ORIGINAL RESEARCH

# The Efficacy and Safety of Bionic Tiger Bone Powder for the Treatment of Knee Osteoarthritis in Early Stage: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial

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## ABSTRACT

**Objective** • This study evaluated the efficacy and safety of bionic tiger bone powder (Jintiange) in comparison to placebo in treating knee osteoarthritis osteoporosis.

**Methods** • A total of 248 patients were randomly allocated to a Jintiange group or a placebo group, undergoing 48 weeks of double-blind treatment. The Lequesne index, clinical symptoms, safety index (adverse events), and Patient's Global Impression of Change score were recorded at pre-determined time intervals. All *P* values ≤ .05 were deemed statistically significant.

**Results** • Both groups showed a decreasing trend in the Lequesne index, with the Jintiange group's reduction significantly larger from the 12th week ($P \leq .01$). Similarly, the effective rate of Lequesne score in the Jintiange group was significantly higher ($P < .001$). After 48 weeks, clinical symptom score differences between the Jintiange group (2.46 ± 1.74) and the placebo group (1.51 ± 1.73) were statistically significant ($P < .05$), as were differences in the Patient's Global Impression of Change score ($P < .05$). Adverse drug reactions were minimal with no significant difference between the groups ($P > .05$).

**Conclusion** • Jintiange demonstrated superior efficacy over placebo in treating knee osteoporosis, with comparable safety profiles. Findings warrant further comprehensive real-world studies. (*Altern Ther Health Med.* 2023;29(6):370-376).

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## INTRODUCTION

Knee osteoarthritis is a chronically progressive synovial disease with joint pain characterized by cartilage degradation, subchondral bone remodeling, osteophyte formation, and synovial inflammation. With increased population aging and obesity, the prevalence of knee osteoporosis is also increasing and seriously impacts the quality of life leading to a greater burden on the society.[1]

According to the theory of Traditional Chinese medicine, tiger bone dispels wind, relieves pain, and strengthens bone. Using modern chemical analysis method, it is found that the main composition of tiger bone is inorganic, accounting for 60%-70% of dried bone, which includes calcium (26.13%-27.13%), phosphorus (12.57%-3.37%), carbonate (5%), magnesium (0.5%), followed by a small amount of potassium, sodium, fluorine, and trace manganese, strontium, boron and barium, after ashing.[2] With the development of society and technology, artificial tiger bone powder was developed

by imitating the composition of natural tiger bone. It consists of biogenic ossein, octapeptide, organic calcium, phosphorus, and a variety of trace elements, and its biochemical properties, nitrogen content, kinematic viscosity, optical rotation, and other physical and chemical properties are similar to natural tiger bone. Fingerprint analysis showed that the characteristic peaks of artificial tiger bone powder and natural tiger bone are the same, and there is no significant difference between artificial tiger bone powder and natural tiger bone in pharmacology and pharmacodynamic indexes.[3]

Bionic tiger bone powder (Jintiange) is a synthetic alternative to natural tiger bone， developed using bionic principles guided by Traditional Chinese Medicine (TCM) theory. This involves calculating the composition ratio of non-endangered animal bones to mimic the natural tiger bone composition and using this ratio to synthesize the product.[4] Based on Chinese medicine theory, knee osteoporosis belongs to arthralgia, bone arthralgia, and knee arthralgia groups, which accord with the efficacy of tiger bone in relieving pain, strengthening tendons and bones, and reducing shock. From a Western medicine perspective, osteoporosis is closely related to osteoarthritis in terms of bone microstructure, changes in subchondral bone pathology, molecular biology, and genetics.[5] Early clinical treatments for knee osteoporosis typically include (i) exercise therapy; (ii) physical therapy, including external fumigation, acupuncture, massage, hydrotherapy, heat therapy, and other traditional medical treatments; (3) medication that improves disease conditions (glucosamine, sodium hyaluronate, calcitonin, etc.) and symptoms (non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, glucocorticoids, etc.); and (4) biological therapy, such as intra-articular injection of platelet-rich plasma, autologous or allogeneic stem cell technology, etc. While knee osteoporosis etiology and pathogenesis are unclear, various treatment methods exist. However, no single therapy delivers complete clinical effects or social benefits.[6]

