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 VAS pain score. There was a significant increase in the cartilage thickness in the central portion of the trochlear articular cartilage. Clarity scores were significantly better in lateral and central portion of the cartilage in the intervention group.

Conclusions: Our study showed that collagen hydrolysate in addition to exercise decreased pain, improved overall functional status and produced 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 decreased pain and improved the cartilage structure as compared to placebo.

Keywords: 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 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 and electrotherapy (heat/cold), 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 (Ameye 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 Ameye 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 appears 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.

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 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	Knee pain + at least 1 of 3: Age > 50 years Stiffness < 30 minutes Crepitus + Osteophytes (radiographic)	Knee pain + at least 3 of 6: Age > 50 years Stiffness < 30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth

SF OA		
92 % sensitive 75 % specific	91 % sensitive 86 % specific	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/mm^3)
† 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 Known hypersensitivity/ allergy to collagen hydrolysate Presence of other arthropathy i.e. rheumatoid arthritis, gouty arthritis, septic arthritis	Intra-articular injection of hyaluronic acid (past 6 months) or corticosteroids (past month) Previous arthroscopy or surgery of the knee	Limited knee range of motion which would prevent proper positioning Severe genu varus or valgus deformity 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. Subgroup

analysis was performed on the participants who did not regularly exercise to determine the effect of collagen hydrolysate on VAS pain score, WOMAC overall and subscale scores and sonographic measurements Intention-to-treat analysis was performed. A *p* value of $\leq$ 0.05 was considered significant for all of the statistical tests.

RESULTS

Participant characteristics

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

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).

