red bars the G20 aggregate. Error bars denote 95% uncertainty intervals.

3.3. Distribution by anatomical site

Figure 3 compares the relative ranking of knee, hip, hand, and other OA in China and the G20. In both settings, knee OA accounted for the highest age-standardized rates, followed by hand OA, other sites, and hip OA. This pattern was consistent for incidence, prevalence, and DALYs. The predominance of knee OA highlights its central role in driving the overall OA burden. Hand OA also contributed substantially, especially in China, where its rates have risen in recent years. By contrast, hip and other-site OA remained at comparatively low levels and made a relatively small contribution to the total OA burden.

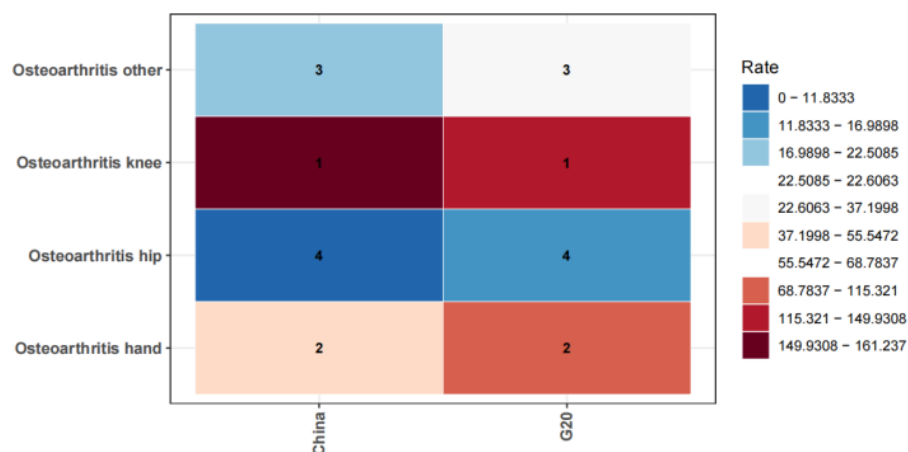


Figure 3. Site-specific burden of osteoarthritis in China and the G20 in 2023. Heat map showing age-standardized rates (per 100,000) of osteoarthritis of the knee, hip, hand, and other sites in China and the G20. Colors indicate the magnitude of the rate according to the legend, and the numbers within each cell represent the within-country rank of each site (1 = highest burden, 4 = lowest burden).

4. Discussion

In this GBD-based analysis, we found that China has experienced a sustained increase in OA burden from 1990 to 2023, with modest rises in age-standardized rates but striking increases in absolute numbers of incident cases, prevalent cases, and DALYs^[4]. Compared with the G20 aggregate, China showed steeper growth in incidence and case numbers, reflecting the combination of rapid population ageing and a very large underlying population base^[5].

The age-specific patterns we observed are typical of a degenerative joint disease. Incidence rates peaked in late middle age, when cumulative mechanical load and occupational exposures intersect with comorbidities such as obesity^[6]. Prevalence and DALY rates remained high into advanced age, underlining that OA is a long-lasting condition that seldom resolves and often leads to progressive functional decline. The concentration of cases and DALYs between 50 and 74 years means that OA disproportionately affects adults in or near retirement age, with implications for labor participation, informal caregiving, and social security systems^[7].

Our site-specific analysis underscores the dominant role of knee OA in both China and the G20. The knee joint bears substantial weight and is strongly influenced by body mass index, occupational kneeling or squatting, and previous injury^[8]. The high burden of knee OA therefore signals the need to intensify interventions targeting obesity, physical inactivity, and workplace ergonomics. The significant contribution of hand OA, particularly in China, suggests that attention should also be given to manual labor, repetitive hand use, and hormonal or genetic factors that may predispose to small-joint degeneration^[9]. Hip and other-site OA currently contribute a smaller share of the burden, but they remain important causes of disability and often require costly surgical treatment^[10].

From a policy perspective, our findings highlight several priorities. Because OA burden rises steeply with age, health systems must prepare for greater demand for orthopedic surgery, rehabilitation, and long-term care as the population ages. Prevention strategies should focus on modifiable risk factors, especially high body mass index and insufficient physical activity, which are increasingly prevalent in urbanizing societies. Early diagnosis and timely non-surgical management, including patient education, exercise therapy, weight management, and appropriate pharmacological treatment, are essential to delay progression and reduce the need for joint replacement. China's rapid increase in OA burden suggests that scaling up community-based rehabilitation and integrating OA management into primary care are urgent tasks.

This study has several limitations. GBD estimates are derived from multiple data sources and modelling procedures, and residual uncertainty may persist, particularly in countries or age groups with limited primary data. We could not distinguish radiographic from symptomatic OA or account for disease severity, treatment patterns, or comorbidities. Furthermore, our analyses were descriptive and did not explore causal relationships between risk factors and OA outcomes. Nonetheless, the GBD framework provides the most comprehensive available picture of global and national OA burden, allowing meaningful comparisons between China and the wider G20.

5. Conclusion

Between 1990 and 2023, the burden of OA in China increased substantially, with modest rises in age-standardized rates but large gains in the number of people affected and the associated DALYs. Compared with the G20 aggregate, China shows steeper growth and a particularly heavy burden of knee and hand OA among adults aged 50 years and older. As China and other G20 countries continue to age, coordinated efforts in prevention, early diagnosis, and rehabilitation will be critical to curb the future impact of OA on individuals and healthcare systems.

Disclosure statement

The authors declare no conflict of interest.

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The Effect of Intra-Articular Injection of PRP Combined with Sodium Hyaluronate and TCM Hot Compress Pack on Serum IL-1 β and IL-6 in Patients with Knee Osteoarthritis

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Abstract: *Objective:* This study aims to investigate the impact of a combined intervention of intra-articular injections of platelet-rich plasma (PRP) and sodium hyaluronate, followed by traditional Chinese medicine (TCM) hot compress therapy, on serum levels of interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) in patients with knee osteoarthritis (KOA). Additionally, it seeks to assess the clinical effectiveness and elucidate the potential mechanisms of this integrated treatment approach. *Methods:* A total of 86 KOA patients admitted to our hospital between August 2024 and July 2025 were randomly assigned to a study group and a control group, each with 43 patients. The control group was treated with intra-articular injection of PRP combined with sodium hyaluronate, while the study group received additional application of a TCM hot compress pack. Clinical efficacy, pain intensity (assessed using the numerical rating scale, NRS), joint function (evaluated using the WOMAC index), serum levels of IL-1 β and IL-6, and quality of life (measured using the SF-36 scale) were compared between the two groups before and after the intervention. *Results:* The study group demonstrated a significantly greater total effective rate compared to the control group ($P < 0.05$). Following treatment, the study group exhibited markedly reduced NRS and WOMAC scores, along with lower serum levels of IL-1 β and IL-6, all significantly superior to the control group ($P < 0.05$). Conversely, SF-36 scores in the study group were significantly elevated compared to the control group ($P < 0.05$). *Conclusion:* Intra-articular injection of PRP combined with sodium hyaluronate, supplemented by TCM hot compress pack, can effectively regulate serum IL-1 β and IL-6 levels in KOA patients, alleviate pain, improve joint function and quality of life, and has good clinical application value.

Keywords: Knee osteoarthritis; Platelet-rich plasma; Sodium hyaluronate; Traditional Chinese medicine hot compress pack; Interleukin-1 β ; Interleukin-6

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1. Introduction

Knee osteoarthritis (KOA) is a prevalent chronic degenerative disease in orthopedics, characterized by cartilage degeneration and osteophyte formation, presenting with pain and limited mobility. The prevalence rate exceeds 30% among individuals over 60 years old, imposing a significant burden on society ^[1,2]. Clinical management primarily aims to alleviate symptoms, with intra-articular injection of platelet-rich plasma (PRP) combined with sodium hyaluronate being a common approach. PRP promotes cartilage repair, while sodium hyaluronate enhances joint lubrication; however, their efficacy in regulating inflammation is limited ^[3,4]. Traditional Chinese medicine (TCM) classifies KOA as “bone arthralgia,” attributing its pathogenesis to liver and kidney deficiency and qi and blood stagnation. Hot compress with a TCM pack can promote blood circulation, remove blood stasis, warm the meridians, and relieve pain ^[5]. This study investigated the combined application of PRP + sodium hyaluronate with a TCM hot compress pack, exploring its effects on serum interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) levels to provide a basis for optimizing treatment protocols.

2. Materials and methods

2.1. General information

Eighty-six patients diagnosed with KOA and admitted to our hospital between August 2024 and July 2025 were enrolled in the study. The inclusion criteria were as follows: (1) Meeting the diagnostic criteria for KOA as defined in the *Guidelines for the Diagnosis and Treatment of Osteoarthritis (2021 Edition)*; (2) Confirmation by knee joint X-ray or MRI of varying degrees of articular cartilage damage and osteophyte formation; (3) Age ranging from 45 to 75; (4) Knee pain NRS score of ≥ 4 ; (5) No intra-articular drug injections or external treatment with TCM in the past month; (6) Both patients and their family members have a clear understanding of the trial content and have signed informed consent forms. Exclusion criteria: (1) Knee joint deformities, suppurative inflammation, tuberculosis, malignant tumors, or other diseases caused by trauma; (2) A history of allergies to PRP, sodium hyaluronate, or TCM preparations; (3) Suffering from severe diseases of the hematopoietic system, cardiovascular system, liver, kidney, or other organs that render them unable to tolerate surgery.

Patients were randomly allocated into a control group ($n = 43$) and a study group ($n = 43$). The control group comprised 19 males and 24 females, with a mean age of 61.25 ± 5.32 years and a mean disease duration of 5.32 ± 1.89 years. Within this group, 20 patients were classified as K-L grade II and 23 as grade III. The study group included 20 males and 23 females, with a mean age of 60.89 ± 5.15 years and a mean disease duration of 5.45 ± 1.92 years. In this group, 21 patients were grade II and 22 were grade III. Baseline characteristics were comparable between the two groups ($P > 0.05$). The study protocol received approval from the relevant ethics committee.

2.2. Treatment methods

2.2.1. Control group

The control group received PRP combined with sodium hyaluronate injection: 8 mL of venous blood was drawn, centrifuged at 1500 r/min for 9 minutes to prepare 2 mL of PRP, which was then injected into the joint cavity through a lateral knee puncture; concurrently, 2 mL of sodium hyaluronate was also injected. The treatment was administered once every two weeks, for a total of two sessions, spanning a four-week period.

