International Journal of Research in Orthopaedics
Sriraam VT et al. Int J Res Orthop. 2025 May;11(3):505-512
http://www.ijoro.org

Original Research Article

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20250900

Clinical benefits of undenatured chicken collagen type II Unstergen® as a nutritional therapy in the management of osteoarthritis: a double-blind, placebo controlled clinical study

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Received: 03 March 2025
Revised: 13 March 2025
Accepted: 18 March 2025

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ABSTRACT

Background: Osteoarthritis (OA) is a degenerative joint disease affecting millions globally, often leading to pain and reduced mobility. Nutraceuticals like undenatured chicken collagen are gaining attention for their potential in symptom relief. This proof-of-concept study evaluates the clinical efficacy of Unstergen® of Titan Biotech Limited in the management of OA.
Methods: This randomised, double-blind, placebo-controlled study studies 48 adults with OA. Subjects received 40 mg/day of Unstergen® (n=32) or placebo (n=16) once a day for 90 days. Outcomes were assessed using WOMAC score, pain scale, quality of life questionnaire (QoL) for all and global rating of change scale (GROC) using X ray of target joint for a cohort of 12 subjects.
Results: Unstergen group demonstrated statistically significant reduction of 20.39% in Western Ontario and McMaster universities osteoarthritis index (WOMAC) scores and 37.77% in pain numerical rating scale (Pain NRS) compared to 7.24% and 8.70% reduction in the placebo arm, respectively. The 90.32% subjects reported improvement in QoL compared to placebo ($p<0.05$). The 87.50% subjects were deemed to have marked improvement on their X ray while no subject in the placebo arm showed improvement after 90 days. No adverse event was attributed to Unstergen and was deemed clinically safe.
Conclusions: Unstergen® demonstrated significant improvement in pain, function and QoL; highlighting its role as a novel nutraceutical supplementation therapy for OA.

Keywords: OA, Undenatured chicken collagen, Type II collagen, Collagen, Unstergen, WOMAC, Pain scale, Nutraceuticals, Joint pain, Joint health

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder affecting a large percentage of the world's population. OA has a strong socioeconomic impact with primary risk factors being age and obesity.[1] OA can be classified as primary OA caused by genetic factors, physiological changes that come with age and secondary OA that comes because of trauma, infection, inflammation, biochemical changes.[2] OA affects 22%-39% of the population in India, being more common in women than men. The burden increases with age and is a major cause of pain and mobility impacting QoL.[3]

Collagen makes up one third of the total protein in the human body and the most common part of the extracellular matrix of the articular cartilage. When cartilage breakdown exceeds synthesis, OA occurs. Collagen derivates have been studied as nutraceutical supplements for the management of OA.[4] The use of hydrolyzed

collagen has been showing satisfactory results with OA, proving benefits greater than glucosamine.[5] Results from a recent meta-analysis shows that collagen supplementation reduces OA symptomatically as evident from reduction in WOMAC and visual analogue scores (VAS) for pain.[6]

Undenatured chicken collagen has shown promise with results that prove prevention of OA development in SD rats with significant reduction in collagen loss in cartilage, upon oral administration of undenatured chicken collagen for 12 weeks.[7] Chen et al who studied the effects of undenatured chicken collagen on 160 patients for 24 weeks, concluded Undenatured Chicken collagen to be a novel holistic solution for mobility by improving joint, muscle and bone health among older adults.[8] Increasingly, there have been several studies on Undenatured Chicken collagen for the symptomatic management of OA. Luo et al conducted a 12 week placebo controlled study on 101 subjects with knee OA, in which undenatured chicken collagen performed better than glucosamine hydrochloride+chondroitin sulphate or a placebo by showing better effects, higher safety profile and improving QoL of patients.[9]

This clinical study evaluated the safety and efficacy of Unstergen® of Titan Biotech Ltd, presented as 40 mg capsules in comparison with a placebo in a randomised, double blinded study design.

METHODS

Study design

This clinical trial was designed as a randomised, double blinded study comparing 40 mg Unstergen® (n=32) and placebo (n=16) for 12 weeks on 48 adults with OA. X ray improvement was studied and marked by the investigator on a GROC for a cohort of 12 subjects. The treatment period was for 90 days with Day 1 as baseline, day 45 as improvement metrics visit and day 90 as end of study visit (Figure 1).

