International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2024; 12(3): 26-31
Received: 24-02-2024
Accepted: 30-03-202

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A randomized, double-blind, placebo-controlled study of proteoglycan and phosphatidylserine tablets for the management of joint pain and mobility

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DOI: https://doi.org/10.22271/flora.2024.v12.i3a.933

Abstract
This randomized, double-blind, placebo-controlled study evaluated daily oral administration of proteoglycan and phosphatidylserine (PG+PS) for 30 days on osteoarthritis symptoms in adults with moderate to severe knee and hip pain. The study was conducted in Denmark from October 2023 to December 2023. A total of 74 participants (37 female, 37 male, mean age 61 years, mean body mass index 24 kg/m^2) were randomized to take 1 table/day placebo (N=34) or 12.5 mg proteoglycan + 60 mg phosphatidylserine (PG+PS, N=40) orally for 30 days. Physical performance was evaluated by stair climb test (SCT) and self-paced walk test (SPWT). Joint pain was evaluated by visual analogue scale (VAS). Statistically significant improvements were observed in the SCT, SPWT, and VAS measure of joint pain for PG+PS vs placebo (all p<.05). Daily administration of PG+PS may be useful in the management of joint pain and mobility in adults with osteoarthritis.

Keywords: Phosphatidylserine, proteoglycan, knee and hip pain, healthy joint mobility, endurance

1. Introduction
Osteoarthritis is a degenerative joint condition that is characterized by deterioration of articular cartilage [1-3]. Individuals with osteoarthritis experience joint dysfunction, pain, and reduced mobility. Approximately 600 million people worldwide were estimated to be living with osteoarthritis in 2020 [4]. Osteoarthritis is the leading cause of chronic pain and disability globally and is responsible for increased healthcare burden and reduced quality of life [1-3].
Articular cartilage is composed of a dense extracellular matrix (ECM) that is primarily made up of water, collagen, and proteoglycans (PGs) [5]. Loss of PG is associated with the progression of osteoarthritis [6], while osteoarthritis treatment is associated with increased PG as well as improvements in joint pain and function [7, 8]. The beneficial effects of PG administration include reduced inflammation as well as reduced type II collagen degradation and enhanced type II collagen synthesis [9, 10]. In animals, oral administration of PG reduces arthritis [10]. Administration of PGs in humans has been shown to have a beneficial effect on mobility, pain, and joint health [5, 9, 11].
Phosphatidylserine (PS) is a glycerophospholipid involved in numerous biological processes including enzyme activation, apoptosis, neurotransmission, and synaptic refinement [12,13]. PS is present in high amounts in soy and sunflower lecithin and oral administration of PS is well tolerated. In humans, oral administration of PS has been shown to have positive effects on cognition, mood, and stress, particularly in elderly individuals [12, 14-19].
We hypothesized that combined daily oral administration of PG and PS would have a positive impact on joint health as well as mood and motivation, resulting in improved mobility and reduced joint pain. This study was designed to evaluate if combined administration of PG and PS for 30 days would improve measures of physical performance and joint pain in adults with moderate to severe knee and hip pain.

2. Materials and Methods
2.1 Study Design and Setting
This randomized, double-blind, placebo-controlled study evaluated once-daily administration of PG+PS for 30 days on physical performance and joint pain in adults with moderate to severe knee and hip pain.
The study was conducted from October 2023 to December 2023 at Vesterbronx Gym (Copenhagen, Denmark).

All experiments were examined and approved by the appropriate committee represented by D. M.Sc., MD Eli Kassis (University of Copenhagen, Gentofte, Denmark) and were performed in accordance with ethical requirements and current standards as indicated by European Good Clinical Practice Guidelines and the 1964 Declaration of Helsinki. Informed and written consent was obtained from all participants prior to participation in the study.

2.2 Participants

Participants were recruited from health clinics and sports centers in Copenhagen and were evaluated for eligibility by a specially trained nurse and a physiotherapist. Generally healthy male and female (not pregnant or breastfeeding) adults between the ages of 30 to 75 (inclusive) with BMI<30 kg/m^2 and moderate to severe knee and hip pain were eligible to participate. Participants were not eligible to participate in the study if they used any of the following supplements withing the prior 90 days: chondroitin, glucosamine, methylsulfonylmethane (MSM), Boswellia, turmeric, type II collagen, or PS. Participants were also excluded from participating if they had a history of any medical or arthritic conditions that could interfere with evaluation of the index knee joint including fibromyalgia, rheumatoid arthritis, or other inflammatory arthropathies affecting the knee joint, arthroscopic or open surgery to the knee within the previous 6 months, or knee injections with corticosteroids within the previous 30 days or hyaluronic acid within the previous 3 months.