2.2.2. Study group

The study group received additional treatment with a TCM hot compress pack: 100 g each of dodder seed, fried

mustard seed, perilla seed, and radish seed, along with 60 g of *Evodia rutaecarpa*, were heated in a constant temperature incubator to 65°C. The compress was applied to the affected area 24 hours after sodium hyaluronate injection, for 30 minutes each time, twice daily, five days a week, for a total of four weeks.

2.3. Observation indicators

2.3.1. Clinical efficacy

The efficacy was evaluated with reference to the “Guidelines for Clinical Research on New Traditional Chinese Medicines”: markedly effective (NRS reduction $\geq 80\%$, symptoms disappeared), effective (NRS reduction 50–79%, symptoms alleviated), and ineffective (NRS reduction $< 50\%$). The overall effective rate was calculated as (markedly effective + effective) / total number of cases $\times 100\%$.

2.3.2. Pain and joint function scores

Assessments were performed pre- and post-treatment. Pain was quantified via the Numerical Rating Scale (NRS, score range 0–10, where higher values denote more intense pain)^[6], while joint function was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, score range 0–96, where higher scores reflect greater functional impairment).

2.3.3. Serum inflammatory cytokine level

Fasting blood samples (5 mL) were collected pre- and post-treatment. Following centrifugation at 3000 rpm for 15 minutes, serum concentrations of IL-1 β and IL-6 were quantified using enzyme-linked immunosorbent assay (ELISA).

2.3.4. Quality of life score

The quality of life of patients was evaluated using the Short Form Health Survey (SF-36) both at baseline and following the completion of treatment^[7]. Scores on this instrument span from 0 to 100, where elevated scores correspond to a more favorable quality of life.

2.4. Statistical methods

Statistical analysis was performed with SPSS software (version 26.0). Continuous variables, presented as mean \pm standard deviation (SD), were compared using *t*-tests. Categorical variables, expressed as *n* (%), were analyzed with chi-square tests. A *P*-value of less than 0.05 was defined as statistically significant.

3. Results

3.1. Comparison of clinical efficacy between the two groups

The study group demonstrated a significantly higher overall response rate compared to the control group (*P* < 0.05), as detailed in **Table 1**.

Table 1. Comparison of clinical efficacy between the two groups [*n* (%)]

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (<i>n</i> = 43)	15 (34.88)	17 (39.53)	11 (25.58)	32 (74.42)
Study group (<i>n</i> = 43)	24 (55.81)	16 (37.21)	3 (6.98)	40 (93.02)
χ^2 -value				5.460
<i>P</i> -value				0.019

3.2. Comparison of NRS and WOMAC scores before and after treatment between the two groups

After the intervention, patients in the study group demonstrated significantly lower NRS and WOMAC scores compared to those in the control group ($P < 0.05$). Details are provided in **Table 2**.

Table 2. Comparison of NRS and WOMAC scores before and after treatment between the two groups (mean \pm SD, points)

Group	NRS pain score		WOMAC index (points)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (<i>n</i> = 43)	6.89 \pm 1.02	3.62 \pm 0.73	68.92 \pm 7.56	45.89 \pm 6.34
Study group (<i>n</i> = 43)	6.92 \pm 1.05	2.15 \pm 0.58	69.34 \pm 7.62	32.67 \pm 5.21
<i>t</i> -value	0.134	10.339	0.257	10.564
<i>P</i> -value	0.893	0.000	0.798	0.000

3.3. Comparison of serum IL-1 β and IL-6 levels before and after treatment between the two groups

Following treatment, the study group exhibited a significant reduction in IL-1 β and IL-6 levels compared to the control group ($P < 0.05$). Details are presented in **Table 3**.

Table 3. Comparison of serum IL-1 β and IL-6 levels before and after treatment between the two groups (mean \pm SD, pg/mL)

Group	IL-1 β (pg/mL)		IL-6 (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (<i>n</i> = 43)	8.62 \pm 1.35	5.31 \pm 1.02	32.56 \pm 4.28	21.45 \pm 3.16
Study group (<i>n</i> = 43)	8.58 \pm 1.41	3.25 \pm 0.86	32.49 \pm 4.35	14.28 \pm 2.89
<i>t</i> -value	0.134	10.125	0.075	10.979
<i>P</i> -value	0.893	0.000	0.940	0.000

3.4. Comparison of quality of life scores before and after treatment between the two groups

After the intervention, the study group demonstrated significantly higher SF-36 scores compared to the control group ($P < 0.05$). For detailed results, refer to **Table 4**.

Table 4. Comparison of quality of life scores before and after treatment between the two groups (mean \pm SD, points)

Group	SF-36 score (points)	
	Before treatment	After treatment
Control group ($n = 43$)	52.34 \pm 5.67	68.45 \pm 5.89
Study group ($n = 43$)	52.67 \pm 5.72	82.35 \pm 6.12
<i>t</i> -value	0.269	10.731
<i>P</i> -value	0.789	0.000

4. Discussion

The core pathogenesis of KOA involves cartilage degradation mediated by inflammatory factors. IL-1 β can activate matrix metalloproteinases (MMPs) to accelerate the degradation of cartilage matrix and inhibit the synthesis of proteoglycans by chondrocytes. As a key pro-inflammatory factor, IL-6 can amplify the inflammatory response and promote synovial hyperplasia and osteophyte formation. PRP contains platelets at a concentration 3 to 5 times higher than normal levels. Upon activation, it releases growth factors such as PDGF and TGF- β , which promote chondrocyte proliferation and repair while inhibiting synovial inflammation. Sodium hyaluronate supplements the viscoelasticity of joint synovial fluid, reducing friction and protecting cartilage^[8]. TCM considers KOA to be a condition of “deficiency in the root and excess in the manifestation.” In this study, the hot compress package demonstrates effects of warming and unblocking meridians, dispersing cold, and relieving pain: the warm-natured herbs *Evodia rutaecarpa* and *Perilla frutescens* seeds, combined with the thermal effect of the hot compress package, can dispel local cold, unblock meridians, and alleviate joint pain and stiffness caused by “cold coagulation and qi stagnation” and “meridian obstruction.” Additionally, it has effects of promoting qi circulation and resolving phlegm, reducing swelling and dispersing nodules: stir-fried *Brassica alba* seeds and *Raphanus* seeds can regulate qi, resolve phlegm, eliminate food stagnation, and reduce bloating, aiding in the relief of swelling and effusion around the joints and alleviating local conditions of “phlegm-dampness and blood stasis obstruction.” Cuscutae seeds nourish the liver and kidneys, strengthen tendons and bones, enhancing the repair capacity of tissues around the joints, making them suitable for joint discomfort associated with liver and kidney deficiency.

The findings of this study demonstrate a significantly higher overall treatment efficacy in the study group compared to the control group, indicating that the combined therapeutic regimen can markedly improve clinical outcomes. The analysis attributes this to the dual effects of warmth and pharmacology produced by the TCM hot compress pack in the study group: on one hand, it improves blood circulation around the patient’s knee joint; on the other hand, it ensures the even distribution and full absorption and utilization of PRP and sodium hyaluronate in the knee joint cavity, further promoting repair of cartilage damage and exerting anti-inflammatory effects^[9]. Additionally, after penetrating the skin and entering the body, the TCM herbs can directly inhibit the inflammatory response of the synovial tissue, achieving effects of promoting blood circulation to remove blood stasis, unblocking meridians, and relieving pain, thereby enhancing treatment efficacy.

In this investigation, the post-treatment NRS scores and WOMAC indices were markedly reduced in the study group compared to those in the control group. The analysis attributes this to the fact that the various growth factors released by PRP possess anti-inflammatory and regenerative properties, while hyaluronic acid can reduce

friction between joint surfaces. The hot compress therapy with TCM herbal packs can achieve the goals of dilating blood vessels and accelerating blood circulation through temperature stimulation, thereby relieving muscle fiber tension, blocking the transmission of pain signals, and exerting effects of promoting blood circulation, removing blood stasis, and relieving pain ^[10]. The improvement in joint function is closely related to cartilage repair, inflammation resolution, and pain relief. The combined treatment effectively improves symptoms such as knee stiffness and limited mobility through multifaceted regulation, thereby enhancing joint function.

After treatment, the serum concentrations of IL-1 β and IL-6 in the study group were markedly reduced compared to those in the control group. This may be attributed to the high platelet content in PRP, which, when activated, secretes multiple growth factors including platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and insulin-like growth factor-1 (IGF-1). PDGF can promote chondrocyte proliferation and matrix synthesis, while TGF- β can inhibit synovial inflammation and reduce the secretion of inflammatory factors. The active ingredients in *Angelicae Sinensis Radix* and *Chuanxiong Rhizoma* can inhibit the expression of inflammatory factors IL-1 β and IL-6, while *olibanum* and *myrrh* can inhibit prostaglandin synthesis and relieve pain. Combined with sodium hyaluronate, they can achieve a dual effect of “anti-inflammation + repair” and synergistically improve joint function.

The quality of life scores were significantly higher in the study group compared to the control group, reflecting an overall improvement in clinical outcomes. Since the daily activities of KOA patients are severely affected and restricted, and the long-term suffering from the disease also imposes a tremendous mental burden on them, the low quality of life in KOA patients is the result of multiple factors working together. Comprehensive treatment approaches can effectively reduce pain and improve the functional level of joints in KOA patients, thereby enabling rapid physiological recovery, enhancing social participation, and subsequently improving psychological well-being and quality of life.

5. Conclusion

In summary, the combined therapeutic approach involving intra-articular injections of PRP and sodium hyaluronate, together with the external application of TCM heat-retaining herbal packs, effectively lowers serum IL-1 β and IL-6 levels in patients with KOA. This regimen not only relieves pain and improves joint mobility but also enhances patients' overall quality of life. The treatment demonstrates significant clinical effectiveness and a favorable safety profile, supporting its broader adoption in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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The Impact of Preemptive Analgesia Combined with Multimodal Analgesia on Perioperative Pain and Postoperative Fracture Healing in Elderly Patients with Hip Fractures

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Abstract: *Objective:* To investigate the impact of preemptive analgesia combined with multimodal analgesia on perioperative pain and postoperative fracture healing in elderly patients with hip fractures. *Methods:* A total of 202 patients who underwent total hip arthroplasty from January 2024 to December 2024 were selected and divided into two groups based on different analgesic methods: a control group receiving routine postoperative multimodal analgesia and a study group receiving preemptive analgesia combined with multimodal analgesia, each with 101 cases. The analgesic effects were compared between the two groups. *Results:* The pain scores of the study group at all postoperative time points were significantly lower than those of the control group ($P < 0.05$); the number of patient-controlled intravenous analgesia pumps and the frequency of rescue analgesia in the study group were significantly lower than those in the control group ($P < 0.05$); the levels of stress response indicators in the study group were significantly lower than those in the control group after surgery ($P < 0.05$); the fracture healing time in the study group was significantly shorter than that in the control group ($P < 0.05$). *Conclusion:* The application of preemptive analgesia combined with multimodal analgesia in elderly patients with hip fractures can provide superior perioperative analgesic effects, effectively reduce surgical stress responses, promote early functional rehabilitation, and have a positive effect on postoperative fracture healing.