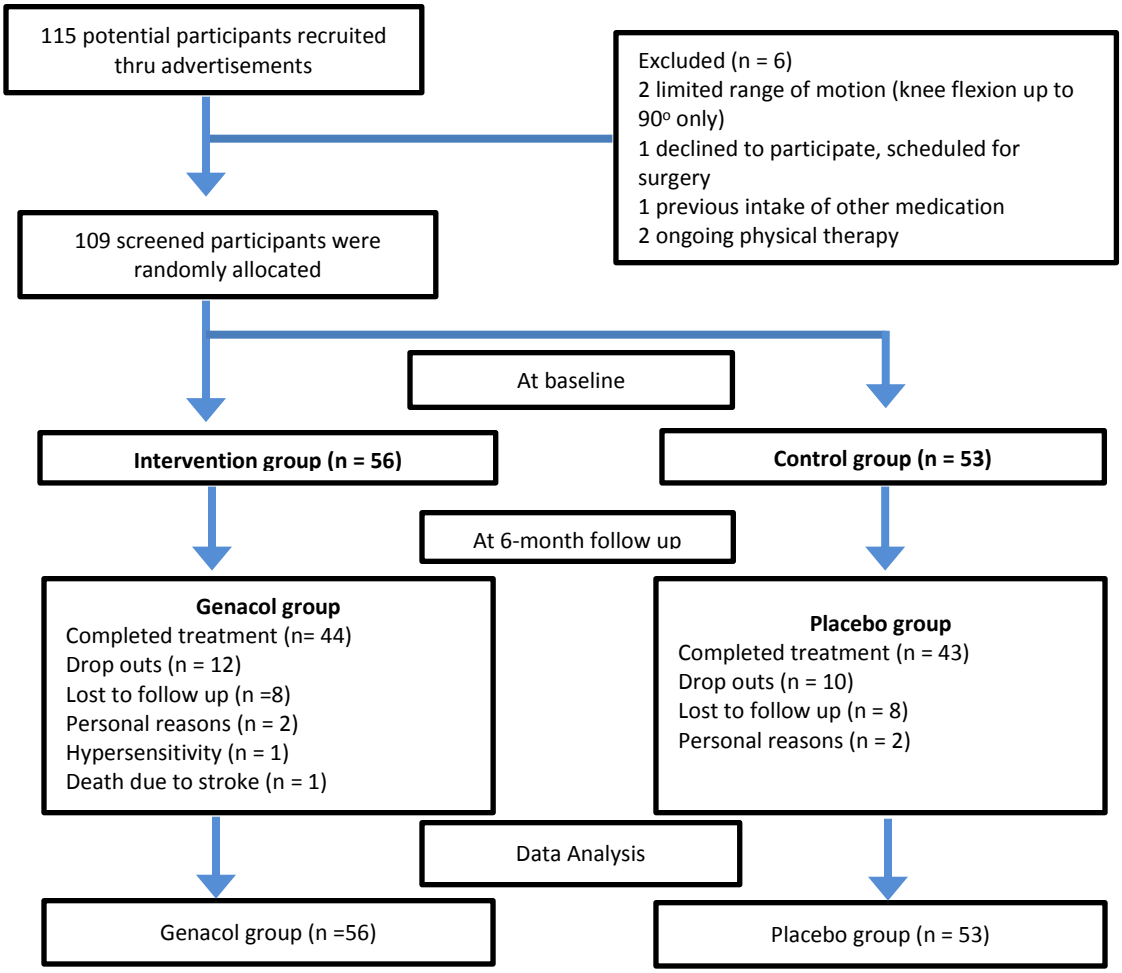


Figure 1. CONSORT Flow diagram

Pain VAS score, WOMAC 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	0.000[a]	0.000[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).

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

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	1.33 (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

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).

Periarticular Soft Tissue Changes

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[b]
Mean change	-0.08 (0.16)	-0.05 (0.19)	0.22

[b] 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[b]
Post-intervention	0.01 (0.07)	0.00 (0.00)	0.09
Mean change	-0.02 (0.09)	0.0 (0.02)	0.07

[b] 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 (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)	-0.05 (0.32)	0.55

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).

Subgroup analysis of participants who were non-compliant with regular exercise.

There were 21 and 14 participants in the intervention and control groups that were non-compliant with performing regular exercise. The pre-intervention VAS score was not statistically different with the two groups. However, during post-intervention, there was a significantly lower VAS score for the intervention group as compared to the control group (3.0 ± 2.9 vs 5.1 ± 3.0; p value 0.03). There was no statistical difference with the WOMAC score of both groups.

Table 11: VAS score of experimental and control groups who were 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[a]
Mean change	-0.8 (1.9)	-0.5 (1.4)	0.54

[a] Significant

Sonographic measurements and findings

There was no statistical difference with the cartilage thickness, clarity and abrasion of the intervention and control group at baseline. After six months, the intervention group had a thicker cartilage measurement in the central portion (0.15 ± 0.04 cm vs 0.12 ± 0.04 cm, p value = 0.03) (Table 12). The intervention group demonstrated significant improvements in the post-intervention cartilage clarity at the central and lateral area as compared with the control group (central area: 2.55 ± 0.71 vs 2.82 ± 0.7 ; p value = 0.05; lateral area: 2.47 ± 0.67 vs 2.82 ± 0.6 ; p value = 0.01). There was also a significant mean difference in the clarity score of the lateral cartilage in the intervention group (-0.28 ± 0.55 vs -0.07 ± 0.60) with a p value of 0.03 (Table 13).

There was no statistical difference between intervention and control groups in the cartilage abrasion scores and peri-articular soft tissue findings at baseline and post-intervention.

Table 12. Baseline and post-intervention sonographic measurements of femoro-tibial articular cartilage thickness (in centimeters)

	Intervention Group (n = 21)	Control Group (n = 14)	*p* value
Medial Cartilage [mean, (SD)]			
Pre-intervention	0.11 (0.05)	0.11 (0.08)	0.48
Post-intervention	0.12 (0.05)	0.11 (0.08)	0.25
Mean change	0.003 (0.03)	-0.003 (0.02)	0.56
Central Cartilage [mean, (SD)]			
Pre-intervention	0.15 (0.04)	0.13 (0.04)	0.06
Post-intervention	0.15 (0.04)	0.12 (0.04)	0.03[a]
Mean change	0.002 (0.02)	-0.001 (0.02)	0.27
Lateral Cartilage [mean, (SD)]			
Pre-intervention	0.15 (0.13)	0.12 (0.03)	0.15
Post-intervention	0.15 (0.13)	0.11 (0.03)	0.54
Mean change	0.004 (0.02)	0.0004 (0.003)	0.50

