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Original Article

Effects of celecoxib combined with glucosamine hydrochloride in the management of knee osteoarthritis

Lv Cheng, Guang-Zheng Li, Xiang Shen, Yang Xie

Department of Orthopaedics, Ma'anshan People's Hospital, Ma'anshan 243000, Anhui, China

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Abstract: Objective: To evaluate the clinical efficacy of combination therapy with celecoxib (CEL) and glucosamine hydrochloride (GH) in patients with knee osteoarthritis (KOA). Methods: A total of 115 KOA patients were retrospectively analyzed and divided into a research group that received CEL combined with GH (n=62), while the control group received CEL alone (n=53). Clinical outcomes, safety, pain severity, knee joint function, quality of life (QoL), bone metabolic markers, and inflammatory indicators were assessed and compared between the groups. Factors associated with treatment efficacy were also analyzed. Results: The research group showed a significantly higher overall response rate (P=0.018), with no increase in adverse events (P>0.05). Compared to the control group, patients receiving combination therapy experienced greater improvements in pain relief, joint function, QoL, and bone metabolism, along with a more pronounced reduction in inflammatory markers (all P<0.05). Multivariate analysis identified advanced age, alcohol consumption, and smoking history as independent risk factors for poor therapeutic response (all P<0.05). Conclusions: Combination therapy with CEL and GH provides superior clinical benefits for KOA management. However, its efficacy may be reduced in older patients and those with a history of alcohol use or smoking.

Keywords: Celecoxib, glucosamine hydrochloride, knee osteoarthritis, clinical efficacy, influence factors

Introduction

Knee osteoarthritis (KOA) is one of the most prevalent chronic musculoskeletal disorders, typically progressing with age and eventually leading to joint dysfunction and disability [1]. By 2040, it is estimated that nearly half of adults over the age of 65 in the United States will develop some form of arthritis, with the knee joint being the most commonly affected site [2]. KOA is primarily characterized by chronic pain and limited mobility, both of which significantly impair patients' quality of life (QoL) [3-5].

Current treatment strategies for KOA are broadly categorized into surgical and conservative pharmacologic approaches. Surgical intervention is generally reserved for end-stage KOA [6]. However, due to the invasive nature of surgery, risk of complications, and potential for reoperation, there is increasing interest in exploring effective non-surgical alternatives [7].

Conservative treatments include both pharmacologic and non-pharmacologic methods such as physical therapy, activity modification, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. These therapies primarily aim to relieve pain and restore joint function. Celecoxib (CEL), a selective cyclooxygenase-2 (COX-2) inhibitor, is a newer-generation NSAID that offers effective symptom relief while minimizing gastrointestinal, renal, and central nervous system side effects compared to earlier NSAIDs [9, 10]. However, monotherapy with CEL often fails to achieve optimal therapeutic outcomes, prompting interest in combination strategies [11].

Glucosamine hydrochloride (GH) is frequently used in KOA treatment for its ability to supply key substrates required for cartilage matrix synthesis - such as proteoglycans and hyaluronic acid - as well as for its anti-inflammatory and anti-apoptotic properties, which collectively help slow disease progression and alleviate symptoms [12, 13]. Preclinical studies, includ-

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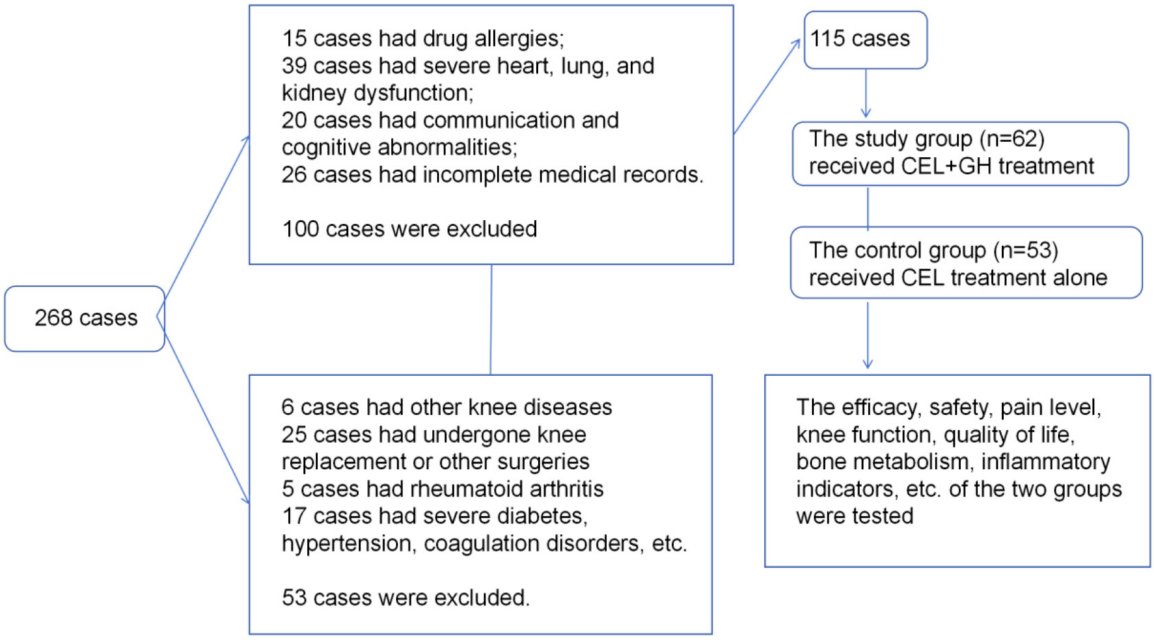

