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Effect of Collagen Hydrolysate as Adjuvant Treatment to Exercise for Knee Osteoarthritis

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ABSTRACT

Objective. To determine the effect of collagen hydrolysate as an adjuvant treatment to exercise for knee osteoarthritis on the following parameters: pain VAS score, WOMAC score, characteristics of femoro-tibial cartilage and periarticular soft tissue changes on sonography.

Design. Triple-blind placebo-controlled randomized controlled trial.

Setting. Out-patient setting within Metro Manila.

Participants. 109 individuals aged 50 years old and above, any gender, occupation and educational attainment, with complaint of knee pain of at least one month duration.

Methods. Participants were randomly allocated into an intervention group (n = 56) who took 3 capsules of collagen hydrolysate 400 mg/capsule daily for six months and a control group (n = 53) who took placebo. Both groups were instructed with a standard home exercise program. Assessments were done at baseline and after 6 months and include medical history taking, physical examination, completion of WOMAC and ultrasonography of both knees. Means

and standard deviations were computed for the demographic data, pain VAS score, WOMAC scores and sonographic measurements. Intention-to-treat analysis was performed.

Main Outcome Measurements. Pain VAS scale, WOMAC Index, sonographic measurements of knee cartilage and soft tissue structures

Results. Overall WOMAC and pain VAS scores decreased compared to baseline in both treatment groups but with no significant difference. There was a significant increase in exercise compliance in both treatment groups by 62.5% for the intervention group and 73.5% for the control group. The intervention group showed significant mean change of cartilage abrasion grading of the medial and central portions of the trochlear articular cartilage and reduction of lateral meniscus protrusion. There was no significant difference in terms of cartilage thickness, cartilage clarity and other soft tissue findings. A subgroup analysis of participants who were not compliant to regular exercise showed that the intervention group had a significant decrease in the pain VAS score. There was a significant increase in cartilage thickness in the central portion of the trochlear articular cartilage. Cartilage clarity scores were significantly better in the lateral and central portion of the articular cartilage in the intervention group.

Conclusions. Our study showed that collagen hydrolysate in addition to exercise may help decrease pain, improve overall functional status and produce intraarticular and periarticular structural modifications

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in patients with knee osteoarthritis. For those who were not compliant with regular exercise, the intake of collagen hydrolysate significantly decreased pain and improved cartilage characteristics compared to placebo.

Key Words: Osteoarthritis, Collagen Hydrolysate, Exercise

Introduction

Osteoarthritis (OA) is the most prevalent of the chronic rheumatic diseases among individuals aged 55 years and older with a prevalence estimate of 9.6-18.0% worldwide and 16.0 to 17.8% locally. It commonly affects the knee and is considered as one of the ten most disabling diseases in developed countries (World Health Organization (WHO), 2016, Fransen et al., 2011, The Philippine Star, 2010, Fantilanan-Soldevilla et al., 2008, Bello and Oesser, 2006 and Jordan et al., 2003). Moreover, the WHO data for the Western Pacific region from the year 2000 to 2012 has shown an increase in years lost to disability (YLD) due to OA from 3.5 million to 5 million which was comparable to that brought about by cardiovascular disease and other medical conditions among elderly persons.

The primary pathologic feature of OA is cartilage loss that is associated with various degrees of synovitis (Tarhan, Unlu and Goktan, 2003). Some studies have shown associations between OA and other abnormalities such as non-destructive synovial proliferations, joint cartilage and capsule thickening, joint effusions, bursitis, meniscal protrusions, erosions, popliteal and mucous cysts (Iagnocco, 2010 and Keen, Wakefield and Conaghan, 2009). Osteophytes, bony projections in the marginal and central regions of the knee joint space, were also seen later in the disease (Jordan et al. 2003 and Tarhan et al. 2003). These findings have then been suggested as part of the possible pain generators in knee OA, therefore, detection and monitoring of these changes may be helpful in the understanding and management of the disease (Ikeuchi, Izumi, Aso, Suigimura and Tani, 2013 and Hunter, McDougall and Keefe, 2008).

Treatment for OA has been focused on reducing joint pain and stiffness, maintaining and improving joint mobility, minimizing disability, improving health-related quality of life, limiting the progression of joint damage and educating patients about the nature and management of the

disorder (De Silva, El-Metwally, Ernst, Lewith and Macfarlane, 2011). Current recommended treatment for OA includes participation in aerobic exercise, tai chi and/or weight loss programs, use of thermal agents (heat/cold) and electrotherapy, joint protection, physical/occupational therapy, provision of orthotic and assistive devices, prescription of medications for pain [i.e. acetaminophen, oral/topical nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol and intraarticular steroid injections] and surgical arthroplasty for the hip and knee as the last resort (Hochberg et al. 2012, The Royal Australian College of General Practitioners (RACGP), 2009, Zhang et al. 2008 and Jordan et al. 2003). Although these strategies are effective in moderating symptoms associated with OA, they do not reverse nor cure the disease. In addition, there are considerable side effects associated with oral intake of NSAIDs and intraarticular steroid injections (Henrotin, Lambert, Couchourel, Ripoll, and Chiotelli, 2011 and RACGP 2009).