It is reported that when compared with ibuprofen in the control group, knee osteoporosis treatment with Jintiange in elderly patients significantly improved their pain symptoms and reduced interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) levels, and other immune factors.[7] Researchers conducted a parallel controlled clinical study comparing Jintiange and NSAIDs and showed that the Jintiange group significantly improved Lequesne indices.[8] Similarly, It is reported that in knee osteoporosis, patients treated with Jintiange and glucosamine hydrochloride for 12 weeks, results of both Western Ontario and McMaster Universities (WOMAC) scores and Lequesne index showed that Jintiange significantly improved the range of motion and quality of life.[9]

In other knee osteoporosis studies using Jintiange, the efficacy and safety of long-term medication use, especially in placebo-controlled studies, is lacking. According to Traditional Chinese medicine concepts, the clinical classification of knee osteoporosis lacks unifying standards. Based on the four syndrome types, knee osteoporosis can be classified into as many as twenty types, with different disease stages. Thus, syndrome type and clinical classifications are often reciprocally used and this poses challenges for classical evidence-based medicine research.[10] Similarly, knee osteoporosis guidelines and expert opinions in traditional medicine lack high-quality clinical evidence for traditional medicines, including Jintiange.[11,12]

Thus, we (i) conducted a clinical study using Jintiange to treat knee osteoporosis in a large cohort using classical evidence-based research methods; and (ii) we investigated the significance of Jintiange to treat early-stage knee osteoporosis. Our study comprised a 48-week treatment with Jintiange, with a parallel placebo control, in 10 nationwide medical centers to evaluate the efficacy and safety of medium and long-term Jintiange treatment in patients with early-stage knee osteoporosis.

## METHODS

### Diagnostic criteria

We adopted diagnostic criteria from the "Guidelines for the Diagnosis and Treatment of Osteoarthritis" (2010 edition) formulated by The Rheumatology Society of Chinese Medical Association.[13]

Clinical criteria: (i) knee pain for most of the previous month; (ii) bony crepitus; (iii) morning stiffness ≤ 30 min; (iv) age ≥ 38 years; and (v) bony enlargement satisfying diagnostic criteria: i + ii+ iii + iv, or i + ii + iv, or i + iii + iv.

Clinical, radiology, and laboratory criteria: (i) knee pain for most of the previous month; (ii) X-ray showing osteophyte formation; (iii) synovial fluid signs of osteoporosis ; (iv) age ≥ 40 years; (v) morning stiffness ≤ 30 min; and (vi) bony crepitus, satisfying diagnostic criteria: i + ii , or i + iii + v + vi, or i + iv + v + vi.

Osteoporosis can be diagnosed based on clinical, radiology, and laboratory criteria.

### Inclusion criteria

Inclusion criteria were: (i) patients who met the diagnostic criteria for primary knee osteoporosis according to the above guidelines,[11] plus unilateral knee joint was affected; (ii) Lequesne index ≤ 4 points, visual analog scale (VAS) ≤ 2 points; (iii) Kellgren-Lawrence scale ≤ level II; (iv) age 38–70 years; (v) body mass index (BMI) 18.5–3 5 $kg{\cdot}m^{-2}$; and (vi) informed consent.

### Exclusion criteria

Exclusion criteria were: (i) patients with joint inflammation such as rheumatoid arthritis, ankylosing spondylitis, and gout (attack stage); (ii) comorbid diseases affecting joints such as psoriasis, neuropathy secondary to syphilis, ochronosis, metabolic bone disease, and acute trauma; (iii) patients having received glucocorticoid treatment within the previous 4 weeks; (iv) patients treated with NSAIDs painkillers within the previous 2 weeks; (v) patients with a history of severe heart disease, hypertension, poor blood glucose control (fasting

blood glucose > 11.1 mmol/L), and severe liver and kidney diseases; and (vi) allergic constitution, or allergies to multiple drugs or the drug used in this study.

### General data

From December 2016 to August 2019, 248 subjects with knee osteoporosis were randomly enrolled, including 124 in the experimental group and 124 in the control group. In the control group, one subject withdrew informed consent during screening. Also, 46 subjects did not finish the whole visit; the loss to follow-up rate was 18.55%. Thirteen subjects were rejected from statistical analyses due to drug use that may have affected therapeutic effects as specified in the protocol or out of the visit window (visit time > 30 days). Thus, the elimination rate was 5.24%, including four subjects in the experimental group (3.23%) and nine in the control group (7.26%). There were no significant differences in drop-out and elimination rates between groups ($P > .05$). Subject enrollment is shown (Figure 1).