Figure 1. Patient selection flowchart. CEL, Celecoxib; GH, Glucosamine Hydrochloride.

ing one using a rabbit KOA model, have demonstrated GH's chondroprotective effects through modulation of transient receptor potential vanilloid 5 (TRPV5), leading to reduced chondrocyte apoptosis [14].

To evaluate this potential therapeutic synergy, the present study compared outcomes between KOA patients treated with CEL alone and those treated with a combination of CEL and GH. Key outcomes included overall efficacy, adverse events, pain reduction, joint function, QoL, bone metabolic markers, and inflammatory indicators. This study provides several notable contributions: (1) it is among the first clinical investigations to evaluate CEL-GH combination therapy in KOA patients, introducing a potentially novel therapeutic approach; (2) it employs a comprehensive assessment framework across multiple outcome domains, thereby enhancing the clinical relevance of the findings; and (3) it identifies high-risk subpopulations with poor treatment responses through both univariate and multivariate analyses, offering insight for personalized KOA management.

Materials and methods

Patient selection

This retrospective study was approved by the Ethics Committee of Ma'anshan People's Hospital. A total of 115 KOA patients treated between October 2022 and October 2024 were included. A non-randomized historical control design was used: 62 patients receiving CEL combined with GH were assigned to the research group, while 53 patients treated with CEL alone formed the control group. The patient enrollment flowchart is shown in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) diagnosis of KOA confirmed by clinical and imaging criteria; (2) no known hypersensitivity to the study medications; (3) absence of severe cardiac, pulmonary, or renal dysfunction; (4) intact cognitive and communication abilities; and (5) complete medical records.

Exclusion criteria included: (1) presence of other knee pathologies, fractures, or traumatic injuries; (2) history of knee replacement or other surgeries; (3) comorbid autoimmune or inflammatory joint diseases such as rheumatoid arthritis, gout, or Sjögren' s syndrome; (4) severe diabetes, hypertension, or coagulation disorders.

Data retrieval

Clinical information (e.g., sex, age, disease duration, lesion site, history of alcohol use, smoking history, marital status, and place of residence) was retrieved from the hospital's electronic medical records system.

Treatment methods

Patients in the research group received CEL + GH. CEL (CSPC Ouyi Pharmaceutical Co., Ltd., H20203297) was administered as one 0.20 g capsule once daily after meals for 6 weeks. GH (Zhejiang Cheng Yi Pharmaceutical Co., Ltd., H20060748) was given at a dose of 0.75 g per tablet, twice daily. The control group received CEL, following the same regimen as the research group. Treatment regimens were determined by the clinical team in accordance with standard clinical guidelines and individualized based on patient condition, after thorough discussion of all therapeutic options and associated risks/benefits with the patient.

Data extraction and outcome measures

Relevant data were extracted and validated by the hospital's medical records system, and evaluated as follows.

Clinical efficacy [15] was assessed at 6 weeks post-treatment using three categories: Cured: symptoms resolved, pain disappeared, joint function restored; Improved: symptoms alleviated, pain reduced, joint function improved; Ineffective: failure to meet the above criteria.

The total effective rate was calculated as the sum of the cured and improved cases.

Adverse reactions [16] covering skin allergies, dizziness, diarrhea, and nausea/vomiting were recorded during treatment to calculate the total adverse reaction rate.