[a] significant

Table 13. Baseline and post-intervention sonographic assessment of femoro-tibial articular cartilage characteristics

	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)	0.85

Post-intervention	2.66 (0.69)	2.82 (0.72)	0.66
Mean change	-0.23 (0.73)	-0.10 (0.57)	0.93
Central Cartilage [mean, (SD)]			
Pre-intervention	2.7 (0.65)	2.86 (0.52)	0.39
Post-intervention	2.55 (0.71)	2.82 (0.7)	0.05[a]
Mean change	-0.21 (0.60)	-0.03 (0.51)	0.15
Lateral Cartilage [mean, (SD)]			
Pre-intervention	2.76 (0.53)	2.89 (0.42)	0.24
Post-intervention	2.47 (0.67)	2.82 (0.6)	0.01[a]
Mean change	-0.28 (0.55)	-0.07 (0.60)	0.03[a]
Abrasion			
Medial Cartilage [mean, (SD)]			
Pre-intervention	1.92 (1.35)	1.93 (1.84)	0.91
Post-intervention	1.95 (1.24)	1.78 (1.81)	0.49
Mean change	0.02 (0.56)	-0.14 (0.59)	0.27
Central Cartilage [mean, (SD)]			
Pre-intervention	1.50 (1.21)	1.21 (1.37)	0.26
Post-intervention	1.50 (1.06)	1.10 (1.31)	0.09
Mean change	0.00 (0.69)	-0.10 (1.10)	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 (1.44)	0.18
Mean change	0.02 (0.84)	-0.03 (0.33)	0.56

[a] 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 (1.e. exercise) on pain score, functional status, articular cartilage characteristics and soft tissue changes using sonography.

Pain and WOMAC scores in both of our treatment groups improved but did not reach statistical significance. The studies of Moskowitz (2000) and McAlindon et al. (2011) also showed similar results. 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. 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. On the other hand, the incongruity of our findings with that of Benito-Ruiz et al. (2009) and Bernardo and Azarcon (2012) may be attributed to the difference in our 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 pain and WOMAC scores of our participants. However, with a subgroup analysis of participants who were not compliant to exercise showed similar results to the study of Benito-Ruiz et al (2009) and

Bernardo and Azarcon (2012) which showed that collagen hydrolysate could significantly decrease pain in knee osteoarthritis.

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 grade 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. In light of these 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 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 may include balancing of participants in terms of occupation and OA severity and recruitment of a larger sample size.

CONCLUSION

Our study showed that collagen hydrolysate in addition to exercise decreased pain, improved overall functional status and produced intraarticular and periarticular structural modifications (i.e. improvement of cartilage abrasion grade and reduction of lateral meniscal protrusion) in patients with knee osteoarthritis.

In the subgroup analysis of participants who were not compliant with the regular exercise, intake of collagen hydrolysate could significantly lower pain VAS score with improvement in the structure of the articular cartilage with regards to its thickness and clarity.

References

1. Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K. et al.(1986). Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis and Rheumatism, 29*, 1039-1049.
2. American College of Rheumatology. (2015*). Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*. Retrieved on January 19, 2016, from http://www.rheumatology.org/I-Am-A/ Rheumatologist/Research/Clinician-Researchers/Western-Ontario-McMaster-Universities-Osteoarthritis-Index-WOMAC#sthash. h8ZaNSEm.zQMPEzWg.dpuf
3. American Geriatrics Society Panel on Exercise and Osteoarthritis. (2001). Exercise prescription for older adults with osteoarthritis pain: Consensus practice recommendations. *Journal of the American Geriatrics Society*, *49 (6)*, 808 – 823.
4. Ameye, LG and Chee, WS.(2006).Osteoarthritis and nutrition. From nutraceuticals to functional foods: A systematic review of the scientific evidence. *Arthritis Research & Therapy*, *8*. Retrieved on January 19, 2016, from http://arthritis-research.com/ content/8/4/R127
5. Bello, AE and Oesser, S. (2006). Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: A review of the literature. *Current Medical Research and Opinion, 22 (11),* 2221-2232. doi: 10.1185/030079906X148373
6. Benito-Ruiz, P., Camacho-Zambrano, MM., Carrillo-Arcentales, JN., Mestanza-Peralta, MA., Vallejo-Flores, CA., Vargas-Lopez, SV. et al. (2009).A randomized controlled trial on the efficacy

