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SHORT-TERM EFFICACY OF A COMBINATION OF GLUCOSAMINE AND CHONDROITIN SULFATE COMPARED TO A COMBINATION OF GLUCOSAMINE, CHONDROITIN SULFATE AND CALCIUM FRUCTOBORATE (CFB) ON IMPROVEMENT OF KNEE DISCOMFORT CONDITIONS IN HEALTHY SUBJECTS. A COMPARATIVE, DOUBLE-BLIND, PLACEBO CONTROLLED ACUTE CLINICAL STUDY

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Abstract: *Purpose:* To compare and evaluate the effects of treatment with a blend of glucosamine and chondroitin sulfate, or a blend of glucosamine, chondroitin sulfate and calcium fructoborate as compared to a placebo, on joint discomfort. *Methods:* Individuals with self-reported knee discomfort were randomized and blinded to treatment with a combo containing glucosamine and chondroitin sulfate or glucosamine, chondroitin sulfate and calcium fructoborate. Both groups were compared to placebo. Symptoms of discomfort and joint function were assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the McGill Pain Questionnaire (MPQ) before treatment and after 7 and 14 days of treatment. *Results:* Ninety individuals were selected for this study and were randomly assigned in groups of 30 containing 15 male and 15 female participants to each of three treatment conditions. Treatment with glucosamine combined with chondroitin sulfate and CFB resulted in a statistically significant 24% reduction of mean WOMAC score and a 25% reduction of mean McGill index at day 14 over baseline (p-value = 0.0006 and p-value < 0.0001, respectively). Treatment with placebo or with glucosamine and chondroitin material did not result in significant improvement of the conditions. *Conclusions:* Results showed that short-term treatment with glucosamine and chondroitin could be efficacious only if used in combination with CFB.

Key words: Calcium fructoborate, glucosamine, chondroitin sulfate, WOMAC, McGill, joint discomfort.

Introduction

Chronic knee discomfort is a common phenomenon among population of older age (1). Many circumstances can cause or contribute to it (2). Individuals experiencing knee discomfort often report long-term distress, swelling, or sensitivity in one or both knees. Conventional management of knee discomfort mainly focuses on relief of symptoms using analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (3, 4). Some dietary supplements have reported to show some potency to reduce symptoms associated with joint discomfort (5-10).

Chondroitin sulfate is an important structural component of cartilage. Chemically, it is a sulfated glycosaminoglycan composed of N-acetyl-galactosamine and glucuronic acid (11). Over the years, this material has been used as a dietary supplement to treat symptoms of joint discomfort. This material is bioavailable at the level 15-24% of orally administered dose (12-15). It has been suggested that ingested chondroitin sulfate may show anti-inflammatory activity, inhibit proteolytic activity, stimulate the synthesis of proteoglycans and hyaluronic acid and reduce catabolic activity of chondrocytes (16). This material has been used to reduce deficiency and degradation of endogenous chondroitin sulfate in the body, to modulate IL-1β and Nf-kB in chondrocytes, activities that have been suggested may improve OA conditions if chondroitin is used over an extended time. (15, 17-19) However, clinical potency of chondroitin sulfate remains a subject of open discussion due to mixed efficacy results (15, 20-22). Recent studies have addressed

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the efficacy of treatment with chondroitin and have concluded that some positive results may be observed after long-term supplementation (23-25).

Another dietary glycan that has been suggested to have beneficial effects on joint discomfort is glucosamine sulfate. Glucosamine sulfate is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids. Glucosamine sulfate ("glucosamine") has been marketed to relieve symptoms of osteoarthritis, which involves the age-dependent erosion of articular cartilage (25, 26).

Glucosamine is marketed to support the structure and function of joints in people suffering from joint discomfort. Commonly sold forms of glucosamine are glucosamine sulfate, glucosamine hydrochloride, and N-Acetyl Glucosamine. Although there is no evidence to suggest that glucosamine sulfate offers advantages over glucosamine hydrochloride, the latest does not need to be stabilized with salt and offers a more concentrated form of glucosamine. Given these facts, the product of choice for consumers should be Glucosamine hydrochloride (27). The use of glucosamine for management of OA conditions has been studied and reported in a manner similar to chondroitin sulfate; however, clinical potency of treatment of OA conditions with glucosamine remains unclear; despite previously performed clinical studies (28) A mixture of these dietary supplements (glucosamine and chondroitin) has been used to help delay or reverse the loss of cartilage (29, 30).

