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Impact of Bone Collagen Peptide on Patients with Knee Osteoarthritis: A Randomized Controlled Clinical Trial

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Abstract [**Objectives**] To explore the impact of bone collagen peptide (BCP) on patients with knee osteoarthritis (KOA). [**Methods**] A total of 100 patients diagnosed with KOA were admitted to the study and randomly assigned to either a control group or a treatment group, with each group comprising 50 participants. The control group received health education along with standard daily treatment protocols. In contrast, the treatment group was administered an additional dosage of 20 g of BCP twice daily, in conjunction with the treatment regimen provided to the control group. Both groups received continuous treatment for 3 months. The WOMAC scores and the WHOQOL-BREF scores of the participants in both groups were assessed both prior to and following treatment. [**Results**] Following treatment, the WOMAC scores of patients in the treatment group demonstrated a significant improvement compared to those in the control group (13.39 ± 2.19 *vs.* 15.46 ± 1.30, $P < 0.05$). Additionally, the WHOQOL-BREF scores for patients in both groups showed improvement, with the treatment group exhibiting superior WHOQOL-BREF scores relative to the control group ($P < 0.05$). [**Conclusions**] For patients diagnosed with KOA, the supplementation of BCP alongside conventional treatment has been shown to significantly enhance knee joint function and improve the overall quality of life for these individuals.

Key words Bone collagen peptide (BCP), Knee osteoarthritis (KOA), Random, Comparison, Clinical trial

1 Introduction

Knee osteoarthritis (KOA) is the most prevalent form of osteoarthritis, characterized by a chronic degenerative condition of the knee joint. This condition is marked by a progressive loss of articular cartilage, alterations in bone substance, and a reduction in joint functionality. The global prevalence of KOA has been rising annually, establishing it as one of the primary health concerns affecting the middle-aged and elderly populations. KOA accounts for approximately 85% of all osteoarthritis cases worldwide[1]. The ongoing intensification of population aging, coupled with the rising prevalence of lifestyle factors such as obesity, is anticipated to lead to a further increase in the incidence of KOA, imposing a heavy burden on the global public health system. This condition not only results in significant joint pain for affected individuals but also severely impacts their daily activities and overall quality of life, thereby exacerbating the burden on both societal and economic systems.

Currently, the treatment of KOA primarily encompasses pharmacological treatment, physical therapy, physical exercise, and surgical intervention when deemed necessary[2]. These therapeutic approaches may alleviate pain, enhance joint functionality, and even decelerate the advancement of the disease. Pharmacological treatment typically encompasses non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, which are intended to alleviate joint pain and inflammation. Additionally, physical therapy contributes to improved functionality by enhancing the flexibility and strength of the joints. Engaging in physical exercise can further promote the stability of the knee joints and mitigate the risk of overloading. Although these treatment methods may offer temporary relief, the pursuit of long-term pain alleviation and symptom enhancement continues to pose a significant challenge. Current treatment strategies frequently provide only temporary relief of symptoms and are unable to fully prevent or reverse joint damage. As a result, many patients experience ongoing pain and functional impairments in the context of long-term management.

Bone collagen peptide (BCP) is a hydrolyzed product derived from animal bones, characterized by its high collagen content and the presence of various essential amino acids. It is noted for its digestibility and absorption efficiency. In recent years, research has demonstrated that BCP has the potential to enhance bone health and mitigate the symptoms of KOA. This efficacy has been substantiated by both animal studies and clinical trials[3]. Although numerous unknown factors persist in this field, BCP, as a natural nutritional supplement, presents a promising avenue for exploring more effective treatment options for KOA.

2 Materials and methods

2.1 Research objects and grouping A randomized controlled trial (RCT) was conducted involving patients with KOA who attended the Osteoporosis/Rheumatology and Immunology Department, the Rehabilitation Department, and the Orthopedics Outpatient Department at No. 4 West China Teaching Hospital, Sichuan University, from January 2022 to December 2023. A total of 100 qualified participants were included in the study, with a mean age of (63.0 ± 9.2) years, comprising 14 males and 86 females. Utilizing the random number table method, the participants were randomly assigned to two groups. The control group, consisting of 50 participants, had a mean age of (65.1 ± 8.9) years, which included 7 males and 43 females. The experimental group, also comprising 50 participants, had a mean age of (60.8 ± 9.5)

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years, with 7 males and 43 females. This study received approval from the Ethics Committee of No. 4 West China Teaching Hospital, Sichuan University (Ethics Approval No.: HXSY-EC-2022075), and all participants provided informed consent.