The study was conducted at ten clinical research centers; all of them are general hospitals and have the qualifications of clinical trial institutions. Institutional review board approval of the trial at clinical research center was obtained (Approval number: LL2019-335). All subjects signed the informed consent.

Of the 248 knee osteoporosis subjects, 192 were female (77.73%), and 55 were male (22.27%), with an average age of 55.55 ± 8.06 years. Knee osteoporosis was determined in 133 left knees (53.85%) and 114 right knees (46.15%). Subject information is shown (Table 1).

### Study compliance

In total, 231 subjects whose medication compliance met the requirements of 80%–120% were included, consisting of 115 subjects in the experimental group (97.46%) and 116 in the control group (95.87%). No significant differences were observed between groups ($P > 0.05$). Overall, the compliance of subjects for medications was > 95%, suggesting subject/medication compliance was good across the groups.

During the study, the average daily dose of Jintiange in the experimental group was 8.58 ± 1.07 tablets, while in the control group, it was 8.69 ± 0.78 tablets. The overall average daily dose was 8.64 ± 0.93 tablets. There were no statistically significant differences between groups ($P > 0.05$). Thus, the drug intensity of the two groups met program requirements.

In total, 46 subjects (18.55%) left the study; 23 subjects in the experimental group (18.55%) and 23 subjects in the control group (18.75%). There was no statistical significant difference between the two groups ($P > 0.05$). Withdrawal reasons were: adverse events (three in the experimental group and one in the control group) and loss to follow-up (20 in the experimental group and 22 in the control group).

### Study design

**Randomization.** This was a randomized, double-blind, placebo-controlled, multicenter clinical study. Using a stratified blocked randomization method, stratified by research centers and using the SAS statistics package PROC PLAN, a randomized treatment schedule (test and control (placebo) drugs) for the 247 subjects was generated.

**Figure 1.** The Flow of the Enrollment of Subjects

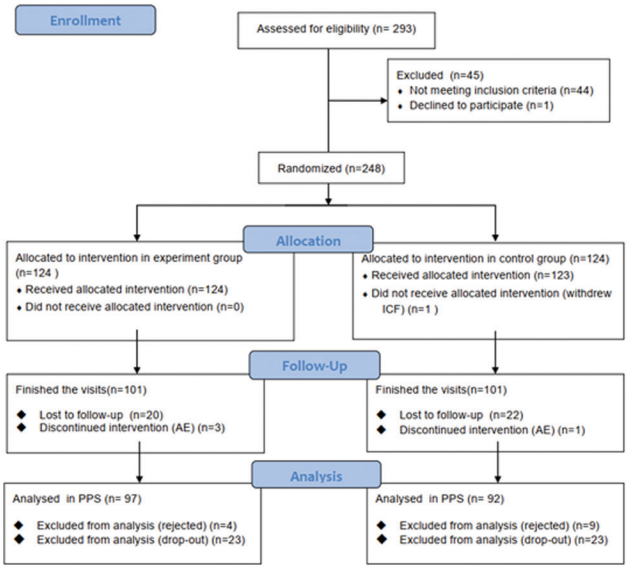



**Table 1.** General Information Compared Between Two Groups

| Parameters | Treatment group (n = 124) | Control group (n = 123) | Statistical value | *P* value |
|---|---|---|---|---|
| Age (years) | 55.82 ± 7.86 | 55.28 ± 8.28 | 0.526 | .600 |
| BMI ($kg.m^{-2}$) | 24.55 ± 3.00 | 24.33 ± 2.66 | 0.610 | .542 |
| Radiological classification (N) | | | | |
| Level 0 | 9 (7.26%) | 4 (3.28%) | 0.246 | .620 |
| Level I | 71 (57.26%) | 79 (64.75%) | - | - |
| Level II | 44 (35.38%) | 35 (28.69%) | - | - |
| Level III | 0 (0.00%) | 4 (3.28%) | - | - |
| Level IV | 0 (0.00%) | 0 (0.00%) | - | - |

Note: BMI, Body Mass Index; Age and BMI were tested by *t* test and radiological grading by The Cochran-Mantel-Haenszel test.

