Article

Impact of Combining Alfacalcidol With Proximal Femoral Nail Antirotation on Bone Mineral Density, Serum Bone Metabolites, and Inflammatory Markers in Elderly Patients With Osteoporotic Intertrochanteric Fractures

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AIM: Proximal femoral nail antirotation (PFNA) fixation remains an effective surgical method in effectively managing intertrochanteric fractures in elderly patients with osteoporosis. While postoperative anti-osteoporotic therapy is essential, only a part of the elderly patients adhere to anti-osteoporosis treatment. Therefore, this study aims to investigate the therapeutic efficacy of combining alfacalcidol (an anti-osteoporotic drug) with PFNA fixation, as well as their effects on serum bone metabolic markers and inflammatory indicators in elderly patients with osteoporotic intertrochanteric fractures.
METHODS: This retrospective study recruited 140 elderly patients with osteoporosis intertrochanteric fractures who were treated at Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, China, between January 2021 and January 2024. Patients were divided into two groups based on their treatment approach: a surgical group (n = 63, who received PFNA with routine postoperative care) and a combined group (n = 77, who received PFNA combined with alfacalcidol). Postoperatively, these patients were followed up for a six-month period. Fracture healing was comprehensively evaluated through functional assessment and X-ray imaging examination. Harris hip scores and bone mineral density (BMD) were assessed before surgery, and then again one month and six months after surgery. Furthermore, serum bone metabolic markers and inflammatory cytokines were evaluated preoperatively and then six months after surgery.
RESULTS: The fracture healing time was significantly shorter in the combined group than in the surgical group ($p < 0.001$). Compared to the surgical group, the Harris scores in the combined group were significantly higher at one and six months postoperatively ($p < 0.001$, $p = 0.003$). Additionally, BMD in the combined group was significantly increased at six months postoperatively ($p = 0.002$). Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), β-Crosslaps (β-CTX), and parathyroid hormone (PTH) were significantly lower in the combined group compared to the surgical group after surgery ($p < 0.001$), whereas 25-hydroxyvitamin D (25-OHD) and procollagen type I C-terminal propeptide (PICP) levels were significantly higher ($p < 0.001$). In the surgical group, there were 4 cases of screw migration, 2 cases of delayed healing, and 1 case of venous embedding in the lower limbs. There was 1 case of infection, 2 cases of screw migration, 1 case of delayed healing, and 2 cases of venous embedding in lower limbs in the combined group. The incidence of postoperative complications was comparable between the combined group (6/77, 7.79%) and the surgical group (7/63, 11.11%) ($p = 0.501$).
CONCLUSIONS: Alfacalcidol combined with PFNA provides superior therapeutic outcomes for elderly patients with osteoporotic intertrochanteric fractures. This treatment approach effectively reduces postoperative fracture healing time, enhances BMD, and promotes functional recovery of the hip joint. Additionally, it improves bone metabolism and alleviates inflammatory responses, thereby enhancing overall clinical outcomes.

Keywords: alfacalcidol; proximal femoral nail antirotation; bone mineral density; serum bone metabolites; inflammatory factors

Introduction

Intertrochanteric fractures are a prevalent type of hip fracture among the elderly, with their incidence rate increasing annually. These fractures account for approximately 30–40% of all hip fractures in older individuals [1,2]. They are typically caused by low-energy trauma and are often associated with unstable, comminuted fracture patterns [3]. Due to an age-related decrease in bone mineral density (BMD) and bone strength, older individuals, particularly those with osteoporosis, are highly vulnerable to fractures from even minor external forces [4]. A study specifically underscored a significant reduction in BMD among elderly Chinese patients with intertrochanteric fractures, with the decline being more pronounced in women [5].
Surgical intervention remains the primary treatment for intertrochanteric fractures, as it promotes postoperative re-

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covery of joint function and improves the patient's quality of life [6]. Among surgical options, intramedullary fixation is recognized as the preferred strategy, with the proximal femoral nail antirotation (PFNA) being a widely used device. The PFNA system has an anti-rotation helical blade that provides resistance to rotational deformities [7] and has shown promising therapeutic outcomes in managing intertrochanteric fractures [7,8]. However, while surgical interventions effectively stabilize the fracture site, it does not improve the underlying issue of osteoporosis. A study conducted in China demonstrated that the early administration of anti-osteoporosis drugs reduced all-cause mortality by 67% in elderly patients with intertrochanteric fractures [9], highlighting the critical significance of initiating anti-osteoporosis treatment following fracture surgery.

Despite the well-established link between osteoporosis and fracture risk in the elderly, adherence to anti-osteoporosis treatment remains considerably low. It has been observed that only 40.3% of patients over 50 years who underwent hip fracture surgery received anti-osteoporosis drugs, and just 39.3% adhered to the treatment regimen one year after the procedure [10]. Furthermore, there is a lack of comprehensive research exploring therapeutic efficacy and clinical outcomes of postoperative anti-osteoporosis treatment, specifically in older individuals with intertrochanteric fractures.

Alfacalcidol, a vitamin D analog and calcium regulator, plays a crucial role in calcium and phosphorus homeostasis, thereby promoting bone formation and alleviating osteoporosis [11]. Previous research has reported that alfacalcidol can significantly reduce the risk of fractures in patients with osteoporosis [12]. Furthermore, alfacalcidol has demonstrated promising outcomes in improving bone health and is highly recommended in clinical practice for managing osteoporosis [13]. Given these observations, we speculate whether the combination of alfacalcidol and PFNA can offer an effective therapeutic approach for elderly patients with osteoporotic intertrochanteric fractures.

Bone metabolism markers are key clinical indicators, reflecting the process of bone formation and resorption, and they are closely correlated to both fracture healing and the pathogenesis of osteoporosis [14,15]. Moreover, immune cytokines play a regulatory role in bone metabolism through various feedback mechanisms and participate in the pathological mechanisms of osteoporosis [16]. However, the impact of alfacalcidol combined with PFNA fixation on clinical efficacy, serum bone metabolites and inflammatory cytokines in patients with intertrochanteric fractures remains unclear.

Therefore, this study aims to explore the therapeutic efficacy of alfacalcidol in combination with PFNA in elderly patients with osteoporosis intertrochanteric fractures and to evaluate its impact on serum bone metabolic markers and inflammatory factors.

Materials and Methods

Recruitment of Study Participants

This retrospective study included 140 elderly patients with osteoporotic intertrochanteric fractures who were treated at the Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, China, between January 2021 and January 2024. The inclusion criteria for patients were as follows: (1) age $\geq$60 years; (2) BMD test confirming osteoporosis (T-score $<$–2.5) [17]; (3) intertrochanteric fracture diagnosis confirmed by imaging and clinical examination [18], caused by low-energy injuries and not involving an open fracture; and (4) fresh, unilateral fracture. Fresh fractures were defined as fractures that occurred within 3 weeks, without evidence of periosteal reaction or callus formation [19].

