e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(12); 82-87

Original Research Article

An Comparative Study to Assess the Efficacy of Undenatured Collagen Type II (NUC) and Chondroitin Sulphate (CS) in the Management of Osteoarthritis

Ashwini Gaurav[1], Nitin Kumar[2]

[1]Assistant Professor, Department of Orthopedics , Netaji Subhash Medical College & Hospital, Bihta, Patna, Bihar, India

[2] Senior Resident, Department of Orthopaedics, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

Received: 12-02-2023 Revised: 16-04-2023 / Accepted: 20-05-2023

Corresponding author: Dr Nitin Kumar

Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the efficacy of nutraceuticals in the management of osteoarthritis.

Methods: The present study was conducted in the Department of Orthopaedics for one year .100 patients were included in the study and the patients were thoroughly informed about the study protocol and those who were interested in participating signed informed consent. 100 patients were randomised to receive the allocated intervention, either Undenatured Collagen Type II (NUC) (N = 50) or chondroitin sulfate (CS) (N = 50).

Results: The two study groups were similar in terms of demographics and clinical characteristics. There were more females in both the groups as compared to male. In the study, there were more married patients as compared to unmarried. There were no significant differences in composite WOMAC and its sub-scales between the two groups at baseline. At follow-up, scores of pain decreased significantly in both groups but patients in the NUC group had significantly lower levels of pain at follow-up as compared to patients in the CS group. Stiffness and physical function were not significantly changed, but score in the composite dimension was decreased significantly only in the NUC group. Subjects in the NUC group reported a significant decrease in pain while pain remained stable for patients in the CS group. In addition, at follow up, patients in the NUC group reported significantly lower levels of pain as compared to those in the CS group.

Conclusion: The nutrition can improve the symptoms of declared OA. However, the role of nutrition in slowing down progression of the disease remains to be seen. The preliminary results of this study support the hypothesis that treatment with the newly introduced multi-compound supplement was effective, as reflected by the self-reported feeling of pain.

Keywords: knee osteoarthritis; nutraceuticals; pain relief; antioxidant

Introduction

Osteoarthritis (OA) as a degenerative chronic joint cartilage disorder is the most prevalent and principal reason for joint pain and functional impairment in the world.[1] OA is more prevalent in older adults and it will inflict incredible economic and societal charges and disturb life quality in different aspects subsequently in the future.[2] On the other hand, discomfort, pain and decreases in functional ability because of OA can consequence a greater risk of overweight/obesity, diabetes mellitus and falls and fractures.[3] Issues that chip into the development of OA consist of general factors (age, sex, overweight/obesity and nutrition) and local biomechanical factors (joint injury, physical activities and joint space).[4]

Nutraceutical supplements, such as Undenatured Collagen Type II (NUC) and chondroitin sulfate (CS) have been applied to manage OA and relieve symptoms in recent years.[5] Nutraceuticals are described as dietary supplements that comprise a condensed form of a considered bioactive ingredient, initially isolated from food, however existing in a nonfood matrix, and consumed to preserve or increase health situation in the amounts beyond those accessible from common foods.[5] Nevertheless, there is no agreement in regard to applying the term “nutraceutical” or “dietary supplement”. The “active ageing” is a principle objective of dietary supplements, as indicated by the developing sales of vitamins and minerals.[6] Dietary bioactive combinations have been revealed to be impressive in the improvement of clinical symptoms and in decreasing inflammatory indices in subjects with OA.[7] Presently 69% of subjects with

OA receive various forms of dietary supplements for their problem.[8]

Today, a cure for OA remains elusive. The management of OA is largely palliative, focusing on the alleviation of symptoms. Current recommendations for the management of OA include a combination of non pharmacological interventions (weight loss, education programs, exercise, and so on) and pharmacological treatments (paracetamol, non steroidal anti-inflammatory drugs [NSAIDs], and so on).[9] Among these pharmacological treatments, NSAIDs, despite serious adverse effects associated with their long-term use, remain among the most widely prescribed drugs for OA.[10] In this context, there is a need for safe and effective alternative treatments while the absence of any cure reinforces the importance of prevention. Such prevention and alternative treatments could come from nutrition. It is now increasingly recognised that, beyond meeting basic nutritional needs, nutrition may play a beneficial role in some diseases.[11]

The aim of the present study was to assess the efficacy of nutraceuticals in the management of osteoarthritis.