and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. *International Journal of Food Sciences and Nutrition, 60 (S2)*, 99-113. doi: 10.1080/09637480802498820

7. Bernardo, MLR and Azarcon, AC. (2012) A randomized controlled trial on the effects of oral collagen treatment on the medial joint space and functional outcome among Veterans Memorial Medical Center patients diagnosed with osteoarthritis of the knee. *PARM Proceedings*, *4*, 1 – 8.
8. Bernardo, MMN., Gonzalez-Suarez, CB., Tan-Sales, BGK., Aycardo, SM., Chan, RY. and Tan-Ong, M.(2015). Development of musculoskeletal ultrasound protocol for the assessment of knee osteoarthritis. *PARM Proceedings, 7 (1),* 13-27.
9. Berthiaume, MJ., Raynauld, JP., Martel-Pelletier, JM., Labonte, F., Beaudoin, G., Bloch, DA. et al.(2005). Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. *Annals of the Rheumatic Diseases, 64*, 556 – 563. doi: 10.1136/ard.2004.023796
10. Bruyère, O., Zegels, B., Leonoria, L., Rabendaa, V., Janssena, A., Bourgesb, C. et al.(2012). Effect of collagen hydrolysate in articular pain: A 6-month randomized, double-blind, placebo controlled study. *Complementary Therapies in Medicine,* 1-7*.* doi:10.1016/j.ctim.2011.12.007
11. Crowley, DC., Lau, FC., Sharma, P., Evans, M., Guthrie, N., Bagchi, M. et al.(2009). Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: A clinical trial. *International Journal of Medical Sciences, 6(6),* 312-321.Retrieved on March 23, 2012, from http://www.medsci.org
12. Cua, RCA., Malvar, AKG., Gonzalez-Suarez, CB., Bernardo, MMN., Feliciano, DDS., Delos Reyes, F. et al.(2016). *Correlation of Sonographic Longitudinal-SagittalTechnique and Transverse-Axial Technique of Articular Cartilage Assessment in Patients with Knee Osteoarthritis.* Manuscript in preparation.
13. De Silva, V., El-Metwally, A., Ernst, E., Lewith, G. and Macfarlane, GJ. (2011). Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: A systematic review. *Rheumatology, 50*, 911-920. doi:10.1093/rheumatology/keq379
14. Fantilanan-Soldevilla, H., Gerona, JG., Cabasan, GA., Ngo, JD., Uy, EA., Tolin, MC, et al. (2009). Prevalence and demographic profile of rheumatic diseases at the University of Santo Tomas: Census report January to December 2008. *Philippine Journal of Internal Medicine, 47* (Sept.-Oct., 2009), 195-201.

