Collagen peptides improve knee osteoarthritis in elderly women
A 6-month randomized, double-blind, placebo-controlled study

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Abstract
As the global population gets older, joint-related health concerns are increasingly common, such as osteoarthritis causing pain and reducing mobility. Collagen peptides have been proposed as nutraceuticals to improve joint health in patients with osteoarthritis. We performed a prospective, randomized, double-blind, placebo-controlled study in elderly women with mild-to-moderate knee osteoarthritis to assess the oral intake of collagen peptides (Peptan®) for a duration of 6 months significantly reduces joint pain and improves physical mobility as assessed by two well-established scoring systems (WOMAC and Lysholm score). This study confirms that collagen peptides are a highly efficient nutraceutical to improve joint health which can help to maintain an active lifestyle throughout ageing.

INTRODUCTION
Population ageing
Worldwide, the population is increasingly ageing, with a greater proportion of people getting old and old people reaching an even higher age than before. In 2009, 10% of the population were 65 years and older and this fraction is estimated to increase to 20% by 2050 (1). This demographic development is associated with an increased incidence of age-related disease currently building a strong case for the maintenance of health throughout ageing and the focus of interest of the pharmaceutical and nutraceutical industry.

Osteoarthritis
One age-related disease with rising prevalence is osteoarthritis with 10% of all men and 20% of all women over 60 years old already suffering from it today (3). Osteoarthritis is a degenerative disease of the articular cartilage in joints of the knee, hip, spine and hand. Pain, stiffness and locking of the joint are key symptoms reducing mobility and strongly impacting on the quality of life of the patient. The hyaline cartilage of the joint consists mainly of extracellular matrix composed of collagen, proteoglycans (e.g. aggrecan) and glycosaminoglycans such as hyaluronic acid. Chondrocytes present in the cartilage maintain the matrix in a finely-tuned turnover process, balancing synthesis and breakdown. In osteoarthritis, a dysregulation of this balance leads to a shift towards degradation with a subsequent loss of cartilage. In addition to cartilage degradation, the inflammation of the lining surrounding the joint space, the synovium, as well as alterations in the bone underlying the joint cartilage, such as sclerosis and the formation of osteophytes, are involved in the pathological manifestation of osteoarthritis (4).

Currently, osteoarthritis cannot be cured and available treatment is mostly symptomatic. To treat pain, mainly non-steroidal anti-inflammatory drugs (NSAIDs) are used, which at long-term or high dose use may cause heavy side effects, such as gastrointestinal bleeding and cardiovascular disease (5, 6). Suggested as a safe alternative, the dietary supplements glucosamine and chondroitin sulfate have been used to treat osteoarthritis. However, a systematic, multi-centred study at a large scale did not find a general beneficial effect of glucosamine or chondroitin sulfate. Only a small subgroup of patients with moderate-to-severe pain significantly benefitted from a combined treatment with glucosamine and chondroitin sulfate (7). Thus, the strong need for alternative symptom modifying therapies has created a highly active field of research.

Collagen peptides
Collagen peptides are a specific mix of peptides of different length, obtained by the enzymatic hydrolysis of native collagen coming from animal connective tissues, and showed that the oral intake of collagen peptides (Peptan®) for a duration of 6 months significantly reduces joint pain and improves physical mobility as assessed by two well-established scoring systems (WOMAC and Lysholm score). This study confirms that collagen peptides are a highly efficient nutraceutical to improve joint health which can help to maintain an active lifestyle throughout ageing.

STUDY DESIGN
A prospective, single-centre, randomized, double-blind, placebo-controlled trial was conducted between January and July 2012 at the 6th People’s Hospital affiliated to Shanghai Jiaotong University, China. The study protocol was approved by the hospital’s ethical committee which works according to the guidelines of Good Clinical Practice. The study was registered in the hospital’s database (Clinical Trial Registration No. 2011-51). All participants gave their informed consent.

Patient recruitment, inclusion criteria and treatment
Hundred women between the age of 40 and 70 presenting themselves with knee joint pain or discomfort were recruited to participate in the study. This effect size assures, at a significance level of α=0.05, a power of 80% (WOMAC score, and of more than 80%, the Lysholm score). Osteoarthritis was diagnosed by x-ray and classified according to the Kellgren-Lawrence x-ray classification (22). According to the guidelines the scores were defined based on the following symptoms: grade i - doubtful narrowing of the joint space and possible osteophytes tipping grade ii - definite narrowing of the joint space and definite osteophytes; grade iii - definite narrowing of the joint space, moderate multiple osteophytes, some sclerosis and possible deformation of the bone contour; grade iv - marked narrowing of the joint space, large osteophytes, severe sclerosis and definite deformation of the bone contour. Only subjects with a Kellgren-Lawrence score of 0 to 18 (excluding stage IV of severe osteoarthritis), without allergies and with normal liver and kidney function were included, who had not used nutraceutical or anti-inflammatory drugs within the last 6 months. Patients were randomly assigned to receive a daily oral dose of 8g collagen peptides or 8g placebo for a duration of 6 months. The administered collagen peptide was Peptan® (19 - 21). The study was approved by the hospital’s ethical committee which works according to the guidelines of Good Clinical Practice. The study was registered in the hospital’s database (Clinical Trial Registration No. 2011-51). All participants gave their informed consent.