Pain severity [17] was measured using the Visual Analogue Scale (VAS; range: 0-10), with higher scores indicating more severe pain. Assessments were conducted before and after 6 weeks of treatment.

Knee joint function [18] was assessed using two validated scales: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; range: 0-96), where higher scores indicate worse symptoms; Lysholm Knee Scale (range: 0-100), with higher scores indicating better joint function.

QoL [19] was evaluated using the Generic Quality of Life Inventory-74 (GQOL-74), covering four domains: physical function, psychological function, social function, and material well-being. Each domain is scored from 0 to 100, with higher scores reflecting better QoL.

To determine the bone metabolic markers (BMMs) and inflammatory indicators [20], Fasting venous blood (5 mL) was collected pre- and post-treatment (6 weeks), and serum was separated by centrifugation. The following biomarkers were quantified by ELISA: BMMs: bone gla protein (BGP), osteoprotegerin (OPG), and calcitonin (CT); Inflammatory markers included interleukin-6 (IL-6), interleukin-18 (IL-18), and matrix metalloproteinase-3 (MMP-3).

All reagents were sourced from Wuhan Bioyeargene Biotech Co., Ltd. and Wuhan Betterarray Biotech Co., Ltd.

Outcome measures

The clinical benefits of CEL-GH combination therapy were evaluated by analyzing its effects on efficacy, safety, pain, joint function, QoL, bone metabolism, and inflammation.

Primary outcomes included clinical efficacy, adverse reactions, pain intensity, and knee function.

Secondary outcomes included QoL metrics, BMMs, and inflammatory biomarkers.

All indicators were part of the hospital's routine clinical evaluation protocol.

Statistical analysis

Statistical analysis was conducted using SPSS 19.0. Quantitative data were presented as mean ± standard deviation ($\bar{x} \pm s$) and were compared using paired t-tests between groups before and after treatment. Categorical data were expressed as counts and percentages [n (%)] and compared using the chi-square test (χ^2).

Univariate and multivariate analyses were performed to identify independent predictors of treatment efficacy. Variables with $P<0.05$ by univariate chi-square tests were selected for multivariate analysis. Variables with >15% missing data, subgroup counts <5, or deemed clinically irrelevant were excluded. Binary logistic regression was conducted using a forward - backward stepwise approach based on maximum likelihood estimation. A *P*-value <0.05 was considered significant.

Table 1. Baseline data analysis of knee osteoarthritis patients

Factor	Control group (n=53)	Research group (n=62)	χ^2/t	P
Sex (male/female)	31/22	35/27	0.049	0.826
Age (years)	53.60±6.21	54.55±7.01	0.447	0.763
Disease duration (years)	3.21±0.63	3.27±0.96	0.389	0.698
Site of onset (bilateral/unilateral)	17/36	23/39	0.318	0.573
History of alcoholism (yes/no)	25/28	28/34	0.046	0.830
History of smoking (yes/no)	23/30	26/36	0.025	0.875
Marital status (married/single)	39/14	41/21	0.750	0.386
Residence (urban/rural)	37/16	40/22	0.362	0.547

Table 2. Clinical curative effect analysis of knee osteoarthritis patients [n (%)]

Factor	Control group (n=53)	Research group (n=62)	χ^2	P
Cured	13 (24.53)	17 (27.42)	-	-
Improved	26 (49.06)	39 (62.90)	-	-
Ineffective	14 (26.42)	6 (9.68)	-	-
Total effective rate	39 (73.58)	56 (90.32)	5.572	0.018

Results

Comparison of baseline data

As shown in **Table 1**, there were no significant differences between the two groups in baseline characteristics, including sex, age, disease duration, lesion site, history of alcohol use or smoking, marital status, or place of residence (all P>0.05).

Comparison of clinical efficacy

The total effective rate was significantly higher in the research group than in the control group (90.32% vs. 73.58%, P<0.05; **Table 2**).

Factors influencing treatment efficacy

Univariate analysis identified four variables significantly associated with treatment efficacy: age, disease duration, history of alcohol use, and smoking history (all P<0.05). These variables were included in a multivariate logistic regression model, which revealed the following independent risk factors for poor treatment response: 55 years (P=0.032, Odds Ratio (OR): 3.446), alcoholism history (P=0.024, OR: 3.733), and smoking history (P=0.041, OR: 3.160). See **Tables 3**-**5**.