In the search for a possible alternative management for OA, patients have also tried nutraceuticals or dietary supplements to ease their pain and discomfort (Crowley et al., 2006 and Henrotin et al., 2011). Nutraceuticals are defined as food ingredients or components that provide some medical or health benefits and are sold as powders, pills or other medicinal forms. The advantages of these substances include having limited biological effects that accumulate over time with minimal to absent adverse side effects (Ameje and Chee, 2006). Several investigators have suggested the benefits of some substances (i.e. glucosamine, chondroitin, collagen, vitamin C, vitamin E, methylsulfonylmethane, S-adenosyl methionine, polyunsaturated fatty acids or fish oil and avocado/soybean unsaponifiables) in promoting collagen formation, repairing damaged articular cartilage and/or decelerating its progressive degeneration (Gregory and Fellner, 2014, Henrotin et al. 2011, Vista and Lau, 2011 and Ameje and Chee, 2006). However, study results show conflicting or insufficient evidence regarding the efficacy of these substances.

One of these substances, collagen hydrolysate, has been the subject of several researches for the past years. Collagen hydrolysate is derived from enzymatic hydrolysis of gelatin originating from porcine and bovine bones and hides. Some experimental studies

have found that it contained several amino acids in a sequence similar to that of native collagen (type II), had good intestinal absorption (10-20%), preferentially accumulated in joint cartilage and stimulated chondrocyte metabolism and collagen synthesis (Kumar, Sugihara, Suzuki, Inoue and Venkateswarathirukumarac, 2014, Henrotin et al., 2011, Benito-Ruiz et al. 2009, Bello and Oesser, 2006, and Moskowitz, 2000). These findings have instigated investigators to further explore the use of collagen hydrolysate as a stimulating and regenerative agent for patients with degenerative cartilage disorders such as OA. (Bello and Oesser, 2006).

Most of the studies regarding the use of collagen for OA and other musculoskeletal disorders used the following outcome measurements to assess its efficacy: VAS pain score, physical examination parameters, patient-reported outcomes or quality-of-life scores, Western Ontario and McMaster Universities OA Index (WOMAC) and imaging tests [Conventional radiography/Magnetic Resonance Imaging (MRI)]. Imaging tests appear to be the most objective of these parameters. Although radiography has been traditionally used to diagnose OA, it has been shown to have low sensitivity in demonstrating cartilage involvement in the early stage of the disease and was also limited in direct visualization of the hyaline cartilage and other soft tissues around the knee. MRI, on the other hand, has been found to be a sensitive and non-invasive technique due to its capability of visualizing soft tissue structures. However, its limitations include cost and availability. On the other hand, musculoskeletal sonography has shown its capability in detecting and evaluating a large number of abnormalities involving the hyaline cartilage, synovial fluid, synovial membrane, menisci, joint capsule, bursae and bony cortex from the early to late stages of OA. Some of its other advantages include its capability for immediate point-of-care assessment, limited cost and non-invasiveness (Iagnocco, 2010). Several studies have also demonstrated the reliability and validity of sonographic assessments of the osteoarthritic knee compared with MRI, anatomic evaluation and clinical examinations (Živanović, Rackov and Mijušković, 2012, Iagnocco, 2010, Keen et al., 2009, Naredo et al., 2005 and Tarhan et al., 2003). Currently, there has been no study that has used musculoskeletal sonography to

monitor the effect of collagen hydrolysate in knee OA and its associated soft tissue changes.

It is therefore the primary objective of our research to determine the effect of collagen hydrolysate as an adjuvant treatment to exercise for knee OA on the following parameters: pain score (VAS), functional outcome score (WOMAC), characteristics of femoro-tibial cartilage, periarticular soft tissue changes using sonography.

Methodology

Research design

Triple-blind placebo-controlled randomized controlled trial.

Setting of the sample

Adults of more than 50 years old, any gender, occupation and educational attainment, with complaint of knee pain of at least one month duration and residing in Metro Manila from January 2013 – June 2015.

Ethical considerations

This study adhered to the principles of the Declaration of Helsinki. Bioethical approval was obtained from the Institutional Review Board (IRB) of the University of Santo Tomas Hospital. Prior to the study, written informed consent was obtained from all the participants. Funding and study medications were provided by JCS Pharmaceuticals, Inc. There was no conflict of interest among the investigators.

Participant screening and recruitment

Potential participants were recruited through written advertisements soliciting “adults with knee pain for more than a month”. The advertisements were posted around the University of Santo Tomas (UST) campus, University of Santo Tomas Hospital, Santisimo Rosario Parish Church within the UST campus and the Marikina Senior Citizens’ Healthy Lifestyle Center. We were contacted by the participants through phone call or face-to-face.

Participants were screened through preliminary medical history review and physical examination. Inclusion criteria were based on the Altman’s clinical criteria for classification of idiopathic osteoarthritis of the knee (see Table 1). Exclusion criteria are shown on Table 2.