The exclusion criteria included: (1) those not eligible for surgery and received conservative or alternative treatments; (2) use of anti-osteoporosis drugs within three months before treatment; (3) pathological fractures caused by bone tumors or tuberculosis; (4) severe impairment of major organ function (heart, liver, kidneys, lungs); (5) history of mental disorders; (6) ovarian or thyroid diseases associated with secondary osteoporosis, including ovarian dysfunction, hyperthyroidism, and hypothyroidism; and (7) incomplete clinical data.

Based on the treatment method, patients (n = 140) were divided into two groups: the surgical group (n = 63), which underwent PFNA with routine postoperative care, and the combined group (n = 77), which received PFNA along with alfacalcidol treatment. The study was approved by the ethics committee of Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine (No. 2024-K056) and complied with the principles outlined in the Declaration of Helsinki. All patients provided informed consent, and patient confidentiality was maintained by anonymizing personal information in all figures.

Surgical Protocol and Treatment

All patients received proximal femoral nail antirotation (PFNA) under epidural anesthesia in the supine position. The affected limb was fixed, and vital signs were continuously monitored throughout the procedure. To reduce fractures, the affected limb was stabilized using a traction frame. Once satisfactory alignment was confirmed, a 5–6 cm lateral incision was made on the lateral aspect of intertrochanteric. Next, a drill was introduced at the apex of the greater trochanter.

Furthermore, a PFNA nail was inserted into the femoral stem under the guidance of a C-arm X-ray machine (PLC7500, Perlove Medical, Nanjing, China). A spiral blade was then guided into the femoral neck and its position was confirmed through intraoperative imaging. Subsequently, 1–2 locking screws were placed in the distal end to secure the PFNA nail. The incision was cleaned, a drainage tube was placed, and the incision was sutured. Fig. 1 shows

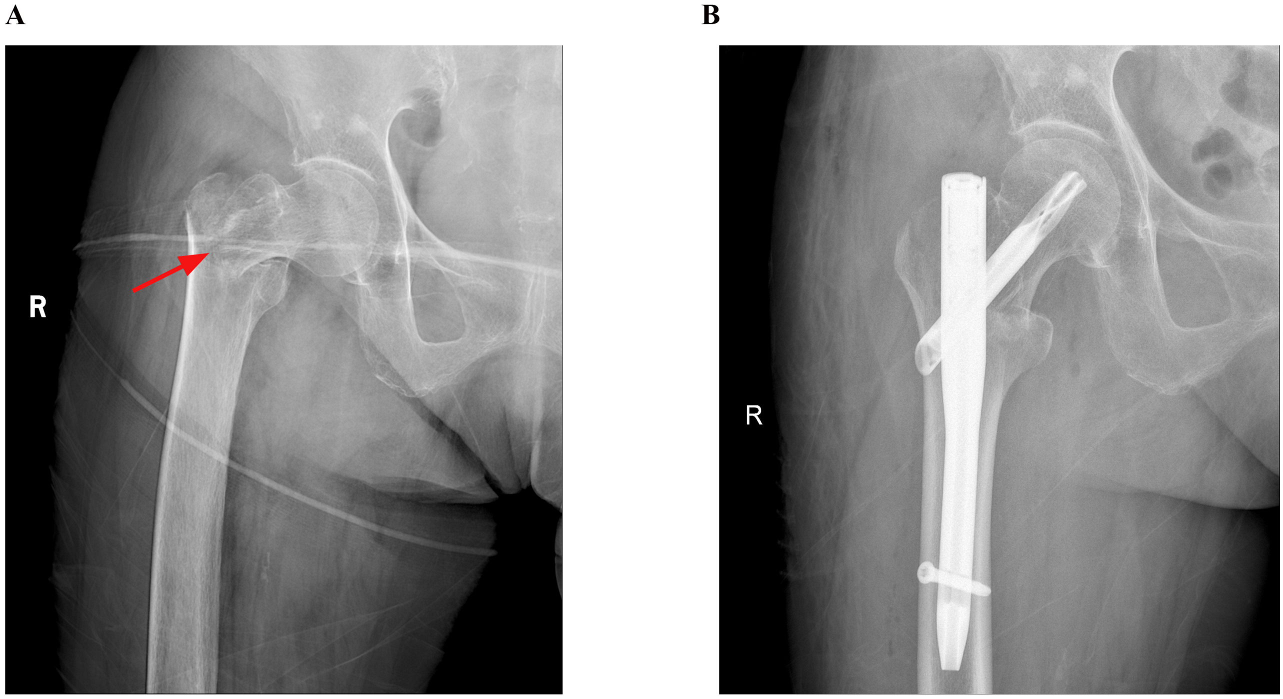

Fig. 1. Representative X-ray images of a patient with an intertrochanteric fracture. (A) The X-ray image before surgery. The red arrow indicates a fracture site. (B) The X-ray image after surgery. R, right.

the preoperative and postoperative X-ray images of a patient with an intertrochanteric fracture.

None of the patients received anti-osteoporosis medication before or during surgery. After surgery, both groups received calcium supplementation, while the combined group received additional alfacalcidol therapy. Patients in the surgical group received calcium carbonate D3 (H10950029, Wyeth Pharmaceuticals Co., Ltd., Suzhou, China) at a dosage of 600 mg/day (one capsule daily for a duration of 6 months. Patients in the combined group received alfacalcidol (H200000065, Nantong Huashan Pharmaceutical, Nantong, China) in addition to the same calcium carbonate D3 (600 mg/day). Alfacalcidol was initiated on the second day after surgery at a dosage of 0.5 µg/day, given orally as two capsules once daily for six months.

Patients in both groups received routine postoperative care and rehabilitation training. Specifically, postoperative drainage was routinely performed. To prevent thrombosis, patients received low molecular weight heparin sodium (2500 IU/day; H20030429, Qilu Pharmaceutical, Jinan, China) through subcutaneous injections for 7–10 days. For infection control, cefazolin sodium (1.0 g; H20163258, Shandong Runze Pharmaceutical Co., Ltd., Heze, China) was administered intravenously 30 minutes before surgery, followed by a dose of 1.0 g twice daily for three days postoperatively. Additionally, rehabilitation care was initiated with in-bed hip extension and knee flexion exercise on the first postoperative day. One week postoperatively, patients started bedside muscle contraction exercises in the seated position. Non-weight-bearing functional exercises with crutches were initiated at 3–4 weeks after surgery. However, weight-bearing functional exercise was performed based on the individual's fracture recovery status. After discharge, patients continued rehabilitation training and nutritional support as per physician recommendations. A flowchart of the treatment protocol is shown in Fig. 2.