Keywords: Hip fracture; Preemptive analgesia; Multimodal analgesia; Pain; Fracture healing

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1. Introduction

Geriatric hip fractures are a common orthopedic emergency. Patients with such fractures often experience severe perioperative pain due to their advanced age, multiple underlying medical conditions, and decreased pain thresholds. This pain can trigger stress responses such as elevated blood pressure and increased heart rate, exacerbating the burden on cerebral blood vessels and adversely affecting fracture healing and prognosis^[1]. While

traditional single-agent analgesic regimens can alleviate some pain, they are limited by inadequate analgesic efficacy and numerous adverse reactions, making it difficult to meet clinical needs ^[2]. Multimodal analgesia, which involves the combined use of analgesic drugs and techniques with different mechanisms of action, aims to achieve synergistic analgesia while reducing the dosage and side effects of individual drugs and has become one of the core principles of modern perioperative management. The core concept of preemptive analgesia is to implement effective analgesic interventions before the onset of noxious stimuli to prevent peripheral and central sensitization, thereby alleviating acute pain and preventing its transition to chronic pain. It is now widely used in clinical surgical analgesia ^[3]. Based on this, the present study explores the effects of preemptive analgesia combined with multimodal analgesia on perioperative pain and postoperative fracture healing in elderly patients with hip fractures, aiming to provide evidence for clinical analgesia.

2. Materials and methods

2.1. General information

A total of 202 patients who underwent total hip arthroplasty from January 2024 to December 2024 were selected and divided into a control group and a study group based on different analgesic methods, with 101 patients in each group. The general information of the two groups was comparable ($P > 0.05$), as shown in **Table 1**.

Table 1. Comparison of general information between the two groups

Group	n	Gender (%)		Age (years)	BMI (kg/m ²)	Type of fracture		ASA classification	
		Male	Female			Femoral neck fracture	Intertrochanteric fracture of the femur	Grade II	Grade III
Control	101	56 (55.45)	45 (44.55)	73.34 ± 6.32	23.66 ± 3.51	53 (52.48)	48 (47.52)	65 (64.36)	36 (35.64)
Study	101	57 (56.44)	44 (43.56)	73.12 ± 6.61	23.75 ± 3.62	51 (50.50)	50 (49.50)	63 (62.38)	38 (37.62)
Statistic (χ^2/t)		0.020		0.242	0.179	0.079		0.085	
P-value		0.887		0.809	0.858	0.778		0.770	

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Age > 65 years; (2) Diagnosed with femoral neck fracture or intertrochanteric fracture of the femur via X-ray or CT, and scheduled for surgical treatment; (3) American Society of Anesthesiologists (ASA) classification grade II–III; (4) Informed consent obtained from the patient or their family members.

Exclusion criteria: (1) Pathological fractures or open fractures; (2) Patients with severe cognitive impairment or mental illness that prevents cooperation in pain assessment; (3) History of long-term opioid abuse or addiction to analgesic drugs; (4) Allergies to anesthesia/analgesic drugs used in the study; (5) Infection at the puncture site or severe abnormalities in blood coagulation function.

2.3. Methods

Both groups of patients received intraspinal anesthesia combined with ultrasound-guided nerve block. The study group utilized preemptive analgesia combined with multimodal analgesia: Preemptive analgesia involved intravenous injection of 0.2 mg of hydromorphone and 50 mg of flurbiprofen axetil 30 minutes before surgery.

Postoperative analgesia involved a patient-controlled intravenous analgesia (PCIA) pump with a formulation consisting of 40 mg of nalbuphine, 200 mg of flurbiprofen axetil, diluted with normal saline to a total volume of 100 ml. The parameters were set as follows: background dose of 1 ml/h, single-press dose of 2 ml, and a lockout time of 15 minutes. Additionally, patients received daily intravenous injections of 50 mg of flurbiprofen axetil for three consecutive days after surgery. The control group received conventional postoperative analgesia: a postoperative PCIA pump with a formulation consisting of 100 mg of sufentanil diluted to 100 ml with normal saline. The parameters were set as follows: a background infusion rate of 1 ml/hour, a bolus dose of 2 ml per press, and a lockout interval of 15 minutes. If necessary, intravenous butorphanol 1 mg was administered for rescue analgesia.

2.4. Observation indicators

2.4.1. Perioperative pain

Assessed using the Visual Analog Scale (VAS) at 1 hour before surgery and at 6, 12, 24, 48, and 72 hours after surgery, with scores ranging from 0 to 10. The score is positively correlated with the degree of pain.

2.4.2. Postoperative analgesia monitoring

The number of PCIA pumps and the frequency of rescue analgesia within 48 hours postoperatively were recorded. Rescue medication was administered when the VAS score was ≥ 4 .

2.4.3. Stress response indicators

Peripheral venous blood samples were collected before and 24 hours after surgery to measure serum cortisol (Cor) and interleukin-6 (IL-6) levels using the ELISA method.

2.4.4. Fracture healing time

The time taken to reach clinical healing criteria was recorded, which included the absence of local tenderness, longitudinal percussion pain, and abnormal movement, as well as the time when X-rays showed blurred fracture lines and continuous callus formation.

2.5. Statistical methods

Measurement data and count data were respectively expressed as mean \pm standard deviation (SD) and n (%), and analyzed using statistical software (SPSS 24.0) with t -tests and chi-square (χ^2) tests. A P -value less than 0.05 was considered statistically significant.

3. Results

3.1. Perioperative pain

There was no significant difference in VAS scores between the two groups 1 hour before surgery ($P > 0.05$). However, at 6, 12, 24, 48, and 72 hours postoperatively, the VAS scores in the study group were significantly lower than those in the control group ($P < 0.05$). See **Table 2**.

Table 2. Perioperative pain (mean \pm SD, points)

Group	<i>n</i>	Pre-op (1h)	Post-op 6h	Post-op 12h	Post-op 24h	Post-op 48h	Post-op 72h
Control group	101	6.73 ± 1.23	3.74 ± 1.01	3.56 ± 0.84	3.02 ± 0.77	2.76 ± 0.65	2.34 ± 0.56
Study group	101	6.74 ± 1.21	2.23 ± 0.67	2.15 ± 0.34	1.83 ± 0.63	1.63 ± 0.45	1.32 ± 0.23
<i>t</i> -value		0.058	12.521	15.637	12.021	14.365	16.933
<i>P</i> -value		0.954	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

3.2. Number of PCIA pumps and rescue analgesia episodes

The number of PCIA pumps and rescue analgesia frequency in the study group were significantly lower than those in the control group ($P < 0.05$). See **Table 3**.

Table 3. Number of PCIA pumps and rescue analgesia frequency (mean ± SD, times)

Group	<i>n</i>	Total PCIA attempts	Effective PCIA attempts	Rescue analgesic doses
Control group	101	25.45 ± 4.43	20.23 ± 3.35	1.84 ± 0.65
Study group	101	12.57 ± 3.24	8.34 ± 2.13	0.36 ± 0.14
<i>t</i> -value		23.585	30.100	22.370
<i>P</i> -value		< 0.001	< 0.001	< 0.001

3.3. Stress response indicators

At 24 hours postoperatively, the levels of Cor and IL-6 in the study group were significantly lower than those in the control group ($P < 0.05$). See **Table 4**.

Table 4. Stress response indicators (mean ± SD)

Group	<i>n</i>	Cortisol (nmol/L)		IL-6 (pg/mL)	
		Pre-op	Post-op 24h	Pre-op	Post-op 24h
Control group	101	385.65 ± 43.43	676.75 ± 68.44	15.63 ± 4.23	121.42 ± 23.23
Study group	101	384.46 ± 45.45	509.43 ± 63.23	15.66 ± 4.29	78.53 ± 18.44
<i>t</i> -value		0.190	18.047	0.050	14.533
<i>P</i> -value		0.849	< 0.001	0.960	< 0.001

3.4. Fracture healing time

The fracture healing time in the study group was 12.42 ± 2.31 weeks, significantly shorter than that in the control group, which was 15.53 ± 1.64 weeks ($P < 0.05$).

4. Discussion

Severe perioperative pain is not only the primary source of suffering for patients but can also trigger a series of pathophysiological changes, including sympathetic nervous excitation, increased heart rate, elevated blood pressure, immunosuppression, hypercoagulability, etc. These changes significantly increase the risk of complications such as cardiovascular and cerebrovascular events, pulmonary infections, thrombosis, and

postoperative delirium, seriously affecting the postoperative rehabilitation process and long-term prognosis of patients ^[4,5]. In recent years, increasing evidence has indicated that effective pain management not only relates to patient comfort but may also influence the final outcome of tissue repair ^[6]. Studies have shown that, compared with traditional analgesic modalities, preemptive analgesia combined with multimodal analgesia can create a more favorable biological environment for fracture healing through more comprehensive pain control and stress inhibition ^[7].