2.3 Intervention

Participants were randomized 1:1 to take 1 tablet per day of placebo or 1 tablet/day of 12.5 mg proteoglycan plus 60 mg phosphatidylserine (PG+PS). Tablets were manufactured by John M. Petersen, M.Sc. (Almega A/S, Ringsted, Denmark). Participants were randomly assigned to treatment groups by a recruiting nurse and were provided with coded containers containing 30 tablets of either PG+PS or matching placebo. The sealed list of container numbers and corresponding contents was kept by an independent auditor until the end of the study. The participants, recruiting nurse, and investigators remained blinded throughout the study. Participants were instructed to take 1 tablet every morning for the 30-day study. Participants could take 200 mg ibuprofen up to 3 times a day during the study. All participants were provided with daily reminders of study procedures via SMS text or virtual meetings.

2.4 Outcomes and Assessments

Study outcomes include the change from baseline to Day 30 in the number of stairs climbed in the stair climb test (SCT), the distance walked in the self-paced walk test (SPWT), and the change from baseline to Day 30 in joint pain. Assessments were conducted at baseline (Day 0) and on Days 4, 7, 14, and 30.

The VAS Score (range 0-10) was a measure of joint pain and was obtained at the beginning of each assessment prior to completing physical performance tests. Participants rated their joint pain by placing their finger on a blank 100-mm visual analog scale (VAS), with 0 defined as no pain, and 100 defined as worst possible pain. The blank ruler was then compared with a 100-mm lined ruler and divided by 10.

Physical performance was assessed with the SCT and the SPWT. The SCT assesses the ability to ascend a flight of stairs, as well as lower extremity strength, power, and balance [20]. The SCT was conducted using a Stairmaster (Life Fitness, Rosemont, IL, USA). Participants could adjust the level and speed as needed during the 5-minute test. The number of floors achieved over a 5-minute test period was recorded. The SPWT assesses the distance participants can walk over a short period of time [20]. The SPWT was conducted using a treadmill (Life Fitness, Rosemont, IL, USA) and participants could adjust the speed as needed. Participants were instructed to walk quickly and safely without overexerting themselves and the distance covered (in kilometers) over a 5-minute test period was recorded.

Participants were asked to report any potential side/adverse effects at each assessment. Participants could also contact study personnel at any time for questions about the study or to report adverse events. Compliance was assessed on Days 7, 14, and 30 by counting the number of tablets.

2.5 Data Analysis

Continuous variables were compared between the groups using the student t-test or its nonparametric equivalent Mann-Whitney U test. A 2-tailed p value of 0.05 was considered statistically significant. A value of $p<0.05$ was considered statistically significant. Continuous variables were summarized using descriptive statistics. Statistical analyses were conducted using RStudio (Version 4.1) and jamovi (Version 2.3).

3. Results & Discussion

3.1 Study Population

A total of 90 individuals were assessed for eligibility and 82 participants were allocated to treatment groups (Fig. 1). Overall, 74 participants completed the 30-day study and were included in the analysis. Of these, 37 (50%) were male. The mean (SD) age was 61.3 (6.8) years and BMI was 24.1 (1.2) kg/m^2. Age and BMI were similar across treatment groups.

No adverse events or tolerability issues were reported in any treatment group during the study.

3.2 Physical Performance

A statistically significant improvement from baseline to Day 30 was observed for PG+PS vs placebo in the SCT and the SPWT (both $p<.001$, Table 1, Fig. 2). Notably, a statistically significant difference between PG+PS and placebo was observed at the earliest timepoint assessed (Day 4) and persisted for all subsequent assessments through Day 30 (Fig. 2).