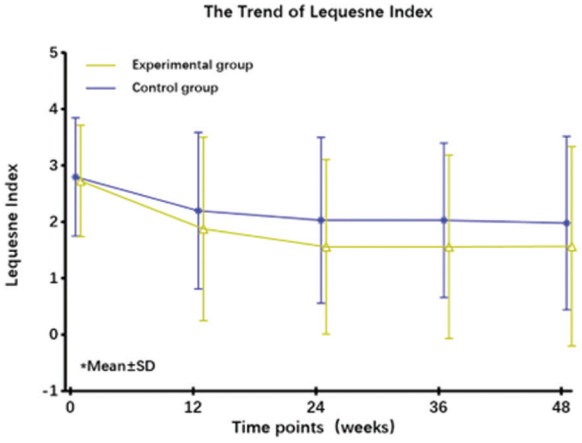
**Blinding.** Researchers and subjects were blinded. Blinding was jointly conducted by the organizers and statisticians, using a two-level blinding method. First-level blinding: a random number corresponding to the intervention group code, i.e., group A and group B. The sponsor produced the study drug and the control drug (placebo). Capsule shape, color, label, and packaging were uniform to ensure no differences in appearance.

**Second-level blinding**. Intervention groups (groups A and B) were set as experimental and control groups, respectively.

### Administration Scheme

The experimental group was orally administered Jintiange (0.4 g/tablet, three tablets/time, three times/day) for 48 weeks. The control group was orally administered a placebo (same

**Figure 2.** The Trend of the Lequesne Index




1. A significant effect was defined as an improvement rate > 90%.
2. Effective was defined as an improvement rate between 61% and 90%.
3. Remission was defined as an improvement rate between 31% and 60%.
4. Invalid was defined as a condition improvement rate ≤ 30%.

capsule, filled with dextrose); the administration schemes were identical. The placebo was similarly shaped and labeled as the experimental drug and was produced by Xi'an Jinhua Pharmaceutical Co., LTD in China. The simulant content met the basic requirements of the placebo.

Emergency treatment was also established for patients in pain. Celecoxib capsules (Celebrex) could be taken orally (0.2 g/tablet, 0.2 mg/time, twice a day) for no more than 48 h of continuous use (the total dose was ≤ 400 mg) when subjects experienced pain. For subjects allergic to sulfonamides, meloxicam tablets could be orally taken at 1.5 mg/day for up to 48 h of continuous use.

In addition to experimental drugs, other Chinese and Western drugs with similar functions to Jintiange or other knee osteoporosis treatment methods, thereby affecting study efficacy evaluations, were prohibited during the observation period.

For subjects who had been treated with knee osteoporosis drugs before pain onset: if the glucocorticoid treatment dose was stable for at least 4 weeks or the non-steroidal anti-inflammatory painkiller dose was stable for at least 2 weeks, patients were included in observations, but the original treatment drugs (type and dose) were to remain unchanged during the study.

If a patient's condition did not improve after at least 12 weeks, investigators assessed whether other treatments, such as oral NSAIDs (non-selective NSAIDs and selective COX-2 inhibitors), glucocorticoid injections, or joint replacement surgery, should be performed. Subjects requiring these remedial treatments were deemed failed and included in the Full Analysis Set (FAS).

**Primary and secondary parameters**

**Lequesne index scores.** Lequesne index scores were used as the main efficacy parameter to determine outcomes. Lequesne curative effect rate = (total score before treatment - total score after treatment)/pre-treatment total score × 100%. The result is shown in Figure 2.

**Secondary efficacy indicators.** Secondary efficacy indicators were the main clinical symptoms and Patient Global Impression of Change (PGIC) scores. The main clinical symptoms were divided into four groups.

1. Recovery: main clinical symptoms and signs had disappeared. The decrease in the syndrome score was ≥ 95%.
2. Significant effects: main clinical symptoms and signs were significantly improved; the decrease in the syndrome score was ≥ 70%.
3. Effective: main clinical symptoms and signs had improved; the decrease in the syndrome score was ≥ 30%.
4. Invalid: main clinical symptoms and signs were not significantly improved or even aggravated; the decrease in the syndrome score was < 30%.