Follow-up

All patients were followed up for a period of six months after surgery. They were advised to attend an outpatient clinic at least once per month to monitor fracture healing and recovery. During each follow-up, the physician assessed limb function, recorded any complications, observation and final confirmation of fracture healing time. Reported complications included incision infection, screw migration, delayed healing, and venous embolism in the lower limbs.

The criteria for fracture healing were as follows [20,21]: (1) presence of callus formation with blurred fracture line and proper alignment at the fracture site; (2) ability to walk independently and remain upright for at least thirty minutes, with no change observed at the fracture site over a two-week period; and (3) absence of compression pain at the fracture site along with good joint mobility. Functional recovery was initially determined clinically, and an X-ray was conducted upon satisfactory functional recovery to confirm bone healing. Additionally, BMD, Harris hip scores, serum bone metabolites, and inflammatory factors were systematically assessed throughout the follow-up period.

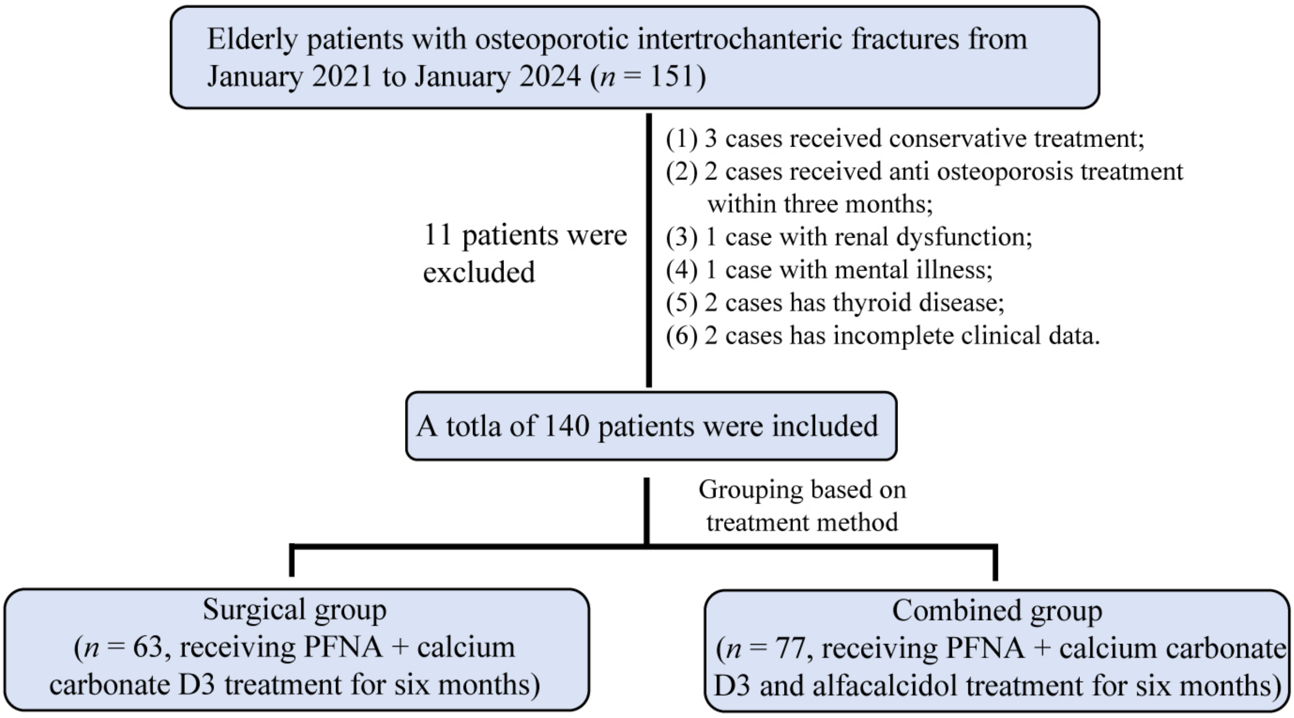

Fig. 2. A flowchart of the treatment protocol. PFNA, proximal femoral nail antirotation.

Assessment of Hip Joint Function Through the Harris Score

Harris hip score is commonly used to evaluate hip joint function [22,23], with its effectiveness and reliability well-established in previous studies [24,25]. Harris scores of patients were recorded before surgery, and at one and six months after surgery. All assessments were performed by a single foot and ankle surgeon with five years of clinical experience, based on a patient's clinical presentation and functional status. The Harris score was used to examine four key domains, including pain, function, deformity, and joint mobility, with a total score of 100 points. Higher scores indicate better hip joint recovery and functional outcomes.

Evaluation of BMD

BMD of the femoral neck on the non-fractured side was evaluated preoperatively, and at one and six months postoperatively, using a dual-energy X-ray bone densitometer (GE Lunar Prodigy Advance, GE Healthcare, Madison, MI, USA). Before each measurement, the instrument was calibrated, followed by a quality assurance check using a dedicated vertebral body phantom. Scanned images were analyzed with enCORE software (v.17.0, GE Healthcare, Madison, MI, USA). All scans were performed and analyzed by the same team of trained technicians to ensure consistency. Fig. 3 shows a dual-energy X-ray image used for BMD assessment.

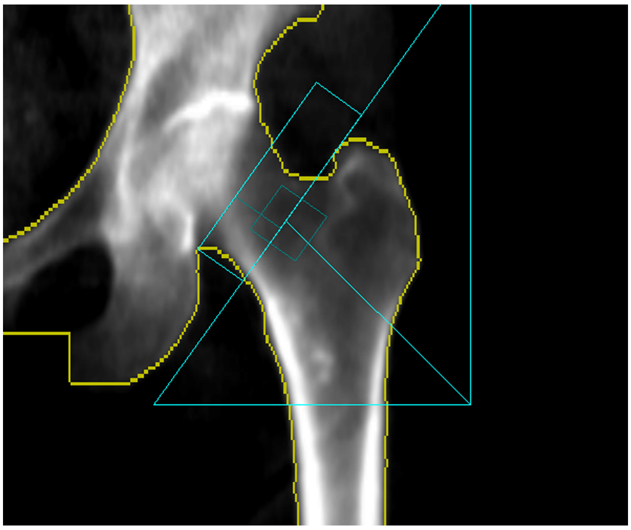

Fig. 3. A representative dual-energy X-ray image used for bone mineral density assessment. The yellow lines indicate the boundaries of the hip bones, while the blue lines represent the regions of interest used for bone density analysis. All lines were automatically generated by the enCORE software (v.17.0, GE Healthcare, Madison, MI, USA).