Materials and Methods

The present study was conducted in the Department of Orthopaedics, Netaji Subhash Medical College & Hospital, Bihta, Patna, Bihar, India for one year.100 patients were included in the study and the patients were thoroughly informed about the study protocol and those who were interested in participating signed informed consent. 100 patients were randomised to receive the allocated intervention, either CS (N = 50) or NUC (N = 50).

The inclusion criteria were male or female patients above the age of 35 with mono- lateral or bilateral knee OA confirmed by radiographic measurements (stage II, III or IV according to Kellgren-Lawrence, K&L), with at least moderate symptoms in the target knee that translated as intermittent or constant pain above 4 in the WOMAC pain subscale and in VAS, that were able to walk without a medical or other support device (such as a walking stick, crutches, or a kneecap). In bilateral knee OA, the target knee was determined as the knee with highest VAS pain score.

The exclusion criteria were patients undergoing physical therapy or transcutaneous electrical nerve stimulation (TENS), with rheumatoid arthritis, fibromyalgia, spinal dis- orders or any other musculoskeletal disorders that according to the physician was a bias, with a scheduled knee surgery or any other programmed surgery during the trial, those with a diagnosis of kidney or liver disease, coagulation disorders, any form of cancer, HIV infection, type I diabetes, those with unregulated type II diabetes, those using illicit substances or with a history of substance or alcohol abuse over the past 2 years (or those who consume more than 2 typical alcoholic beverages/day at present), those using corticosteroids within 2 months prior to randomisation and during the trial, those who changed their diet or supplementation 1 month prior or during the recruitment/trial, those using CS supplement or any phytochemical-rich supplement, women on oestrogen-replacement therapy, pregnant or lactating and those judged by the researcher as unable to perceive and comply with the obligations laid down in the protocol for which consent and voluntary participation was sought.

On intense pain, patients were allowed to use rescue medication, either analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), as prescribed by the study physician.

Baseline Assessment & Outcome Measures

A complete medical history with information about the demographic characteristics of the patients, habits that affected their general health (smoking, alcohol), heredity data, age at diagnosis, the cause of the onset of the disease, current medication/ supplementation and surgeries was collected.

Anthropometric measurements, such as height (cm), body weight (kg), as well as waist circumference (cm), measured with a flexible non-stretch tape halfway between the lower ribs and the iliac crest, and hip circumference (cm), measured at the level of the widest circumference over the great trochanters, for the calculation of waist-hip ratio (WHR), were obtained. Estimation of body composition (fat%, fat mass and lean mass) was performed through bioelectrical impedance analysis (BIA). Body weight was measured to the nearest 0.1 kg. Height was measured to the nearest millimeter and body mass index (BMI) was computed as weight (kg)/height (m^2).

For the assessment of pain, the validated pain VAS, a numeric scale from 0 (no pain) to 10 cm (worst pain), was used to depict the worst feeling of pain the patient had the day before the interview or in the last week. Additionally, the Greek-validated WOMAC questionnaire was also employed as its three dimensions, pain (5 items), stiffness (2 items) and functional limitations (17 items), reflect the severity of the cardinal symptoms of OA. Higher scores indicate worse symptoms.

After completing the baseline assessment, the patients were randomly assigned to one of the following arms: Undenatured Collagen Type II (NUC), or Chondroitin Sulphate (CS). Sample 1:1 randomisation was performed using an algorithm that allocated subjects to the two arms of the intervention based on their gender and age. The per os administration dosage was two capsules daily, taken approximately 20 min before meals. In order

to mitigate biases, blinding of the involved researchers, as well as the volunteers, was ensured through the identical containers and organoleptic characteristics of the capsules.