Calcium fructoborate (CFB) is a natural borate complex first described by Miljkovic (31) CFB has been tested in clinical studies to verify its potency to reduce joint discomfort symptoms and certain inflammatory markers (32, 33). Previous studies have shown that treatment with CFB resulted in statistically significant reduction of blood C-Reactive Protein (CRP) levels in subjects with angina pectoris (34, 35) and in subjects with increased risk of cardiovascular conditions (36). CFB is a patented, nature-identical compound produced according to a proprietary process described by Miljkovic (US Patent #5,962,049) (31). Chemical structure and identity of CFB has been previously described (32). Based upon these previous observations, we have designed this short term pilot clinical trial wherein CFB has been combined with glucosamine and chondroitin sulfate in order to observe possible effects on knee discomfort.

Materials and Methods

Materials

CFB was provided by VDF FutureCeuticals, Inc., (Momence, IL, USA). Glucosamine hydrochloride, chondroitin sulfate, silica oxide and fructose were from Sigma-Aldrich (St Louis, MO, USA),

Inclusion criteria for study subjects: Age range: >35 and<65 years; BMI: >21 and <30; no visible evidence of having a cold or other infections; non-diabetic; free of allergies; McGill Score >35 but less than 60.

Exclusion criteria

Age range: <35 and >65 years; BMI: <21 or >30 (kg/m^2); diabetes; subjects who were pregnant, nursing, or planning to get pregnant; subjects currently enrolled in another study; subjects with cardiovascular diseases; subjects taking medications for pain or NSAIDs, subjects taking supplements or vitamin D within two weeks of this trial.

Consent

This study was conducted according to the guidelines put forth in the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Board at Vita Clinical S.A. (Avenida Circunvalacion Norte #135, Guadalajara, JAL, Mexico 44270) (IRB Number: ABC-NCI-13-08-FRXB). All study subjects were generally healthy and had not used any type of medication or supplement for a period of 15 days prior to the start of the study. Study was performed by NutraClinical Inc. (San Diego, USA) according to the study protocol designed by VDF FutureCeuticals, Inc./ Applied Bioclinical Lab (Irvine, CA, USA).

Study description

After protocol had been approved by the Institutional Review Board, male and female subjects between 35-65 years of age were prescreened according to the inclusion and exclusion criteria. Subjects were recruited through advertisement in local papers. Distribution of the treatments and data collection was performed by NCI (NutraClinical Inc. 16259 Laguna Canyon Rd., Irvine, CA 92618). A total of 96 subjects were selected to participate in the study. All admitted participants had McGill scores between 35 and 60 (per inclusion criteria) and all had given written consent. Participants were randomly assigned into three (3) groups of 32 subjects. Each group contained an equal number of males and females. Each group was subjected to one of three treatment conditions. On Day 1 (baseline) medical history and physical examinations were performed on all subjects. Blood collections were performed on days 1 (baseline), 7 and 14 and always under fasting conditions (12h). On day 1, all subjects received their test products and were instructed to take the first dose immediately after blood collection. All bottles containing the tested materials and all capsules were similar in appearance. McGill and WOMAC Questionnaires were administered at baseline and at 7 and 14 days.

Experimental Groups

Placebo contained 80mg of fructose and 15mg of silica oxide per capsule. Subjects in the placebo group were instructed to take one (1) capsule twice per day before meals. Treatment 1 (TR1) capsules contained a mixture of 375 mg glucosamine, 100 mg chondroitin sulfate and 55 mg CFB. Treatment 2 (TR2) capsules contained a mixture of only 375mg of Glucosamine and 100mg of Chondroitin sulfate. Subjects in TR1 and TR2 experimental groups were advised to take two capsules twice per day before meals. All subjects were instructed to take the capsules before breakfast and lunch and minimum fifteen minutes prior to eating.

Western Ontario and McMaster Universities Arthritis Index. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a widely used questionnaire used to calculate physical function of joints (37). The WOMAC consists of 24 items divided into 3 subscales: pain (5 questions; scores range from 0 to 20), stiffness (2 items; scores range from 0 to 8), and functional limitations (17 items; scores range from 0 to 68). Total scores range from 0 (best) to 96 (worst). The WOMAC index was administered on day 1, day 7 and day 14 of treatment.

McGill Pain Questionnaire. The McGill Pain Questionnaire (MPQ) is a multidimensional pain questionnaire used to quantify the quality and intensity of pain (38, 39). The questionnaire was designed to provide quantitative measures of clinical pain that can be treated statistically. The scale contains 4 subscales consisting of 78 words that participants use to describe feelings of pain. On the first category, subjects have to select a word that "describes" the pain (like "quivering", "pounding"). The second category includes the pain components ("tiring", "suffocating"). The third category is the evaluation of the pain (from "no pain" to "excruciating"). The last part includes a miscellaneous description ("spreading", "torturing", "miserable"). After completing the questionnaire, users will have selected seven words that best describe their pain. Each chosen word has an associated numerical value, giving a total score ranging from 0 (no pain) to 78 (severe pain). The McGill pain questionnaire was administered on day 1 (pre-treatment) and after 7 and 14 days of treatment.