RESULTS
Patient characteristics and adherence
The hundred osteoarthritis patients that entered the study were equally randomized to the two treatment groups, placebo or collagen peptides. Over the course of the study, two patients dropped out of the placebo group (for reasons of non-adherence and lateral thigh pain), and four patients dropped out of the collagen peptide group (three had already taken collagen peptides before the study and one presented septic arthritis). As shown in Table 1, there were no significant differences at baseline between both groups regarding age, height, weight, body mass index (BMI), WOMAC score and Lysholm score.

Table 1. Baseline characteristics of the recruited patients.

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<tr>
<th>Age (years)</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
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<td>Height (cm)</td>
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Table 1. Baseline characteristics of the recruited patients. Values are presented as means ± standard deviation. Statistical significance of differences was calculated by Student’s t-test. BMI=body mass index.

Statistical analysis
All values are indicated as mean with standard deviation unless indicated otherwise. Statistical analysis was performed by means of an unpaired t-test. A paired measurement ANCOVA or Fisher’s exact test. Differences were considered significant when p<0.05.

Numerical data were analyzed using SPSS software. All data are presented as mean ± standard deviation.

The WOMAC score and Lysholm score
WOMAC and Lysholm scores improved significantly in the collagen peptide group compared to the placebo group (p<0.05). The WOMAC score increased in the placebo group by 3.1 points, while it decreased by 11.5 points in the collagen peptide group. The Lysholm score increased by 15.1 points in the placebo group, while it decreased by 23.0 points in the collagen peptide group. The difference of the WOMAC and Lysholm score between the placebo and the collagen peptide group after 6 months of treatment is significant.

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Importantly, the level of osteoarthrits quantified using the Kellgren-Lawrence X-ray classification (Table 2) was distributed in a comparable manner without significant differences between the placebo and the collagen peptide group. Around half the patients of each group presented mild osteoarthritis in one or both knees (score I-II). Differences between the placebo and the collagen peptide group after 6 months of treatment (Table 3) were distributed in a comparable manner without significant differences between baseline and after 6 months of treatment (Table 3). Compared to baseline, the improvement of liver parameters and blood urea nitrogen was significant in the collagen peptide group, even though the change from baseline was very small. Serum creatinine showed a small but significant increase from baseline in the placebo and to a lesser extent in the collagen peptide group. Overall, this result demonstrates that the treatment of osteoarthrits patients with 8g collagen peptides daily over a duration of 6 months is safe.

**Treatment efficacy**

The effect of the treatment on joint pain and function was evaluated by the WOMAC and the Lysholm scoring system. The WOMAC score is composed of subscales measuring pain, stiffness and physical function. As shown in Figure 1, the values of the WOMAC score decreased over time in patients treated with collagen peptides indicating a gradual improvement of joint pain and function. At 3 months of treatment, a small but already highly significant effect was visible (treatment difference of 0.002 in the placebo vs. -1.07 in the collagen peptide group, p<0.001) which continued into a pronounced and highly significant improvement of knee osteoarthritis after 6 months of treatment with collagen peptides (treatment difference of 0.77 in the placebo vs. -3.93 in the collagen peptide group, p<0.001). The WOMAC score is a comprehensive evaluation of joint function and disability, including pain, stiffness and physical function (Figure 1, Table 4). Table 4 demonstrates an improvement in knee pain and stiffness as well as in physical function.

The WOMAC score is in line with the results of several other clinical studies using collagen peptides at a dose of 8g/d and is considered a valuable alternative for the treatment of knee osteoarthritis. The Lysholm score has been developed specifically to evaluate knee function, by integrating information on limping, stair climbing, locking, giving way of the knee during activity and the ability to squat the joint. Corresponding to the results of the WOMAC rating, the Lysholm score significantly improved over the study duration in patients treated with collagen peptides in comparison to the placebo group. This finding is remarkable since only one other study has described such an effect (20). Two other trials assessed joint function by WOMAC or Quality of Life scores but did not find an effect of collagen peptide treatment (19, 21). However, both studies used a much more heterogeneous group of subjects presenting with general joint pain, not diagnosed osteoarthritis. We performed a combined evaluation of different joints (knee, hip, spine, etc.), which might explain why no effect on joint function was observed. The presented data provide strong evidence for the symptom-relieving effect of collagen peptides in knee osteoarthritis, but the study design does not allow to conclude on potential mechanisms of action. A recent study has investigated the effect of collagen peptides on joint structure in a small group of patients using a MRI technique which can visualise cartilage (29). The result suggests that collagen peptides increase the proteoglycan content in knee cartilage after 6 months of treatment, which is consistent with the in vitro data showing a stimulation of extracellular matrix synthesis by collagen peptides (15, 16). Even if differences observed after 6 months are highly significant in the current study, more investigations should be initiated in future to confirm the efficacy of collagen peptides as a protective factor of cartilage in randomized, placebo-controlled clinical studies of bigger scale, and with diverse patient characteristics to overcome the current study’s limitations of sex, ethnicity of the subjects and the cause and location of osteoarthritis. In addition, mechanical and biochemical parameters (e.g. MRI, UCTJ, UCTX2) could be assessed, and efforts could be made to investigate the potential differences between collagen peptide products from different sources and different production processes. The present study demonstrates a clear beneficial effect of collagen peptides (Peptan®) treatment on joint pain and function in patients with mild knee osteoarthritis. Their safety record and demonstrated absence of side effects make collagen peptides a valuable alternative for the symptom-modifying treatment for osteoarthritis. Thus, they present a highly useful nutriceutical to help maintain the quality of life during ageing.

**Acknowledgments**

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**References**