2.2 Inclusion criteria According to the diagnostic criteria established in the *Guidelines for Diagnosis and Treatment of Osteoarthritis* by the Orthopedics Branch of the Chinese Medical Association in 2018[4], the inclusion criteria for participants were as follows: individuals must have experienced recurrent knee pain within the preceding month; must have received a diagnosis of KOA confirmed by X-ray examination; must exhibit noticeable bone friction during limb movement; must be aged between 40 and 80 years, with no restrictions on gender; must be capable of completing at least two outpatient follow-ups (the first occurring after initial oral administration and the second three months post-administration) within a three-month period; and must possess the ability to comprehend and voluntarily sign the informed consent form, as well as willingly participate in the trial procedures and follow-up examinations.

2.3 Exclusion criteria The study excluded the following groups of patients: those diagnosed with rheumatic arthritis, individuals with a history of knee joint surgery, patients with incomplete clinical data, and those suffering from mental disorders, cognitive impairments, or consciousness disorders. Additionally, participants who did not voluntarily consent to participate in the study were excluded, as well as patients who had previously taken glucosamine, chondroitin, or other substances that could potentially influence the results of the experiment.

2.4 Elimination standards The study eliminated individuals who were identified as misdiagnosed during the research process, those who received other pertinent treatments during the treatment period, and those who did not complete the prescribed course of treatment in the cost assessment.

2.5 Therapeutic methods The control group received health education and basic daily treatment, while the treatment group implemented a combination of health education, basic daily treatment, and BCP adjuvant therapy. The specific method involved the oral administration of 20 g of BCP (produced by Sichuan Raybo Biotechnology Co., Ltd., 5 g/bag, batch No.: 220101) on an empty stomach in the morning and 1 – 2 h prior to bedtime for adjuvant therapy. Both groups underwent treatment for a continuous duration of 3 months.

2.6 Observation indicators Prior to and following treatment, the WWOMAC scores and the WHOQOL-BREF scores were assessed for both groups of participants. The WOMAC score was assessed based on the patient's actual situation. Each item was categorized into five levels of severity: none, mild, moderate, severe, and extremely severe. The corresponding scores ranged from 0 to 4 points, culminating in a total score of 96 points. A higher score indicates a greater impairment in knee joint function. The WHOQOL-BREF scale was capable of producing scores across four distinct domains. This scale included two question items that were analyzed independently. Specifically, Question 1 (G1) inquired about individuals' overall subjective perceptions of their quality of life. The domain score was computed on a positive scale, indicating that a higher score corresponds to an improved quality of life. This score was derived by multiplying the average score of the relevant item by a factor of 4. A series of investigations were conducted on patients both prior to and following the use of BCP, examining various aspects including physical health, mental health, social relationships, and the surrounding environment. This approach aimed to further elucidate the changes in the quality of life experienced by patients with osteoarthritis as a result of BCP usage. The therapeutic effects of BCP on various parameters, including pain, joint function, stiffness, and quality of life in patients with KOA, were observed based on the aforementioned scoring results.

2.7 Statistical methods The data were analyzed utilizing SPSS 26.0 statistical software. Measurement data were presented as means ± standard deviations ($\bar{x} \pm s$), and the independent samples *t*-test was employed for group comparisons. Count data, such as gender, were expressed as percentages, and the *chi*-square (χ^2) test was applied for group comparisons. A *P*-value of less than 0.05 was deemed statistically significant.

3 Results and analysis

3.1 WOMAC scores The WOMAC scores of the two groups of patients were compared both prior to and following treatment, as presented in Table 1. Prior to treatment, no significant difference in WOMAC scores was observed between the two groups. However, post-treatment analysis revealed a significant improvement in the WOMAC scores of the treatment group compared to the control group (13.39 ± 2.19 *vs.* 15.46 ± 1.30, $P < 0.05$). This finding suggests that, in addition to conventional treatment, the administration of BCP can significantly enhance knee joint function in patients with KOA.