Comparison of safety profile

As summarized in **Table 6**, adverse reactions including skin allergies, dizziness, diarrhea, and nausea/vomiting occurred in 5 patients in the control group and 7 in the research group. The incidence of adverse reactions was not significantly different between groups (11.29% vs. 9.43%, P>0.05).

Comparison of pain assessment

As shown in **Figure 2**, no significant difference in baseline VAS scores was observed between groups (P>0.05). After treatment, both groups showed significant reductions in VAS scores (P<0.05), with the research group achieving greater pain relief compared to the control group (P<0.05).

Comparison of knee joint function

Baseline WOMAC and Lysholm scores did not differ significantly between groups (both P> 0.05). Post-treatment, WOMAC scores decreased and Lysholm scores increased significantly in both groups (both P<0.05). Moreover, the research group demonstrated significantly lower WOMAC and higher Lysholm scores compared to the control group (both P<0.05; **Figure 3**).

Comparison of quality of life

As shown in **Figure 4**, no significant differences were observed between groups in any of the four dimensions (social function, psychological function, physical function, and material life) prior to treatment (all P>0.05). After treatment,

Table 3. Univariate analysis of clinical factors affecting treatment efficacy in knee osteoarthritis patients

Factor	Ineffective group (n=20)	Effective group (n=95)	χ^2	P
Gender			0.573	0.449
Male	13 (65.00)	53 (55.79)		
Female	7 (35.00)	42 (44.21)		
Age (years)			4.771	0.029
<55	6 (30.00)	54 (56.84)		
≥55	14 (70.00)	41 (43.16)		
Disease duration (years)			6.256	0.012
<4	8 (40.00)	66 (69.47)		
≥4	12 (60.00)	29 (30.53)		
Site of onset			0.291	0.590
Bilateral	8 (40.00)	32 (33.68)		
Unilateral	12 (60.00)	63 (66.32)		
History of alcoholism			5.572	0.018
Yes	14 (70.00)	39 (41.05)		
No	6 (30.00)	56 (58.95)		
History of smoking			4.964	0.026
Yes	13 (65.00)	36 (37.89)		
No	7 (35.00)	59 (62.11)		
Marital status			0.238	0.625
Married	13 (65.00)	67 (70.53)		
Single	7 (35.00)	28 (29.47)		
Residence			0.101	0.750
Urban	14 (70.00)	63 (66.32)		
Rural	6 (30.00)	32 (33.68)		

Table 4. Assignment analysis

Factor	Variables	Assignments
Age (years)	X1	<55 =0, ≥55 =1
Disease duration (years)	X2	<4 =0, ≥4 =1
History of alcoholism	X3	No =0, Yes =1
History of smoking	X4	No =0, Yes =1

all QoL scores increased significantly in both groups (all P<0.05), with the research group showing significantly higher scores across all domains compared to the control group (all P<0.05).

Comparison of bone metabolism markers

No significant differences were noted between groups before treatment (all P>0.05). Following treatment, BGP and OPG levels significantly increased in both groups (both P<0.05), with higher levels in the research group (both P< 0.05). CT levels showed no significant change within or between groups (P>0.05, **Figure 5**).

Comparison of inflammatory markers

No significant intergroup differences were found in the levels of IL-6, IL-18, and MMP-3 at baseline (all P> 0.05). After treatment, all three inflammatory markers decreased significantly in both groups (all P<0.05), with greater reductions observed in the research group compared to the control group (all P<0.05, **Figure 6**).

Discussion

The global burden of chronic joint diseases is rising, partly due to increasingly unhealthy lifestyles featuring obesity and physical inactivity [21]. Simultaneously, the incidence of KOA in younger populations is also increasing, placing greater demands on healthcare systems and escalating socioeconomic costs [22]. Although surgical intervention remains an effective treat-

Table 5. Multivariate analysis of factors influencing treatment efficacy in knee osteoarthritis patients

Factor	β	SE	Wald	P	OR	95% CI
Age (years)	1.237	0.576	4.616	0.032	3.446	1.115-10.655
Disease duration (years)	0.999	0.554	3.246	0.072	2.715	0.916-8.044
History of alcoholism	1.317	0.582	5.116	0.024	3.733	1.192-11.692
History of smoking	1.151	0.564	4.156	0.041	3.160	1.045-9.551

Table 6. Safety analysis of knee osteoarthritis patients [n (%)]

