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EFFICACY AND TOLERABILITY OF PROKNEE COLLAGEN II™ ON JOINT HEALTH IN INDIVIDUALS WITH MILD TO MODERATE JOINT PAIN: A RANDOMIZED, DOUBLE -BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Osteoarthritis (OA) is a progressive joint disease resulting from degeneration of articular cartilage, thereby leading to a loss of joint function and debilitating pain. The present study aimed to investigate the effect of Proknee Collagen II™ on joint health and quality of life. A 12-week, randomized, double-blind, placebo-controlled, parallel study was conducted in participants with joint pain. Adults aged 40-65 years (n = 60) with joint pain diagnosed as Grade II knee OA were enrolled in the study and were randomized in a 1:1:1 ratio to receive either Proknee Collagen II™, Glucosamine hydrochloride (G) + Chondroitin sulfate (C), or placebo for 12-weeks. Improvement in the joint health was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Quality of life was assessed by the change in the EQ-5D-5L scores. At day 84, Proknee Collagen II™ demonstrated a statistically significant result in the joint health when compared to placebo (p=0.0021). Furthermore, Proknee Collagen II™ demonstrated a statistically significant change in the "usual activities" domain (p=0.0392) and in the "pain or discomfort" domain (p=0.0274) of the EQ-5D-5L questionnaire when compared to placebo at day 84. A statistically significant change was noted for the EQ-5D VAS scores in the Proknee Collagen II™ group (p=0.0081) when compared with placebo at day 84. Thus, Proknee Collagen II™ was able to significantly improve the joint health and quality of life of participants, and was well-tolerated.

KEYWORDS: Osteoarthritis, joint health, WOMAC, quality of life, joint pain.

INTRODUCTION

Osteoarthritis (OA) is a progressive degenerative joint disease that affects around 250 million people worldwide.[1] It has been stated to increase the health burden by ~ 303 billion dollars annually in the form of medical costs and lost earnings.[2] OA is a slow progressing joint disorder that initially may not present any symptoms, despite radiological evidences of degeneration. Progression of OA is attributed to a degeneration of articular cartilage. It not only affects joint health, but also leads to debilitating pain.[3] However, in the later stages of life, the disease progression can be rapid over several weeks or months even in patients with normal X-rays. Epidemiological studies indicate that joint health is affected by several modifiable risk factors such as the overuse of joints, sedentary lifestyle, obesity, etc.[4,5,6] These factors lead to the wear and tear of type II collagen fibres, which are the basic components of the cartilage.[7] Luyten et al.[8] suggested that early interventions may be effective in minimizing the structural and symptomatic progression of cartilage damage. Moreover, Crowley et al.[9] suggested that undenatured collagen type II has shown a significant improvement in joint health, especially when compared to the widely used supplement combination of glucosamine and chondroitin (G+C). Proknee Collagen II™ is an orally administered form of undenatured collagen type II, which creates an oral tolerance - a mechanism whereby the immune system distinguishes between innocuous material in the gut and potentially harmful foreign invaders that help cartilage repair.[10,11]

Undenatured collagen type II has been found to be effective in the symptomatic treatment of OA and reducing pain in the affected joints.[10] Evidence from a previously conducted study has also demonstrated a positive effect of type II collagen in modulating knee OA symptoms.[12] It also reported a significantly better effect

and a high safety profile on OA as well as improved the quality of life of patients.[12] Considering the evident efficacy of this nutraceutical compound in previous studies, the current study was designed to evaluate the effectiveness of Proknee Collagen II™ in improving the joint health and thereby the quality of life in people facing joint pain.

MATERIALS AND METHODS

Study design

This study was designed as a 12-week, randomized, double-blind, placebo-controlled parallel clinical trial in adults reporting knee joint pain. The study was conducted between July 2020 and April 2021 at 4 sites in Mumbai, India and 1 site in Varanasi, India under the supervision of orthopaedics at each study site. Participants were randomly assigned to either Proknee Collagen II™, G+C, or placebo arm.