Serum Bone Metabolites and Inflammatory Cytokines

Fasting venous blood samples were collected from all patients before surgery and again six months after surgery to evaluate serum bone metabolites and inflammatory cytokines. The levels of inflammatory factors, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), as well as bone metabolism markers, such as 25-hydroxyvitamin D (25-OHD), β-Crosslaps (β-CTX), procollagen type I C-terminal propeptide (PICP), and N-terminal/mid-region osteocalcin (N-

MID), were quantified using enzyme-linked immunosorbent assay (ELISA) kits. The ELISA kits for IL-6 (EK0410), TNF-α (EK0525), and IFN-γ (EK0373) were obtained from BOSTER Biological Technology Co., Ltd. (Wuhan, China). However, kits for 25-OHD (RD-RX10021), β-CTX (RD-RX10155), PICP (RD-RX10046), and N-MID (RD-RX10181) were purchased from Beijing Ruida Henghui Technology Development Co., Ltd. (Beijing, China).

C-reactive protein (CRP) levels were measured using rate-scattering turbidimetry following the manufacturer's instructions for the reagent kit (SNM262, Baiolebo, Beijing, China). Parathyroid hormone (PTH) levels were determined using an automatic biochemical analyzer (Cobas 8000, Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS software (version 20.0, IBM, Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro-Wilk method. Normally distributed data were expressed as mean $\pm$ standard deviation (SD). Between-group comparisons were conducted using the independent-sample t-test, and within-group comparisons before and after the procedure were performed using paired t-tests. Furthermore, within-group comparisons across multiple time points, including preoperative, one-month, and six-month postoperative, were performed using repeated measures analysis of variance (ANOVA) followed by the Bonferroni test. Moreover, non-normally distributed data were presented as the median (interquartile range), and between-group comparisons were performed using the Mann-Whitney U test. Categorical data were presented as frequencies and percentages [n (%)], and the chi-square test was used for comparison. When a chi-square test of a 2×2 contingency table is performed, and the sample size is small or the expected frequency is between 1 and 5, Yates' continuity correction can be applied to reduce errors; if the expected frequency in any cell is $<$1, Fisher's exact test should be used instead. A p-value of $<$0.05 was considered statistically significant.

Results

Comparison of Baseline Data Between the Two Groups

The surgical group included 63 patients, comprising 33 females and 30 males, with a mean age of 73.22 $\pm$ 6.04 years. The combined group consisted of 77 patients, including 43 females and 34 males, with a mean age of 74.04 $\pm$ 6.53 years. There were no significant differences between the two groups in baseline characteristics, including age, sex, body mass index (BMI), Evans classification, fracture site, preoperative hospitalization time, smoking and drinking history, or the presence of comorbidities such as hypertension, coronary heart disease, and diabetes (all $p > 0.05$, Table 1).

Comparison of Fracture Healing Time and Harris Scores Between the Two Groups

The fracture healing time was significantly shorter in the combined group compared to the surgical group ($p < 0.001$). In both groups, Harris scores improved after surgery and continued to increase over time ($p < 0.05$). Repeated measurement ANOVA showed that the time factor, treatment group, and their interaction had a significant effect on the Harris score ($p < 0.001$). Furthermore, the Harris scores at one month and six months postoperatively were significantly higher in the combined group than in the surgical group ($p < 0.001$, $p = 0.003$, Table 2).

Comparison of BMD Between the Combined and Surgical Groups

In both groups, BMD increased slightly one month after surgery compared to baseline; however, the difference was statistically insignificant ($p > 0.05$). By 6 months postoperatively, a substantial increase in BMD was observed ($p < 0.05$). Repeated measurement ANOVA revealed that both the time factor and the time-by-group interaction had significant effects on BMD ($p < 0.001$, 0.002), whereas the group factor alone demonstrated no significant effect ($p = 0.082$). Notably, BMD in the combined group was significantly higher than in the surgical group six months after surgery ($p = 0.002$, Table 3).

Comparison of Serum Bone Metabolites and Inflammatory Indicators Between the Two Groups

Before surgery, there were no significant differences between the two groups regarding serum bone metabolites (25-OHD, β-CTX, PICP, N-MID, and PTH) and inflammatory markers (IL-6, TNF-α, IFN-γ, and CRP) (all $p > 0.05$). After surgery, levels of IL-6, TNF-α, IFN-γ, and CRP significantly decreased in both groups (all $p < 0.05$). Furthermore, the postoperative levels of IL-6, TNF-α, and IFN-γ were considerably lower in the combined group compared to the surgical group (all $p < 0.001$). However, there was no significant difference in CRP levels between the two groups after surgery ($p = 0.093$, Table 4).

Additionally, the postoperative levels of 25-OHD and PICP increased significantly in both groups compared to preoperative levels ($p < 0.05$), while β-CTX, N-MID, and PTH levels decreased ($p < 0.05$). Postoperatively, the combined group showed substantially higher levels of 25-OHD and PICP ($p < 0.001$), and considerably lower levels of β-CTX and PTH ($p < 0.001$). No significant difference in N-MID levels was observed between the two groups after surgery ($p = 0.201$) (Table 4).

Comparison of Complications Between the Two Groups

In the surgical group, there were 4 cases of screw migration, 2 cases of delayed healing, and 1 case of venous embolism in the lower limbs. There was 1 case of infection, 2 cases of screw migration, 1 case of delayed healing, and 2 cases of venous embedding in the lower limbs in the combined

Table 1. Comparison of baseline characteristics between the two groups.