The results of this study showed that the postoperative pain scores in the study group were lower, and both the number of PCIA pumps and the number of rescue analgesic administrations were significantly lower than those in the control group. Preemptive analgesia blocks pain transmission pathways before the occurrence of noxious stimuli, preoccupies pain receptors in advance, inhibits central sensitization, and lays the foundation for postoperative analgesia. Multimodal analgesia achieves synergistic effects by combining analgesic drugs with different mechanisms of action. The combined application can provide effective perioperative analgesia. Pain is the core stressor in elderly patients with hip fractures during the perioperative period. It activates the hypothalamic-pituitary-adrenal (HPA) axis and peripheral inflammatory pathways through noxious stimuli, leading to the massive release of cortisol and IL-6 ^[8]. The results of this study indicate that the levels of stress response indicators in the study group after surgery were all lower. Preemptive analgesia, achieved through preoperative ultrasound-guided nerve block combined with pretreatment with hydromorphone and flurbiprofen axetil, blocks the transmission of pain signals to the central nervous system, inhibits the formation of central sensitization, and reduces stress triggers at their source. Multimodal analgesia, through the synergistic effects of opioid drugs and non-steroidal anti-inflammatory drugs, not only reduces the dosage of a single drug to minimize stress accumulation but also doubles-inhibits the excessive activation of the HPA axis by suppressing prostaglandin synthesis and κ -receptor agonistic effects, thereby reducing cortisol secretion. Simultaneously, it inhibits peripheral inflammatory cascade reactions and blocks the release of IL-6 induced by fracture trauma and pain. Fracture healing is a complex repair process influenced by various factors such as pain, stress response, and local blood circulation. Severe perioperative pain can enhance the body's stress response, increase the release of stress hormones such as cortisol and adrenaline, inhibit osteoblast activity, promote osteoclast proliferation, and delay fracture healing ^[9]. Meanwhile, pain can restrict early patient mobility, leading to poor local blood circulation and slow callus growth. The research findings of Wu *et al.* ^[10] indicate that the absence of preemptive analgesia is one of the risk factors for poor prognosis in elderly patients undergoing hip surgery. Therefore, effective analgesia has a significant impact on fracture healing and prognosis in patients. The results of this study show that the fracture healing time in the study group was significantly shorter than that in the control group. The combination of preemptive analgesia and multimodal analgesia demonstrated remarkable analgesic effects. Effective pain control alleviated the body's stress response, thereby avoiding the impact of inflammation and other factors on fracture healing. Meanwhile, effective analgesia enabled patients to engage in functional activities earlier. Functional exercises can produce beneficial mechanical stress stimulation at the fracture site, promoting callus remodeling and maturation. Through these various mechanisms, fracture healing was facilitated.

5. Conclusion

In summary, the combination of preemptive analgesia and multimodal analgesia can effectively alleviate perioperative pain, reduce stress responses, promote fracture healing, and facilitate postoperative rehabilitation in

elderly patients with hip fractures. However, this study has limitations. Firstly, it was a single-center study with a limited sample size. Secondly, the follow-up period was relatively short, which may introduce selection bias. Additionally, the optimization of different analgesic drug dosage combinations was not explored. Therefore, future research should involve multi-center, large-sample, and long-term follow-up studies to further validate the long-term efficacy and safety of this approach.

Disclosure statement

The author declares no conflict of interest.

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Research Progress on the Role of Exosomes and the PI3K/Akt Pathway in Osteoporosis

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Abstract: Osteoporosis (OP) is a metabolic bone disease characterized by decreased bone mineral density and microstructural deterioration, leading to an elevated risk of fragility fractures. Bone remodeling relies on the dynamic balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Exosomes, as key mediators of intercellular communication, regulate the differentiation and function of bone marrow mesenchymal stem cells (BMSCs), osteoblasts, and osteoclasts by delivering bioactive molecules (e.g., miRNAs), thereby playing a pivotal role in OP pathogenesis. Recent studies have revealed that the PI3K/Akt signaling pathway not only serves as a central regulator of BMSC osteogenic differentiation but also synergizes with exosomes to promote bone formation by activating downstream targets (e.g., RUNX2, BMP2). This review systematically summarizes the synergistic mechanisms of exosomes and the PI3K/Akt pathway in osteogenesis, focusing on how specific miRNAs (e.g., miR-19a-3p, miR-935) modulate key molecules (e.g., PTEN, STAT1) to restore bone metabolic homeostasis. These findings provide novel insights into the molecular mechanisms of OP and lay a theoretical foundation for developing targeted therapeutic strategies.

Keywords: Exosomes; PI3K/Akt; Osteoporosis; Bone marrow mesenchymal stem cells; Osteogenic differentiation

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1. Introduction

Osteoporosis (OP) is a disease that affects bone across the body and shows low mass in bone and damage to the structure of bone at a small scale, and this leads to bone that breaks more easily and shows a higher risk for breaks that occur^[1]. The population across the world shows increasing age, and the rate of osteoporosis continues to increase. The most serious problem that results from this condition is fractures that occur with low force, and these fractures create a substantial burden in medical costs and economic impact on individuals who have the disease and on society in general^[2,3]. This indicates that examination of the processes that produce osteoporosis in the body and investigation of approaches that provide prevention and treatment that work well are important to conduct.

The process that changes bone structure involves the balance between forming bone and removing bone. Bone formation occurs through cells that develop from bone marrow stem cells. These stem cells represent the main source for cells that form bone and play an important role in OP. When bone marrow stem cells show reduced potential for developing into cells that form bone or show an increased tendency for developing into fat cells, this produces insufficient bone formation. This represents a main factor in OP development ^[4]. In recent years, small particles that cells release have received significant attention in OP research. These particles that cells release can contain proteins, lipids, and miRNAs. The particles regulate the function and development of bone marrow stem cells, cells that form bone, and cells that remove bone. This affects the balance of the process that changes bone ^[5]. The PI3K/Akt pathway has received confirmation as a main pathway that regulates the development of cells forming bone and their function. However, the interaction between particles from bone marrow stem cells and the PI3K/Akt pathway remains unclear. The interaction between these particles and this pathway, and the combined regulation of OP development, requires systematic examination. This article examines the combined mechanisms of particles from bone marrow stem cells and the PI3K/Akt pathway in OP. This examination provides a basis for understanding OP development and developing treatment approaches.

2. Overview of BMSCs and exosomes

2.1. Bone marrow mesenchymal stem cells (BMSCs)

BMSCs are cells with multiple functions that occur in the bone marrow and show the capacity for division and development into different forms. These cells develop into cells forming bone, cells storing fat, cells in cartilage, and other types. The development of BMSCs follows regulation by factors that include aspects relating to biological processes, physical conditions, and chemical signals. The factor TAZ, which functions to activate processes in the cell, plays a major role in maintaining the balance between the development into bone-forming cells and the development into fat-storing cells in BMSCs. This factor promotes development into bone-forming cells and limits development into fat-storing cells. In the condition involving reduced bone density, BMSCs show decreased potential for development into bone-forming cells and increased development into fat-storing cells. This pattern produces insufficient formation of bone and an increase in fat in bone marrow, and these changes disrupt the balance that maintains bone structure. **Figure 1** shows the characteristics of mesenchymal stem cells.

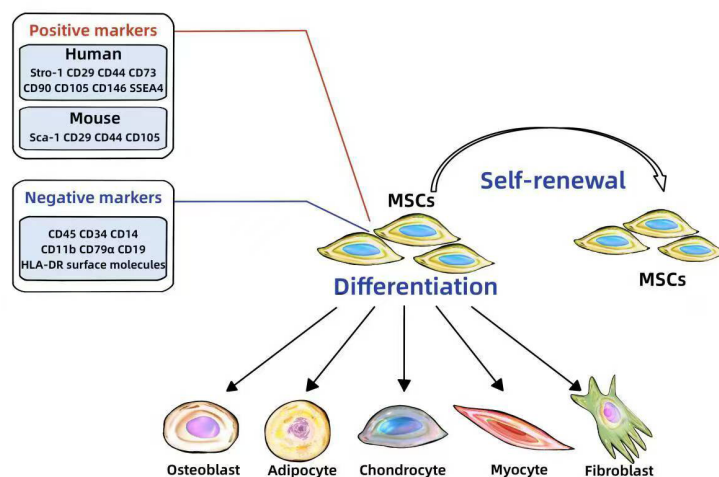


Figure 1. Schematic diagram of the characteristics of mesenchymal stem cells (MSCs). There are both positive markers and negative markers for identifying MSCs. MSCs possess the characteristics of self-renewing and differentiating into multiple cell types, including osteoblast, adipocyte, chondrocyte, myocyte, and fibroblast ^[10]

2.2. Exosomes

Cells produce small structures that move outside the cell, and these structures show a size of approximately 30 to 150 units in measure. The structures appear in different fluids in the body. These small structures contain various molecules that provide biological activity, and the molecules include specific forms of proteins, lipids, and genetic material. The structures function as important means for communication between cells, and this communication involves the process of control in different conditions relating to normal function and disease ^[6]. In the area of examining bone change and development, research shows that the small structures can change the activity of cells that form bone and cells that break down bone. The structures affect this activity through molecules that provide signals, and specific genetic material represents one form of these molecules. The process influences the relationship between bone loss and bone formation. The small structures show a significant role in the development and occurrence of the condition involving bone weakness ^[5,7].

2.3. Exosomes derived from BMSCs (BMSCs-Exos)

Small structures from bone marrow stem cells show characteristics that these cells demonstrate and indicate important roles in tissue repair and regulation of immune processes. These structures also show potential in promoting tissue development. Studies indicate that small structures from stem cells of different tissue sources, such as bone marrow and fat tissue, show effects that promote bone development, and research examining structures from bone marrow stem cells provides the most extensive data. For example, small structures that originate from human stem cells of a particular type show significant effects in promoting blood vessel formation and bone formation processes ^[8]. Liu and other researchers found that structures from stem cells showed effects that limited bone loss and promoted blood vessel formation in a rat model examining hormone effects on bone tissue death in the upper leg bone ^[9]. These structures also affected a particular signaling pathway involving specific factors to promote bone cell development. Additionally, these small structures from bone marrow stem cells provide a means for carrying specific small molecules. For example, structures enriched with a particular small molecule designated miR-196a promoted bone healing in rat skull defects, and this finding suggests possible applications in treating diseases that affect bone processes ^[10].

3. The role of BMSCs-Exos in bone metabolism

3.1. The effect of BMSCs-Exos on osteoblasts

The main cells that produce new bone are called osteoblasts. Studies show that small particles released by these cells, or by cells from bone marrow, can affect how osteoblasts develop and form mineral deposits. This occurs through signals between cells. Cui *et al.* found that small molecules in particles from osteoblasts that already contain minerals can increase the development of bone-forming cells ^[10]. These molecules increase levels of RUNX2 and alkaline phosphatase. Other studies report that miR-30d-5p, miR-133b-3p, and miR-140-3p show higher levels in particles from osteoblasts. These molecules may increase osteoblast development and function through multiple pathways. The pathways include Wnt, insulin, TGF- β , and calcium signaling ^[10]. Evidence indicates that these particles use a complex network of signaling molecules to control osteoblast development in a

precise manner.

3.2. The effect of BMSCs-Exos on osteoclasts

Large cells with multiple internal structures that function in removing bone material develop from cells in the blood-forming system. The process that produces these cells and the process that makes these cells active involve factors that cells supporting bone formation provide. Small structures that cells release show effects in both directions on the process of forming these large bone-removing cells. Studies indicate that structures from cells developing into bone-removing cells appear to support the formation process, but structures from cells that complete development contain a factor that binds to a signal molecule. This factor competes with the signal molecule for binding sites on cells forming bone-removing structures, and this competition limits the formation process. Also, a molecule that modifies other molecules gets released in these small structures. This molecule changes a factor important for bone-removing cell function by adding specific modifications. The modifications increase on a factor that controls the process in these cells, and this increase reduces the activity that removes bone material. The findings provide an approach for affecting the process that removes bone.