The PGIC was rated by subjects across seven levels: 1 = significant improvement to 7 = significant deterioration.

**Safety evaluations**

General vital signs were recorded during the follow-up. Laboratory examinations included, routine blood tests (Red Blood Cell [RBC], Hemoglobin [Hb], White Blood Cell [WBC], Platelet [PLT]), routine urine tests, liver functions (Alanine transaminase [ALT], Aspartate transaminase [AST], Alkaline phosphatase [AKP], total bilirubin [TBIL], γ-glutamyltransferase [GGT]), renal functions (creatinine [Cr], blood urea nitrogen [BUN], glomerular filtration rate [GFR]), blood calcium levels, blood phosphorus, and an electrocardiogram (ECG) (heart rate, QTc interval, ST-T change, and ECG diagnosis). Adverse and serious adverse events were recorded concerning "Quality Management Standards for Drug Clinical Trials ," and causal relationships were determined. These were divided into five groups: 1) positively relevant, 2) likely relevant, 3) possibly relevant, 4) suspicious, and 5) impossibly related.

**Statistical methods**

Treatment and control groups were 1:1 parallel controlled, and an optimal experimental design was adopted. The effective rate of Lequesne index scores was used to calculate the sample size. The effective rate of the Lequesne index score for the experimental group was predicted to be 85%, and 60% for the placebo group, with a power of 80%, $\alpha = 0.025$ (one-sided). Subjects were allocated to the experimental and control groups in a 1:1 ratio, with an

anticipated sample size of 100 in each group. Accounting for potential drop-outs and withdrawals during the study, the sample size was expanded to 247. The full analysis set (FAS) comprised 124 subjects in the experimental group and 123 in the control group.

The SAS9.4 software package (SAS Institute Inc, US) was used for statistical analysis. Following the Intention-to-treat (ITT) principle, statistical analyses were conducted as a Full Analysis Set (FAS). Missing data were transferred to the latest observation data. The main study efficacy indicators were analyzed using a one-sided test, and statistical hypothesis tests for baseline balance, secondary efficacy indicators, and safety analyses were conducted using a two-sided test. *P* values ≤ .05 were considered statistically significant.

General group information was statistically compared. Quantitative data such as Lequesne index scores were compared using group *t* tests (homogeneity of variance, normal distribution) or Wilcoxon rank sum tests according to data distributions. Chi-square or exact probability tests (if the chi-square test was inapplicable) were used for categorical data such as gender and image grading. The Wilcoxon rank sum or CMH $\chi^2$ tests were used for ranked data.

## RESULTS

### Outcomes of Lequesne Index score

The Lequesne index scores of both groups showed a decreasing trend at 12, 24, 36, and 48 weeks after treatment, with the largest decrease at 24 weeks. The decrease in the experimental group was more obvious than in the control group. No statistically significant differences were observed between groups before treatment ($P = .439$), but from 12 weeks after treatment, significant differences were identified ($P \leq .01$) between groups (Table 2).

After 12, 24, 36, and 48 weeks, the effective rate of the Lequesne Index for both groups increased gradually. The rate was maximum at 24 weeks, and the increase in the experimental group was more obvious than in the control group. Statistically significant differences were observed between groups ($P < .001$) (Table 3).

**Table 2.** Comparison of the Lequesne Index of the Two Groups Before and After Treatment

| | Lequesne index (Mean ± SD) | | | |
|---|---|---|---|---|
| Time points | Experimental group (n = 124) | Control group (n = 123) | Statistical value | *P* value |
| -2-0 weeks | 2.73 ± 0.99 | 2.80 ± 1.05 | 0.774 | .439 |
| 12 weeks | 1.88 ± 1.63 | 2.20 ± 1.39 | 2.581 | .010 |
| 24 weeks | 1.56 ± 1.55 | 2.03 ± 1.47 | 3.375 | <.001 |
| 36 weeks | 1.56 ± 1.63 | 2.03 ± 1.37 | 3.720 | <.001 |
| 48 weeks | 1.57 ± 1.77 | 1.98 ± 1.54 | 2.996 | .003 |

Note: Wilcoxon rank sum test was used for comparison between the two groups.