Factor	Control group (n=53)	Research group (n=62)	χ^2	P
Skin allergies	1 (1.89)	2 (3.23)	-	-
Dizziness	1 (1.89)	1 (1.61)	-	-
Diarrhea	2 (3.77)	1 (1.61)	-	-
Nausea/vomiting	1 (1.89)	3 (4.84)	-	-
Total incidence	5 (9.43)	7 (11.29)	0.105	0.746

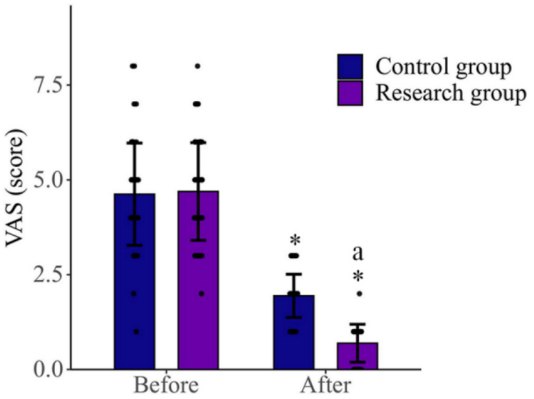

Figure 2. Degree of pain of knee osteoarthritis patients. Note: * represents P<0.05 compared to the score before treatment; a represents P<0.05 compared to control group. VAS, Visual Analogue Scale.

ment for advanced KOA, clinical outcomes and recovery times vary substantially, highlighting the need to optimize conservative management strategies [23].

In this study, the total effective rate was significantly higher in the research group compared to the control group (90.32% vs. 73.58%), indicating that adding GH enhances treatment efficacy. CEL provides rapid relief from inflammatory pain by selectively inhibiting COX-2 and reducing prostaglandin synthesis. GH, on the other hand, promotes cartilage matrix repair and suppresses inflammatory cytokines. The combination of CEL and GH produces synergistic effects, offering both symptomatic relief and structural joint protection in KOA management [24, 25].

Further univariate and multivariate analyses identified age ≥55 years, along with a history of alcohol use or smoking, as independent predictors of suboptimal treatment response. Patients with these risk factors may face greater therapeutic challenges and worse outcome.

In terms of safety, common adverse reactions such as skin allergies, dizziness, diarrhea, and nausea/vomiting were recorded. No significant difference in adverse reaction incidence was found between the two groups, suggesting that CEL-GH combination therapy does not substantially increase treatment-related risks. This favorable safety profile may be attributed to the absence of metabolic interaction between GH and CEL, as well as GH's well-established tolerability [26]. Supporting this, Wang et al. [27] reported that GH combined with diacerein improved treatment outcomes and reduced adverse reactions in KOA patients, which is consistent with our results.

Both groups experienced significant reductions in pain following treatment, with the research group showing greater improvement. CEL's analgesic effect results from COX-2 inhibition and reduced prostaglandin production through the arachidonic acid pathway [28]. GH may further alleviate pain by restoring the balance between synthesis and degradation of type II collagen, thereby preserving cartilage integrity [29].

To assess knee function recovery, we recorded WOMAC and Lysholm scores for both groups. Post-treatment, the research group exhibited significantly lower WOMAC scores and higher Lysholm scores compared to the control group, indicating superior functional recovery under combination therapy. In a murine KOA model, GH was shown to impede disease progression

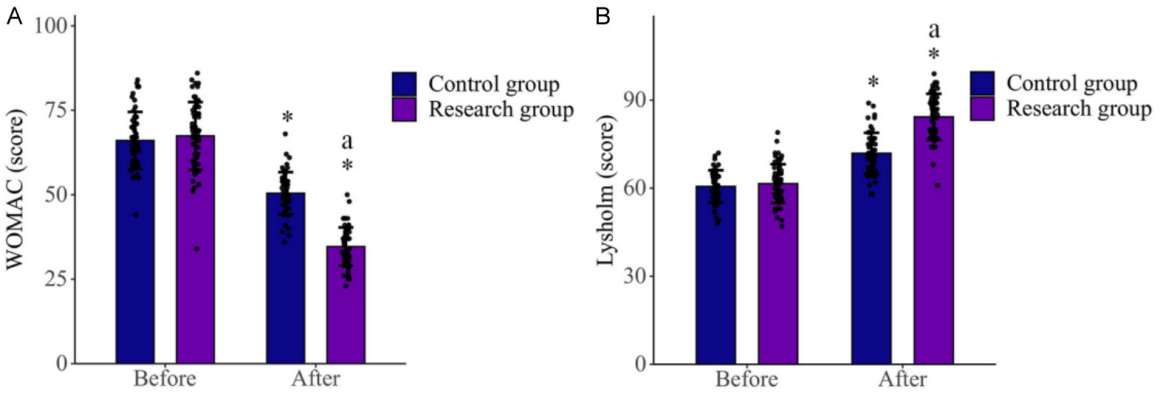

Figure 3. Analysis of knee joint function of knee osteoarthritis patients. A. WOMAC scores of both groups. B. Lysholm scores of both groups. Note: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. * represents P<0.05 compared to the score before treatment; a represents P<0.05 compared to control group.