General information	Surgical group (n = 63)	Combined group (n = 77)	$t/\chi^2/Z$	p-value
Age (years)	73.22 ± 6.04	74.04 ± 6.53	0.764	0.446
Sex, n (%)			0.167	0.682
Female	33 (52.38%)	43 (55.84%)		
Male	30 (47.62%)	34 (44.16%)		
Body mass index (kg/m^2)	23.55 ± 3.07	24.16 ± 3.09	1.165	0.246
Evans classification#, n (%)			0.867	0.833
Type I	26 (41.27%)	32 (41.56%)		
Type II	25 (39.68%)	26 (33.77%)		
Type III	8 (12.70%)	12 (15.58%)		
Type IV	4 (6.35%)	7 (9.09%)		
Fracture site, n (%)			0.005	0.946
Left side	29 (46.03%)	35 (45.45%)		
Right side	34 (53.97%)	42 (54.55%)		
Preoperative hospitalization time (days)	3 (2, 4)	3 (2, 5)	1.470	0.141
Smoking history, n (%)			0.396	0.529
Yes	32 (50.79%)	35 (45.45%)		
No	31 (49.21%)	42 (54.55%)		
Drinking history, n (%)			0.471	0.493
Yes	29 (46.03%)	31 (40.26%)		
No	34 (53.97%)	46 (59.74%)		
Hypertension, n (%)			0.093	0.760
Yes	22 (34.92%)	25 (32.47%)		
No	41 (65.08%)	52 (67.53%)		
Coronary heart disease, n (%)			0.026	0.873
Yes	10 (15.87%)	13 (16.88%)		
No	53 (84.13%)	64 (83.12%)		
Diabetes, n (%)			0.111	0.739
Yes	12 (19.05%)	13 (16.88%)		
No	51 (80.95%)	64 (83.12%)		

#Evans classification: Type I: Undisplaced two-part fragment fracture; Type II: Displaced two-part fragment fracture, large and small rotors are complete; Type III: Three-part fragment fracture without posterolateral support due to dislocated greater trochanter fragment; Type IV: Three-part fragment fracture without dislocated lesser trochanter or femoral arch fragment.

group. The overall complication rate was slightly lower in the combined group (6/77, 7.79%) than in the surgical group (7/63, 11.11%); however, the difference was not statistically significant (p = 0.501, Table 5).

Discussion

Intertrochanteric fractures are common conditions in the elderly, primarily involving the region of the femur between the greater and lesser trochanters. The local symptoms include the pain and restricted movement of hip. The Clinical manifestations are affected limb shortening and abduction deformity [1–3]. Osteoporosis is a significant risk factor for intertrochanteric fractures in the elderly [26]. Prompt surgical intervention is essential to realign the fracture site [27]. Surgical fixation methods include intramedullary nailing, dynamic hip screw fixation, and artificial joint replacement. Artificial hip replacement surgery is typically preferred for patients with complex comminuted fractures, coexisting degenerative arthritis, or failed internal fixation. However, it is associated with unique complications, such as periprosthetic fractures, thromboembolism, prosthetic loosening or wear, and joint dislocation [28]. A dynamic hip screw is usually appropriate for stable fractures, but it is not recommended for patients with osteoporosis due to inadequate fixation strength [29]. Intramedullary nailing can provide sufficient biomechanical stability with minimal soft-tissue destruction and has become the preferred clinical treatment approach. Furthermore, this strategy facilitates early postoperative rehabilitation, which is especially crucial in the elderly to reduce the risks associated with prolonged bed rest [30,31].

Our study confirmed that PFNA effectively enhances hip joint function in elderly patients with intertrochanteric fractures, as evidenced by a substantial increase in Harris scores. During follow-up, some complications, including incision infection, screw migration, and venous embolism in the lower limbs, were observed and managed with appropriate interventions. PFNA offers better anti-rotation

Table 2. Comparison of fracture healing time and Harris scores between the two groups.

Group	n	Fracture healing time (weeks)	Harris score					
			Before surgery	1 month after surgery	6 months after surgery	Time	Group	Time by group
Surgical group	63	18.83 ± 2.27	36.44 ± 5.11	60.06 ± 4.05*	82.73 ± 7.17*#	F = 2577.633; $p < 0.001$	F = 32.155; $p < 0.001$	F = 12.560; $p < 0.001$
Combined group	77	15.40 ± 2.56	35.88 ± 4.27	66.19 ± 5.21*	86.42 ± 7.00*#			
t		8.295	0.706	7.638	3.069			
p-value		<0.001	0.481	<0.001	0.003			

*$p < 0.05$ vs. before surgery, #$p < 0.05$ vs. 1 month after surgery.

Table 3. Comparison of bone mineral density between the two groups.

Group	n	Bone mineral density (g/cm^2)					
		Before surgery	1 month after surgery	6 months after surgery	Time	Group	Time by group
Surgical group	63	0.56 ± 0.06	0.57 ± 0.05	0.59 ± 0.08*	F = 24.009; $p < 0.001$	F = 3.070; $p = 0.082$	F = 6.320; $p = 0.002$
Combined group	77	0.55 ± 0.07	0.57 ± 0.08	0.64 ± 0.10*#			
t		0.896	0.007	3.215			
p-value		0.372	0.995	0.002			

*$p < 0.05$ vs. before surgery, #$p < 0.05$ vs. 1 month after surgery.

stability than traditional screw systems, especially suitable for patients with osteoporosis [32,33]. A previous study evaluating the impact of PFNA on patients with unstable intertrochanteric femoral fractures combined with severe osteoporosis found progressive enhancement in Harris scores over time after surgery, with satisfactory hip function achieved after 12 months of follow-up [33], which is consistent with our findings.

While PFNA offers effective short-term fracture stabilization in elderly patients with osteoporosis, it does not address the underlying bone condition. Among these patients, reduced bone formation and poor microcirculation often result in delayed fracture healing and suboptimal outcomes [34]. Thus, the administration of anti-osteoporosis drugs is essential to achieve optimal therapeutic effects.

In our study, patients in the surgical group received calcium carbonate D_3 after surgery for calcium supplementation, whereas those in the combined group received alfacalcidol in addition to calcium carbonate D_3. The results showed that the fracture healing time was significantly shorter in the combined group than in the surgical group, along with significant improvement in the Harris score and BMD after surgery. These findings indicate that the combination of alfacalcidol and calcium carbonate D_3 offers enhanced therapeutic effects for postoperative recovery in elderly patients with intertrochanteric fractures, promoting fracture healing, restoring hip joint function, and improving osteoporosis. Alfacalcidol, an anti-osteoporosis drug, is rapidly metabolized into its active form 1,25-(OH)2-vitamin D3, which enhances the absorption of calcium and phosphorus in the intestine and renal tubules, raises serum calcium and phosphorus levels, and promotes bone formation [11]. Additionally, alfacalcidol reduces plasma parathyroid hormone (PTH) levels and inhibits bone resorption, thereby improving osteoporosis [12].

Bone metabolism involves a dynamic equilibrium between bone resorption, mediated by osteoclasts, and bone formation by osteoblasts [35]. Osteoporosis results when this balance is disrupted, exceeding bone resorption over bone formation [36]. β-CTX is derived from the degradation of type I collagen and serves as a marker of osteoclast activity and bone resorption. PTH, the primary regulator of calcium and phosphorus homeostasis, stimulates the formation and activation of osteoclasts [37]. PICP reflects the synthesis of type I collagen and is an essential indicator of bone formation. Similarly, N-MID, secreted by osteoblasts, reflects bone formation as well as the activity and status of newly formed osteoblasts [38].