4. PI3K/Akt signaling pathway

4.1. Overview of the PI3K/Akt pathway

The pathway involving enzymes that change lipid molecules in cell membranes plays a major role in regulating different activities in cells, including processes relating to cell growth, development, cell death, use of energy, and survival. The enzyme that changes lipid molecules is a group of related enzymes that can be divided into three forms based on structure and how activation occurs. The first form of this enzyme, particularly one type in this form, is associated with receptors on cell surfaces that respond to signals and is activated by factors that promote growth, causing conversion of one lipid molecule in the membrane to a different molecule that provides signals. The enzyme that follows in the pathway is a key enzyme that changes proteins at specific sites and contains a region at one end that binds to the signal molecule, bringing it to the membrane. At the membrane, one site in this enzyme is changed by a different enzyme, and a second site is typically changed by a complex of proteins, leading to full activation. The activated enzyme regulates what happens to cells and how cells function by changing a series of target proteins that follow, such as proteins that control gene activity, proteins that regulate cell growth, and proteins that affect energy use.

4.2. The PI3K/Akt pathway and bone metabolism

The pathway involving PI3K and Akt shows important effects in processes relating to bone. Studies indicate that Akt and factors that follow in signaling function as main elements in the development of bone and in changes occurring in bone over time. Work using the removal of specific genes reveals that animals lacking both Akt1 and Akt2 show formation of bone that occurs more slowly than in other cases, and animals lacking Akt1 show bones that differ in length and centers for later bone formation that develop with delay ^[11]. In cells that produce bone, processes that increase activity in the pathway involving PI3K and Akt show effects on genes that indicate bone formation, such as BMP2 and ALP, and these effects support changes in cells that produce bone and an increase in the number of these cells ^[12]. The pathway also works together with BMP2 in processes that guide cells of a particular type to develop into cells that produce bone ^[13]. Akt also adds phosphate groups to a factor that controls

other genes, the FoxO factor, and this leads to the factor remaining in the part of the cell outside the central structure, and these processes support the continued function of cells that produce bone and the formation of bone.

In osteoclasts, the PI3K/Akt signaling pathway is also indispensable for their generation. Lee *et al.* confirmed that inhibiting PI3K activity using LY294002 significantly reduces osteoclastogenesis induced by RANKL and M-CSF ^[14]. Although Akt is not absolutely essential for osteoclast survival, it is crucial for the proliferation and differentiation of osteoclasts. The Akt signaling pathway may regulate osteoclast differentiation by affecting the DNA-binding activity of NF- κ B.

PTEN, the element that removes phosphate groups from position ten on the chromosome, provides important control that limits activity in the pathway involving PI3K and Akt. This element functions by removing phosphate groups from PIP3, and the process terminates signals that increase Akt activity. In cells that form bone, the loss of PTEN results in phosphorylation of Akt that remains at high levels for extended periods. This condition produces increased differentiation in these cells and also produces reduced rates of cell death ^[15]. The findings suggest that control of activity in the pathway involving PI3K and Akt requires specific regulation. This regulation appears important for maintaining the balance in bone tissue that supports normal function.

5. The impact of BMSCs-Exos synergizing with the PI3K/Akt pathway on osteoporosis

Multiple studies show the main role of BMSCs-Exos in bone remodeling. The mechanisms that these factors use relate to the PI3K/Akt signaling pathway. BMSCs-Exos contain high levels of miRNAs. These miRNAs show different patterns during the process of forming bone. For example, miR-218, let-7a, and miR-135b increase in level. However, miR-155 and miR-320c decrease in level. These miRNAs provide possible targets for the treatment of osteoporosis, also called OP ^[16].

Recent work shows more small structures in cells that relate to forming bone. For example, miR-144 increases the process where cells with multiple possible forms produce more cells and develop into bone forms by reducing SFRP1 levels through the pathway using Wnt signals. miR-27a-3p supports the formation of bone by reducing the factor ATF3, which increases the production of other factors. miR-935 produces effects relating to bone by reducing STAT1 levels in cells ^[17]. In contrast, miR-1297 reduces the process where cells develop into bone forms and increases the progression of the condition involving reduced bone strength by limiting the Wnt pathway and reducing levels of Runx2 and Osterix.

Data show that bone formation effects from small particles released by bone cells relate in part to activation of one particular process involving PI3K and Akt. Kawamura and other researchers indicate that this PI3K and Akt process provides important control for both bone breakdown and bone formation. The studies that follow provide direct confirmation of these patterns. In these studies, researchers use substances that block the PI3K and Akt process, such as LY294002, before treatment with the small particles. Results show that the small particles from bone cells produce less promotion of bone cell development and mineral formation when this blocking occurs. The difference appears significant. These findings suggest that the small particles released by bone cells produce their effects through a process involving PI3K and Akt signaling. This process appears to provide the main means for the observed changes in bone cell function and bone formation that the studies examine ^[18].

At the level of molecular mechanisms, particles that cells release carry specific forms of small molecules that can affect and change important factors in the pathway involving PI3K and Akt. Zhou *et al.* found that PTEN

is a direct target that miR-19a-3p affects. The particles carrying miR-19a-3p can reduce PTEN in cells, and this reduces the limiting effect that PTEN provides on the pathway involving PI3K and Akt. This process makes Akt more active and increases the development of cells that form bone ^[19]. The work that Burger *et al.* present also indicates the limiting role that PTEN provides in the pathway involving PI3K and Akt and in the processes relating to bone ^[20].

In conclusion, BMSCs-Exos deliver specific functional miRNAs that target and regulate key nodes in the PI3K/Akt signaling pathway (such as PTEN), activating downstream osteogenic gene expression, and thereby synergistically promoting the osteogenic differentiation and bone formation of BMSCs. This provides new theoretical insights and potential strategies for targeted therapy of osteoporosis.

6. Conclusion and outlook

This review systematically summarizes the synergistic regulatory effects of BMSCs-derived exosomes and the PI3K/Akt signaling pathway in osteoporosis. Existing studies show that BMSCs-Exos, as important information carriers, can regulate the PI3K/Akt pathway through molecules such as miRNAs (e.g., miR-19a-3p, miR-935) that they carry, influencing osteoblast differentiation and bone formation, and playing a key role in the pathophysiological process of osteoporosis.

Progress in the field shows significant development, but challenges remain. The mechanisms that underlie the interaction between exosomes and the pathway involving PI3K and Akt are not fully understood. Research requires further work to reveal the complete picture of these mechanisms. Issues in delivery to specific targets, stability of exosomes, and possible responses from the system that provides protection in the body present major obstacles. These factors limit the use of exosomes in treatment. Strategies that modify exosomes through design need development to address these issues. The pathway involving PI3K and Akt shows complexity in structure and function. This pathway interacts with other pathways that provide signals in the body. These interactions complicate efforts to regulate the pathway with precision.

Looking ahead, further elucidating the detailed map of the synergistic interaction between BMSCs-Exos and the PI3K/Akt pathway, optimizing the exosome preparation process and targeted delivery systems, and exploring their safety and efficacy in large animal models and preclinical studies, will strongly promote the translation of exosome- and signaling pathway-based therapies for osteoporosis from basic research to clinical application.

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Ferroptosis Mechanism in the “Secondary Injury” Phase of Osteoporotic Fractures: From Laboratory to Perioperative Intervention

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Abstract: Delayed healing of osteoporotic fractures is a common and challenging clinical problem, traditionally attributed to insufficient local blood supply. However, recent years have seen increasing attention on the critical role of ferroptosis during the “secondary injury” phase of osteoporotic fractures. Ferroptosis damages chondrocytes through iron overload and lipid peroxidation, having a significant impact on bone repair. This article explores the molecular mechanisms of ferroptosis, focusing on the role of osteoclasts in secreting free iron and the impact of changes in GPX4 and FSP1 expression on ferroptosis regulation, highlighting the significance of ferroptosis chondrocyte subpopulations in fracture healing. It also evaluates the application potential and existing controversies of perioperative intervention strategies such as iron chelators and vitamin K2, discussing the development trends of bone-targeted iron chelating nanoparticles and rapid detection technologies for ferroptosis evaluation. This review aims to provide new theoretical bases and intervention ideas for the treatment of clinical osteoporotic fractures, promoting solutions to delayed fracture healing.

Keywords: Ferroptosis; GPX4; FSP1; Iron chelator (DFO); Delayed healing of osteoporotic fractures; Perioperative intervention

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1. Introduction

Osteoporotic fractures are a common and serious health issue among the elderly, with increasing incidence and associated burden due to population aging. Osteoporosis significantly reduces bone strength, making older patients more likely to fracture, especially in the spine, hip, and long bones. These fractures not only have high disability rates but also severely impact patients' quality of life and survival rates. Current clinical data show that about 30% of patients with osteoporotic fractures experience delayed healing or nonunion after treatment, leading to limited

functional recovery and increased complications, putting a strain on both patients and the healthcare system^[1]. Traditional research on fracture healing mechanisms has mainly focused on insufficient local blood supply, poor mechanical stability, and bone metabolism disorders, but these factors fail to comprehensively explain the complex issues encountered in the healing of osteoporotic fractures.

In recent years, studies have found that factors such as apoptosis, oxidative stress, and abnormal iron metabolism during the “secondary injury” phase of fracture healing significantly affect healing quality. In particular, ferroptosis, a novel form of iron-dependent programmed cell death, has gradually gained attention for its role in bone tissue. Ferroptosis triggers lipid peroxidation through iron overload, leading to cell membrane damage and cell death, thereby affecting bone cell function and the bone remodeling process. Basic and clinical studies have revealed that an iron metabolism imbalance is closely related to osteoporosis and delayed fracture healing, where iron overload not only inhibits osteoblast activity but also promotes osteoclast activation, leading to enhanced bone resorption and bone structure degradation^[2,3]. Additionally, oxidative stress plays an important role during the “secondary injury” phase of osteoporotic fractures, with antioxidants such as tanshinone IIA showing potential in protecting bone marrow mesenchymal stem cells from oxidative damage and promoting bone repair^[4].