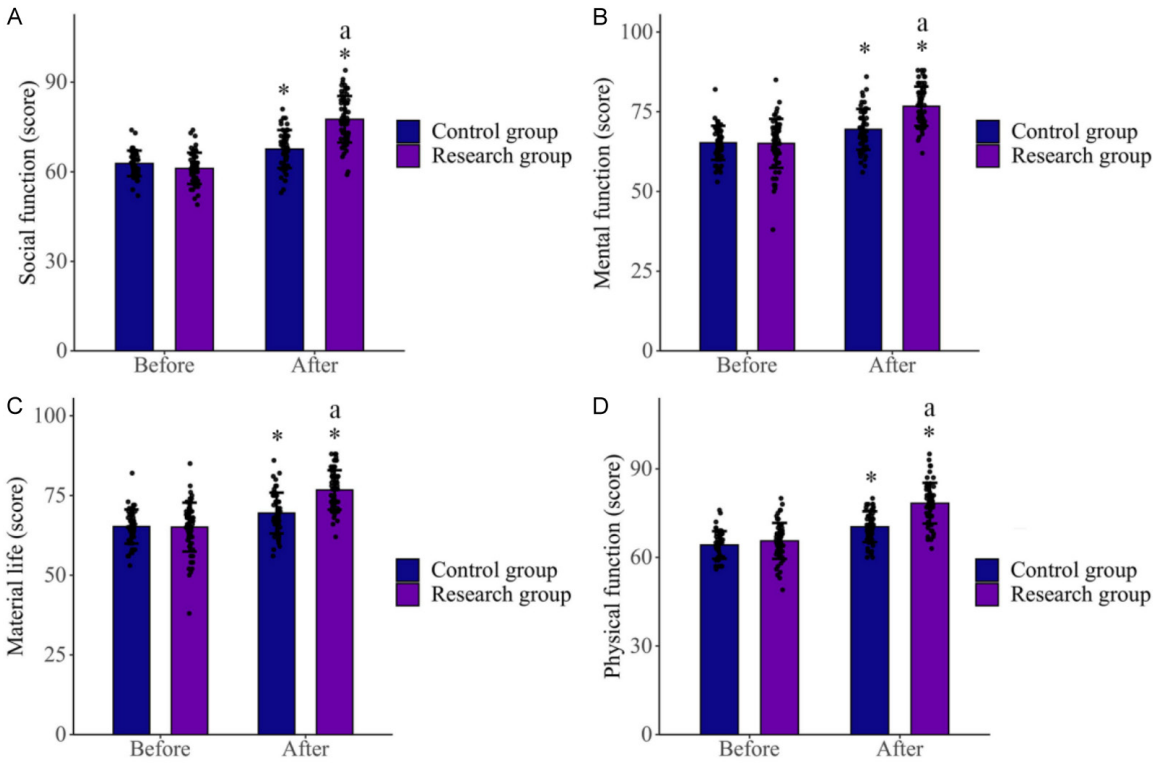

Figure 4. Analysis of quality of life in knee osteoarthritis patients. A. Social function scores of both groups. B. Mental function scores of both groups. C. Material life scores of both groups. D. Physical function scores of both groups. Note: * represents P<0.05 compared to the score before treatment; a represents P<0.05 compared to control group.

by downregulating inflammatory mediators, oxidative stress markers, and matrix-degrading enzymes, which may partially account for the improved joint function observed in our study [30]. Consistent with these findings, Wang et al. [31] reported that combining GH with NSAIDs significantly reduced knee pain, relieved arthritis symptoms, and enhanced joint function in KOA patients.