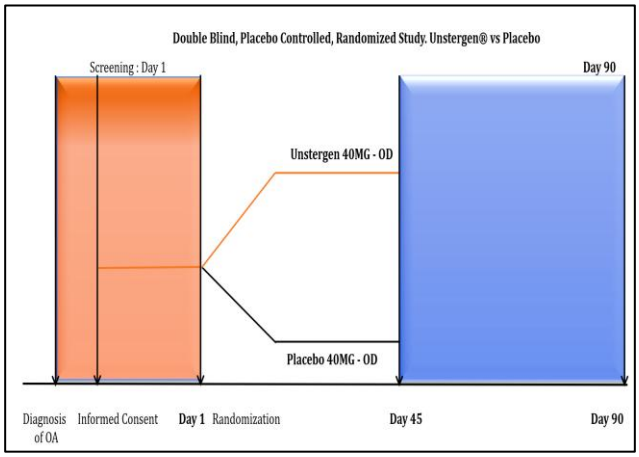

Figure 1: Study design.

The objective of the study was to evaluate the safety and efficacy of Unstergen® as a nutritional supplement for adults with OA.

Ethical approval

Universal ethics committee (CDSCO Reg no ECR/125/Indt/TN/2013/RR-20 and OHRP reg No IORG0007234), an independent ethics committee reviewed and approved the research study, prior to initiation.

Regulatory compliance

The study was registered with Indian council of medical research (ICMR)-clinical trial registry of India (CTRI) holding reference number CTRI/2023/09/058043. This study followed the ethical principles as given in declaration of Helsinki, The ICH harmonized tripartite guideline-guideline for good clinical practice E6 (R2), and Indian council for medical research (ICMR) ethical guidelines for biomedical research on human participants and new drugs and clinical trial rules. The study is CONSORT (Consolidated standards of reporting trials) compliant.

Study inclusion and exclusion criteria

Adults with OA of the hip or knee between the ages of 30 and 65 years were screened for this study in the months of October 2023. Subjects who were willing to abstain from use of other products-topical, supplements etc targeted at improving joint pain (to negate bias) and who were willing to consume animal origin collagen for the duration of this study were screened. Subjects who were ambulatory but not currently receiving or not satisfied with anti-inflammatory or anti analgesic medication were screened. Subjects with a pain score of 5-7 on a 10-point NRS at the time of screening in a minimum of one joint were selected. Subjects who were known to be sensitive to collagen, immunocompromised, with history of surgery in target joint, clinically present infection/inflammation or any musculoskeletal condition that would impede measurement of efficacy at target joint were excluded. Female subjects who were pregnant, breastfeeding were excluded.

The study was conducted in Raam Clinic, Chennai. India.

Randomisation and blinding

Subjects were randomised based on SAS generated alphanumeric codes that were printed in similar containers to maintain double blind. Only the statistician and the designated unblinded personnel were aware of the treatment details for emergency decoding in the event of any serious adverse event (SAE). Both Unstergen® and placebo was presented in capsules holding 40 mg product, undistinguishable from one another.

Interventions

Titan Biotech Ltd.'s Unstergen® is a undenatured chicken collagen type 2 derived from chicken sternum cartilage. This ingredient aids in joint repair, reducing pain, increasing mobility, flexibility, and promoting long-term joint health.

Native type II collagen, a nutraceutical ingredient from chicken sternum cartilage, can be beneficial for joint diseases due to its oral tolerance mechanism. It interacts with Peyer's patches in the gut, preventing T-cell attacks on collagen type 2 in the cartilage. This desensitization process, also known as oral tolerance, prevents the immune system from recognizing collagen type 2 as an antigen, potentially reducing inflammation and degradation.[10] Methylcellulose was used as the placebo for this study. This study permitted the use of SOS analgesics which was recorded. The use of SOS medication was due to the pain and limiting nature of the indication being studied with a placebo arm.

Treatment protocol

Written informed consent was obtained from the subjects before undertaking any study procedure. The patient information sheet and informed consent document was also made available in vernacular language for the ease and convenience of the subject. Care was taken to ensure complete transparency and impartiality during translation. This was also reviewed and ensured by ethics committee.

The 48 subjects were screened and enrolled in to the study in two treatment arms. The 12 subjects (selected randomly) were assigned to the cohort group where additionally improvement via X ray was assessed. The subjects were followed up for 12 weeks with one visit at day 45 and one visit at day 90 after baseline. There were no changes made to the trial design and trial outcome after the commencement. The trial was not interrupted or terminated and ended with the enrolled subjects completing their follow up.