Changes in lifestyle or medication, general health status and possible occurrence of adverse effects were monitored biweekly via telephone calls. The participants' compliance with the protocol was based on subject self-reporting and pill count. After 8 weeks, VAS and WOMAC were re-evaluated. The primary outcome measures were the changes in WOMAC pain subscale and VAS. The secondary outcome measures were the changes in WOMAC stiffness and functionality sub scales.

Statistical Analysis

Quantitative variables were expressed as mean values (SD), while qualitative variables were expressed as absolute and relative frequencies. Quantitative variables were tested for normality using the Kolmogorov–Smirnov criterion. For the comparison of proportions, Fisher's exact tests were used. For the comparison of means between two groups, Student's t-tests were used. Repeated measurements analysis of variance (ANOVA) was adopted to evaluate the changes observed in VAS and WOMAC scales between the two treatment groups over the follow-up period. All reported p values are two-tailed. Statistical significance was set at $p < 0.05$. Analyses were conducted using SPSS statistical software (version 22.0).

The primary outcome of the trial was a significant reduction in pain in OA patients. Pain measure is a patient-reported outcome, particularly common for treatments developed for conditions where intentions are to ameliorate symptoms, facilitate functioning and improve quality of life. The data derived can be used to measure the benefit and risk of a treatment, such as any side effects or inconvenience. Furthermore, we aimed to determine the population size of our ongoing prospective randomised controlled trial based on the preliminary outcomes of measures of pain.

Results

Table 1: Demographics, anthropometrics and clinical characteristics of OA patients

	CS N (%)	NUC N (%)	P Value
Gender			
Male	16 (32)	19 (38)	1.000
Female	34 (68)	31 (62)	
Age (years), mean (SD)	61.4 (12.8)	62.6 (10.8)	0.912
Marital status			
Married, divorced	45 (90)	37 (74)	0.512
Unmarried	5 (10)	13 (26)	
Education			
1–9 years	16 (32)	11 (22)	0.324
10–12 years	13 (26)	4 (8)	
>12 years	21 (42)	35 (70)	
Smoking			
No	29 (58)	42 (84)	0.200
Yes	21 (42)	8 (16)	
Fat %, mean (SD)	37.3 (9.1)	30.5 (10.5)	0.092
BMI (kg/sqm), mean (SD)	31.9 (6.1)	28.4 (4.7)	0.120
WHR, mean (SD)	0.91 (0.08)	0.92 (0.06)	0.743
K&L (disease severity)			
2	4 (8)	15 (30)	0.120
3	20 (40)	27 (54)	
4	26 (52)	8 (16)	

Table 2: Changes in WOMAC scales during the follow-up for the two study groups

	Baseline		Follow Up		P Value
Treatment	**Mean**	**SD**	**Mean**	**SD**	
WOMAC (pain)					
CS	8.90	3.07	6.34	3.07	0.025
NUC	7.33	3.87	3.63	3.08	0.001
p	0.270		0.036		
WOMAC (stiffness)					
CS	2.08	1.84	1.46	1.52	0.072
NUC	1.54	1.66	1.32	1.36	0.276
p	0.546		0.806		

WOMAC (physical function)					
CS	27.03	13.77	21.19	9.21	0.314
NUC	17.15	10.55	15.30	12.97	0.180
p	0.391		0.244		
WOMAC (composite)					
CS	39.68	17.85	29.36	12.88	0.100
NUC	26.84	15.55	19.21	15.40	0.036
p	0.283		0.109		

The two study groups were similar in terms of demographics and clinical characteristics. There were more females in both the groups as compared to male. In the study, there were married patients as compared to unmarried.

There were no significant differences in composite WOMAC and its sub scales between the two groups at baseline. At follow-up, scores of pain decreased significantly in both groups but patients in the NUC group had significantly lower levels of pain at follow-up as compared to patients in the CS group. Stiffness and physical function were not significantly changed, but score in the composite dimension was decreased significantly only in the NUC group.