In 2023, a study first confirmed the involvement of ferroptosis in the mechanism of delayed healing of osteoporotic fractures, marking a new phase in research in this field. The study indicated significant changes in the activity of ferroptosis-related signaling pathways, affecting the survival of bone cells and the bone healing microenvironment, suggesting that ferroptosis may become a new target for the treatment of osteoporotic fractures^[3]. However, current clinical guidelines do not cover the mechanisms of ferroptosis and its perioperative intervention strategies, and clinical awareness and application of ferroptosis-related treatments are still in the early stages.

2. Mechanisms of ferroptosis in delayed healing of osteoporotic fractures

2.1. Osteoclast-mediated release of free iron and chondrocyte injury

The delayed healing process of osteoporotic fractures is closely related to abnormal osteoclast activity. In osteoporotic conditions, osteoclast activity is significantly enhanced, leading to excessive bone resorption and a large release of free iron. Free iron promotes local iron overload, inducing lipid peroxidation reactions within chondrocytes, becoming one of the key factors for the occurrence of ferroptosis. The iron-dependent lipid peroxidation reaction is the core mechanism of ferroptosis, primarily manifested by the accumulation of lipid peroxides, which subsequently leads to cell membrane damage, resulting in cell dysfunction or even death.

Specifically, the excessive presence of free iron promotes the progression of lipid peroxidation reactions, leading to the downregulation of glutathione peroxidase 4 (GPX4) expression. GPX4, as an important intracellular antioxidant enzyme, can reduce lipid peroxides and protect the integrity of cell membranes; its reduced expression directly weakens the antioxidant capacity of chondrocytes, making them more susceptible to ferroptosis. The impaired function of chondrocytes hinders callus formation and bone repair, resulting in delayed fracture healing.

Multiple studies have confirmed the close relationship between iron overload and bone metabolism disorders. Iron generates a large amount of reactive oxygen species (ROS) through the Fenton reaction, exacerbating lipid peroxidation and inducing ferroptosis. Furthermore, iron overload may also exacerbate the development of osteoporosis by regulating the functional imbalance between osteoclasts and osteoblasts. The free iron released by osteoclasts not only directly affects chondrocytes but may also enhance inflammatory responses, indirectly

promoting bone resorption and bone loss, leading to a vicious cycle^[5].

Therefore, osteoclast-mediated release of free iron induces chondrocyte ferroptosis by promoting lipid peroxidation reactions and downregulating GPX4 expression, which is one of the important mechanisms for delayed healing of osteoporotic fractures. This mechanism reveals the key role of ferroptosis in bone metabolism disorders, providing a theoretical basis and potential therapeutic targets for interventions targeting osteoclast activity and iron metabolism.

2.2. Changes in the expression and function of ferroptosis suppressor protein FSP1

Ferroptosis suppressor protein 1 (FSP1), as another important ferroptosis suppressor besides GPX4, has recently gained attention. A recent study reported that in an osteoporotic mouse model, FSP1 expression was significantly downregulated by about 40%. This finding suggests the important regulatory role of FSP1 in the processes of osteoporosis and fracture healing. FSP1 prevents ferroptosis by regulating the inhibition of lipid peroxidation reactions. The specific mechanism includes FSP1 acting as an NAD(P)H coenzyme-dependent reductase, promoting the reduction of coenzyme Q10 (CoQ10) to form reduced coenzyme Q10 (CoQ10H2), thereby capturing lipid peroxidation free radicals, inhibiting lipid peroxidation reactions, and maintaining cell membrane stability. The activity of FSP1 provides cells with an alternative defense pathway against ferroptosis beyond the GPX4 system, enhancing the cell's resistance to ferroptosis.

The downregulation of FSP1 expression leads to a weakened ability to inhibit lipid peroxidation, accelerating the occurrence of ferroptosis due to the accumulation of lipid peroxidation products. The significant reduction of FSP1 in osteoporotic mice further exacerbates the ferroptosis process in bone tissue cells, hindering bone repair and fracture healing. Additionally, the downregulation of FSP1 may lead to increased oxidative stress levels in the bone metabolic environment, promoting osteoclast activity and creating an unfavorable microenvironment for bone formation.

This mechanism not only deepens our understanding of the ferroptosis regulatory network but also offers new potential targets for treating delayed healing in osteoporotic fractures. Regulating FSP1 expression or inhibiting ferroptosis by activating the FSP1 pathway may become effective strategies to promote bone repair and improve osteoporosis^[6].

2.3. Ferroptosis chondrocyte subpopulations and their impact on bone resorption

With the development of single-cell sequencing technology, significant breakthroughs have been made in the study of cellular heterogeneity during the delayed healing of osteoporotic fractures. Recent research has revealed a specific “ferroptosis chondrocyte subpopulation” that not only exhibits ferroptosis-related molecular characteristics but also secretes receptor activator of nuclear factor kappa-B ligand (RANKL), playing a key role in bone metabolism regulation.

RANKL is the main regulatory factor for osteoclast formation and activity, and its excessive expression promotes osteoclast activation and bone resorption. The RANKL secreted by the ferroptosis chondrocyte subpopulation enhances osteoclast activity, forming a positive feedback loop: increased osteoclast activity releases more free iron, promoting more chondrocytes to undergo ferroptosis, thereby producing more RANKL, exacerbating bone resorption and bone loss.

This finding provides a new perspective on cellular heterogeneity in delayed healing of osteoporotic fractures and reveals the complex interplay between ferroptosis and bone metabolism. Ferroptosis not only affects the

survival of bone cells as a mode of cell death but also regulates bone metabolic signals through specific cell subpopulations, influencing the balance between bone resorption and formation. This mechanism suggests that interventions targeting the ferroptosis chondrocyte subpopulation and its RANKL secretion may break the positive feedback loop of bone resorption and promote fracture healing. Future research could focus on the molecular characteristics and regulatory mechanisms of this subpopulation to develop more precise therapeutic strategies to improve the clinical prognosis of osteoporotic fractures ^[7].

3. Intervention strategies for ferroptosis mechanisms in the perioperative period

3.1. Local application and effects of the iron chelator DFO

Deferoxamine (DFO), a classic iron chelator, is widely used to treat iron overload-related diseases because of its strong ability to bind iron ions. In recent years, the potential application of DFO in the repair of osteoporotic fractures has attracted attention. A study published in 2023 in *Bioactive Materials* reported that continuous application of local sustained-release DFO gel at the fracture site for 7 days significantly increased callus density by 32%, effectively promoting the bone healing process. This local application of DFO effectively chelates excess free iron, reducing iron-catalyzed lipid peroxidation reactions, inhibiting ferroptosis in chondrocytes, thereby improving the microenvironment for bone repair and promoting the regeneration and repair of bone tissue.

Mechanistically, DFO inhibits ferroptosis by lowering the intracellular excess iron ion content, reducing the generation of iron-dependent free radicals, and blocking cell membrane damage caused by lipid peroxidation. Additionally, DFO may also activate the cell's antioxidant defense system, further alleviating oxidative stress damage and protecting bone cell function. The advantage of local application is that it avoids the risk of systemic iron deficiency, reducing interference with systemic iron metabolism, making it suitable for precise interventions at the fracture site during the perioperative period, maximizing the bone repair-promoting effect of DFO.

Moreover, drug delivery technologies for DFO are continuously innovating, such as using chitosan nanoparticles as carriers for sustained release, improving local drug concentration and duration of action, further enhancing the therapeutic effect and safety of DFO. These advancements provide new strategies and directions for intervening in the ferroptosis mechanism in osteoporotic fractures during the perioperative period, making DFO a key candidate for targeted treatment ^[8,9].

3.2. Protective role of vitamin K2 in activating the NRF2/GPX4 axis

Vitamin K2, a fat-soluble vitamin, has been shown to play a crucial role in bone metabolism and antioxidant activity. A study published in 2024 in *Bone Research* revealed that vitamin K2 can promote the expression of GPX4 by activating the nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway, significantly enhancing the antioxidant capacity of cells, thereby inhibiting the occurrence of ferroptosis and helping protect against delayed healing in osteoporotic fractures.

The specific mechanism is that NRF2, as an important transcription factor within cells, plays a central role in regulating antioxidant responses. Vitamin K2 can promote the nuclear translocation of NRF2, activating the expression of its downstream target gene *GPX4*. GPX4 is a key antioxidant enzyme in the ferroptosis process, capable of catalyzing the reduction of lipid peroxides, preventing lipid peroxidation chain reactions, and protecting cell membranes from damage. Through the activation of the NRF2/GPX4 axis by vitamin K2, intracellular oxidative stress levels are reduced, ferroptosis is effectively inhibited, and bone cell function is maintained,

promoting the bone healing process.

This mechanism provides a new therapeutic approach for non-iron chelator drug interventions in ferroptosis, especially suitable for the later stages of perioperative management and long-term management of osteoporosis patients. Compared to iron chelators, the application of vitamin K2 is safer, with fewer side effects, suitable for chronic use, and its multiple regulatory functions on bone metabolism and antioxidant activity further enhance its clinical value. Future development of vitamin K2 and its analogs is expected to become an emerging drug for intervening in the ferroptosis mechanism in osteoporotic fractures ^[10].

3.3. Controversies and challenges in perioperative iron metabolism regulation

Despite the important potential of iron metabolism regulation in intervening in the ferroptosis mechanism during the perioperative period, its clinical application still faces many controversies and challenges. First, systemic iron chelators like DFO can effectively reduce body iron load but may affect normal blood cell production, leading to adverse reactions such as anemia. Therefore, the risks and benefits must be weighed when applying them perioperatively to avoid excessive iron deficiency, causing other complications. Second, there are also differences in the choice of iron supplementation methods during the perioperative period. Intravenous iron can quickly correct iron deficiency but carries risks of allergic reactions and iron overload; oral iron supplements are convenient but have unstable absorption and more gastrointestinal side effects. Currently, there is a lack of unified clinical guidelines to clarify the best strategies for regulating iron metabolism during the perioperative period, resulting in considerable variations in practice. Additionally, perioperative patients often have complex conditions and variable iron metabolism states, making it urgent to accurately assess iron load and ferroptosis status and develop individualized intervention strategies. Future large-scale, multicenter clinical trials are needed to systematically evaluate the safety and efficacy of different iron metabolism regulation plans, clarify the optimal time window, dosage, and administration methods for ferroptosis intervention during the perioperative period, and integrate iron metabolism regulation into the comprehensive management system of the perioperative period to improve patient prognosis quality ^[11].