The study protocol was approved by an independent ethics committee (ACEAS-IEC; Reg. No. ECR/65/Indt /GJ/2013) registered with the Office for Human Research Protections in the US Department of Health and Human Services. The study was conducted in compliance with the Declaration of Helsinki, and ICH-GCP guidelines. The investigators explained the study procedures, objectives, as well as risks and benefits involved in the study to the participants. Only participants willing to give written informed consent were recruited for the study. The study results have been reported as per the Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants

Adults aged between 40 and 65 years with knee joint pain, defined as radiographically proven grade II based on the Kellgren and Lawrence (KL) classification system, were enrolled in the present study. Written informed consent forms were voluntarily obtained from all study participants. Only participants fulfilling the eligibility criteria as stated in **Table 1** were enrolled in the study.

Table 1: Eligibility Criteria.

Inclusion Criteria	1. Individuals aged between ≥ 40 to ≤ 65 years, suffering from knee joint pain for at least 3 months prior to screening. 2. Body Mass Index (BMI) ≥ 18.5 and ≤ 29.9 kg/m^2. 3. Non-vegetarians. 4. Knee joint pain ≥ 60 on a 100-point Pain VAS. 5. Radiographic evidence of grade II knee OA. 6. Willingness to stop the restricted supplements and medications prior to inclusion and throughout the study period. 7. Willingness to stop the use of study designated rescue medication 48 hours prior to all assessment visits. 8. Female participants of childbearing age willing to use the accepted methods of contraception during the study.
Exclusion Criteria	1. Prior or ongoing medical conditions. 2. History of type II diabetes and uncontrolled hypertension. 3. Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. 4. Radiographic evidence of Grade I or Grade IV OA based on the Kellgren and Lawrence (KL) radiographic criteria for osteoarthritis. 5. Any planned surgery to the index joint during the participation in the study. 6. Participants with deformity of the knee joint or with planned surgery (diagnostic or therapeutic intervention) to the index joint during the participation in the study. 7. Any history or evidence of allergy to chicken, eggs, shellfish or protein products in the past.

Interventions

The rationale for dosage of Proknee Collagen II™ was determined through earlier conducted preclinical and clinical trials.[9,12,13,14] Based on previous findings, the present study was designed to evaluate the efficacy of Proknee Collagen II™ at a dose of 40 mg/day in participants with knee OA. This dosage of Proknee Collagen II™ was compared with G+C which was consumed at a dose of 2700 mg/day. In order to preserve blinding, the study products were matched for size, shape, colour, and texture and thus 450 mg of capsule was prepared for all three groups. The details of the study products are provided in **Table 2**.

Participants were randomized in blocks of six using the Stats Direct software (version 3.1.1.17) in a 1:1:1 allocation rate to either receive the investigational product (IP), Proknee Collagen II™; comparator, G+C; or placebo. The participant IDs were arranged in a chronological order as per the computer generated randomization chart. This master randomization chart was password protected, saved and maintained in the electronic Trial Master File (eTMF). The treatment allocation was blinded to the participants, investigators and the research team directly involved in the study.

Table 2: Details of study products.

Active Ingredient	Proknee Collagen II™	G+C	Placebo
Undenatured Type II Collagen + D-Glucose	40 mg + 2660 mg	-	-
Glucosamine Hydrochloride+ Chondroitin Sulfate	-	1500 mg + 1200 mg	-
D-Glucose	2660 mg	-	2700 mg
Total Weight	2700 mg	2700 mg	2700 mg
Dosage form	Capsule		
Route	Oral		
Strength	450 mg		
Dosage regimen	Three capsules post-breakfast and three capsules post-dinner		
Duration	84 days		

Abbreviation: G+C Glucosamine hydrochloride and Chondroitin sulfate

The Proknee Collagen II™ sample was used in this study with a batch number of AM/1906271. For severe pain, acetaminophen was permitted as rescue medication at a dose up to 1000 mg/day, but was prohibited for 48 hours prior to each study visit. The study products were manufactured in a "Good Manufacturing Practices" certified facility.