Table 1. Altman's Criteria for Classification of Idiopathic Osteoarthritis (OA) of the Knee (Altman et al. 1986)

Clinical and Laboratory*	Clinical and Radiographic	Clinical†
Knee pain + at least 5 of 9: Age > 50 years Stiffness < 30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth ESR < 40 mm/hr RF < 1:40 SF OA 92 % sensitive 75 % specific	Knee pain + at least 1 of 3: Age > 50 years Stiffness < 30 minutes Crepitus + Osteophytes (radiographic) 91 % sensitive 86 % specific	Knee pain + at least 3 of 6: Age > 50 years Stiffness < 30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth 95 % sensitive 69 % specific

*ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous or white blood cell count < 2,000/mm³)

† Alternative for the clinical category would be 4 of 6, which is 84 % sensitive and 89 % specific.

Table 2. Exclusion criteria for participants

Medical History	Procedures	Objective Findings
Previous intake of collagen hydrolysate or any form of supplement in the past week	Intra-articular injection of hyaluronic acid (past 6 months) or corticosteroids (past month)	Limited knee range of motion which would prevent proper positioning
Known hypersensitivity/allergy to collagen hydrolysate	Previous arthroscopy or surgery of the knee	Severe genu varus or valgus deformity
Presence of other arthropathy i.e. rheumatoid arthritis, gouty arthritis, septic arthritis		Minimal or absent knee joint space on x-ray

Sample Size Calculation

Based on the study of Bruyere et al. in 2012 and using the statistical software Stata 11, a sample size of 50 participants per treatment arm or a total of 100 was necessary to achieve an 80% power of the study at an alpha level of 0.05. We decided to add at least 10% more participants to compensate for possible drop-outs during the conduct of the study.

Methods

Participants included in the study were allocated into an intervention group and a control group using a random list of numbers generated through Microsoft Excel. Both groups were instructed with a standard home exercise

program for knee osteoarthritis which has been validated by Mercado et al. in 2012. Members of the intervention group were asked to take 3 capsules of collagen hydrolysate 400 mg/capsule (Brand name: Genacol) daily for six months while the control group took placebo. Each participant was also instructed to keep a daily journal/diary for documentation of the occurrence of knee pain, performed exercises, and intake of additional medications during the study.

Standard Treatment for Knee OA

Standard treatment for both groups included instructions on proper effective exercises for knee OA (see Appendix A). The exercise program was composed of strengthening exercises for the hip and knee musculature, stretching exercises and walking as a form of aerobic exercise. The brochure was produced by the Apolinario Mabini Rehabilitation Center of the University of Santo Tomas Hospital and has been proven effective in decreasing pain, improving functional outcome and increasing cardio-respiratory endurance (Mercado et al. 2012). These exercises were to be done at least twice a week for six months. Paracetamol 500 mg-tablets were also provided as rescue medications for episodes of severe pain warranting intake of medication.

Study Medications

The medications were prepared by JCS Pharmaceuticals, Inc. and contained 400 mg of collagen hydrolysate for the intervention group and an equal amount of maltodextrin as placebo for the control group. Both sets of medications were placed in identical white capsules and were coded by the manufacturer. The code was revealed by the manufacturer to the investigators only after all the follow-up participant data have been collected. The allocator of the study medications was also blinded to the capsules' contents.

Criteria for Study Termination or Participant Withdrawal

The following criteria for termination of the study or subject participation were used:

1. Participant's voluntary refusal
2. Increasing knee pain even with intake of NSAID or other medications
3. Presence of adverse events related to intake of the study medications (i.e. fever, eructation, severe gastrointestinal disorder, allergic reaction) or other unrelated medical conditions that would prevent further participation

Outcome measures

Pain Visual Analogue Scale (VAS)

The Pain VAS used in this study is a graphic rating scale format composed of a horizontal line 100 mm in length, divided equally with 6 vertical lines to produce a 0-10 scale (with intervals of 2) and anchored by word descriptors and different faces at each line. The participant marks the point that represents their current state of pain. The VAS score is measured in millimeters from the left hand end of the line to the point that the participant marks. It has an excellent test-retest reliability ($r = 0.94$) and moderate to good construct validity ($r = 0.62 - 0.91$) compared with similar pain rating scales (Pagare, Buxton and Thomas, 2016).

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC is a self-administered questionnaire used to assess pain, stiffness and physical function among patients with hip and/or knee OA. It is composed of 24 items divided into the subscales of pain (5 items), stiffness (2 items) and physical function (17 items). This study used the 100-mm VAS format Tagalog version with anchors of *hindi masakit/walang paninigas/hindi mahirap* and *masakit na masakit/matinding paninigas/napakahirap*. The participant marks the point on the line that represents their current symptom with regarding the context described by the items. The item score is determined by measuring in millimeters from the left hand end of the line to the point that the participant marks. Possible score ranges per subscale area as follows: pain=0-500, stiffness=0-200, physical function=0-1700. The total WOMAC score is the sum of the scores for all of the items (max score = 2400) with higher scores indicating worse pain, stiffness and functional limitations. Its psychometric properties showed acceptable to excellent internal consistency and test-retest reliability (Cronbach alpha 0.70 - 0.91; ICC 0.58 - 0.92) and moderate to high construct validity correlations with other similar instruments (American College of Rheumatology, 2015).