Table 1 WOMAC scores of the two groups of patients prior to and following treatment ($\bar{x} \pm s$, $n = 50$)

Group	Prior to treatment	Following treatment
Control	15.72 ± 1.32	15.46 ± 1.30
Treatment	15.89 ± 1.79	13.39 ± 2.19 *

NOTE * $P < 0.05$ indicates statistical significance when compared to the control group following treatment.

3.2 WHOQOL-BREF scores The comparison of WHOQOL-BREF scores between the two groups of patients, both prior to and following treatment, is presented in Table 2. Prior to treatment, no significant difference was observed in the WHOQOL-BREF scores between the two groups. However, the WHOQOL-BREF scores for post-treatment patients in both groups demonstrated improvement, with the treatment group exhibiting significantly higher scores than the control group ($P < 0.05$).

Table 2 WHOQOL-BREF scores of the two groups of patients prior to and following treatment ($\bar{x} \pm s$, $n = 50$)

Group	Time	Mental health	Physical health	Surrounding environment	Social relation	Health condition	Quality of life
Control	Prior to treatment	73.26 ± 6.21	76.20 ± 7.63	81.36 ± 8.94	83.63 ± 7.18	2.03 ± 0.20	2.15 ± 0.30
	Following treatment	80.15 ± 7.32#	83.19 ± 8.03#	88.70 ± 9.02#	88.60 ± 7.39#	2.43 ± 0.23#	2.52 ± 0.32#
Treatment	Prior to treatment	72.67 ± 6.84	75.46 ± 7.81	80.72 ± 9.06	83.04 ± 7.23	2.01 ± 0.20	2.11 ± 0.32
	Following treatment	95.69 ± 7.50 *#	96.32 ± 8.55 *#	90.21 ± 9.98 *#	90.25 ± 8.46 *#	3.26 ± 0.26 *#	3.16 ± 0.45 *#

NOTE * $P < 0.05$ indicates statistical significance when compared to the control group following treatment; # $P < 0.05$ indicates statistical significance when comparing measurements taken prior to treatment within the group.

4 Discussion

For an extended period, researchers and healthcare professionals have dedicated significant effort and resources to the development of treatment methods for KOA, with the objective of enhancing patient care, improving quality of life, and alleviating pain. Non-pharmacological interventions, such as patient education, physical exercise, and weight management, constitute fundamental components of KOA management[5]. Furthermore, the pharmacological strategy primarily emphasizes the alleviation of symptoms while also striving to prevent or halt the underlying biological mechanisms responsible for tissue damage. KOA not only impacts the cartilage but also extends its effects to the entire joint structure[6]. The central characteristic of KOA is the deterioration of articular cartilage. An imbalanced biomechanical microenvironment and a range of biological factors disrupt cartilage homeostasis. Consequently, this disruption leads to the degradation of the extracellular matrix (ECM), which is abundant in collagen and proteoglycans. Additionally, it is associated with various phenomena, including joint surface fibrosis, cellular apoptosis, and vascular invasion[7]. The progressive degradation of cartilage stimulates chondrocytes to enhance anabolic activity through compensatory hypertrophy. This results in the concurrent production of matrix degradation products and pro-inflammatory mediators, which further accelerates the progression of KOA. Moreover, the involvement of surrounding tissues is frequently observed alongside the advancement of KOA[8]. Despite the extensive body of research conducted to date, a definitive treatment for KOA has yet to be established, and there are currently no pharmacological agents available that can halt the progression of this condition. Existing clinical guidelines have recommended a variety of treatment modes derived from medical literature, including NSAIDs, analgesics, intra-articular corticosteroid injections, *etc.* However, the long-term efficacy of these treatment options has been limited. For example, the implementation of opioid analgesic regimens may result in adverse outcomes[9].