Table 3: VAS at baseline and at follow-up for the two study groups

Treatment	**VAS**				
	Baseline		**Follow up**		**P Value**
CS	6.14	1.96	6.00	1.54	>0.999
NUC	7.03	2.04	3.97	2.26	<0.001
P Value	0.212		0.012		

Subjects in the NUC group reported a significant decrease in pain while pain remained stable for patients in the CS group. In addition, at follow up, patients in the NUC group reported significantly lower levels of pain as compared to those in the CS group.

Discussion

Osteoarthritis (OA) is the most common joint malady and one of the major debilitating diseases, with an increasing social burden for most countries owing to the ageing of the population. The global prevalence increased 9.3% from 1990 to 2017 with greater affliction on the female sex.[12] A comprehensive understanding of the risk factors and the long-term advantages of the management of OA, while abolishing social disparities that may inhibit proper access to health services, is of paramount importance. OA affects the whole joint and is strongly mediated by age-related cellular senescence[13], genetics, and injury/malalignment[14] and is possibly exacerbated and/or induced by obesity and metabolic syndrome.[15,16]

The two study groups were similar in terms of demographics and clinical characteristics. There were more females in both the groups as compared to male. In the study, there were married patients as compared to unmarried. The selection of clinically important outcomes in an OA trial is challenging given the fact that its pathophysiology, presented as joint space narrowing, osteophytes and bone cysts, does not correlate well with the clinical manifestation of its symptoms such as pain.[17] The major two entities implicated in OA pain are bone marrow lesions and synovitis, inflammation of the synovial membrane.[18] Changes in the perception of pain are frequently used as first-line indicators of the course of an intervention. However, there is great heterogeneity in pain sensitivity that can be attributed to person-level factors i.e., psychological and the individual's pain thresholds, and systemic-level factors summed up in the delicate balance between nociceptive pain, neuropathic pain and the affected joint.[19,20] Carlesso et al[21] proposed the identification of a pain susceptibility phenotype to shed light to the transition from acute pain to chronic as a new means of managing more efficiently pain in symptomatic OA in the context of pre-emptive therapy.

There were no significant differences in composite WOMAC and its subscales between the two groups at baseline. At follow-up, scores of pain decreased significantly in both groups but patients in the NUC group had significantly lower levels of pain at follow-up as compared to patients in the CS group. Stiffness and physical function were not significantly changed, but score in the composite dimension was decreased significantly only in the NUC group. Subjects in the NUC group reported a significant decrease in pain while pain remained stable for patients in the CS group. In addition, at follow up, patients in the NUC group reported significantly lower levels of pain as compared to those in the CS group. In this study, CS was chosen as the reference intervention to the active comparator NUC in order to provide benefit to the patients and to avoid ethical implications that would arise from not treating a painful debilitating disease

such as OA.[22] CS was also used in a 2008 RCT that evaluated Garcinia kola seeds, high in bioflavonoid compounds, in knee OA.[23] After a 6-week intervention with Garcinia kola, WOMAC pain and VAS score were significantly decreased compared to placebo ($p < 0.001$). Furthermore, intake of the supplement caused a faster onset of pain relief and longer duration of the beneficial effect when compared to placebo. These findings of the superiority of a flavonoid-rich supplement against CS are corroborated by our preliminary results.

Conclusion

The nutrition can improve the symptoms of declared OA. However, the role of nutrition in slowing down progression of the disease remains to be seen. The preliminary results of this study support the hypothesis that treatment with the newly introduced multi-compound supplement was effective, as reflected by the self-reported feeling of pain.