15. Fransen, M., Bridgett, L., March, L., Hoy, D., Penserga, E., and Brooks, P. (2011). The epidemiology of osteoarthritis in Asia. *International Journal of Rheumatic Diseases*, *14*, 113–121. doi: 10.1111/j.1756-185X.2011.01608.x
16. Gregory, PJ and Fellner, C.(2014). Dietary supplements as disease-modifying treatments in osteoarthritis: A critical appraisal. *Pharmacology & Therapeutics*, 39 (6), 436-452.
17. Halpern, B., Chaudhury, S., Rodeo, SA., Hayter, C., Bogner, E., Potter, HG. et al. (2013).Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis. *Clinical Journal of Sport Medicine, 23(3),* 238-239.doi: 10.1097/JSM.0b013e31827c3846
18. Henrotin, Y, Lambert. C., Couchourel, D., Ripoll, C. and Chiotelli, E.(2011). Nutraceuticals: do they represent a new era in the management of osteoarthritis? A narrative review from the lessons taken with five products.*Osteoarthritis and Cartilage 19*. 1-21. doi: 10.1016/j.joca.2010.10.017
19. Hochberg, M., Altman, RD., April, KT., Benkhalti, M., Guyatt, G., McGowan, J. et al. (2012). Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research, 64, (4)*, 465–474. doi: 10.1002/acr.21596
20. Hunter, DJ., McDougall, JJ., and Keefe, FJ. (2008). The symptoms of OA and the genesis of pain. *Rheumatic Disease Clinics of North America, 34(3)*, 623–643. doi:10.1016/j.rdc.2008.05.004.
21. Hunter, DJ., Zhang, YQ., Niu, JB., Tu, X., Amin, S., Clancy, M. et al.(2006).The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. *Arthritis & Rheumatism, 54 (3)*, 795–801. doi: 10.1002/art.21724
22. Iagnocco, A. (2010). Imaging the joint in osteoarthritis: a place for ultrasound? *Best Practice & Research Clinical Rheumatology, 24*, 27–38.doi: 10.1016/j.berh.2009.08. 012
23. Ikeuchi, M., Izumi, M., Aso, K., Sugimura, N. and Tani, T. (2013). Clinical characteristics of pain originating from intra-articular structures of the knee joint in patients with medial knee osteoarthritis. *SpringerPlus*, *2,* 628*.* doi: 10.1186/2193-1801-2-628. Retrieved on January 19, 2016, from http://www.springerplus.com/ content/2/1/628
24. Jordan, KM., Arden, NK., Doherty, M., Bannwarth, B., Bijlsma, JWJ., Dieppe, P. et al. (2003). EULAR recommendations 2003: An evidence-based approach to the management of knee osteoarthritis: Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the Rheumatic Diseases, 62*, 1145–1155. doi: 10.1136/ard.2003.011742

25. Keen, HI., Wakefield, RJ. and Conaghan, PG. (2009). A systematic review of ultrasonography in osteoarthritis. *Annals of the Rheumatic Diseases, 68*, 611–619. doi:10.1136/ard.2008.102434
26. Kumar, S., Sugihara, F., Suzuki, S., Inoue, N. and Venkateswarathirukumarac, S.(2014).A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. *Journal of the Science of Food and Agriculture*. doi: 10.1002/jsfa.6752. Retrieved on January 19, 2016, from Wiley Online Library database
27. McAlindon, TE., Nuite, M., Krishnan, N., Ruthazer, R., Price, LL., Burstein, D. et al.(2011). Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: A pilot randomized controlled trial. *Osteoarthritis and Cartilage, 19,* 399-405. doi:10.1016/j.joca.2011.01.001
28. Mercado, VF., Gonzalez-Suarez, CB., Regino, JM., Aguinaldo, JB., Yu, MJ., and Oquiñena, MTI.(2013). *Videotape instruction vs brochure on the effectiveness of unsupervised home exercise program in patients with knee osteoarthritis.* Manuscript in preparation, University of Santo Tomas Hospital, Manila, Philippines.
29. Moskowitz, R.(2000). Role of collagen hydrolysate in bone and joint disease. *Seminars on Arthritis and Rheumatism, 30,* 87-99. doi:10.1053/sarh.2000.9622
30. Naredo, E., Cabero, F., Palop, MJ., Collado, P., Cruz, A., and Crespo M.(2005). Ultrasonographic findings in knee osteoarthritis: A comparative study with clinical and radiographic assessment. *Osteoarthritis and Cartilage, 13,* 568 – 574. doi:10.1016/j.joca.2005.02.008
31. Pagare, V., Buxton, S. and Thomas, E. (Eds.).(2016). *Visual Analogue Scale.* Retrieved on January 19, 2016, from http://www.physio-pedia.com/Visual_Analogue_Scale #References
32. Tarhan, S., Unlu, Z. and Goktan, C.(2003). Magnetic resonance imaging and ultrasonographic evaluation of the patients with knee osteoarthritis: a comparative study. *Clinical Rheumatology, 22*, 181–188. doi: 10.1007/s10067-002-0694-x
33. The Philippine Star. (2010). *Delaying the progression of osteoarthritis.* Retrieved January 19, 2016, from http://www.philstar.com:8080/science-and-technology/566128/delaying-progression-osteoarthritis
34. The Royal Australian College of General Practitioners. (2009, July). *Guideline for the non-surgical management of hip and knee osteoarthritis*. Victoria, Australia: The Royal Australian College of General Practitioners College House.

