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Original article

Efficacy and safety of a compound supplement containing glucosamine, chondroitin, and five bioactive ingredients in volunteers with knee joint pain

Takeshi Katayoshi [a], Masakatsu Kageyama [a], Riyo Kobashi [a], Junko Minakuchi [a], Naoko Suzuki [b], Tsuyoshi Takara [c], Tomofumi Negishi [d], Seika Kamohara [d, e], Kentaro Naito [a, *]

[a] DHC Corporation Laboratories, Division 2, 2-42 Hamada, Mihama-ku, Chiba 261-0025, Japan
[b] Research and Development Department, Orthomedico Inc., Tokyo 113-8519, Japan
[c] Seishin-kai Medical Association Inc., Takara Medical Clinic, Tokyo 141-0022, Japan
[d] DHC Corporation, Minami-azabu 2-7-1, Minato-ku, Tokyo 106-8571, Japan
[e] Health Science University, Fujikawaguchiko-machi, Yamanashi 401-0380, Japan

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ABSTRACT

Purpose: This study was designed to evaluate the efficacy and safety of a compound supplement containing glucosamine (GS), chondroitin sulfate (CS), and five bioactive ingredients for improvement of knee osteoarthritis (OA).

Methods: Sixteen volunteers aged ≥40 years with knee pain and without ambulant treatment participated in a 6-week randomized, double-blind, placebo-controlled study. They were assigned to the dietary supplement or placebo groups (n = 8, respectively) and ingested six capsules twice daily. The OA symptoms of each subject were determined in pre- and post-treatment periods using a visual analog scale for pain (VAS pain) and four Japanese Knee Osteoarthritis Measure (JKOM) subscales ("joint stiffness," "daily living," "social activities," and "general health condition"). For safety and biomarker assessments, blood and urine samples were tested.

Results: In the treatment group, the subjective symptoms of VAS pain and three JKOM subscale scores except for "social activities" were significantly improved compared to pre-treatment. Among them, the pattern of change in "joint stiffness" and total JKOM scores showed a significant difference between groups ($p = 0.008$ and 0.041, respectively). The serum level of interleukin-6, a systemic inflammation biomarker, was significantly decreased in the treatment group after 6 weeks ($p = 0.019$), whereas the level remained stable in the placebo group ($p = 0.690$). Diagnostic urine and hematological parameters revealed no serious adverse differences following dietary supplementation over the 6-week study.

Conclusion: These findings suggest that the compound supplementation of functional food ingredients has potential as an adjunctive and safe therapy for knee OA.

1. Introduction

Identifying effective therapies for osteoarthritis (OA) has become a major general public health challenge globally. This prevalent disease begins with early joint stiffness and progressively deteriorates over many years. Eventually, pain and reduced function manifest as severe symptoms of OA [1]. In an aging society, although the prevalence of OA has been shown to be increasing, there are currently no established treatments to delay disease progression. The standard treatments used for OA include pain control with oral or topical analgesic drugs, such as non-steroidal anti-inflammatory agents (NSAIDs), accompanied by physical therapies to maintain joint function. For patients for whom medical management is insufficient to control OA symptoms, joint

Abbreviations: GS, glucosamine; CS, chondroitin sulfate; OA, osteoarthritis; VAS, visual analog scale; JKOM, Japanese Knee Osteoarthritis Measure; NSAIDs, non-steroidal anti-inflammatory agents; MSM, methylsulfonylmethane; IL-6, iterleukin-6; CTX-II, C-terminal telopeptides of type II collagen; SD, standard deviation.

* Corresponding author. Fax: +81 43 275 4831.
E-mail address: knaito@dhc.co.jp (K. Naito).

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replacement surgery for hip or knee joints is considered. Therefore, it is important that preventive measures for OA be implemented at an earlier stage.

During recent years, several studies have reported the effects of dietary supplements containing glucosamine (GS) or chondroitin sulfate (CS) for the treatment of OA-associated symptoms [2,3]. The results of such studies mainly concluded that GS and CS alleviate knee pain without any serious adverse effects. In addition, some distinctive clinical studies have shown that these ingredients suppress disease progression and alleviate OA-related symptoms, such as joint pain. For example, Bruyere et al. have shown that a 3-year treatment of knee OA by GS supplementation resulted in decreased cumulative incidence of total knee replacements [4]. Michel et al. have shown positive effects of CS on joint space narrowing [5]. Although many lines of clinical evidence support the above assertions, the therapeutic efficacy of GS and CS on OA remains highly debated due to conflicting data obtained in an equal number of studies [6]. The following factors are considered as possible causes for this conflict: 1) the intervention effects of ingredients used in dietary supplements are relatively weaker than those of pharmaceutical ingredients and 2) evaluation of responses in OA are easily affected by potential confounding factors. To resolve this discrepancy, combined supplementation of CS and/or other functional ingredients (e.g., an anti-inflammatory or anti-oxidant agent) with GS has attracted attention [7–9]. This therapeutic approach is expected to be more effective than conventional treatments using GS or CS alone. The purpose of the present study was to investigate the safety and efficacy of a compound supplement containing GS, CS, and five bioactive-ingredients, each of which has been reported to resolve OA-related symptoms in *in vitro* and preclinical studies [10–14]. Results from the present clinical study using a compound supplement may provide a new approach to treating knee joint conditions associated with OA.