Sonographic measurements of the knee cartilage and soft tissue structures

The musculoskeletal ultrasound protocol for knee osteoarthritis developed by Bernardo et al. in 2014 was adopted for the sonographic assessments in this study (see Appendix B). The

following structures were scanned and the subsequent parameters were measured thrice according to the protocol:

1. Articular cartilage (medial and lateral femoral condylar area)
 - a. Narrowest anteroposterior diameter of the articular cartilage (in centimeters)
 - b. Cartilage clarity - how well the cartilage borders could be distinguished from the overlying intra-articular soft tissues and scored as follows: 1 - excellent; 2 - good; 3 - poor; and 4 - worst.
 - c. Cartilage grade - the severity of focal cartilaginous lesions and scored as follows: 0 - normal; 1 - minimal abrasion; 2 - partial defect; 3 - defect extending down to intact subchondral bone; and 4 - defect involving the subchondral bone.
2. Suprapatellar and infrapatellar recess
 - a. Largest anteroposterior diameter of effusion (in centimeters)
 - b. Degree of synovitis
Thickness of the synovial tissue was graded as follows: normal - no synovitis; mild - flat, thickened synovium; moderate - thickened synovium with few villi-like protrusions; severe - marked thickening with multiple villi-like protrusions.
 - c. Power Doppler Signal (PDS)
Blood flow in the synovial membrane was evaluated using the power Doppler signal and graded as follows: 1 - normal or minimal tissue perfusion, 2 - mild hyperemia, 3 - moderate hyperemia, and 4 - marked hyperemia.
3. Medial and lateral menisci
 - a. Meniscal protrusion
A line is drawn from the femur to the tibia and the height of a perpendicular line drawn from this line to the highest point of the meniscus is measured in centimeters
4. Pes anserine bursitis
 - a. Widest antero-posterior diameter of bursitis (in centimeters)
 - b. Power Doppler Signal
5. Posterior knee (Baker's cyst)
 - a. Widest transverse diameter of the cyst (in centimeters)

Other findings noted during the scans were also noted such as the presence of osteophytes, tendinopathies, panniculitis and meniscal breaks.

Data collection

All participants were assessed at baseline and after 6 months. In each assessment, the following procedures were conducted: medical history taking, physical examination, completion of WOMAC and ultrasonography of both knees.

Medical history and physical examination

Participants filled out a data sheet which obtained the following data: name, age, gender, address, occupation, contact information, comorbid diseases, previous surgeries, current medications and treatments. Data pertinent to OA were also obtained: affected knee, worst pain score on the affected knee rated using pain VAS, number of years diagnosed with OA (if previously diagnosed through x-ray or consultation), exercise compliance and medications taken for pain.

The following physical parameters were subsequently assessed: range of motion of both knees, knee deformity (genu valgus/varus), swelling and/or warmth, height and weight.

Sonography of the Knee

Gray scale ultrasound using *Sonosite M-Turbo* ultrasound machines (Washington, USA) with linear transducers (bandwidth 13-6MHz, scan depth 6cm) and Power Doppler capabilities were used. Five certified sonologists (one orthopedic surgeon, one rheumatologist, three physiatrists) who were part of the musculoskeletal ultrasound protocol development team performed the procedure on the participants. They were blinded to participant allocation.

Treatment of Data

Prior to the statistical analysis, the measurement of the femoro-tibial cartilage thickness and grading of cartilage quality using the two methods (longitudinal and transverse views) were correlated and showed significant correlation (Cua et al. 2016). Thus, the investigators decided to use the cartilage measurements in the trochlear region obtained through the transverse view which provided articular cartilage thickness measurements of the central region. Exercise compliance, on the other hand, was interpreted as performance of the standard exercise regimen at least twice a week during the period of the study (Mercado et al. 2012).

Statistical analysis

Means and standard deviations were computed for the demographic data, VAS pain score, WOMAC overall and subscale scores and sonographic measurements. Mann-Whitney, Fisher's Exact and McNemar's Change tests were used when applicable to detect significant differences between treatment groups for categorical and continuous variables. Intention-to-treat analysis was performed. A p value of ≤ 0.05 was considered significant for all of the statistical tests.

Results

I. Participant characteristics

A total of 109 participants were included in the study and randomly allocated to treatment groups (Please refer to Figure 1). The number of participants who withdrew from the study was similar and the reasons for drop out are indicated on the diagram. Majority of the participants were females, had bilateral knee pain and were non-compliant to exercise recommendations before intervention. Height, weight, body mass index, pain VAS and WOMAC scores were similar for both treatment groups with no significant differences (see Table 3).

Table 3. Baseline characteristics of study participants

	Total	Intervention Group	Control Group	p value
No. of participants	109	56	53	
Males/Females	23/86	13/43	10/43	0.64
Age in years, mean (SD)	64.1 (8.3)	64.1 (8.6)	62.7 (10.2)	0.96
Weight in kg, mean (SD)	62.2 (7.0)	61.6 (10.4)	62.7 (10.2)	0.42
Height in cm, mean (SD)	152.5 (7.1)	152.7 (7.4)	152.7 (9.0)	0.60
Body mass index in kg/m^2 , mean (SD)	26.8 (2.9)	26.4 (3.9)	27.0 (4.8)	0.84
Knee involvement (unilateral/bilateral)	3/106	1/55	2/51	0.61
Pain VAS score, mean (SD)	4.6 (3.1)	4.6 (3.0)	4.6 (2.9)	1.00
WOMAC Overall Score, mean (SD)	790.0 (520.6)	795.4 (545.2)	752.2 (490.4)	0.75
Exercise compliance (compliant/non-compliant)	10/99	3/53	7/46	0.20