Study Conduct

On the screening visit, individuals were assessed for the eligibility criteria and only participants fulfilling the eligibility criteria were enrolled into the study. Before randomization, every participant completed a 7-day placebo run-in period to identify and exclude placebo responders. Once randomized on baseline (day 0), participants were to report for a follow up visit at a frequency of every 4 weeks (days 28 and 56) till the end of the study visit on day 84. During the course of the study, participants were provided a diary to record missed doses as well as use of rescue medication. This diary was reconciled at each of the study visit in order to record the compliance of the study products.

Outcome Measures

Primary Outcome

Modified western Ontario and McMaster Universities Index Total score (mWOMAC) is a self-administered validated instrument that has been extensively used in several clinical research. Total WOMAC score is a validated predictor of joint health.[16] For evaluating the efficacy of Proknee Collagen II™, the change in the WOMAC total score from day 0 to days 28, 56, and 84 was compared to that of the comparator (G+C), and placebo.

Secondary Outcomes

The secondary outcome for the study consisted of a change in WOMAC subscale scores of pain, stiffness, and physical function.[16] Furthermore, health-related quality of life (hr-QoL) was evaluated by the validated EQ-5D-5L questionnaire. It covers 5 domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[17,18] Moreover, the EQ-5D VAS score assessed the participant's self-rated health on a 20 cm vertical, visual analogue scale (VAS).[19] Change from day 0 to day 84 was compared to that of the G+C group and placebo for assessment of the efficacy of Proknee Collagen II™ in the aforementioned variables.

Safety Assessments

Vital signs (blood pressure and pulse rate), laboratory parameters (liver – Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) and kidney profile – creatinine) were monitored. The frequency and occurrence of adverse events or serious adverse events were also monitored throughout the study. Blood samples were collected on day 0 and day 84, and were investigated using standard laboratory techniques by a lab accredited by The College of American Pathologists (CAP), Mumbai (India).

Statistical Analysis

Based on data from similar studies, a sample size of 60 participants, was chosen.[20] The type I error probability associated with the null hypothesis test was set to 0.05. For analysis, the modified intent-to-treat (mITT) population, which consisted of participants that at least completed the Day 28 visit, was chosen. The efficacy and safety parameters were compiled using ANCOVA (comparison between all three groups), paired t-test (within-group analysis), two-sample t-test/test (inter-group analysis). The normality of data was assessed using the Shapiro-Wilk test.

Quality Assurance

The investigator and the research team were GCP certified and the study was conducted in compliance with the ICH-GCP guidelines. A pre-approved monitoring and audit plan was finalized to ensure data quality.

RESULTS

A total of 60 participants with radiological evidences of KL Grade II for osteoarthritis were randomized in the ratio of 1:1:1 and were stratified based on WOMAC total score ≥76. The enrolled population consisted of 20 participants each in Proknee Collagen II™, G+C group, and placebo groups. As the study progressed, a total of 5 participants from all groups were lost to follow-up or

were withdrawn. 55 participants completed the study, with 18 in the Proknee Collagen II™ group, 19 in the G+C group, and 18 in the placebo group. The disposition of study participants is illustrated in **Figure 1**.