QoL, evaluated across four domains including social function, also improved significantly in the research group compared to controls. Similarly, Lila et al. [32] found that long-term

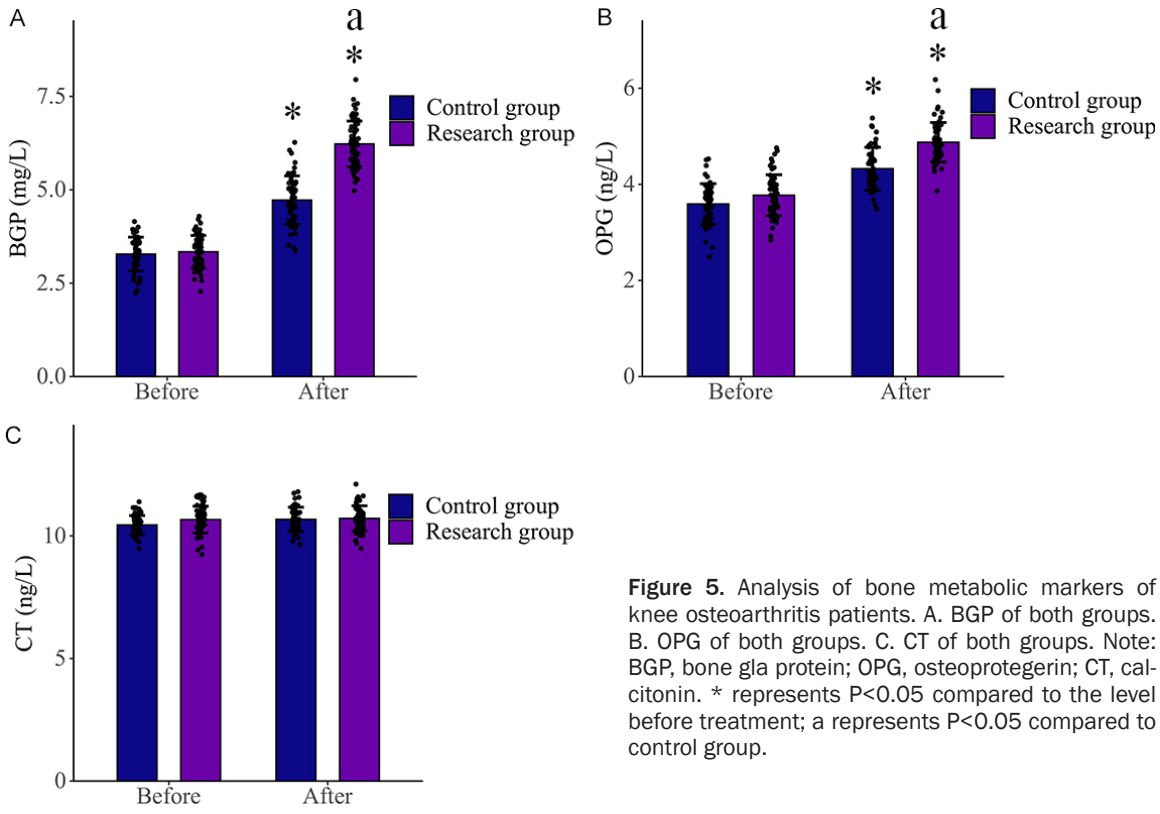

Figure 5. Analysis of bone metabolic markers of knee osteoarthritis patients. A. BGP of both groups. B. OPG of both groups. C. CT of both groups. Note: BGP, bone gla protein; OPG, osteoprotegerin; CT, calcitonin. * represents P<0.05 compared to the level before treatment; a represents P<0.05 compared to control group.