Blood Collection

Blood was collected at baseline prior to treatment. For each participant, two 9 mL blood samples were drawn from an antecubital vein in anticoagulant-free (dry tubes) (BD Vacutainer Franklin Lakes, NJ, USA). Blood again was drawn at Day 7 and Day 14 of the treatment, and always under fasted conditions.

Statistical Methods

In order to address the a priori hypothesis that treatment would improve mean reported discomfort in study subjects with self-reported discomfort in knee joint, the primary analysis tested the effect of treatment on the mean 7-day and 14-day change from baseline in WOMAC score (Western Ontario and McMaster Universities Arthritis Index) and McGill score (pain index of McGill University). A repeated measures analysis of variance (ANOVA) (40) was used to estimate treatment effects on within-subject changes in mean WOMAC and McGill scores over the 7- and 14-day period. Specifically, each score was regressed on an indicator of treatment group, post-treatment day, and the treatment-day interaction. In this case, a test of the coefficients for the treatment-day interaction equaling zero is equivalent to a test of the treatment effect at day 7 and day 14. Both the WOMAC and McGill scores were analyzed using this approach.

Results

Age and BMI characteristics of the study population are presented in Table 1. The average age of the 92 study participants was 49.2 years. The groups were comparable with respect to BMI (26.6 kg/m^2 for all 92 study subjects). Fifty percent of subjects in each treatment group were male. Two participants on the control group and 2 on TR1 did not follow compliance and were dropped from the study. A total of 92 participants remained on study through visits 1, 2 and 3. Numerical summaries of WOMAC and MPQ scores are listed in Table 2. At baseline, range of WOMAC values was 41.6-53.5 and range of McGill score values was 49.2-51.5. It is noticeable that the average value of WOMAC in TR2 was lower comparing to control and TR1 at baseline. However,

Table 1

Characteristics of study subjects as presented by an average values (mean+/-SEM) at Day 1 (baseline)

Treatment	Age (Years)	BMI (kg/m^2)	WOMAC	MPQ
Control	51.4+/-1.2	26.6+/-0.5	52.70 ± 12.66	51.47 ± 5.87
TR1	49.2+/-1.6	26.9+/-0.5	52.17 ± 16.20	49.34 ± 5.40
TR2	47.8+/-1.4	26.2+/-0.5	41.66 ± 11.96	49.66 ± 5.77

Abbreviations: BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Arthritis index; McGill, McGill Pain Questionnaire; SE, Standard Error of the Mean

MPQ score average values were in the same range in all experimental groups. The analysis of treatment effects was based on mean within subject change from baseline.

Table 2
Numerical Summaries of WOMAC and MPQ score by Treatment and Day. Reporting AVE ± SD. WOMAC and MPQ values were determined at baseline and on day 7 and 14

	Treatment Condition		
Variable	**Control (n=30)**	**TR1 (n=30)**	**TR2(n=32)**
WOMAC Score			
Baseline	52.70 ± 12.66	52.17 ± 16.20	41.66 ± 11.96
Day 7	44.70 ± 11.79	44.60 ± 11.42	42.84 ± 12.04
Day 14	51.03 ± 10.36	*40.83 ± 11.55	40.03 ± 9.90
MPQ Score			
Baseline	51.47 ± 5.87	49.34 ± 5.40	49.66 ± 5.77
Day 7	47.67 ± 6.98	42.66 ± 6.32	45.78 ± 5.36
Day 14	47.90 ± 5.86	**37.50 ± 6.07	42.94 ± 9.24

Abbreviations: WOMAC, Western Ontario and McMaster Universities Arthritis Index; MPQ, McGill Pain Questionnaire; AVE, average; SD, standard deviation. *Significant difference from baseline P-value=0.006. **Significant difference from baseline P-value >0.00001

Table 3 shows the estimated effects of active treatment versus placebo at 7 and 14 days follow up. In each case the mean within-subject change from baseline for active compounds is compared to the mean within-subject change for the placebo. A negative estimate indicates that treatment was involved in greater reductions in reported discomfort. The within-subject change in mean WOMAC score over 14 days was estimated to be 9.67 points lower on TR1 (glucosamine, chondroitin sulfate plus CFB) when compared to control (Estimate effect = -9.67, P-Value = 0.006). The within-subject change in mean McGill score over 14 days was estimated to be 8.28 points greater on TR1 when compared to control (Estimated effect = -8.28, P-Value < 0.00001). TR2 (glucosamine and chondroitin, alone) appeared to have an effect on WOMAC scores at day 7, but it is in the wrong direction. This is interpreted to be an artifact associated with the lower mean WOMAC score in group TR2 at baseline. The apparent effect vanished at day 14, and no effect of TR2 is reported on McGill scores throughout the follow-up period. Generally, for both the WOMAC and McGill score, TR1 was more effective than TR 2 at reducing knee discomfort over the two week period.