4. Future prospects and technological innovations in ferroptosis mechanism research

4.1. Development of bone-targeted iron-chelating nanoparticles

Using nanocarriers can effectively improve the stability and bioavailability of iron chelators. For example, functionalized polydopamine nanoparticles have good iron chelation ability and biocompatibility, enabling targeted delivery to bone tissue through surface modification. Their pH-dependent iron ion release characteristics are suitable for the acidic environment of fracture sites, promoting local inhibition of ferroptosis and improving the fracture healing process ^[12]. Additionally, nanoparticles mediating iron ion chelation can also synergistically scavenge reactive oxygen species, reducing oxidative stress and further protecting bone cells from ferroptosis damage ^[13]. Current research is also exploring iron-chelating nanosystems using biodegradable materials like chitosan, which not only have good drug-carrying capacity but can also achieve long-lasting treatment by regulating drug release rates ^[9,14]. In the future, developing multifunctional nanocarriers that simultaneously carry factors promoting bone formation and iron chelators is expected to become an innovative treatment method for the delayed healing of osteoporotic fractures. In summary, the development of bone-targeted iron-chelating nanoparticles represents a cutting-edge direction for ferroptosis intervention strategies. Achieving precise targeted

delivery and controlled release to bone tissue through nanotechnology not only enhances the therapeutic effects of iron chelators but also significantly reduces systemic side effects, holding great clinical translational potential and providing new ideas and methods for the treatment of osteoporotic fractures ^[15].

4.2. Application prospects of rapid test strips for ferroptosis evaluation in the perioperative period

Core biomarkers of ferroptosis include iron ion levels, lipid peroxidation products (such as malondialdehyde, 4-HNE), and the expression status of key regulatory proteins (such as GPX4, SLC7A11). By combining nanomaterials and biosensing technology, highly sensitive biosensors can be designed for rapid detection of these biomarkers. Existing studies have shown that magnetic and optical signal carriers like nano-ferrite particles have excellent performance in biological imaging and sensing fields ^[16], and this technology can be referenced for the development of rapid detection platforms. Combining artificial intelligence and big data analysis, a perioperative ferroptosis scoring system can integrate patient clinical data, biochemical indicators, and imaging information to achieve individualized risk assessment and treatment decision support ^[17]. Utilizing machine learning models for pattern recognition and prognosis prediction of ferroptosis-related indicators is expected to improve diagnostic accuracy and treatment safety. Furthermore, the portability and ease of use of rapid test strips make them suitable for operating rooms and intensive care environments, allowing real-time monitoring of patients' ferroptosis status and timely adjustment of treatment plans to reduce postoperative complication rates. In the future, with the continuous discovery of biological markers and advancements in nanosensing technology, the application prospects of rapid test strips for ferroptosis evaluation in the perioperative period are broad, becoming an important tool for promoting precise treatment of osteoporotic fractures during the perioperative period ^[17,18].

4.3. Multidisciplinary integrated research promoting in-depth analysis of ferroptosis mechanisms

Ferroptosis, as a novel regulatory mode of cell death, involves iron metabolism, lipid metabolism, oxidative stress, and various signaling pathways. Researching its complex biological characteristics and clinical relevance requires deep integration of multiple disciplines. The future development trend of ferroptosis mechanism research is to combine molecular biology, cell biology, bone metabolism, and clinical medicine to construct a systematic panorama of ferroptosis.

Cutting-edge technologies such as single-cell sequencing provide powerful means to reveal the heterogeneity of ferroptosis cells, allowing for the analysis of specific gene expression and regulatory networks in different cell subpopulations during ferroptosis ^[19]. Gene editing technologies (such as CRISPR/Cas9) can precisely intervene in key regulatory factors to verify their functions in the ferroptosis process, advancing mechanism research towards in-depth exploration of causal relationships ^[20].

At the same time, research on the association between ferroptosis and osteoporosis, fracture healing, and perioperative complications requires close integration of clinical data and basic research. For example, analyzing molecular biomarkers from clinical samples, combined with imaging and functional assessments, can reveal the specific mechanisms of ferroptosis in skeletal pathology, providing scientific evidence for clinical diagnosis and treatment ^[21].

Multidisciplinary integration can also promote the development of new therapeutic strategies, such as drug screening based on ferroptosis mechanisms, design of nanoparticle drug delivery systems, and formulation of

precise intervention plans during the perioperative period. Cross-disciplinary collaboration will drive the clinical translation of ferroptosis research results, accelerate innovations in the treatment of osteoporotic fractures, and improve patient prognosis and quality of life ^[22]. In summary, through multidisciplinary integration and advanced technology applications, the in-depth analysis of ferroptosis mechanisms will continue to advance, potentially providing a new theoretical basis and treatment strategies for the prevention and treatment of osteoporotic fractures, helping translate basic research into clinical use.

5. Conclusion

An important role of ferroptosis mechanisms in the delayed healing of osteoporotic fractures marks a significant shift in fracture repair research. Traditionally, delayed fracture healing has been attributed mainly to factors such as insufficient blood supply, while discovering ferroptosis adds a new perspective to this complex process, showing how abnormal iron metabolism and ferroptosis signaling pathways critically affect bone tissue repair. This enriches the theoretical framework of bone metabolism regulation. It also offers new targets and strategies for clinical diagnosis and treatment. Looking ahead, advancing the clinical application of ferroptosis mechanisms needs teamwork across multiple disciplines. First, accelerating the development of bone-targeted drugs using nanotechnology and biomaterials for precise drug delivery and controlled release; second, developing detection technologies for ferroptosis that are rapid and sensitive, combining molecular markers with imaging techniques for real-time monitoring and assessment of the fracture healing process. Furthermore, closely integrating basic research with clinical trials will help reconcile different viewpoints in various studies and find the most valuable intervention strategies for clinical use. Multi-center, large-sample clinical studies will provide strong evidence for the safety and efficacy of ferroptosis-related treatments, helping to include them in standard treatment for osteoporotic fractures.

Disclosure statement

The authors declare no conflict of interest.

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Application of Joint Line Incision + Precise Pre-Bent Plate via Three-Dimensional Reconstruction of the Proximal Tibia *In Vitro* + Transparent Retractor in Tibial Plateau Fractures

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Abstract: *Objective:* To analyze the combined application effects of the joint line incision approach, precise pre-bent plates via three-dimensional reconstruction of the proximal tibia *in vitro*, and transparent retractors in the clinical treatment of Schatzker types III to VI tibial plateau fractures, and their impact on the functional recovery of the knee joint. *Methods:* A retrospective analysis was conducted on the surgical treatment outcomes of 28 patients with tibial plateau fractures admitted from January 2023 to January 2025. All patients underwent internal fixation surgery via the joint line incision approach after admission, with the combined use of precise pre-bent plates via three-dimensional reconstruction of the proximal tibia *in vitro* and transparent retractors for auxiliary treatment during surgery. Surgical treatment indicators, treatment outcomes, and the occurrence of complications were analyzed. Knee joint range of motion and knee joint function scores [New York Special Surgery Hospital Score (HSS), International Knee Documentation Committee Score (IKDC)] were compared before and after surgery. *Results:* At six months post-surgery, the overall excellent and good reduction rate of tibial plateau fractures in 28 patients was 89.29%. The overall incidence of surgical complications within six months post-surgery was 14.29%, with no cases of severe complications observed. The average surgical duration was 145.32 ± 15.07 minutes, the average intraoperative blood loss was 53.52 ± 6.71 ml, and the average time to fracture healing post-surgery was 14.65 ± 2.21 weeks. Compared to pre-surgery, the range of motion of the knee joint, as well as the HSS and IKDC scores of the knee joint, significantly increased at three and six months post-surgery, with statistically significant differences ($P < 0.05$). *Conclusion:* The application of three-dimensional reconstruction-based precise pre-bent plates for the proximal tibia and fluoroscopically visible retractors in internal fixation surgery via a joint line incision approach for patients with Schatzker type III–VI tibial plateau fractures can actively enhance surgical efficiency and the effectiveness of internal fixation. Additionally, it can assist in optimizing postoperative fracture reduction and the rehabilitation of knee joint function in patients.

Keywords: Tibial plateau fracture; Internal fixation surgery; Joint line approach; Three-dimensional reconstruction; Pre-bent plate; Fluoroscopically visible retractor

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1. Introduction

Tibial plateau fractures are a severe type of lower limb fracture, typically caused by high-energy stress injuries to the affected knee joint. These fractures can lead to swelling, pain, and mobility impairment of the knee joint. If not treated properly, they can further affect the weight-bearing and functional health of the knee joint, necessitating active treatment ^[1]. As the primary surgical treatment for tibial plateau fractures at the current stage, internal fixation can assist in promoting fracture reduction after the internal fixation plate is inserted through the incision, thereby maintaining the bone structure and functional health of the knee joint. However, upon analyzing traditional internal fixation plates and surgical outcomes, it has been found that factors such as inadequate pre-preparation of the plate, insufficient surgical precision, and poor fluoroscopic visibility of the retractor may fail to meet the precise surgical needs of some patients and affect the quality of postoperative functional rehabilitation of the knee joint. Therefore, surgical procedures should be improved in response to these factors ^[2,3]. Hence, to analyze the combined effects of the joint line incision approach, precise pre-bending of three-dimensional reconstructed plates for the proximal tibia *in vitro*, and fluoroscopically visible retractors in the clinical treatment of Schatzker type III–VI tibial plateau fractures, as well as their impact on the functional recovery of the knee joint, a therapeutic study was conducted. The details are as follows.

2. Data and methods

2.1. Clinical data

A retrospective analysis was conducted on the surgical treatment outcomes of 28 patients with tibial plateau fractures admitted from January 2023 to January 2025. Among the 28 patients, there were 17 males and 11 females, aged between 27 and 68 years (47.55 ± 4.98 years). The affected side was the left knee in 7 cases and the right knee in 21 cases. The causes of injury were traffic accidents in 21 cases, sports injuries in 4 cases, and falls from heights in 3 cases. According to the Schatzker classification, there were 5 cases of type III, 12 cases of type IV, 8 cases of type V, and 3 cases of type VI.

Inclusion criteria: (1) Closed tibial plateau fractures with a disease course of ≤ 7 days; (2) Preoperative imaging findings consistent with the diagnostic criteria for Schatzker type III to VI fractures; (3) Meeting the indications for internal fixation surgery; (4) Having intact cognitive and language communication functions and confirming acceptance of surgical treatment. Exclusion criteria: (1) Open tibial plateau fractures or fractures caused by pathological factors; (2) Preoperative imaging findings indicating fractures in other areas around the knee joint or severe meniscal injury; (3) Having a history of previous knee surgery or degenerative knee disease; (4) Having motor dysfunction in the affected lower limb; (5) Having a history of stroke or mental disorders; (6) Confirming intolerance to surgery or having surgical contraindications.