35. Trojian, TH., Concoff, AL., Joy, SM., Hatzenbuehler, JR., Saulsberry, WJ., and Coleman, CI. (2016) AMSMM scientific statement concerning viscosupplementation injections for knee osteoarthritis: Importance for individual patient outcomes. *British Journal of Sports Medicine, 50*, 84 – 92. doi:10.1136/bjsports-2015-095683
36. Vista, E. and Lau, C. (2011). What about supplements for osteoarthritis? A critical and evidenced-based review. *International Journal of Rheumatic Diseases, 14,* 152–158.
37. World Health Organization. (2012). Years of healthy life lost due to disability (YLDs) in the Western Pacific Region (Lower to Middle Income). Retrieved on January 19, 2016, from http://apps.who.int/gho/data/ view.main.YLDNUMREG7WPRV?lang=en
38. World Health Organization. (n.d.). *Chronic rheumatic conditions*. Retrieved January 19, 2016, from http://www.who.int/chp/topics/rheumatic/ en/
39. Zhang, W, Moskowitz, RW., Nuki, G., Abramson, S., Altman, RD., Arden, N., et al. (2008).OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and Cartilage 16*, 137-162.doi:10.1016/ j.joca.2007.12.013
40. Živanović, S., Rackov, LP. and Mijušković, Z.(2012).Biomarkers and Ultrasound in the Knee Osteoarthrosis Diagnosis. In Rothschild, BM. (Ed.), *Principles of Osteoarthritis - Its Definition, Character, Derivation and Modality-Related Recognition* (chap. 5). Retrieved on January 19, 2016, from http://www.intechopen.com/books/principles-of-osteoarthritis-its-definition-character-derivation-and-modalityrelated-recognition/biomarkers-and-ultrasound-in-the-knee-osteoarthrosis-diagnosis

Appendix A

Standard Treatment Exercise for Knee Osteoarthritis (Brochure)

- *unang parte ng ehersisyo kung saan inuunat ang mga importanteng muscle at maiwasan ang injury habang nagehersisyo.*
2. Exercise Proper – main exercise program for the following muscles:
- *ang pinakamalaking parte ng ehersisyo.*
a. quadriceps (front part of the thigh)
quadriceps (harap ng parte ng hita)
b. hip abductors (side part of the thigh)
hip abductors (gilid ng hita)
c. hamstring (back part of the thigh)
hamstrings (likod ng parte ng hita)
3. Cool down – last part of the exercise to relax the muscle
- *huling parte ng ehersisyo kung saan ang musle ay kailangan magrelaks.*

Exercise

Stretching Exercise (Warm up and Cool down)

Exercise #1 Calfstretching
1. Face a wall and stand 12 inches away from it.
Humarap ka sa pader and tumayo kay ng may labingdalawang pulgada ang layo sa pader.
2. Extend one leg behind you, keeping both feet flat on the floor and your rear knee straight.
Ihakbang ang kanang paa sa harapan at patalikod naman ang kaliwang paa.
3. Lean toward the wall until you feel tension in the calf muscle of the extended leg. (you can put your arms on the wall for support.)
Itulak ang dingding gamit ang mga kamay at pakiramdaman ang pag-unat ng kalamnan sa paa.
4. Hold the stretch for 30 seconds, then relax
Magbilang ng 30 segundo habang nakaposisyon at pagkatapos ay magpahinga.
5. Repeat 3 times on each leg
Ulitin ng 3 beses sa bawat binti