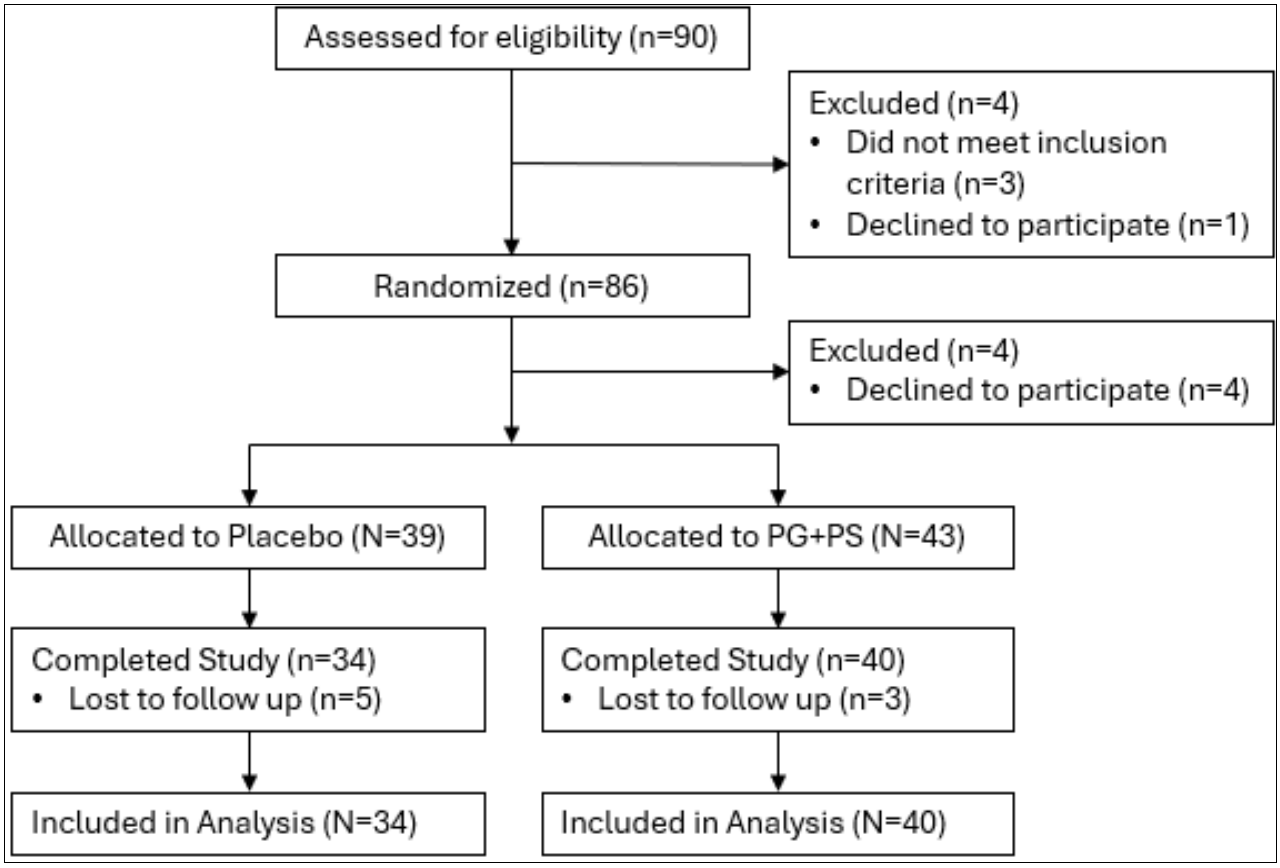

Fig 1: Study Population

Table 1: Efficacy Measures: Change from Baseline to Day 30

	Placebo (N=34)	PG+PS (N=40)	*P* value
SCT			
Baseline	17.7 (1.6)	18.7 (3.3)	*p*<.001
Day 30	22.2 (2.1)	27.2 (5.8)	
Absolute Change	4.5 (1.3)	8.5 (2.9)	
Percentage Change	26 (8)	45 (10)	
SPWT			
Baseline	0.36 (0.05)	0.40 (0.09)	*p*<.001
Day 30	0.54 (0.07)	0.64 (0.13)	
Absolute Change	0.17 (0.01)	0.23 (0.01)	
Percentage Change	48 (13)	60 (12)	
VAS Score			
Baseline	4.2 (0.7)	5.0 (1.3)	*p*<.001
Day 30	3.4 (0.7)	3.3 (0.9)	
Absolute Change	-0.9 (0.5)	-1.7 (1.1)	
Percentage Change	20 (12)	32 (18)	

SCT=Stair Climb test. Numbers indicate floors completed during the 5-minute test. SPWT=Self-Paced Walk Test. Numbers indicate distance in km covered during the 5-minute test. VAS Score indicates level of joint pain on a scale of 0-10 where 0=no pain. Baseline and Day 30 data are mean and standard deviation (SD). Change data are mean and standard error of the mean (SEM) for the change from baseline to Day 30. P values are shown for comparison of change data for PG+PS vs Placebo.