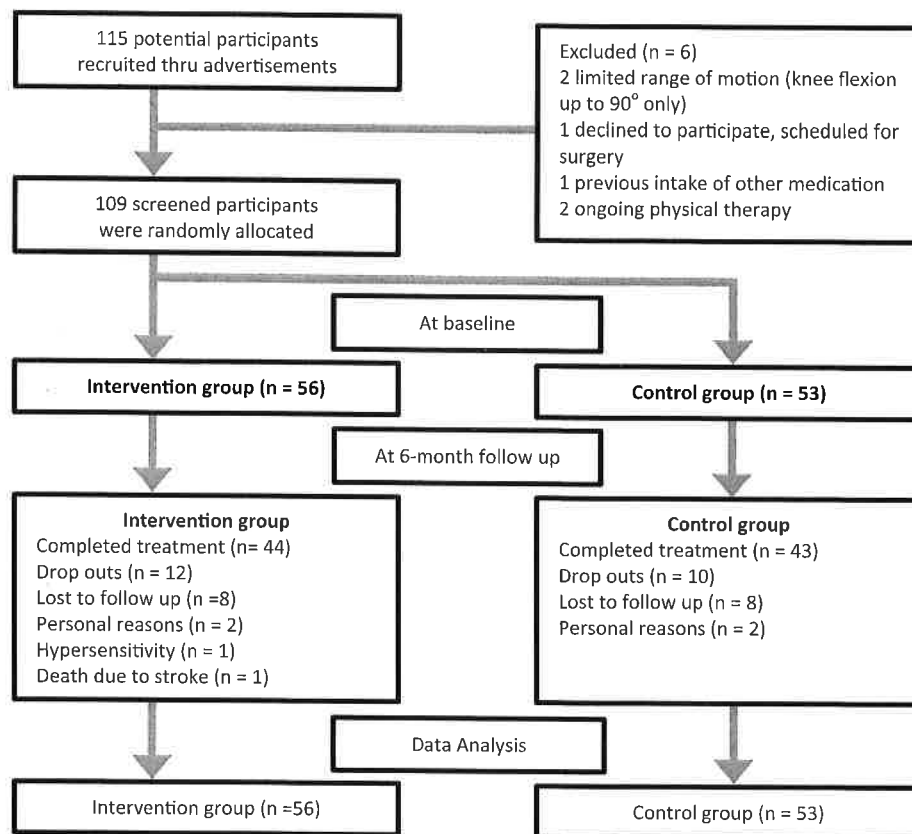


Figure 1. CONSORT Flow diagram.

II. WOMAC Score, Pain VAS Score and Exercise Compliance

Table 4. Baseline and post-intervention overall WOMAC scores, pain VAS scores and exercise compliance count

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Overall WOMAC Score [mean, (SD)]			
Pre-intervention	795.4 (545.2)	752.2 (490.4)	0.75
Post-intervention	596.4 (549.8)	537.5 (400)	0.99
Mean change	-16.1 (41.5)	-21.5 (60.4)	0.46
Pain VAS score [mean, (SD)]			
Pre-intervention	4.6 (3.0)	4.6 (2.9)	1.00
Post-intervention	2.2 (2.6)	2.2 (2.9)	0.66
Mean change	-2.4 (2.9)	-2.4 (3.3)	0.75
Exercise Compliance (Compliant/Non-compliant)			
Pre-intervention	3/53	7/46	0.20
Post intervention	35/21	39/14	0.23
P value	0.00 ^a	0.00 ^a	

^a Significant

Overall WOMAC and pain VAS scores decreased compared to baseline in both treatment groups. However, there was no statistically significant difference between the two groups for these two outcome measures. However, there was a significant increase in exercise compliance

by 62.5% in the intervention group and 73.5% in the control group (see Table 4).

III. Sonographic measurements and findings

There were minimal though statistically significant differences between the baseline values of the two treatment groups with regard to medial meniscus protrusion and deep infrapatellar bursitis measurements. The rest of the baseline values for femoro-tibial articular cartilage thickness and characteristics as well other soft tissue findings were similar and not statistically different for both groups (see Tables 5-10).

Cartilage thickness, clarity and abrasion

After the intervention, there was a significant mean change of cartilage abrasion grading of the medial (-0.13 ± 1.22 , $p = 0.009$) and central (-0.6 ± 1.25 , $p = 0.013$) portions of the articular cartilage in the trochlear area for the intervention group. The cartilage thickness and clarity of the articular cartilage was not significantly different between the two groups (see Tables 5-6).