**Table 3.** Description and Comparison of the Effective Rate of Lequesne Index Between Two Groups

| | The effective rate of the Lequesne index | | | | |
|---|---|---|---|---|---|
| Time points | Experimental group (n = 124) | Control group (n = 123) | Difference 95% CI | Statistical value | *P* value |
| 12 weeks | | | | | |
| Effective (n, %) | 86 (69.35%) | 59 (47.97%) | 0.094, 0.334 | 12.617 | <.001 |
| Ineffective (n, %) | 38 (30.65%) | 64 (52.03%) | | | |
| 24 weeks | | | | | |
| Effective (n, %) | 98 (79.03%) | 70 (56.91%) | 0.108, 0.334 | 16.156 | <.001 |
| Ineffective (n, %) | 26 (20.97%) | 53 (43.09%) | | | |
| 36 weeks | | | | | |
| Effective (n, %) | 97 (78.23%) | 70 (56.91%) | 0.099, 0.327 | 14.790 | <.001 |
| Ineffective (n, %) | 27 (21.77%) | 53 (43.09%) | | | |
| 48 weeks | | | | | |
| Effective (n, %) | 100 (80.65%) | 67 (54.47%) | 0.150, 0.374 | 23.176 | <.001 |
| Ineffective (n, %) | 24 (19.35%) | 56 (45.53%) | | | |

Note: Significantly effective, effective, and remission were regarded as effective in Lequesne's total effective rate. The difference in effective rate between groups was calculated as the experimental group minus the control group.

### Secondary efficacy indicator outcomes

After continuous medication for 48 weeks, the main clinical symptom score in the experimental group was 2.28 ± 1.55 and 2.85 ± 1.68 in the control group. The difference was statistically significant ($P < .05$).

After continuous medication for 48 weeks, the major symptom score difference in the experimental group was 2.46 ± 1.74; the difference was statistically significant when compared with baseline data ($P < .05$). The control group was 1.51 ± 1.73, and the difference was statistically significant compared to baseline data ($P < .05$).

The change of rate in the main clinical symptom score was 0.51 ± 0.38 in the experimental group and 0.31 ± 0.47 in the control group; the difference was statistically significant when compared between groups, as well as groups and baseline data ($P < .05$).

The PGIC in the experimental group was 2.33 ± 0.91, and in the control group was 2.67 ± 1.08; the difference was also statistically significant ($P < .05$).

### Safety results

Of 248 patients enrolled in the study, 247 were included in the FAS, consisting of 124 in the experimental group and 123 in the control group. In terms of adverse events leading to drop-out, there were four cases (4 adverse events, 3.25%) in the experimental group and 0 cases in the control group, with no significant differences between groups ($P > .05$).

In terms of adverse reactions, we observed five cases (5 adverse reactions, 4.07%) in the experimental group and three cases (4 adverse reactions, 2.44%) in the control group,

with no significant differences between groups ($P > .05$). Adverse reactions in the experimental group mainly involved increased GGT levels, constipation, abdominal discomfort, upper abdominal pain, and blepharitis, whereas the control group mainly experienced abdominal discomfort, flatulence, and toothache.

No serious adverse drug-related events were recorded during this study.

## DISCUSSION

### The theoretical basis and status of long-term knee osteoporosis treatment using Jintiange

The main pathogenesis of knee osteoporosis is articular cartilage degeneration, loss of cartilage, adjacent cartilage hyperplasia, and ossification, which all affect the joint function. TNF-α and matrix metalloproteinases (MMPs) have important roles in disease progression, with MMP-3 being the main protease involved in cartilage degradation. Studies have shown that artificial tiger bone powder regulates osteopontin and MMP-3 expression, thus affecting articular cartilage and subchondral bone metabolism. The latest research shows that artificial tiger bone powder improves trabecular bone's thickness, number, and spacing and enhances bone biomechanical properties by improving bone microstructure.[11] According to traditional medical theory, Jintiange strengthens tendons and bones, and exerts anti-inflammatory and analgesic effects. A study has also shown that Jintiange protects articular cartilage, promotes the surface repair of articular cartilage, inhibits subchondral bone remodeling, alleviates osteoporosis symptoms, and delays joint degeneration. Thus, its efficacy is consistent with knee osteoporosis etiology and pathogenesis.[12] Few parallel controlled clinical studies have investigated osteoporosis treatment using Jintiange, with administration periods no longer than 3 or 4 months. The mechanism of traditional medicines is to improve disease via regulating human body functions. Knee osteoporosis is a chronic orthopedic disease. Thus, this study has accumulated experience in treating knee osteoporosis with a long course of Jintiange.