2. Material and methods

2.1. Experimental subjects

Eligible subjects were initially screened for the following attributes: 1) males and females aged ≥40 years with knee pain and without ambulant treatment; 2) no history of treatment for disorders, such as cardiac failure or infarction; 3) no disorders, such as atrial fibrillation, arrhythmia, hepatic dysfunction, nephropathy, cerebrovascular accident, rheumatoid arthritis, diabetes, dyslipidemia, hypertension, or other chronic disease; 4) no asthma sufferers; 5) no daily use of medicinal drugs, including Chinese herb or supplement tablets; 6) no use of analgesics; 7) no allergies to shellfish, milk, or gelatine; 8) no patients who are currently pregnant or have planned a pregnancy in near future; 9) not routinely receiving acupuncture and moxibustion therapy, massage therapy, or manipulative treatment; and 10) not currently receiving treatment for knee pain. Written informed consent was obtained from each subject.

2.2. Research design

The present study employed a randomized, double-blind, placebo-controlled design with two groups and was performed from November, 2012 to May, 2013 at a clinical service organization center in Japan. All subjects were recruited in Japan through a contract research organization managed by Orthomedico, Inc. (Tokyo, Japan) and had no relationship with DHC Corporation (Tokyo, Japan). The protocol of the present study was approved by Ethics Committee of Seishin-kai Medical Association Inc., Takara Medical Clinic, (chairman: Tsuyoshi Takara, M.D.; No.: 1212-1211-NH01-TC) and was conducted in accordance with the principles of the amended Declaration of Helsinki and "Ethical Guidelines for Epidemiological Research (issued by the Japanese Government in 2008)". Written informed consent was obtained from all participants included in the present study. The 16 screened subjects previously completed the Japanese Knee Osteoarthritis Measure (JKOM) questionnaire, as described in next section. Briefly, the criteria comprised two measures: 1) the visual analog scale for pain (VAS pain) score as JKOM item I and 2) total JKOM score as JKOM items II–V. Subjects were randomly assigned to the dietary supplement group (n = 8) or the placebo group (n = 8) using Statlight #11 (Yukms, Kawasaki, Japan) to ensure a similar level of VAS pain and total JKOM score between groups. Supplements were administered in a double-blind fashion during a 6-week period. Blood and urine samples were drawn from subjects in the pre- and post-study periods. During the pre-study laboratory visit, subjects reviewed and signed the consent form, completed a medical-health questionnaire to verify their medical history and lifestyle habits, and were measured for height, weight, body mass index, body fat percentage, systolic and diastolic blood pressure, and cardiac rate. Finally, each subject received a supplement organizer tray with a 6-week supply and written instructions for taking the supplements. These outcome measures were repeated during the second laboratory visit.

2.3. JKOM questionnaire

The clinical manifestations of knee pain were evaluated by the JKOM score. JKOM is a patient-based, self-administered questionnaire specifically assessing knee pain by VAS pain on a scale of 1–10 and assessing the quality of life comprising four subscales, each on a scale of 1–5, of joint stiffness, daily living, social activities, and general health condition. The total JKOM score was calculated by summing the individual scores of the above-mentioned subscales, except for the VAS pain score, for a total score with a maximum of 100. The JKOM score is higher in patients experiencing more pain and physical disability, and this evaluation modality is considered to have sufficient reliability and validity for studies of the clinical outcomes of Japanese subjects with knee OA.

2.4. Study drug

Supplements (treatment, placebo) were prepared in the form of hard brown capsules (six per day, identical in appearance) and provided to subjects in supplement organizer trays. Each subject ingested six capsules/day: three in the morning and three in the evening. The placebo capsules contained inert substances, such as calcium stearate and starch. Compliance was monitored by submitting a daybook via a Web-based application or posting. The combined supplement contained the following ingredients (in six capsules): GS hydrochloride (1200 mg), methylsulfonylmethane (MSM, 420 mg), CS (275 mg), type II collagen (50 mg), collagen peptide (90 mg), olive extract (12 mg), and concentrated bovine protein (6 mg).

2.5. Blood measures

Using standard hematology tests, the following nine items were measured: 1) leukocyte count; 2) erythrocyte count; 3) hemoglobin; 4) hematocrit; 5) platelet count; 6) mean corpuscular volume; 7) mean corpuscular hemoglobin; 8) mean corpuscular hemoglobin concentration; and 9) leukocyte fractionation. Using standard biochemical tests, the following 25 items were measured: 1) aspartate transaminase; 2) alanine aminotransferase; 3) γ-glutamyl transpeptidase; 4) alkaline phosphatase; 5) lactate dehydrogenase;

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