Exercise #2 Hamstring Stretching
1. Lie on your back with both knees bent so that the feet are resting comfortably in a flat position.
Humiga at ibaluktot ang dalawang tuhod na nakalapat ang dalawang paa sa kama.
2. Raise the one leg with knee in full straight using a towel around the foot.
Itaas ang isang paa na ang tuhod ay nakadiretso gamit ang tuwalya na nakapalupot sa paa.
3. Hold the stretch for 30 seconds, and then relax
Panatilihin ang pagkakabanat sa loob ng 30 segundo, pagkaraan ay ipahinga.
4. Repeat 3 times on each leg
Ulitin ng 3 beses sa bawat binti

Exercise#3 Quadriceps Stretching
1. Lie on your side with one hand supporting your head.
Humiga ng nakatagilid habang ang isang kamay ay nakasuporta sa ulo.
2. Bend your upper leg back and grab your ankle with your hand.
Ibaluktot ang binti na nasa ibabaw and hilahin ang paa gamit ang isa mong kamay.
3. Stretch your leg back. Be sure your calf is lined up with your thigh so that your knee is not twisted.
Banatin ang hita patalikod. Siguraduhin ang iyong binti ay paniay sa iyong mga hita upang ang iyong mga tuhod ay hindi nakabaluktot.
4. Hold the stretch for 30 seconds, then relax
Panatilihin ang pagkakabanat sa loob ng 30 segundo, pagkaraan ay ipahinga.
5. Repeat 3 times on each leg
Ulitin ng 3 beses sa bawat binti.

owards your knee.
galaw ng paa papunta

relax
syon ng sampung

n a 45°, and your foot

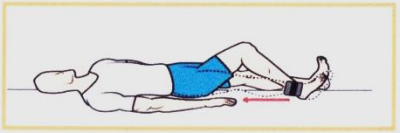
45°,at ang isang paa

n the back of your

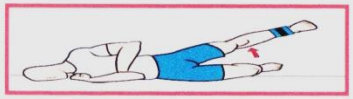
sa likod sa likod ng
sa kama.
relax
syon ng sampung

ang binti.

Exercise#1 Quadriceps
1. Lie on your back .
Humiga na ang likod ay nakasandal sa higaan.
2. Bend the left knee at 90° angle, keeping foot flat on floor.
Ibaluktot ang kaliwang tuhod ng 90°,at ang isang paa ay nakalapat sa kama.
3. Keeping the right leg straight lift it until right foot is the height of the left knee.
Panatilihin ang kanang binti na tuwid, iangat ito hanggang sa kanang paa ay ang taas ng kaliwang tuhod.
4. Do it for 20 times, then relax.
Gawin ito ng 20 beses, pagkatapos ay mag-relaks.
5. Repeat on the other leg.
Ulitin sa kabilang binti.



Exercise #2 Hamstring
1. Lie on your back.
Humiga na ang likod ay nakasandal sa higaan.
2. Bend both knees at 30° angle.
Ibaluktot ang dalawng tuhod ng may 30 ° anggulo
3. Straighten one leg.
Ituwid ang isang binti.
4. Do it for 20 times, then relax.
Gawin ito ng 20 beses, pagkatapos ay mag-relaks.
5. Repeat on the on the other leg.
Ulitin sa kabilang binti.



Exercise #3 Abductors
1. Lie on your right side, shoulder and hips aligned.
Humiga ng nakatagilid sa kanan, panatilihin ang balikat at hita ay pantay.
2. Bend the right leg(leg on floor) to 90°
Ibaluktot ang kanang binti ng 90°.
3. Slowly raise the left leg about 18 inches
Dahan-dahan itaas abg kaliwang binti na may 18 pulgada ang taas.
4. Do it for 20 times, then relax.
Gawin ito ng 20 beses, pagkatapos ay mag-relaks
5. Repeat on the other leg.
Ulitin sa kabilang binti.