Outcome measures and end points

The effectiveness of Unstergen® was evaluated using WOMAC scale.[11] Pain scale NRS, QoL questionnaire EQ-5D-5L and GROC based on X ray for subjects in the cohort group.[12-14] Clinical safety was evaluated by complete blood count (hemogram) and biochemistry parameters (liver and kidney function tests) at baseline and end of the study.

WOMAC questionnaire was developed to measure symptoms and physical disability in OA with the aim to clinically evaluate the relevant changes in the health status as a result of an intervention. WOMAC has 24 questions that elicit responses for symptoms of pain, stiffness and physical function. Pain NRS is a widely used method to assess the reduction of pain in OA. Subjects mark their pain levels on a numerical scale of 0-10 where 0 marks no pain and 10 marks maximum pain possible. Both of these tools are studied, validated and prominently used while evaluating new approaches in clinical orthopaedics.[6] EQ-5D-5L is a standardised questionnaire to understand the improvement in QoL brought on by symptomatic relief upon treatment with Unstergen®. GROC is a scale that spans between-5 denoting very much worse after treatment, 0 denoting unchanged and +5 denoting completely recovered after intervention. Demographic data (Table 1) was captured at baseline and vital signs such as pulse rate, respiratory rate, temperature and blood pressure was recorded on day 1, day 45 and day 90 of the study (Table 2).

Table 1: Demographic data: Unstergen® versus placebo.

Demographics	Unstergen®		Placebo	
Gender	Female	10 (32%)	Female	7 (50%)
	Male	21 (68%)	Male	7 (50%)
	Total	31 (100%)	Total	14 (100%)
Age (in years)	41.45±5.55		42.21±7.27	
Height (m)	1.70±0.09		1.69±0.08	
Weight (kg)	77.83±8.16		76.78±7.52	
BMI (kg/m^2)	27.08±4.16		26.94±3.16	

Table 2: Vital signs: Unstergen® versus placebo.

Vital signs	Unstergen®		Placebo	
	Day 1 (Baseline)	**Day 90 (End of study)**	**Day 1 (Baseline)**	**Day 90 (End of study)**
Pulse rate (Beats/min)	79.52±10.47	82.00±11.43	79.43±11.78	79.21±13.17
Respiratory rate (Breaths/minute)	15.77±3.33	16.87±3.02	15.57±2.38	16.86±3.06
Temperature (F)	98.07±0.56	98.03±0.57	97.80±0.63	98.01±0.60
Systolic BP (mmHG)	112.90±8.64	113.55±7.98	111.43±8.64	112.14±8.02
Diastolic BP (mmHG)	75.48±8.88	73.87±9.72	73.21±12.19	75.36±10.28

Statistical analysis

Being a proof-of-concept study, the sample size was decided by the sponsor-Titan Biotech Ltd. All statistical analyses was done in accordance with international council on harmonisation (ICH) E9 (R1) guideline for statistical principles for clinical trials, using SAS (Version 9.4) was used to perform both proportion test and t test and for the generation of tables, graphs and reports. Statistical tests were carried out at 5% level of significance. One sample t-test was used for intra analysis of the treatment arms and two sample t test was used for inter group analysis between Unstergen® and placebo. Descriptive summary statistics was provided for all demographic data. Box and whisker plots were used to graphically represent the results of this study.

RESULTS

A total of 51 adults with OA were screened for this study. Of this 48 subjects were enrolled into the study in two treatment arms. Three subjects were lost to follow up (Personal reasons, not interested to continue, moved out of the city) and the data of 45 subjects (31 on Unstergen® and 14 on placebo) was analysed as presented as per the statistical analysis plan (SAP).

Unblinding

No subject was unblinded during the course of the study, Unblinding was done by the statistician during analysis upon completion of the study. After unblinding it was found that a total of 31 subjects were treated with Unstergen® and 14 were treated with placebo.

The 80.65% of subjects on Unstergen® showed statistically significant reduction on WOMAC score, whereas no subject on the placebo arm was able to reach said end point. The average reduction after 90 days of treatment with Unstergen® was 12.19 compared to 4.36 in the placebo arm. (t=8.87, p=0.000). The subjects on Unstergen® showed a 20.39% reduction in WOMAC score compared to 7.24% of the placebo arm showing subjective improvement in OA symptoms (t=9.2738, p=0.000).