Table 5. Baseline and post-intervention sonographic measurements of femoro-tibial articular cartilage thickness (in centimeters)

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Medial Cartilage [mean, (SD)]			
Pre-intervention	0.11 (0.05)	0.11 (0.06)	0.52
Post-intervention	0.14 (0.05)	0.14 (0.05)	0.61
Mean change	0.03 (0.04)	0.03 (0.05)	0.56
Central Cartilage [mean, (SD)]			
Pre-intervention	0.14 (0.04)	0.15 (0.05)	0.47
Post-intervention	0.16 (0.04)	0.16 (0.05)	0.80
Mean change	0.02 (0.04)	0.01 (0.04)	0.27
Lateral Cartilage [mean, (SD)]			
Pre-intervention	0.14 (0.11)	0.12 (0.04)	0.52
Post-intervention	0.15 (0.08)	0.14 (0.04)	0.54
Mean change	0.01 (0.08)	0.02 (0.04)	0.51

Table 6. Baseline and post-intervention sonographic assessment of femoro-tibial articular cartilage characteristics

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Clarity			
Medial Cartilage [mean, (SD)]			
Pre-intervention	2.85 (0.56)	2.91 (0.59)	0.41
Post-intervention	2.59 (0.74)	2.61 (0.72)	0.66
Mean change	-0.26 (0.87)	-0.29 (0.79)	0.93
Central Cartilage [mean, (SD)]			
Pre-intervention	2.79 (0.62)	2.86 (0.62)	0.39
Post-intervention	2.39 (0.75)	2.51 (0.71)	0.17
Mean change	-0.40 (0.86)	-0.35 (0.79)	0.54
Lateral Cartilage [mean, (SD)]			
Pre-intervention	2.82 (0.54)	2.86 (0.52)	0.50
Post-intervention	2.36 (0.68)	2.42 (0.63)	0.45
Mean change	-0.46 (0.83)	-0.43 (0.78)	0.64
Abrasion			
Medial Cartilage [mean, (SD)]			
Pre-intervention	2.22 (1.29)	1.99 (1.39)	0.19
Post-intervention	2.10 (1.07)	2.37 (1.30)	0.07
Mean change	-0.13 (1.22)	0.38 (1.31)	0.009 ^b
Central Cartilage [mean, (SD)]			
Pre-intervention	1.83 (1.29)	1.52 (1.27)	0.06
Post-intervention	1.77 (0.95)	1.82 (1.06)	0.64
Mean change	-0.06 (1.25)	0.30 (1.10)	0.013 ^b
Lateral Cartilage [mean, (SD)]			
Pre-intervention	1.83 (1.31)	1.57 (1.30)	0.12
Post-intervention	1.83 (0.80)	1.83 (1.10)	0.71
Mean change	0 (1.27)	0.26 (1.27)	0.16

^b Significant

Periarticular Soft Tissue Changes

There was a significant difference between the two groups post-intervention with regard to lateral meniscus protrusion. The intervention group showed a notable reduction (from 0.20 ± 0.16 cm to 0.13 ± 0.16 cm) compared to the control group (from 0.23 ± 0.17 cm to 0.18 ± 0.21 cm). There was no significant difference between the treatment groups for the other soft tissue findings (see Tables 7-10).

Table 7. Baseline and post-intervention sonographic measurement of meniscal protrusion in centimeters [mean, (SD)]

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Medial meniscus			
Pre-intervention	0.20 (0.19)	0.26 (0.19)	0.02 ^b
Post-intervention	0.20 (0.23)	0.25 (0.23)	0.06
Mean change	0.00 (0.20)	-0.01 (0.18)	0.94
Lateral meniscus			
Pre-intervention	0.20 (0.16)	0.23 (0.17)	0.08
Post-intervention	0.13 (0.16)	0.18 (0.21)	0.05 ^c
Mean change	-0.08 (0.16)	-0.05 (0.19)	0.22

^c Significant**Table 8.** Baseline and post-intervention sonographic assessment of the suprapatellar recess

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Synovitis (with/without)			
Pre-intervention	58/54	69/37	0.16
Post-intervention	58/54	66/40	0.20
Suprapatellar bursitis			
Anteroposterior diameter, in centimeters [mean, (SD)]			
Pre-intervention	0.23 (0.29)	0.30 (0.36)	0.17
Post-intervention	0.14 (0.26)	0.19 (0.32)	0.40
Mean change	-0.09 (0.29)	-0.11 (0.37)	0.41

Table 9. Baseline and post-intervention sonographic assessment of the infrapatellar recess

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Infrapatellar panniculitis (with/without)			
Pre-intervention	6/106	3/103	0.50
Post-intervention	32/80	42/64	0.09
Bursitis			
Anteroposterior diameter, in centimeters [mean, (SD)]			
Superficial infrapatellar area			
Pre-intervention	0.00 (0.02)	0.01 (0.10)	0.94
Post-intervention	0.00(0.02)	0.00 (0.00)	0.33
Mean change	0.0 (0)	-0.01 (0.10)	0.52
Deep infrapatellar area			
Pre-intervention	0.03 (0.11)	0.00 (0.02)	0.014 ^d
Post-intervention	0.01 (0.07)	0.00 (0.00)	0.09
Mean change	-0.02 (0.09)	0.0 (0.02)	0.07

^d Significant**Table 10.** Baseline and post-intervention sonographic assessment of other periarticular soft tissue findings

	Intervention Group (n = 56)	Control Group (n = 53)	p value
Pes anserine bursitis			
Anteroposterior diameter in centimeters [mean, (SD)]			
Pre-intervention	0.02 (0.07)	0.03 (0.13)	0.87
Post-intervention	0.01 (0.04)	0.00 (0.02)	0.06
Mean change	-0.01 (0.07)	-0.03 (0.13)	0.11
Popliteal (Baker's) cyst			
Transverse diameter in centimeters [mean, (SD)]			
Pre-intervention	0.23 (0.59)	0.34 (0.82)	0.25
Post-intervention	0.18 (0.59)	0.30 (0.84)	0.20
Mean change	-0.05 (0.36)	-0.04 (0.32)	0.55

IV. Subgroup statistical analysis of data from participants non-compliant to exercise

Additional statistical analyses were conducted to determine the effect of collagen hydrolysate intake independent from exercise on the different outcome measures. Data from participants who were not compliant with the performance of regular exercise were used. This subgroup was composed of 21 participants from the intervention group and 14 from the control group.