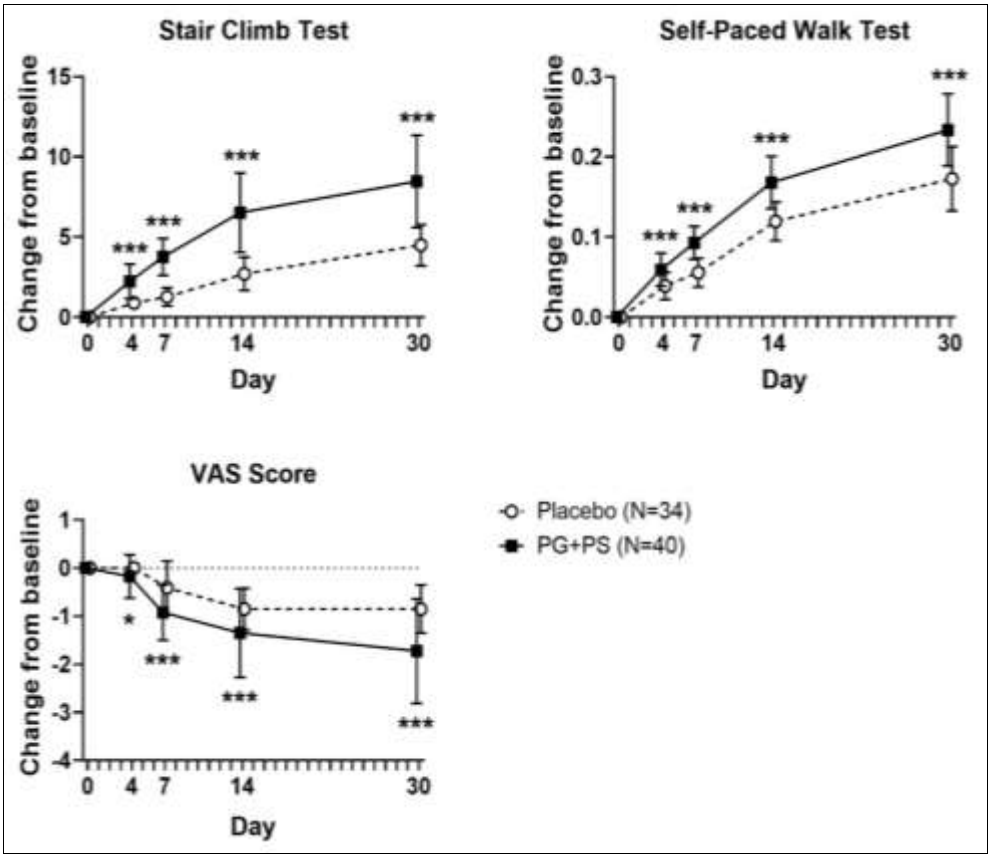

Fig 2: Change from Baseline in Efficacy Measures

Stair Climb test numbers indicate floors completed during the 5-minute test. Self-Paced Walk Test. numbers indicate distance in km covered during the 5-minute test. VAS Score indicates level of joint pain on a scale of 0-10 where 0=no pain. Data are mean and standard deviation (SD) for the change from baseline (Day 0) for each group (N=74). * p<.05, *** p<0.001 for comparison of Placebo vs PG+PS.

In the PG+PS group, the percent change from baseline to Day 30 in the SCT and SPWT was 45% and 60%, respectively (Table 1). The SCT and SPWT are reliable measures of knee and hip osteoarthritis and are generally responsive to improvements in physical performance [20]. Although an MCID for both measures has yet to be determined, these results are consistent with another study (*manuscript in preparation*). The consistent results for the 2 different physical performance tests strengthen the validity of the current findings. The SCT and SPWT are brief measures of physical performance that would not be expected to improve with limited repeated assessments (eg, performance would not improve due to training) [20]. However, any effects of repeated testing on performance would be expected to also be observed in the placebo group. These results indicate that the combination of PG+PS produces beneficial effects on multiple relevant measures of physical performance.