The domains of the WOMAC questionnaire were analysed and results showed reductions of 16.05% vs 6.18% in pain domain, 18.95% vs 4.17% in the stiffness domain and 19.22% vs 8.56% in physical function domain for subjects on Unstergen® (p<0.05) vs placebo respectively.

The 93.55% of subjects on Unstergen® reported less joint pain during walking, climbing stairs etc evident by reduction in scores in pain domain of WOMAC, while 70.97% reported improvement in the joint stiffness domain of WOMAC and 67.74% of subjects reported improvement in everyday activities (Physical function domain of WOMAC).

The average reduction in pain NRS with Unstergen® was 2.29 scores from baseline as reported by 87.10% of subjects, while the scores dropped only 0.57 in the placebo arm, which was not statistically significant (p=1.000) (Figure 3). NRS reduction was higher with subjects who consumed Unstergen® for 3 months-reported as 37.77% compared to 8.70% on the placebo arm (t=6.5061, p=0.000).

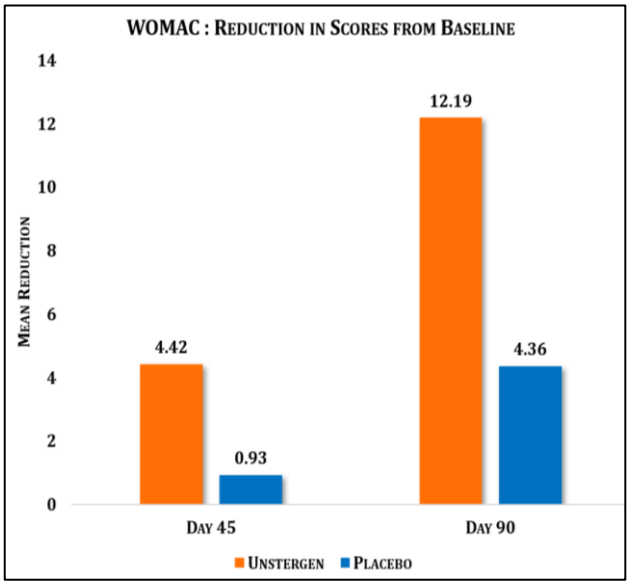

Figure 2: WOMAC: reduction in scores from baseline.

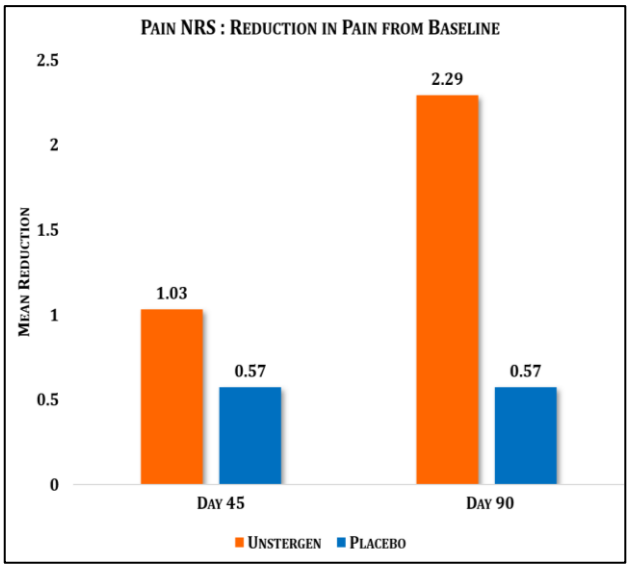

Figure 3: Pain NRS: reduction in pain from baseline.

The 90.32% of subjects who took Unstergen® for 90 days, reported improvement in QoL (p=0.000) while only 7.14% in the placebo arm reported improvement (p=0.999) (Figure 4). Subjects reported a reduction of 40.34% in symptoms compared to just 11.25% in the placebo arm which translated to marked improvement in QoL (t=9.8941, p=0.000)