Exercise # 4 Adductors
1. Lie on your back.
Humiga na ang likod ay nakasandal sa higaan.
2. Both legs straight, place a rolled towel in between the knees and slowly take your leg inwards tightening the muscles in the inner thigh.
Parehong binti ay tuwid, maglagay ng isang pirasong tuwalya sa pagitan ng mga tuhod at dahan-dahan dalhin ang mga binti papasok.
3. Do it for 20 times, then relax.
Gawin ito ng 20 beses, pagkatapos ay mag-relaks.

References (Sanggunian):
1. Deyle G., Allison S, Matekel R. (2005) Physical Therapy Treatment Effectiveness for Osteoarthritis of the knee: Randomized Comparison of Supervised Clinical Exercise and Manual Therapy Procedure versus a Home Exercise Program. Physical Therapy, Vol 85.
2. Ettinger B.A, Mentes J (1997) A Randomized Trial Comparing Aerobic Exercise and Resistance with a Health Education Program in Older Adults with knee osteoarthritis. Journal of American Medical Association Vol 277.
3. Fransen M, Mc Connell S (2009). Exercise for Osteoarthritis of the knee (Review) The Cochrane Collaboration.
4. Miller ME, Rejeski WJ (2000). Physical Activity, functional limitations and disability in older adults. Journal of American Geriatic Society 48;1264-72.
5. Rogind H., Nielsen B., Jensen B. (1998) The Effects of a Physical Training Program on patients with Osteoarthritis of the knees. Archives Physical Medicine Rehabilitation Vol 79.

Appendix B

Musculoskeletal Ultrasound Protocol for the Knee (Bernardo et al. 2014)

1. ARTICULAR CARTILAGE
    a. Transverse anterior view
        i. Patient supine with knee fully flexed
        ii. Position transducer immediately above the patella, perpendicular to the long axis of the extremity with the depth and focal zone optimised to visualize the trochlear articular cartilage on the medial trochlea, trochlear notch and lateral trochlea on the same axial image.
        iii. Divide the image into three, zooming in on the image to enhance visualization.
        iv. Measure the narrowest cartilage thickness in three locations: medial, lateral and central/trochlear notch. Each measurement will be done three times.
        v. Evaluate the clarity and grade of the femoral hyaline cartilage
    b. Longitudinal sagittal view
        i. Knee flexed at 90 degrees
        ii. Position transducer longitudinally close to the medial/lateral border of the patella as possible
        iii. Measure the narrowest portion of the articular cartilage at the medial longitudinal and lateral longitudinal planes. Each measurement will be done 3 times.
        iv. Evaluate the clarity and grade of the femoral hyaline cartilage
2. SUPRAPATELLAR AND INFRAPATELLAR RECESS
    a. Suprapatellar recess
        i. Knee flexed 45 degrees
        ii. Scan for effusion and/or synovitis. If with effusion, perform compression test and measure largest anteroposterior diameter 3 times.
    b. Infrapatellar recess
        i. Knee flexed 30 degrees

        ii. Scan for effusion and/or synovitis over the superficial and deep infrapatellar areas. If with effusion, perform compression test and measure largest anteroposterior diameter 3 times.
    c. Evaluate the degree of synovitis
    d. Evaluate the power Doppler signal of the synovial membrane in relation to the surrounding tissue of the quadriceps muscle by placing the transducer head on the suprapatellar and infrapatellar recesses for 10 secs.
3. MEDIAL AND LATERAL MENISCUS
    a. Knee flexed at 10 degrees
    b. Internal rotation and mild varus stress to examine the lateral meniscus; external rotation and mild valgus stress to examine the medial meniscus.
    c. Measure meniscal protrusion 3 times.
4. PES ANSERINE BURSITIS
    a. Knee fully extended
    b. If a bursitis is found, measure the largest anteroposterior diameter 3 times and evaluate power Doppler signal
5. BAKER'S CYST
    a. Patient in prone position.
    b. Position transducer head at the level of the midcalf in the transverse plane and visualize the medial gastrocnemius, lateral gastrocnemius and soleus muscles.
    c. Continue scanning superiorly to the level of the knee joint with visualization of the semimembranosus tendon medial to the gastrocnemius tendon. If there is a Baker's cyst found, measure the widest transverse diameter in short axis 3 times.