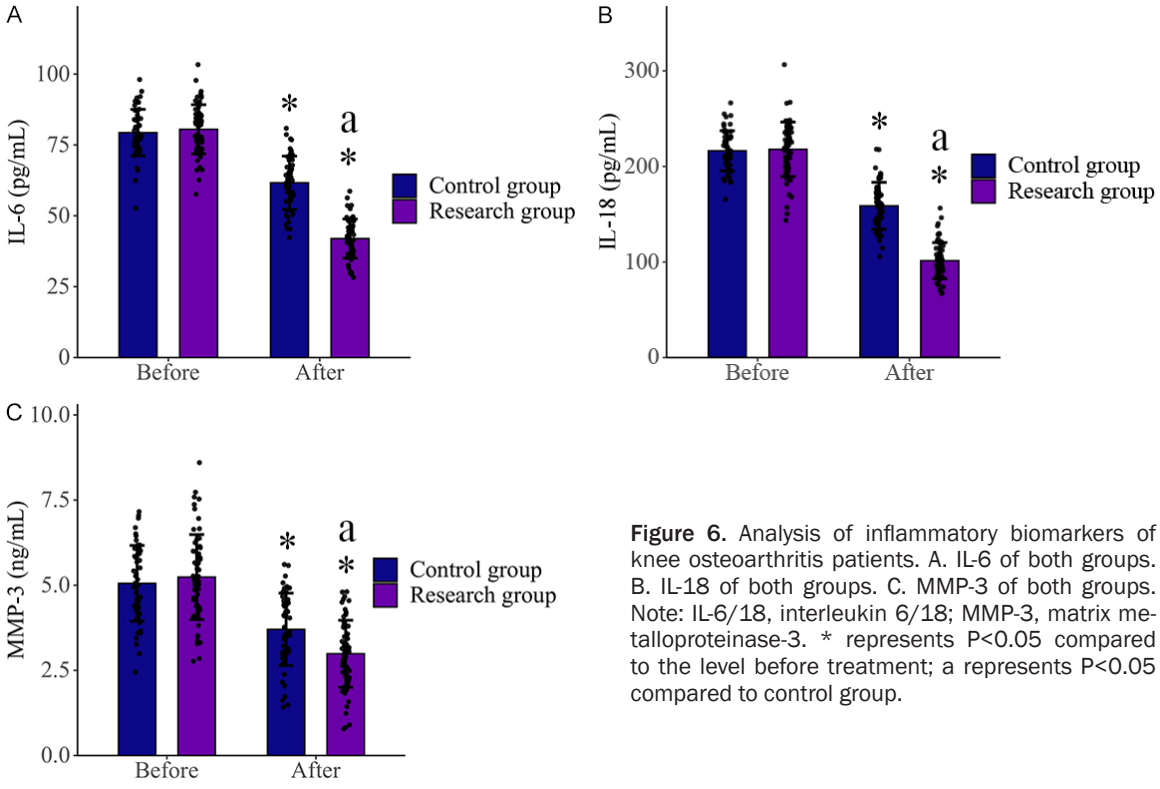

Figure 6. Analysis of inflammatory biomarkers of knee osteoarthritis patients. A. IL-6 of both groups. B. IL-18 of both groups. C. MMP-3 of both groups. Note: IL-6/18, interleukin 6/18; MMP-3, matrix metalloproteinase-3. * represents P<0.05 compared to the level before treatment; a represents P<0.05 compared to control group.

oral GH supplementation markedly enhanced QoL in KOA patients.

Bone metabolism was assessed using BGP, OPG, and CT levels. The combination therapy

showed superior efficacy over CEL monotherapy in improving bone metabolic markers. Supporting this, Yang et al. [33] demonstrated that co-administration of GH and sodium hyaluronate in KOA patients with osteoporosis not only reduced pain and promoted functional recovery but also restored bone metabolic balance.

Moreover, serum levels of IL-6, IL-18, and MMP-3 were significantly more reduced in the research group. Zhang et al. [34] similarly reported that CEL-GH combination therapy lowered inflammatory cytokine levels and improved pain outcomes. Liu et al. [35] further confirmed that combining GH with compound bone peptide injections enhanced clinical efficacy, reduced systemic inflammation, and improved immune function in KOA patients.

Despite these promising findings, this study has several limitations. First, it was conducted at a single center, which may limit generalizability despite the relatively large sample size. Future multicenter studies with larger cohorts are needed to minimize selection bias. Second, the evaluation criteria were limited to short-term outcomes; future studies should incorporate long-term efficacy and prognostic follow-up to more comprehensively assess the benefits of CEL-GH therapy. Third, no basic experimental research was included. *In vivo* and *in vitro* studies are warranted to clarify the mechanistic basis of CEL-GH synergy and the pathophysiological progression of KOA. These limitations will be addressed in future investigations to enhance the robustness of clinical evidence.

In conclusion, combined CEL with GH demonstrates significant clinical efficacy and favorable safety in the treatment of KOA. It provides pain relief, improves knee joint function, enhances quality of life, promotes bone metabolism, and suppresses inflammatory responses. These findings support its broader clinical adoption. Furthermore, identifying high-risk subgroups enables targeted intervention and more efficient healthcare resource use.

Disclosure of conflict of interest

None.

Address correspondence to: Yang Xie, Department of Orthopaedics, Ma'anshan People's Hospital, No. 45 Hubei Road, Huashan District, Ma'anshan 243000, Anhui, China. Tel: +86-0555-8222278; E-mail: xieyang20240601@163.com

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