### Considerations of applying Lequesne scores

The clinical evaluation of a drug depends on its function and the characteristics of the study population. Therefore, it is practical and scientific to use clinical functional scores in early-stage knee osteoporosis subjects than biochemical markers or cartilage imaging changes.[13,14] The Lequesne score consists of three components: pain or discomfort scores, walking distance scores, and daily mobility scores, with total scores ranging from 1 to 24. The index is one of the most common tools for assessing knee osteoporosis severity and the functional status of subjects with knee osteoporosis. The Chinese version of the scale has been verified with good reliability.[15] Compared with WOMAC scores, Lequesne indexes include walking distances and daily basic activity evaluations such as walking up and down stairs. For early-stage knee osteoporosis subjects in this study, average ages were relatively low (young); 55.82 ± 7.86 years in the experimental group and 55.28 ± 8.28 years in the control group; hence, the influence of disease on subjects' daily life quality can more accurately reflect the progression of disease and treatment effect. During the 48-week trial, subjects were evaluated five times using Lequesne scores. With adequate health education and training in scoring, Lequesne's scores were highly reliable. In the early stage of osteoporosis, the subjects may also gradually increase their pain tolerance or tolerance to the disease over time, which may affect the results of the Lequesne's score. In this study, a placebo was used as the control, so the above influence of the placebo effect on efficacy and safety could be excluded.[4]

### The practical significance of patients participating in a clinical study

In this study, the PGIC scale was used to analyze clinical efficacy from the subjects' perspective, as patients and doctors must participate in medical decisions. The PGIC scale has shown some significance in evaluating therapeutic effects and disease management, especially for patients with early-stage knee osteoporosis who are more sensitive to pain and functional changes.[16] In early disease stages, patients and doctors must choose from a wide variety of interventions, with factors ultimately deciding medical decisions, usually including clinical efficacy, side effects or risks, economic factors, access to interventions, and doctor-patient relationships. The subjects enrolled in this study were outpatients from 10 first-class hospitals in China, with similar characteristics: (i) subjects were relatively young, had a relatively mild illness, and had higher expectations in terms of quality of life, and (ii) subjects were informed, understood, and agreed to the purpose, process, and significance of the trial, so they generally displayed good compliance with medium- and long-term drug therapy.

Further PGIC analysis using the per-protocol set (PPS) data set showed that the experimental group (n = 97) was 2.33 ± 0.92, and the control group (n = 92) was 2.67 ± 1.09, with no statistical significance between groups ($P > 0.05$). Possible reasons were: (i) subjects scored their overall impression with treatments at the last visit (48$^{th}$ week). Only one option was required to be checked during scoring, which was checked at the researcher's request. Affected by the doctor-patient relationship, the subjective evaluation of the subjects might be interfered with. (ii) In this trial, all subjects were provided free drugs, all related examination expenses were reimbursed, and some transportation allowances were provided. While these measures protected subjects' interests, they may also have affected their "preference" for this study. Some subjects established good relationships with investigators during the 48-week follow-up, with investigators providing more medical and humanistic attention to some patients than others. Therefore, this may affect objectivity concerning PGIC.

Our study indicated that subjects should participate in treatment decisions and score their global impressions of

disease change. Also, a more humane medical approach should be integrated into clinical research, with clinical evaluations being more evidence-based and accompanied by realistic significance. Evaluation tools and methods should be improved to incorporate more intelligent and intimate multi-dimensional evaluation methods. Similarly, we advocate larger real-world studies on Jintiange to reduce or eliminate the influence of non-medical factors on clinical efficacy and safety during knee osteoporosis treatment.[17]

## CONCLUSIONS

We observed that knee osteoporosis treatment with Jintiange displayed good efficacy and safety. However, further clinical research incorporating more extensive and comprehensive cohorts could have far-reaching clinical significance for Jintiange therapy for knee osteoporosis.

### AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

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