3.3 Joint Pain

A statistically significant improvement from baseline to Day 30 was observed for PG+PS vs placebo was observed for the VAS Score (both p<.001, Table 1, Fig. 2). Additionally, a statistically significant difference for PG+PS vs placebo was observed at the earliest timepoint measured (Day 4), and persisted for the duration of the study (Fig. 2).

In this study, daily oral administration of PG+PS resulted in an improvement from baseline to Day 30 of 32% in the VAS Score measure of joint pain. VAS measures of pain on a 100-mm scale such as the one used in this study are commonly used for assessing pain and the change in pain [21]. The minimal clinically important difference (MCID) for VAS measures of pain on a 100-mm scale such as the one used in this study have been shown to range between 11 to 14 mm and do not depend on the severity of the pain experienced at baseline [21]. Thus, the mean change from baseline to Day 30 in VAS Score in the PG+PS group of 1.6 corresponds to a change of 16 on a 100-mm scale and reflects a clinically meaningful improvement in joint pain.

4. Conclusions

We observed improvements in multiples measures of physical performance and joint pain in participants with moderate to severe knee and hip pain who received PG+PS vs those who received placebo. Moreover, improvements were observed within 1 week of administration. The results of this study are consistent with another study in which PG+PS resulted in statistically significant improvements in physical performance and joint pain vs placebo (*manuscript in preparation*). Furthermore, that study included another comparator group that received PG alone and statistically significant differences were observed between PG+PS vs PG alone, indicating that PS provides additional benefit.

The mechanism for the improvement in physical performance tests and joint pain in individuals in the PG+PS group is likely due to a combined effect of PG and PS. The improvements in both physical performance and joint pain occurred remarkably early (within the first week of the study). We expect that PS may have improved mood and motivation and may also have had anti-inflammatory effects that led to increased performance on the SCT and SPWT and reduced joint pain [12-15, 18, 22-24]. These effects of PS, combined with the beneficial effects of PG on joint health [5, 9, 11], may have led to the rapid improvements observed here.

Osteoarthritis treatments range from over-the-counter pain relievers to surgical interventions, eg, steroid injections and joint replacements. Supplements commonly used in management of osteoarthritis symptoms include glucosamine and chondroitin, which have demonstrated mixed results in studies of adults with osteoarthritis [8, 25, 26]. Larger longer studies of combined administration of PG+PS in this population would provide insight into the long-term benefits of this novel combination on osteoarthritis and how they compare with other treatments.

Study strengths include the randomized, placebo-controlled design and participants were blinded to the treatment. These qualities strengthen the external validity of our findings. Potential limitations of the study include the relatively small number of participants, the single study site, and the lack of a PS and PG comparator groups. Larger longer studies in a more diverse population would benefit our understanding of the impact of PG+PS.

Overall, results of this study support a benefit of PG+PS on mobility and pain in adults with moderate to severe joint pain.

5. Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

6. Conflict of Interest

The authors have declared that no competing interests exist.

Funding for the study was provided by ZANDA LLC (Atlanta, GA, USA).

Special thanks to Ahmed Elaraby, MD whose statistical expertise was essential in the analysis of our study's data.