In our study, postoperative serum levels of 25-OHD and PICP were significantly increased in both groups, while levels of β-CTX, PTH, and N-MID demonstrated a substantial decrease, indicating improved bone metabolism following PFNA surgery. Additionally, the combined group showed significantly higher postoperative levels of 25-OHD and PICP, along with lower levels of β-CTX and PTH compared to the surgical group, suggesting that alfacalcidol improves bone metabolism in elderly patients with osteoporosis intertrochanteric fractures after PFNA surgery. These findings were consistent with previous studies reporting that alfacalcidol elevates serum calcium (Ca), phosphorus (P), and insulin-like growth factor 1 (IGF-1) levels while reducing PINP and β-CTX in patients with osteoporosis [39].

The balance between osteoblast and osteoclast activity is also regulated by immune system cytokines. Immune cells and their secreted cytokines, which play a crucial role in immune regulation, influence bone metabolism through receptor activator of nuclear factor-kappa B ligand (RANKL)-dependent or -independent pathways [40]. He *et al*. [41] reported that lymphocyte count and CRP levels could predict three-year postoperative mortality in elderly patients with intertrochanteric fractures, with an area under the receiver

Table 4. Comparison of serum bone metabolites and inflammatory factors between the two groups.

Indicator	Time	Surgical group (n = 63)	Combined group (n = 77)	t	p-value
IL-6 (pg/mL)	Before surgery	118.78 ± 20.75	125.34 ± 22.14	1.794	0.075
	After surgery	83.65 ± 17.22*	66.94 ± 17.71*	5.623	<0.001
TNF-α (pg/mL)	Before surgery	70.12 ± 10.25	73.43 ± 11.11	1.815	0.072
	After surgery	45.58 ± 9.52*	34.95 ± 8.82*	6.845	<0.001
IFN-γ (pg/mL)	Before surgery	93.75 ± 8.99	94.12 ± 10.02	0.228	0.820
	After surgery	50.34 ± 6.88*	30.46 ± 4.42*	20.679	<0.001
CRP (mg/L)	Before surgery	49.59 ± 7.11	50.86 ± 8.59	0.939	0.349
	After surgery	3.45 ± 0.86*	3.22 ± 0.75*	1.690	0.093
25-OHD (ng/mL)	Before surgery	12.77 ± 3.58	11.95 ± 4.05	1.255	0.212
	After surgery	15.58 ± 3.11*	18.78 ± 3.64*	5.521	<0.001
β-CTX (pg/mL)	Before surgery	584.34 ± 33.77	594.25 ± 30.12	1.834	0.069
	After surgery	448.31 ± 30.49*	374.69 ± 37.59*	12.532	<0.001
PICP (ng/mL)	Before surgery	89.13 ± 10.91	88.99 ± 10.00	0.079	0.937
	After surgery	106.32 ± 18.78*	145.21 ± 16.65*	12.978	<0.001
N-MID (pg/mL)	Before surgery	24.56 ± 3.86	24.18 ± 3.02	0.653	0.515
	After surgery	21.01 ± 3.15*	20.33 ± 3.09*	1.284	0.201
PTH (pg/mL)	Before surgery	37.58 ± 7.52	36.96 ± 8.65	0.447	0.655
	After surgery	33.95 ± 7.11*	28.76 ± 6.58*	4.477	<0.001

$^{*}p < 0.05$ vs. before surgery. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; CRP, C-reactive protein; 25-OHD, 25-hydroxyvitamin D; β-CTX, β-Crosslaps; PICP, procollagen type I C-terminal propeptide; N-MID, N-terminal/mid-region osteocalcin; PTH, parathyroid hormone.

Table 5. Comparison of postoperative complications between the two groups.

Complications (n, %)	Surgical group (n = 63)	Combined group (n = 77)	χ^2	p-value
Infection$^{\&}$	0 (0)	1 (1.30%)	/	>0.999
Screw migration$^{\&}$	4 (6.35%)	2 (2.60%)	0.450	0.502
Delayed healing$^{\&}$	2 (3.17%)	1 (1.30%)	0.031	0.860
Venous embolism in lower limbs$^{\&}$	1 (1.59%)	2 (2.60%)	0.031	0.860
Total	7 (11.11%)	6 (7.79%)	0.453	0.501

$^{\&}$chi-square test with Yates' continuity correction.

operating characteristic curve of 0.686. Similarly, Fisher *et al*. [42] analyzed inflammatory markers in patients with osteoporotic hip fractures and found that postoperative mortality was associated with inflammatory indicators such as the platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, albumin, red cell distribution width, and anemia. Surgical trauma inevitably induces an inflammatory response, resulting in increased levels of inflammation markers. Our study confirmed that alfacalcidol significantly alleviated the postoperative inflammatory response in patients with intertrochanteric fractures undergoing PFNA fixation, as evidenced by reduced serum IL-6, TNF-α, and IFN-γ levels. However, CRP levels were also reduced in the alfacalcidol group 6 months after the difference was not statistically significant. These observations suggest that alfacalcidol may help reduce postoperative inflammation levels in older patients with osteoporotic intertrochanteric fractures.

We acknowledge some limitations in our study. As a retrospective study, all data were obtained from patient medical records, which may introduce selection bias and restrict the strength of causal inferences. Therefore, postoperative studies are necessary to validate these findings. Additionally, the short follow-up period did not allow the assessment of long-term outcomes, such as the risk of re-fracture and changes in quality of life. Future investigations with long-term follow-up are needed to evaluate the correlation between postoperative outcomes and treatment methods. Furthermore, since this study focused on intertrochanteric fractures, it remains unclear whether the observed benefits of the treatment method are applicable to other types of fractures. Similarly, this study did not assess the systemic effects of treatment on BMD at other skeletal sites, including the lumbar vertebra, wrist, or foot, which should be investigated in future studies. Given the high risk of fractures in elderly patients with osteoporosis, our study suggests that combining surgical intervention with postoperative anti-osteoporosis therapy may offer considerable therapeutic benefits. This study provides a reference for clinicians in optimizing treatment approaches for elderly fracture patients with osteoporotic fractures.

Conclusions

Combining alfacalcidol with PFNA demonstrates significant therapeutic effects in elderly patients with osteoporotic intertrochanteric fractures. This combination approach effectively reduces postoperative fracture healing time, enhances BMD, and promotes functional recovery of the hip joint. Furthermore, it improves bone metabolism and alleviates inflammatory responses, thereby contributing to improved overall clinical outcomes. This is the first study to evaluate the clinical efficacy of combining alfacalcidol with PFNA in the treatment of elderly patients with osteoporosis intertrochanteric fractures. Additionally, this study provides a reference to elucidating the role of inflammation and bone metabolism in fracture healing by monitoring changes in serum inflammatory markers and bone metabolism indicators. These findings provide a basis for optimizing treatment approaches for intertrochanteric fractures of osteoporosis.