BCP, recognized as a potential nutritional supplement for the management of KOA, has garnered significant interest in clinical research. Collagen serves as a crucial component of articular cartilage, contributing to the support and maintenance of joint structure. As individuals age, the degradation of collagen in cartilage occurs due to joint damage, resulting in joint dysfunction and pain. BCP, a small molecule peptide derived from hydrolyzed collagen, possesses a relatively low molecular weight ranging from 2 000 to 5 000 Da. This peptide can be absorbed directly through the small intestinal mucosa in its intact form and subsequently accumulates in articular cartilage. This accumulation generates a polypeptide effect that promotes the synthesis of type II collagen and proteoglycans[10]. Numerous studies have investigated the clinical effects of collagen peptides on joint pain and function in patients with KOA[2-3]. This study further corroborated these findings through a randomized controlled clinical trial, demonstrating that BCP can significantly enhance the WOMAC and the WHOQOL-BREF scores in patients with KOA. These results indicate a positive impact on the improvement of knee joint function, pain alleviation, and overall quality of life for these patients. Long-term supplementation with BCP has been shown to facilitate the repair of articular cartilage, mitigate joint inflammatory responses, enhance knee joint functionality, and substantially reduce pain symptoms. Research findings indicate that varying doses and durations of BCP administration not only significantly alleviate joint pain in patients with KOA but also enhance their overall quality of life. Given their favorable bioavailability and minimal side effects, BCP is considered a safe and effective adjunctive treatment option.

Although contemporary clinical research has yielded some promising outcomes in the assessment of BCP for the treatment of KOA, it continues to encounter numerous challenges and limitations. Firstly, the sample sizes in current studies are relatively small, and there are notable discrepancies among various studies regarding their design, methods, and data analysis techniques. These factors, to a certain extent, impact the generalizability and reproducibility of the findings. Consequently, there is a need for additional large-sample, multi-center randomized controlled trials in the future to further validate the reliability and generalizability of these preliminary findings. Furthermore, while BCP demonstrates potential in the treatment of KOA, the specific therapeutic mechanisms remain inadequately understood. Current research predominantly emphasizes clinical observations and superficial effects, thereby lacking comprehensive investigations into the underlying molecular biological mechanisms. Therefore, there is an urgent need for additional fundamental research, particularly utilizing animal models and cellular experiments, to elucidate the mechanism of action of BCP and to clarify its specific role in cartilage repair and the inflammatory response. Moreover, the treatment protocol for BCP requires optimization, as the most effective strategies regarding treatment duration, dosage, and course of treatment remain undefined. These variables may have a direct impact on the clinical efficacy of BCP. Consequently, future research should prioritize the investigation of these critical parameters related to clinical applications in order to establish a scientific foundation for the standardized implementation of BCP.

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the treatment group was 96.00%, which was significantly greater than the response rate observed in the control group, which was 78.00%.

According to traditional Chinese medicine theory, the eye is considered an orifice of the liver. The liver's role as the primary reservoir of blood and its regulation of blood flow have a direct impact on the blood supply and regulation of the eye[8]. Massaging the Ganyu, Guangming, and other Qinggan Mingmu acupoints can facilitate the dispersion of stagnant liver qi and alleviate symptoms of depression, thereby enhancing blood circulation in the ocular region, and relieving spasms of the ciliary muscles. Modern research has demonstrated that the stimulation of periocular and liver meridian acupoints can modulate the function of ocular nerves and facilitate the relaxation of ciliary muscles[9]. Characterized by its gentle force and profound stimulation, Yizhichan Pushing Manipulation effectively targets the deeper layers of acupoints, thereby activating the flow of meridians and contributing to the overall enhancement of the refractive state of the eyeball[10-12].

Ciliary muscle dysfunction serves as a fundamental pathological factor in the development of pseudomyopia, playing a crucial role in the regulation of ocular function. The application of stimulation to the Qinggan acupoints, in conjunction with massage of the periocular muscle groups, yields a synergistic effect on the ciliary muscle. This combined therapeutic approach significantly enhances the sensitivity of ciliary muscle regulation. Simultaneously, the therapy reflects the holistic perspective inherent in traditional Chinese medicine. By identifying and selecting specific acupoints and employing manipulative techniques, this approach establishes a comprehensive intervention system that connects acupoints, meridians, organs, and orifices. The therapy not only enhances visual acuity but also mitigates eye fatigue and regulates emotional states, aligning with the principles of preventive treatment of disease. The data obtained from the study indicated that the combined treatment significantly decreased the occurrence of null cases. This finding is crucial for the early intervention of pseudomyopia and the rehabilitation of visual function in children.

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