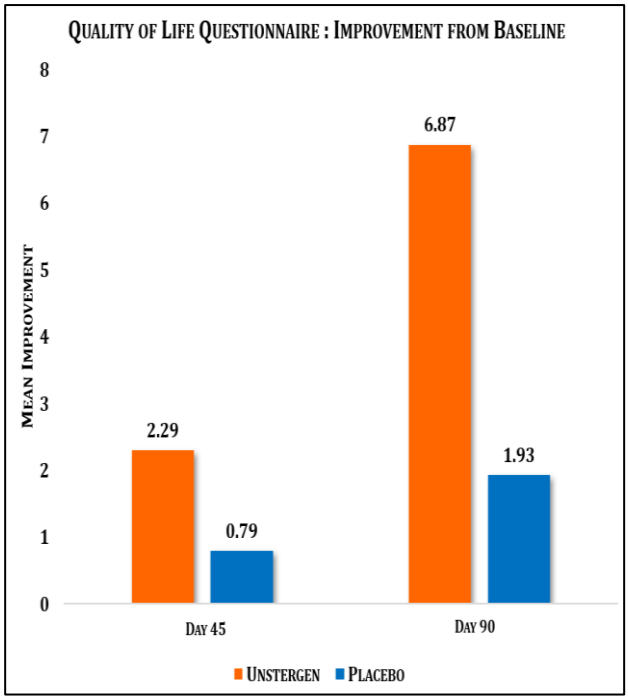

Figure 4: Improvement in QoL from baseline.

GROC score was evaluated by the Investigator by comparing X ray at the baseline to the images at the end of the 90 day treatment period to evaluate improvement. The 87.50% of subjects showed an average of 2.88 scores denoting improvement in OA (p=0.021) compared to the average in placebo which was -0.25 denoting worsening of OA from baseline. (p=0.999) (Figure 5) (Table 3).

A total of 6 adverse events (AE) were reported during the study (Table 5). Upon unblinding at the end of study, it was found that 4 AE (2 common cold, 1 common cold with fever, 1 food poisoning due to pani puri) was reported by subjects on the Unstergen® arm and the 2 AE (1 sore throat, 1 fever) was reported in the placebo arm. All AE was ruled not related to the respective intervention. All AE was followed up and ensured that there was complete recovery with no sequelae. There was no SAE reported during the study and no drop outs were attributed to AE.

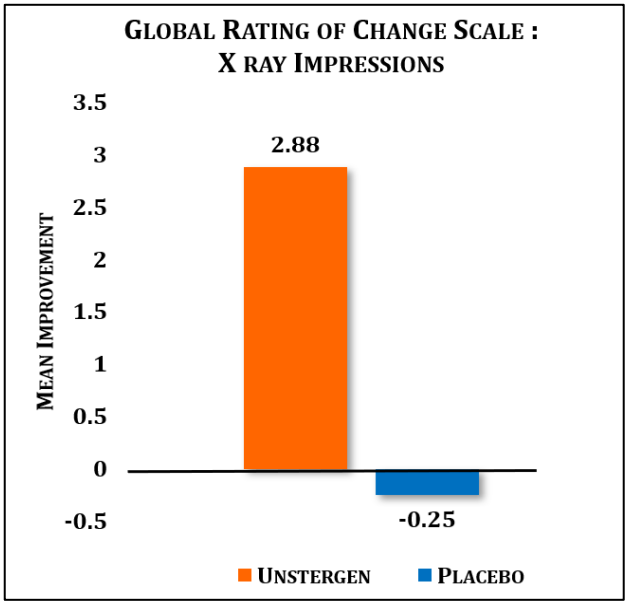

Figure 5: Improvement in X ray marked on GroC.

Seven out of 48 subjects availed SOS medication owing to increased pain and worsening of symptoms. Upon unblinding at the end of study, it was found that 1 subject (3/90 days) was from the Unstergen® treatment arm while the other 5 subjects were from placebo (6/90 days, 6/90 days, 6/90 days, 7/90 days, 6/90 days, 4/90 days) was treatment arm (Table 4).

Clinical safety assessments (complete blood count, biochemistry-liver and kidney parameters) showed no significant difference between baseline and end of treatment period of 90 days, proving clinical safety profile.

Table 3: Summary of efficacy outcomes.

Vital signs	Unstergen®		Placebo	
	Day 1 to day 45	Day 1 to day 90	Day 1 to day 45	Day 1 to day 90
WOMAC score	4.42±3.22	12.19±3.04*	0.93±2.73	4.36±1.91
Pain NRS	1.03±1.20	2.29±0.82*	0.57±0.85	0.57±0.94
QoL questionnaire	2.29±1.87	6.87±1.82*	0.79±0.97	1.93±1.27
Global rating of change scale (X ray)	----	2.88±0.99*	----	-0.25±0.50

*Indicates statistically significant values (p≤0.05).