Availability of Data and Materials

The data analyzed are available on request from the corresponding author.

Author Contributions

OC designed the research study. YSH and BX performed the research. WX and OC analyzed the data and drafted the first manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine ethics committee (No. 2024-K056), and all procedures complied with the principles outlined in the Declaration of Helsinki. All patients provided informed consent, and all personal information has been removed from the figures to ensure confidentiality.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Yang M, Zhang Y. Epidemiological features of 1,332 cases of hip fracture in Shanghai, China (2015-2020). Arthroplasty (London, England). 2024; 6: 18. https://doi.org/10.1186/s42836-024-00236-4.

[2] Fan J, Lv Y, Xu X, Zhou F, Zhang Z, Tian Y, *et al*. The Efficacy of Multidisciplinary Team Co-Management Program for Elderly Patients With Intertrochanteric Fractures: A Retrospective Study. Frontiers in Surgery. 2022; 8: 816763. https://doi.org/10.3389/fsurg.2021.816763.

[3] Zhou X, Chen T, Jiang YL, Chen DB, Tian ZY. Comparison of the clinical outcomes between proximal femoral nail anti-rotation with cement enhancement and hemiarthroplasty among elderly osteoporotic patients with intertrochanteric fracture. BMC Musculoskeletal Disorders. 2024; 25: 290. https://doi.org/10.1186/s12891-024-07414-0.

[4] Lu GL, Li SJ, Li WX. Biomechanical study of extramedullary and intramedullary fixation in the treatment of unstable intertrochanteric reversed-tilt fractures of the femur. Annals of Translational Medicine. 2022; 10: 191. https://doi.org/10.21037/atm-22-93.

[5] Li M, Lv HC, Liu JH, Cui X, Sun GF, Hu JW, *et al*. Differences in Bone Mineral Density and Hip Geometry in Trochanteric and Cervical Hip Fractures in Elderly Chinese Patients. Orthopaedic Surgery. 2019; 11: 263–269. https://doi.org/10.1111/os.12456.

[6] Hongku N, Woratanarat P, Nitiwarangkul L, Rattanasiri S, Thakkinstian A. Fracture fixation versus hemiarthroplasty for unstable intertrochanteric fractures in elderly patients: A systematic review and network meta-analysis of randomized controlled trials. Orthopaedics & Traumatology, Surgery & Research: OTSR. 2022; 108: 102838. https://doi.org/10.1016/j.otsr.2021.102838.

[7] Loh J, Huang D, Lei J, Yeo W, Wong MK. Early Clinical Outcomes of Short versus Long Proximal Femoral Nail Anti-rotation (PFNA) in the Treatment of Intertrochanteric Fractures. Malaysian Orthopaedic Journal. 2021; 15: 115–121. https://doi.org/10.5704/MOJ.2107.017.

[8] Liang Y, Liu S, Li L, Zhong F. Proximal femoral nail antirotation versus external fixation for unstable intertrochanteric fractures in elderly patients: A randomized controlled trial. Medicine. 2022; 101: e29384. https://doi.org/10.1097/MD.0000000000029384.

[9] Li XP, Zhang P, Zhu SW, Yang MH, Wu XB, Jiang XY. All-cause mortality risk in aged femoral intertrochanteric fracture patients. Journal of Orthopaedic Surgery and Research. 2021; 16: 727. https://doi.org/10.1186/s13018-021-02874-9.

[10] Chau YT, Nashi N, Law LSC, Goh RKH, Choo SX, Seetharaman SK. Undertreatment of osteoporosis following hip fracture: a retrospective, observational study in Singapore. Archives of Osteoporosis. 2020; 15: 141. https://doi.org/10.1007/s11657-020-00816-2.

[11] Stuss M, Michalska-Kasiczak M, Sewerynek E. Clinical efficacy and safety of use of alfacalcidol and calcitriol in daily endocrinological practice. Endokrynologia Polska. 2023; 74: 16–24. https://doi.org/10.5603/EP.a2023.0008.

[12] Itoi E, Uemura Y, Ohta H, Nakamura T, Fukunaga M, Orimo H, *et al*. Impact of bone mineral density in reducing fracture risk in patients receiving alendronate plus alfacalcidol therapy. Journal of Orthopaedic Science: Official Journal of the Japanese Orthopaedic Association. 2021; 26: 1085–1093. https://doi.org/10.1016/j.jos.2020.10.017.

[13] Huang S, Li J, Hu X, Chen J. A Health Technology Assessment Based on Chinese Guideline: Active Vitamin D and Its Analogs in the Treatment of Osteoporosis. Drug Design, Development and Therapy. 2024; 18: 2593–2608. https://doi.org/10.2147/DDDT.S465960.

[14] Wawrzyniak A, Balawender K. Structural and Metabolic Changes in Bone. Animals: an Open Access Journal from MDPI. 2022; 12: 1946. https://doi.org/10.3390/ani12151946.

[15] Kushchayeva Y, Pestun I, Kushchayev S, Radzikhovska N, Lewiecki EM. Advancement in the Treatment of Osteoporosis and the Effects on Bone Healing. Journal of Clinical Medicine. 2022; 11: 7477. https://doi.org/10.3390/jcm11247477.

[16] Zhang W, Gao R, Rong X, Zhu S, Cui Y, Liu H, *et al*. Immunoporosis: Role of immune system in the pathophysiology of different types of osteoporosis. Frontiers in Endocrinology. 2022; 13: 965258. https://doi.org/10.3389/fendo.2022.965258.

[17] Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, *et al*. Fragility fractures in Europe: burden, management and opportunities. Archives of Osteoporosis. 2020; 15: 59. https://doi.org/10.1007/s11657-020-0706-y.

[18] Chen XP, Wang JP. Surgery. People's Medical Publishing House: Beijing. 2013. (In Chinese)

[19] Zura R, Xu ZJ, Della Rocca GJ, Mehta S, Steen RG. When Is a Fracture Not "Fresh"? Aligning Reimbursement With Patient Outcome After Treatment With Low-Intensity Pulsed Ultrasound. Journal of Orthopaedic Trauma. 2017; 31: 248–251. https://doi.org/10.1097/BOT.0000000000000778.