Blood chemistry analysis performed at Days 1, 7 and Day 14 did not indicate any significant changes in blood levels of key electrolytes, enzymes, lipids and glucose. All subjects completed this trial without any indications of unusual effects.

Table 3
Treatment Effects over 7 and 14 Days for WOMAC and MPQ Scores

Treatment-Day	**Estimated Effect (95% CI)**	**Naive P-value**
WOMAC Score		
Comparison to Control		
TR1-Day 7	0.43 (-5.11, 5.98)	0.8782
TR1-Day 14	-9.67 (-15.21, -4.12)	0.0006
TR2-Day 7	9.19 (3.73, 14.64)	0.0010
TR2-Day 14	0.04 (-5.41, 5.50)	0.9881
Average effect (TR1 + TR2)/2 versus Control		
Average Effect TR1-Day 7	4.81 (0.03, 9.59)	0.0242
Average Effect TR1-Day 14	-4.81 (-9.59, -0.04)	0.0241
MPQ Score		
Comparison to Control		
TR1-Day 7	-2.89 (-6.26, 0.48)	0.0930
TR1-Day 14	-8.28 (-11.65, -4.91)	< 0.00001
TR2-Day 7	-0.08 (-3.44, 3.29)	0.9652
TR2-Day 14	-1.84 (-5.21, 1.53)	0.2846
Average Effect (TR1 + TR2)/2 versus Control		
Average effect TR1-Day 7	-1.48 (-4.41, 1.45)	0.1612
Average Effect TR1-Day 14	-5.06 (-7.99, -2.12)	0.0004

Discussion

Chronic knee discomfort is a condition that significantly affects the quality of life due to its impact on physical movements. Conventional treatment for joint discomfort involves the use of NSAIDs and dietary supplements such as glucosamine and chondroitin supplements. Since NSAIDs are associated with potential side effects(3, 4, 41, 42); the rationale behind the use of dietary supplements is to improve chronic joint discomfort while reducing the need for NSAIDS. Chondroitin sulfate and glucosamine supplements have been commonly used as dietary supplements to reduce and/or slow down cartilage damage in subjects with joint discomfort (43-47).

Calcium fructoborate (CFB) is a natural plant mineral borate complex produced by a patented process first described by Miljkovic (Miljkovic et al., US Patent #5,962,049) (31). Of the existing boron and borate supplements available, CFB might be the most researched and might offer the most potential for human health (31, 48). CFB, a potential anti-inflammatory agent (35, 49, 50) with the ability to modulate key markers associated with inflammation-related conditions, such as osteoarthritis (32, 50, 51), has been recently reported to subjectively improve feelings of flexibility, comfort, and quality of life in a period of only 14 days (33). For this study, we chose a combination of CFB, along with glucosamine hydrochloride and chondroitin sulfate to assess any synergistic effect. The objective of this study was to investigate any possible short-term benefits in decreasing discomfort and improving physical mobility in participants during a short period of time (only 14 days). We also observed the effects of using a combination of chondroitin sulfate and glucosamine alone. Even

though the recruited participants had not been previously diagnosed, the criterion of selection was based on the McGill Pain Questionnaire, which is not only used to evaluate and monitor pain, but also to determine the effectiveness of any intervention. Discomfort and physical function of the joints were recorded for baseline, Day 7 and Day 14 of the study period. The data tables from the study show that at the start of the study all participants had similar discomfort and physical function scores (Table 2). Results presented in Table 3 showed that TR1 (a combination of CFB, chondroitin and glucosamine) significantly reduced mean WOMAC and McGill scores when compared to placebo. In contrast, TR2 using only chondroitin sulfate and glucosamine had no effect under these experimental conditions. Although our study showed that the combination of all 3 nutrients can result in significant rather rapid improvement in knee discomfort and improved mobility, further investigation is justified and can yield additional insight into these materials.

Conclusions

Data from our study clearly indicate that short-term use of CFB in combination with chondroitin sulfate and glucosamine was effective in reducing knee discomfort and improving the physical mobility of the joints. Future investigations conducted with a larger cohort of subjects and for a longer duration; may provide better understanding of the short and long term effects of supplementation. The present study could be repeated as a crossover; in order to observe any withdrawal effects of the combination therapy in subjects.

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