Table 4: Summary of adverse event.

Adverse events	Unstergen®	Placebo
Common cold	2*	----
Fever	1*	1*
Sore throat	----	1*
Food poisoning	1*	----

*Denotes adverse events were ruled as not related to investigational products, No SAE was reported in this study.

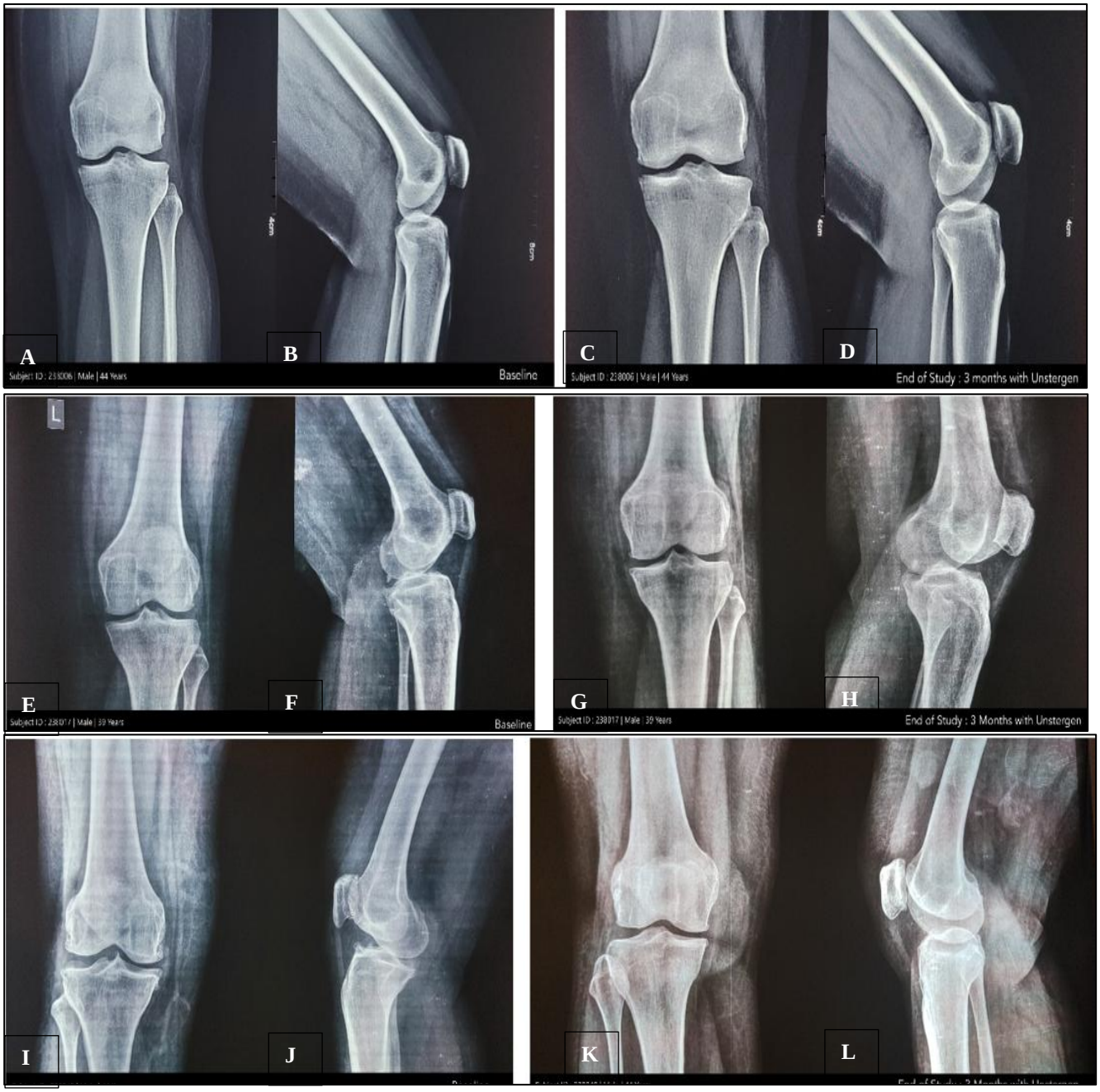

Figure 6 (A-L): Baseline versus 3 months post treatment with Unstergen®. X-ray comparison of 3 subjects.