[20] Ge MY, Duan ZM, Guo YY, Zhao Y. Effect of alfacalcidol combined with tonifying the kidneys and invigorating blood circulation on bone metabolism and bone mineral density in osteoporotic hip fractures in elderly women. Modern Journal of Integrated Traditional Chinese and Western Medicine. 2018; 17: 1915–1918. (In Chinese)

[21] Corrales LA, Morshed S, Bhandari M, Miclau T, 3rd. Variability in the assessment of fracture-healing in orthopaedic trauma studies. The Journal of Bone and Joint Surgery. American Volume. 2008; 90: 1862–1868. https://doi.org/10.2106/JBJS.G.01580.

[22] Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. The Journal of Bone and Joint Surgery. American Volume. 1969; 51: 737–755.

[23] Phruetthiphat OA, Pinijprapa P, Satravaha Y, Kitcharanant N, Pongchaiyakul C. An innovative scoring system for predicting an excellent Harris hip score after proximal femoral nail anti-rotation in elderly patients with intertrochanteric fracture. Scientific Reports. 2022; 12: 19939. https://doi.org/10.1038/s41598-022-24177-7.

[24] Vishwanathan K, Akbari K, Patel AJ. Is the modified Harris hip score valid and responsive instrument for outcome assessment in the Indian population with pertrochanteric fractures? Journal of Orthopaedics. 2018; 15: 40–46. https://doi.org/10.1016/j.jor.2017.12.001.

[25] Mahomed NN, Arndt DC, McGrory BJ, Harris WH. The Harris hip score: comparison of patient self-report with surgeon assessment. The Journal of Arthroplasty. 2001; 16: 575–580. https://doi.org/10.1054/arth.2001.23716.

[26] Hu ZS, Liu XL, Zhang YZ. Comparison of Proximal Femoral Geometry and Risk Factors between Femoral Neck Fractures and Femoral Intertrochanteric Fractures in an Elderly Chinese Population. Chinese Medical Journal. 2018; 131: 2524–2530. https://doi.org/10.4103/0366-6999.244118.

[27] Fu H, Hu L, Zou F, Liao X, Zheng Y, Jin P, *et al*. A Comparative Study of the Early Postoperative Outcome of Three Intramedullary Fixation Modalities in the Treatment of Intertrochanteric Fractures of the Femur in the Elderly. Journal of Musculoskeletal & Neuronal Interactions. 2024; 24: 310–317.

[28] Taylor-Williams O, Inderjeeth CA, Almutairi KB, Keen H, Preen DB, Nossent JC. Total Hip Replacement in Patients with Rheumatoid Arthritis: Trends in Incidence and Complication Rates Over 35 Years. Rheumatology and Therapy. 2022; 9: 565–580. https://doi.org/10.1007/s40744-021-00414-9.

[29] Chang JZ, Xiao YP, Li L, Bei MJ. The efficacy of dynamic compression locking system vs. dynamic hip screw in the treatment of femoral neck fractures: a comparative study. BMC Musculoskeletal Disorders. 2022; 23: 661. https://doi.org/10.1186/s12891-022-05631-z.

[30] Viberg B, Eriksen L, Højsager KD, Højsager FD, Lauritsen J, Palm H, *et al*. Should Pertrochanteric and Subtrochanteric Fractures Be Treated with a Short or Long Intramedullary Nail?: A Multicenter Cohort Study. The Journal of Bone and Joint Surgery. American Volume. 2021; 103: 2291–2298. https://doi.org/10.2106/JBJS.20.01904.

[31] Wang C, Li X, Chen W, Wang C, Guo Y, Guo H. Three-dimensional finite element analysis of intramedullary nail with different materials in the treatment of intertrochanteric fractures. Injury. 2021; 52: 705–712. https://doi.org/10.1016/j.injury.2020.10.102.

[32] Zhang WQ, Sun J, Liu CY, Zhao HY, Sun YF. Comparing the Intramedullary Nail and Extramedullary Fixation in Treatment of Unstable Intertrochanteric Fractures. Scientific Reports. 2018; 8: 2321. https://doi.org/10.1038/s41598-018-20717-2.

[33] Li K, Yang H, Jiang Z, Peng W, Zhou X. Effect of proximal femoral nail antirotation on clinical outcome, inflammatory factors and myocardial injury markers in patients with femoral trochanteric fracture. American Journal of Translational Research. 2022; 14: 4795–4803.

[34] Prisby RD. The clinical relevance of the bone vascular system: age-related implications. Clinical Reviews in Bone and Mineral Metabolism. 2019; 17: 48–62. https://doi.org/10.1007/s12018-019-09259-x.

[35] Srivastava RK, Sapra L, Mishra PK. Osteometabolism: Metabolic Alterations in Bone Pathologies. Cells. 2022; 11: 3943. https://doi.org/10.3390/cells11233943.

[36] Al Saedi A, Stupka N, Duque G. Pathogenesis of Osteoporosis. Handbook of Experimental Pharmacology. 2020; 262: 353–367. https://doi.org/10.1007/164_2020_358.

[37] Rendina-Ruedy E, Rosen CJ. Parathyroid hormone (PTH) regulation of metabolic homeostasis: An old dog teaches us new tricks. Molecular Metabolism. 2022; 60: 101480. https://doi.org/10.1016/j.molmet.2022.101480.

[38] Schini M, Vilaca T, Gossiel F, Salam S, Eastell R. Bone Turnover Markers: Basic Biology to Clinical Applications. Endocrine Reviews. 2023; 44: 417–473. https://doi.org/10.1210/endrev/bnac031.

[39] Rui Z, Yan C, Wang Z, Yuan Y, Luan C, Wang L. The effects of alfacalcidol combined with calcitonin in the treatment of osteoporosis and its influence on levels of inflammation. American Journal of Translational Research. 2024; 16: 1690–1700. https://doi.org/10.62347/ZMAL4724.

[40] Ono T, Hayashi M, Sasaki F, Nakashima T. RANKL biology: bone metabolism, the immune system, and beyond. Inflammation and Regeneration. 2020; 40: 2. https://doi.org/10.1186/s41232-019-0111-3.

[41] He Z, Zhang C, Ran M, Deng X, Wang Z, Liu Y, *et al*. The modified lymphocyte C-reactive protein score is a promising indicator for predicting 3-year mortality in elderly patients with intertrochanteric fractures. BMC Geriatrics. 2023; 23: 432. https://doi.org/10.1186/s12877-023-04065-z.

[42] Fisher A, Fisher L, Srikusalanukul W. Prediction of Osteoporotic Hip Fracture Outcome: Comparative Accuracy of 27 Immune-Inflammatory-Metabolic Markers and Related Conceptual Issues. Journal of Clinical Medicine. 2024; 13: 3969. https://doi.org/10.3390/jcm13133969.