Pain VAS score and WOMAC Score among participants not compliant to regular exercise

Pre-intervention pain VAS scores were not statistically different between the two groups. However, post-intervention measurements showed significantly lower VAS scores for the intervention group compared to the control group (3.0 ± 2.9 and 5.1 ± 3.0 , respectively, with $p = 0.03$).

WOMAC scores improved in both groups after the intervention with greater mean change observed in the intervention group. However, statistical significance was not reached (see Table 11).

Table 11. Baseline and post-intervention overall WOMAC scores and pain VAS scores of participants non-compliant to regular exercise

	Intervention Group (n = 21)	Control Group (n = 14)	p value
Overall WOMAC Score [mean, (SD)]			
Pre-intervention	805.3 (569.4)	686.2 (528.1)	0.55
Post-intervention	646.5 (519.1)	627.8 (403.5)	0.74
Mean change	-16.7 (27.4)	-3.2 (10.6)	0.23
Pain VAS score [mean, (SD)]			
Pre-intervention	3.7 (2.7)	5.6 (3.0)	0.09
Post-intervention	3.0 (2.9)	5.1 (3.0)	0.03 ^e
Mean change	-0.8 (1.9)	-0.5 (1.4)	0.54

^e Significant

V. Sonographic measurements and findings among participants not compliant to regular exercise

Baseline measurements of cartilage thickness, clarity and abrasion showed no statistical difference. At post-intervention, there was a significant difference ($p = 0.03$) between the two groups with regard to cartilage thickness of the central portion of the articular cartilage. The intervention group demonstrated a thicker central cartilage (0.15 ± 0.04 cm) compared to the control group (0.12 ± 0.04 cm) (see Table 12).

The intervention group demonstrated improvements in the post-intervention cartilage clarity scores and was significant at the central (2.55 ± 0.71 vs. 2.82 ± 0.70 ; $p = 0.05$) and lateral

(2.47 ± 0.67 vs 2.82 ± 0.6 ; $p = 0.01$) portions compared to the control group. There was also a significant mean difference in cartilage clarity scores of the lateral portion of the articular cartilage with greater change in the intervention group (-0.28 ± 0.55 vs. -0.07 ± 0.60 ; $p = 0.03$) (see Table 13). Post-intervention cartilage abrasion scores and periarticular soft tissue findings were not statistically different between the two groups.

Table 12. Baseline and post-intervention sonographic measurements of femoro-tibial articular cartilage thickness (in centimeters) of participants non-compliant to regular exercise

	Intervention Group (n = 21)	Control Group (n = 14)	p value
Medial Cartilage [mean, (SD)]			
Pre-intervention	0.12 (0.05)	0.12 (0.08)	0.49
Post-intervention	0.12 (0.05)	0.12 (0.08)	0.26
Mean change	0.00 (0.03)	-0.00 (0.02)	0.34
Central Cartilage [mean, (SD)]			
Pre-intervention	0.15 (0.04)	0.13 (0.04)	0.06
Post-intervention	0.15 (0.05)	0.13 (0.04)	0.03 ^f
Mean change	0.00 (0.02)	0.00 (0.02)	0.98
Lateral Cartilage [mean, (SD)]			
Pre-intervention	0.15 (0.13)	0.12 (0.03)	0.15
Post-intervention	0.15 (0.13)	0.12 (0.03)	0.54
Mean change	0.00 (0.02)	0.00 (0.00)	0.50

^f Significant

Table 13. Baseline and post-intervention sonographic assessment of femoro-tibial articular cartilage characteristics of participants non-compliant to regular exercise

	Intervention Group (n = 21)	Control Group (n = 14)	p value
Clarity			
Medial Cartilage [mean, (SD)]			
Pre-intervention	2.90 (0.53)	2.93 (0.54)	0.86
Post-intervention	2.67 (0.69)	2.82 (0.72)	0.22
Mean change	-0.24 (0.73)	-0.11 (0.57)	0.18
Central Cartilage [mean, (SD)]			
Pre-intervention	2.76 (0.66)	2.86 (0.52)	0.44
Post-intervention	2.55 (0.71)	2.82 (0.72)	0.05 ^g
Mean change	-0.21 (0.61)	-0.04 (0.51)	0.16
Lateral Cartilage [mean, (SD)]			
Pre-intervention	2.76 (0.53)	2.89 (0.42)	0.25
Post-intervention	2.48 (0.67)	2.82 (0.61)	0.01 ^g
Mean change	-0.29 (0.55)	-0.07 (0.60)	0.04 ^g
Abrasion			
Medial Cartilage [mean, (SD)]			
Pre-intervention	1.93 (1.35)	1.93 (1.84)	0.91
Post-intervention	1.95 (1.25)	1.79 (1.81)	0.50
Mean change	0.02 (0.56)	-0.14 (0.59)	0.28
Central Cartilage [mean, (SD)]			
Pre-intervention	1.50 (1.21)	1.21 (1.37)	0.26
Post-intervention	1.50 (1.06)	1.11 (1.31)	0.09
Mean change	0.00 (0.70)	-0.11 (0.42)	0.45
Lateral Cartilage [mean, (SD)]			
Pre-intervention	1.69 (1.35)	1.39 (1.42)	0.36
Post-intervention	1.71 (1.15)	1.36 (1.45)	0.19
Mean change	0.02 (0.84)	-0.03 (0.33)	0.57