2.2. Methods

- (1) Preparation of precisely pre-bent plates for three-dimensional reconstruction of the proximal tibia *in vitro*: Prior to surgery, based on CT scan images of the affected knee joint, a 1:1 three-dimensional solid model of the fracture was prepared after three-dimensional image reconstruction using image processing software (MIMICS17.0). The attending physician performed simulated fracture reduction based on the model, selected the appropriate type and number of internal fixation plates as needed, pre-bent the plates according to surgical requirements, and recorded the steps of the simulated surgical procedure in detail to refine surgical preparation.

- (2) Surgical procedure: After anesthesia induction, a lateral (or medial) arthrotomy incision (transverse) along the joint line was made. Through this incision, tissues were dissected to expose the joint capsule, which was then incised transversely beneath the meniscus. The meniscus was sutured and suspended above the incision. Two Kirschner wires were inserted into the distal femur and the area distal to the tibial fracture, respectively, and connected to a fluoroscopically visible retractor for distraction. According to the preoperative plan, a separate 1.5 cm skin incision was made approximately 5 cm distal to the tibial plateau. A window was created in the tibia, and through the use of a percutaneous reduction device, the collapsed plateau fracture was precisely reduced. Multiple fine Kirschner wires were temporarily inserted through the subchondral bone on the lateral aspect of the plateau for fixation. After confirming accurate reduction of the plateau through anteroposterior and lateral fluoroscopy, a pre-bent plate was inserted through the incision for internal fixation.

Postoperatively, all patients received standardized analgesia, anti-infection treatment, and functional rehabilitation therapy, with continuous follow-up for 6 months.

2.3. Observation indicators

- (1) Surgical treatment indicators: Based on surgical records, the mean surgical duration and intraoperative blood loss were calculated. Based on postoperative follow-up information, the mean time to fracture healing was calculated.
- (2) Treatment outcomes: At the 6th month postoperatively, the reduction effect of tibial plateau fractures was evaluated. Based on CT images of the affected knee joint obtained on the follow-up day, the Rasmussen imaging score was used to assess joint surface collapse, knee varus/valgus deformity, and condylar width changes, with a total score ranging from 0 to 18. Based on the assessment results, the reduction effect was classified as excellent (18 points), good (12–17 points), fair (6–11 points), or poor (≤ 5 points) ^[4].
- (3) Incidence of complications: The overall incidence of surgery-related complications within six months postoperatively was recorded, including five categories: incision infection, delayed fracture healing, joint stiffness, traumatic arthritis, and internal fixation failure.
- (4) Range of motion (ROM) of the knee joint: The maximum extension and flexion ROM of the patients' knee joints were evaluated before surgery and during follow-up visits at the third and sixth months postoperatively, and the mean values for each group were calculated.
- (5) Knee joint function scores: The Hospital for Special Surgery (HSS) score and the International Knee Documentation Committee (IKDC) score were employed to assess the patients' knee joint function before surgery and during follow-up visits at the third and sixth months postoperatively. Both the HSS and IKDC scores range from 0 to 100, with higher scores indicating better knee joint function ^[5,6].

2.4. Statistical methods

Statistical analysis was performed using SPSS 23.0 software. Categorical data were expressed as n (%), and the composition ratio data were analyzed using the chi-square test. Continuous data conforming to a normal distribution were presented as mean \pm standard deviation (SD), and paired t -tests were used for within-group comparisons. A P -value of less than 0.05 was considered statistically significant.

3. Results

3.1. Analysis of surgical treatment indicators, therapeutic effects, and complication incidence rates

The average surgical duration for patients was 65.32 ± 15.07 minutes, with a mean intraoperative blood loss of 53.52 ± 6.71 ml. The average time for fracture healing after surgery was 14.65 ± 2.21 weeks.

The Rasmussen imaging score assessment results at 6 months postoperatively indicated that among the patients, 11 cases had excellent reduction of tibial plateau fractures, 14 cases had good reduction, 3 cases had fair reduction, and 0 cases had poor reduction, with an overall excellent and good rate of 89.29%.

Within 6 months postoperatively, the overall incidence of surgical complications was 14.29%, including 2 cases of incision infection, 1 case of delayed fracture healing, and 1 case of joint stiffness. All these conditions improved or resolved after symptomatic clinical intervention, and no cases of traumatic arthritis or internal fixation failure were observed.

3.2. Comparison of knee joint mobility before and after surgery

The range of knee extension and flexion increased postoperatively compared to preoperative levels, and the knee joint mobility at 3 and 6 months postoperatively was higher than that before surgery, with statistically significant differences ($P < 0.05$). See **Table 1**.

Table 1. Comparison of knee joint mobility before and after surgery (mean \pm SD)

Time point/n	Extension ROM (°)	Flexion ROM (°)
Preoperative/28	-17.58 ± 2.16	35.15 ± 5.21
3 months postoperative/28	$-11.21 \pm 1.45^*$	$94.56 \pm 7.39^*$
3 months postoperative/28	$-2.18 \pm 0.47^{*#}$	$126.58 \pm 14.32^{*#}$
<i>F</i>	27.056	25.677
<i>P</i>	< 0.001	< 0.001

Note: $*P < 0.05$ indicates a statistically significant difference compared to preoperative values; $^{\#}P < 0.05$ indicates a statistically significant difference compared to values at 3 months postoperatively.

3.3. Comparison of HSS and IKDC scores before and after surgery

After surgery, the patients' knee extension and flexion range of motion showed a significant increase compared to pre-surgery levels. Moreover, the HSS and IKDC scores at 3 and 6 months post-surgery were higher than those before surgery, with statistically significant differences ($P < 0.05$). See **Table 2**.

Table 2. Comparison of HSS and IKDC scores before and after surgery (mean \pm SD)

Time point/28	HSS score	IKDC score
Preoperative/28	51.74 ± 7.36	53.08 ± 6.85
3 months postoperative/28	$68.93 \pm 5.68^*$	$71.04 \pm 5.54^*$
6 months postoperative/28	$85.14 \pm 4.37^{*#}$	$87.25 \pm 4.12^{*#}$
<i>F</i>	14.134	15.277
<i>P</i>	< 0.001	< 0.001

Note: $*P < 0.05$ indicates a statistically significant difference compared to pre-surgery levels; $^{\#}P < 0.05$ indicates a statistically significant difference compared to the scores at 3 months post-surgery.

4. Discussion

Surgical treatment, as the preferred treatment option for patients with complex tibial plateau fractures, can repair knee joint collapse and maintain the morphology and functional health of the knee joint's bone tissue after surgical reduction and internal fixation, yielding definite therapeutic effects. However, an analysis of the efficacy of previous traditional internal fixation surgeries revealed that the traditional anterolateral surgical approach (combined with medial or posterior incisions when necessary) involves relatively extensive soft tissue dissection. It requires the use of retractors to maintain the incision field and operative range, which can increase the risk of related surgical complications and affect the quality of intraoperative fluoroscopic image acquisition. Additionally, the lack of adaptability in adjusting the shape of the steel plate during surgery can impact the actual internal fixation effect and postoperative rehabilitation, as well as prolong the time required for pre-bending and shaping the steel plate during surgery. Therefore, adjustments and improvements are needed based on the current advancements in surgical techniques to optimize the actual surgical outcomes for patients with complex tibial plateau fractures^[7].

As an auxiliary technology widely applied in the treatment of complex fractures in recent years, three-dimensional (3D) reconstruction technology can provide a basis for surgical plan evaluation and simulation operations after collecting CT scan images of the patient's preoperative fracture site, followed by 3D image reconstruction and model printing. This technology optimizes the individual adaptability of surgical treatment operations for patients and has demonstrated definite clinical application effects^[8]. Using fracture models, steel plates are precisely shaped *in vitro* to achieve an exact fit between the plates and the bones. After intraoperative fracture reduction, the steel plate is inserted through a soft tissue tunnel created via an incision along the joint line, simplifying the surgical procedure and significantly reducing the operation time. The radiolucent retractor, a surgical instrument made of carbon fiber material, offers advantages such as being lightweight, having high load-bearing capacity, and being radiolucent. It actively enhances the clarity of intraoperative fluoroscopic images and avoids the impact of artifacts on the operation. Therefore, the aforementioned techniques have definite application advantages in the treatment of complex tibial plateau fractures.

This study indicated that among the 28 patients, the overall excellent and good rate of tibial plateau fracture reduction at 6 months postoperatively was 89.29%, and the overall incidence of surgical complications within 6 months postoperatively was 14.29%, with no cases of severe complications observed. Compared to preoperative values, the range of motion of the knee joint and the HSS and IKDC scores of the knee joint at 3 and 6 months postoperatively were significantly increased, with statistically significant differences ($P < 0.05$). The analysis suggests that the combined application of precisely pre-bent steel plates through three-dimensional reconstruction *in vitro* and radiolucent retractors can, after improving preoperative preparations for patients, provide a convenient foundation for effective treatment through individually designed surgical plans and plate shaping. During actual surgical procedures, the use of radiolucent retractors can effectively avoid radiographic artifacts, offering clear images for evaluating fracture reduction and fixation outcomes, thereby reducing the number of intraoperative fluoroscopic examinations. This, in turn, actively optimizes surgical efficiency for patients, minimizes the exposure time of surgical incisions, and, through refined internal fixation techniques, comprehensively reduces the risk of surgical complications, providing a positive basis for patients' postoperative recovery^[9,10].

5. Conclusion

In summary, the application of 3D reconstruction for precise *in vitro* pre-bending of steel plates and radiolucent retractors in the internal fixation surgery of Schatzker type III to VI tibial plateau fractures via an arthrotomy

approach can actively enhance surgical efficiency and the effectiveness of internal fixation. Furthermore, it aids in optimizing postoperative fracture reduction and the rehabilitation of knee joint function in patients.

Disclosure statement

The authors declare no conflict of interest.

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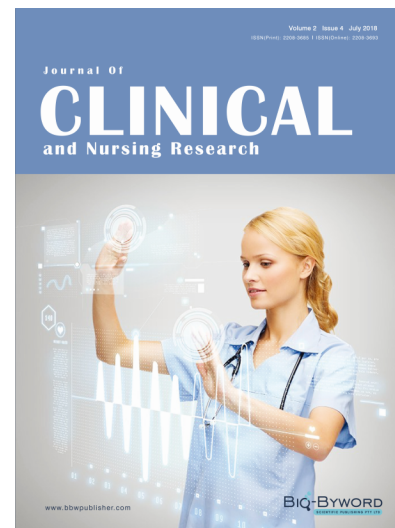
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