References

1. Szychlinska MA, Trovato FM, Di Rosa M, Malaguarnera L, Puzzo L, Leonardi R, Castrogiovanni P, Musumeci G. Co-expression and co-localization of cartilage glycoproteins CHI3L1 and lubricin in osteoarthritic cartilage: morphological, immunohistochemical and gene expression profiles. International journal of molecular sciences. 2016 Mar 11;17(3):359.
2. Ameye LG, Chee WS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. Arthritis research & therapy. 2006 Aug;8:1-22.
3. Concetta Aiello F, Maria Trovato F, Anna Szychlinska M, Imbesi R, Castrogiovanni P, Loreto C, Musumeci G. Molecular links between diabetes and osteoarthritis: The role of physical activity. Current diabetes reviews. 2017 Feb 1;13(1):50-8.
4. Fajardo M, Di Cesare PE. Disease-modifying therapies for osteoarthritis: current status. Drugs & aging. 2005 Feb;22:141-61.
5. Castrogiovanni P, Trovato FM, Loreto C, Nsir H, Szychlinska MA, Musumeci G. Nutraceutical supplements in the management and prevention of osteoarthritis. International journal of molecular sciences. 2016 Dec 6;17(12):2042.
6. Szychlinska MA, Imbesi R, Castrogiovanni P, Guglielmino C, Ravalli S, Di Rosa M, Musumeci G. Assessment of vitamin D supplementation on articular cartilage morphology in a young healthy sedentary rat model. Nutrients. 2019 Jun 3;11(6):1260.
7. Eftekharsadat B, Aghamohammadi D, Dolatkhah N, Hashemian M, Salami H. Lower serum levels of alpha tocopherol and lycopene are associated with higher pain and physical disability in subjects with primary knee osteoarthritis: A case-control study. International Journal for Vitamin and Nutrition Research. 2020 Jan 23.
8. Shen CL, Smith BJ, Lo DF, Chyu MC, Dunn DM, Chen CH, Kwun IS. Dietary polyphenols and mechanisms of osteoarthritis. The Journal of nutritional biochemistry. 2012 Nov 1;23(11):1367-77.
9. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S. 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. 2003 Dec 1;62(12):1145-55.
10. Abramson SB: The role of NSAIDs in the treatment of osteoarthritis. In Osteoarthritis Edited by: Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press; 2003:251-258.
11. German B, Schiffrin EJ, Reniero R, Mollet B, Pfeifer A, Neeser JR. The development of functional foods: lessons from the gut. Trends in Biotechnology. 1999 Dec 1;17(12):492-9.
12. Safiri S, Kolahi CS, Smith E, Hill C, Bettampadi D, Mansournia MA, Hoy D, Ashrafi-Asgarabad A, Sepidarkish M, Almasi-Hashiani A, Collins G. 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 Jun 1;79(6):819-28.
13. Hou A, Chen P, Tang H, Meng H, Cheng X, Wang Y, Zhang Y, Peng J. Cellular senescence in osteoarthritis and anti-aging strategies. Mechanisms of ageing and development. 2018 Oct 1;175:83-7.
14. Palazzo C, Nguyen C, Lefevre-Colau MM, Rannou F, Poiraudeau S. Risk factors and burden of osteoarthritis. Annals of physical and rehabilitation medicine. 2016 Jun 1;59(3):134-8.
15. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. Current opinion in rheumatology. 2013 Jan 1;25(1):114-8.
16. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Current opinion in rheumatology. 2017 Mar 1;29(2):214-22.
17. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. The Lancet. 2005 Mar 12;365(9463):965-73.

18. O'Neill TW, Felson DT. Mechanisms of osteoarthritis (OA) pain. Current osteoporosis reports. 2018 Oct;16:611-6.
19. Schaible HG. Osteoarthritis pain. Recent advances and controversies. Current opinion in supportive and palliative care. 2018 Jun 1;12(2):148-53.
20. Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. InSeminars in arthritis and rheumatism 2014 Oct 1 (Vol. 44, No. 2, pp. 145-154). WB Saunders.
21. Carlesso LC, Segal NA, Frey-Law L, Zhang Y, Na L, Nevitt M, Lewis CE, Neogi T. Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: the multicenter osteoarthritis study. Arthritis & rheumatology. 2019 Apr;71(4):542-9.
22. Millum J, Grady C. The ethics of placebo-controlled trials: methodological justifications. Contemporary clinical trials. 2013 Nov 1;36(2):510-4.
23. Adegbehingbe OO, Adesanya SA, Idowu TO, Okimi OC, Oyelami OA, Iwalewa EO. Clinical effects of Garcinia kola in knee osteoarthritis. Journal of Orthopaedic Surgery and Research. 2008 Dec;3(1):1-0.