^g Significant

Adverse Events

Two participants from the intervention group and one participant from the control group experienced a feeling of bloatedness after two to three days of taking their assigned medications. They were advised to discontinue their medication for one week. Upon resumption of medication intake, no recurrence of previous symptoms was noted for all three patients. One participant from the intervention group experienced a hypersensitivity skin reaction after the second day of taking his assigned medication. This participant was given appropriate medical management and was advised to terminate his participation from the study. The manufacturer was also informed of this adverse reaction.

Discussion

This study, to our knowledge, is the first to determine the effect of collagen hydrolysate in combination with a standard treatment for knee osteoarthritis (i.e. exercise) on pain score, functional status, articular cartilage characteristics and soft tissue changes using sonography.

Pain VAS scores improved in both of our treatment groups and was statistically significant among participants who were compliant with collagen hydrolysate intake but not with exercise. This result is congruent with the findings of Moskowitz (2000), McAlindon et al. (2011), Benito-Ruiz et al. (2009) and Bernardo and Azarcon (2012). WOMAC scores, on the other hand, also improved in both treatment groups but did not reach statistical significance. One plausible explanation for this result is that the participants in both groups probably had milder OA symptoms as demonstrated by their baseline mean pain VAS and WOMAC scores not exceeding 50% of the highest possible score. Moskowitz and McAlindon et al. also mentioned that variability in clinical severity at the onset may affect the expected magnitude of change as patients with more severe symptoms have a greater potential for improvement. The results may also be attributed to the difference in the standard treatments. Utilization of a 6-month exercise program as our standard treatment, in accordance to the general consensus for OA (Trojian et al., 2016), translated into an increase in exercise compliance and expected manifestation of its benefits among the participants from both treatment groups in terms of improved function

and well-being. This may very well explain the observed improvement in both pain and WOMAC scores of our participants.

Several investigators have studied different dietary supplements and interventions to identify the best approach that can delay the structural progression of OA (Gregory and Fellner, 2014). Our study on collagen hydrolysate may be the first to document structural modifications in osteoarthritic knees. We have found significant improvement in the cartilage thickness, clarity and abrasion scores as well as a significant reduction in lateral meniscus protrusion in our intervention group. These changes pose relevant implications for the management of OA.

Previous studies on collagen hydrolysate have found that it preferentially accumulates in cartilage and stimulates chondrocyte metabolism and collagen synthesis. This, in theory, will strengthen the cartilage and possibly delay the progression of OA. The studies of Berthiaume et al. (2005) and Hunter et al. (2006), on the other hand, have emphasized the significant association between the severity of meniscal tears and extrusions and the progression of cartilage volume loss. The menisci provide some protection to cartilage when they are positioned properly within the knee (Hunter et al., 2006). However, due to numerous mechanical and biological factors, the meniscus may protrude and lose articulation with the cartilage which may then contribute to degeneration. Exercise may then play a role in strengthening the structures surrounding the knee to provide external support to the meniscus. In light of this information, it may be probable that the combination of exercise and collagen hydrolysate intake can promote structural modification and delay the progression of cartilage loss in normal and osteoarthritic knees.

A possible limitation of our study is the duration of intervention. Although most of the previous studies on collagen were conducted between three to six months, it may be prudent to extend the follow-up period (nine months and/or 12 months) to be able to observe more prominent changes in the outcome measures as there has been no established onset of effect for collagen hydrolysate as of date. A case report by Halpern et al. (2013) which studied the effect of intraarticular injection of platelet-rich plasma (PRP) in patients with knee osteoarthritis also supports this recommendation because no

change in the articular cartilage using MRI was observed until one year after the injection of PRP. Other recommendations for future studies include the following: 1) comparison of the effects of different concentrations of collagen hydrolysate, 2) comparison of the effect of timing of intake (on empty stomach or at bedtime), 3) balancing or grouping of participants according to occupation, level of physical exertion and OA severity, 4) identification and assessment of other OA risk factors such as foot deformities (i.e. pes planus) and changes in the biomechanical chain, and 5) recruitment of a larger sample size.

Conclusion

Our study showed that collagen hydrolysate in addition to exercise may help decrease pain, improve overall functional status and produce intraarticular and periarticular structural modifications (i.e. improvement of cartilage abrasion grade and reduction of lateral meniscal protrusion) in patients with knee osteoarthritis. For those who were not compliant with regular exercise, the intake of collagen hydrolysate significantly decreased pain and improved cartilage characteristics (i.e. increase in cartilage thickness and improvement of cartilage clarity) compared to placebo.

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