7. References

1. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, *et al*. Global, regional and national burden of Osteoarthritis 1990-2017: A systematic analysis of the Global Burden of Disease Study 2017. Annals of the Rheumatic Diseases. 2020;79(6):819-828.
2. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee Osteoarthritis in population-based studies. EClinicalMedicine. 2020;29-30:100587.
3. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. Current Opinion in Rheumatology. 2018;30(2):160-167.
4. Collaborators GBDO. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023;5(9).
5. Alcaide-Ruggiero L, Cugat R, Dominguez JM. Proteoglycans in Articular Cartilage and Their Contribution to Chondral Injury and Repair Mechanisms. International Journal of Molecular Sciences. 2023;24(13).
6. Alberton P, Dugonitsch HC, Hartmann B, Li P, Farkas Z, Saller MM, *et al*. Aggrecan Hypomorphism Compromises Articular Cartilage Biomechanical Properties and Is Associated with Increased Incidence of Spontaneous Osteoarthritis. International Journal of Molecular Sciences. 2019;20(5).
7. Marouf BH. Effect of *Resveratrol* on Serum Levels of Type II Collagen and Aggrecan in Patients with Knee Osteoarthritis: A Pilot Clinical Study. BioMed Research International. 2021;2021:3668568.
8. Henrotin Y, Marty M, Mobasheri A. What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas. 2014;78(3):184-7.
9. Tomonaga A, Takahashi T, Tanaka YT, Tsuboi M, Ito K, Nagaoka I. Evaluation of the effect of salmon nasal proteoglycan on biomarkers for cartilage metabolism in individuals with knee joint discomfort: A randomized double-blind placebo-controlled clinical study. Experimental and Therapeutic Medicine. 2017;14(1):115-126.
10. Yoshimura S, Asano K, Nakane A. Attenuation of collagen-induced arthritis in mice by salmon proteoglyc*an*. BioMed Research International. 2014;2014:406453.
11. Naraoka Y, Harada H, Katagiri M, Yamamura H, Shirasawa T. *N*-acetyl glucosamine and proteoglycan containing supplement improves the locomotor functions of subjects with knee pain. Drug Discoveries & Therapeutics. 2017;11(3):140-145.
12. Ma X, Li X, Wang W, Zhang M, Yang B, Miao Z. Phosphatidylserine, inflammation, and central nervous system diseases. Frontiers in Aging Neuroscience. 2022;14:975176.
13. Fadok VA, Bratton DL, Rose DM, Pearson A, Ezekewitz RA, Henson PM. A receptor for phosphatidylserine-specific clearance of apoptotic cells. Nature. 2000;405(6782):85-90.
14. More MI, Freitas U, Rutenberg D. Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with Alzheimer's disease and dementia. Advances in Therapy. 2014;31(12):1247-62.
15. Hellhammer J, Vogt D, Franz N, Freitas U, Rutenberg D. A soy-based phosphatidylserine/phosphatidic acid complex (PAS) normalizes the stress reactivity of hypothalamus-pituitary-adrenal-axis in chronically stressed male subjects: a randomized, placebo-controlled study. Lipids in Health and Disease. 2014;13:121.
16. Vakhapova V, Cohen T, Richter Y, Herzog Y, Kam Y, Korczyn AD. Phosphatidylserine containing omega-3 Fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. Dementia and Geriatric Cognitive Disorders. 2014;38(1-2):39-45.
17. Wells AJ, Hoffman JR, Gonzalez AM, Stout JR, Fragala MS, Mangine GT, et al. Phosphatidylserine and caffeine attenuate postexercise mood disturbance and perception of fatigue in humans. Nutrition Research. 2013;33(6):464-72.
18. Hellhammer J, Hero T, Franz N, Contreras C, Schubert M. Omega-3 fatty acids administered in phosphatidylserine improved certain aspects of high chronic stress in men. Nutrition Research. 2012;32(4):241-50.
19. Baumeister J, Barthel T, Geiss KR, Weiss M. Influence of phosphatidylserine on cognitive performance and cortical activity after induced stress. Nutritional Neuroscience. 2008;11(3):103-10.
20. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car

Task. Arthritis Care & Research (Hoboken). 2011;63 Suppl 11.
21. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal. 2001;18(3):205-7.
22. Cruz MAE, Ferreira CR, Tovani CB, de Oliveira FA, Bolean M, Caseli L, *et al*. Phosphatidylserine controls calcium phosphate nucleation and growth on lipid monolayers: A physicochemical understanding of matrix vesicle-driven biomineralization. Journal of Structural Biology. 2020;212(2):107607.
23. Hoffmann PR, Kench JA, Vondracek A, Kruk E, Daleke DL, Jordan M, *et al*. Interaction between phosphatidylserine and the phosphatidylserine receptor inhibits immune responses *in vivo*. The Journal of Immunology. 2005;174(3):1393-404.
24. Ma HM, Wu Z, Nakanishi H. Phosphatidylserine-containing liposomes suppress inflammatory bone loss by ameliorating the cytokine imbalance provoked by infiltrated macrophages. Laboratory Investigation. 2011;91(6):921-31.
25. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. The New England Journal of Medicine. 2006;354(8):795-808.
26. Hochberg MC, Martel-Pelletier J, Monfort J, Moller I, Castillo JR, Arden N, *et al*. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Annals of the Rheumatic Diseases. 2016;75(1):37-44.