DISCUSSION

The present study was designed and executed with the intention of evaluating the safety and efficacy of Unstergen® of Titan Biotech. The results prove that oral supplementation of Unstergen® decreases the symptoms associated with OA in 90 Days. The results were validated by the decrease observed in both overall WOMAC index and pain scale scores. The WOMAC is a widely used, validated questionnaire designed to assess pain, stiffness, and physical function in individuals with OA, particularly in the hip and knee. It consists of 24 items divided into three subscales: pain (score range 0-20), two for stiffness (score range 0-8), and 17 for functional limitation (score range 0-68). The NRS serves as a tool for screening pain, frequently utilized to evaluate the intensity of pain experienced at a specific moment. It operates on a scale from 0 to 10, where 0 indicates "no pain" and 10 represents "the most pain possible."

Pain that interferes and limits everyday life is one of the most important symptoms of OA; reduction in this pain upon treatment with Unstergen® is to be considered a mark of symptomatic improvement in OA. It is considered that oral supplementation with undenatured chicken collagen helps recover the extracellular matrix of the articular cartilage thereby aiding with lessening symptoms of OA.

Several studies on type II collagen or undenatured chicken collagen have demonstrated significant reduction of collagen loss of cartilage, improved overall joint health as early as 4 weeks, proved to be safe and efficacious in improving knee flexibility and mobility, reducing knee and lower back pain and enhancing motor function.[7,9,15] A similar double blind, placebo controlled study showed that hydrolyzed chicken collagen type II was effective in reducing joint pain and stiffness upon oral supplementation for 8 weeks.[16]

In the present study using "Unstergen®" showed a significant reduction in symptoms of OA. WOMAC showed a significant reduction in Unstergen® group, the mean reduction value at the end of the study from the baseline was 12.19 for Unstergen® and 4.36 for placebo group respectively (Figure 2). On days 45 and 90 of supplementation, the pain NRS score in the Unstergen® group was significantly lower than that of the placebo group ($p \leq 0.05$). Subjects on Unstergen® reported marked improvement in QoL. 87.5% of subjects showed marked improvement in the X ray while no subject showed improvement in the placebo arm (Figure 6 shows the comparison X ray images of three subjects at baseline and after 3 months on Unstergen®).

All the efficacy results showed a significant improvement compared to the placebo ($p \leq 0.05$). In the course of the study, the subjects were instructed to stick to their usual routine and lifestyle as before without implementing any significant changes to their eating or exercise habits. The only addition to their everyday routine lifestyle was the blinded intervention capsules; thus, an unbiased inter-comparison analysis was performed. No elements of bias, inaccuracy, or multiple analyses are present in the proposed study protocol.

The sample size is considerably small but this is to be considered a proof-of-concept study that would eventually further exploration with larger sample size across varied population typically grouped by severity of OA, occupational wear and tear marked and other comorbidities.

CONCLUSION

The current study showed that oral supplementation of Unstergen® (undenatured chicken collagen type II) is a potential supportive nutraceutical therapy in the management of OA. Supplementation of 40 mg of "Unstergen®" for a minimum of 12 weeks shows significant potential for use in patients with OA due to its safety profile. Clinical safety was established with blood test at baseline and end of study, proving the tolerability and safety of the product. Though, further research with a larger sample size is warranted, this study has proved that Unstergen® is a safe, clinically verified and validated nutraceutical for managing OA with reducing progression, providing symptomatic relief, improving functional capacity and overall QoL.

ACKNOWLEDGEMENTS

The author would like to thank, Titan Biotech Limited, Delhi.

Funding: Titan Biotech Limited, with Aurous HealthCare Research and Development India Pvt. Ltd. (CRO)
Conflict of interest: None declared
Ethical approval: The study was approved by the Universal Ethics Committee (CDSCO Registration Number: ECR/125/Indt/TN/2013/RR-20) holding approval number UEC/APP/018/19-20.

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Cite this article as: Sriraam VT, Pillai S, Singla R, Singla S. Clinical benefits of undenatured chicken collagen type II Unstergen® as a nutritional therapy in the management of osteoarthritis: a double-blind, placebo controlled clinical study. Int J Res Orthop 2025;11:505-12.