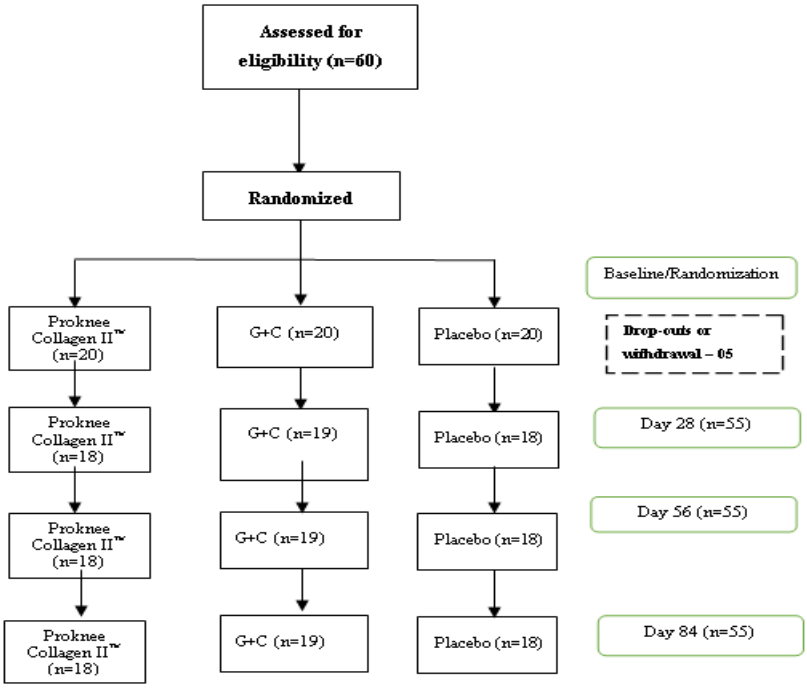

Figure 1: Participant disposition.

Participant Demographics and Baseline Characteristics

At baseline, the three groups were comparable in terms of demographic characteristics. The pain VAS score for each of study group was >60. A summarized description of participant demographics and baseline characteristics is provided in **Table 3.**

Table 3: Demographics and Baseline Characteristics.

Characteristics		**Proknee Collagen II™ (n = 20)**	**G+C (n = 20)**	**Placebo (n = 20)**	**p-value**
		Mean (SD)			
Age (years)		51.4 (7.49)	49.3 (5.75)	46.05 (5.63)	0.0335*
Gender, n (%)	Male	7 (35.00%)	10 (50.00%)	8 (40.00%)	0.6188#
	Female	13 (65.00%)	10 (50.00%)	12 (60.00%)	
BMI (kg/m^2)		24.15 (2.81)	24.77 (3.28)	25.01 (2.33)	0.6188*
Pain VAS Score		68 (6.16)	68 (7.68)	67 (5.71)	0.8572*
WOMAC Index	Total Scores	83.95 (7.80)	84.25 (7.43)	85.58 (6.73)	0.7645*
	Pain Scores	13.50 (1.96)	14.30 (1.66)	14.55 (2.11)	0.2046*
	Stiffness Scores	5.80 (1.15)	6.15 (0.93)	6.05 (0.89)	0.5241*
	Physical Function Scores	64.65 (5.95)	63.80 (6.40)	64.65 (4.86)	0.8657*
EQ-5D-5L	Mobility	2.85 (0.59)	3.00 (0.56)	3.00 (0.73)	0.6862*
	Self-care	2.60 (0.75)	2.90 (0.72)	2.90 (0.79)	0.3547*
	Usual activities	3.10 (0.64)	3.10 (0.79)	3.35 (0.67)	0.4354*
	Pain or discomfort	3.15 (0.59)	3.00 (0.92)	3.20 (0.41)	0.6215*
	Anxiety or depression	2.85 (0.88)	2.75 (0.79)	3.00 (0.65)	0.5937*
EQ-5D VAS		58.50 (15.40)	50.75 (19.62)	57.75 (12.51)	0.2530*
Notes: *p-value was calculated using ANOVA (A) for continuous variables #p-value was calculated using paired t-test					
Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; FBS, fasting blood sugar; G+C, Glucosamine Hydrochloride plus chondroitin sulphate; n, number of participants; SD, standard deviation; VAS, visual analogue scale.					

Effect of Proknee Collagen II™ on Joint Health

The overall joint health of participants was assessed using the total WOMAC scores. WOMAC scores for the three groups were identical at baseline. The change in WOMAC scores are depicted in **Table 4**. Compared to placebo, a significant reduction was seen in the Proknee Collagen II™ group at day 84, and a similar change was observed in the G+C group. At day 84, the total WOMAC scores decreased by 31.44 in the Proknee Collagen II™ group and 36.84 in the G+C group; whereas in the placebo group it decreased by only 12.50. Thus, the decline in the score for the Proknee Collagen II™ group remained statistically significant and clinically comparable with G+C. After 12 weeks of product administration, Proknee Collagen II™ demonstrated a significant improvement in joint health when compared with placebo (p=0.0021).

Effect of Proknee Collagen II™ on Joint Pain

WOMAC pain scores for the three groups were identical at the baseline. As demonstrated in **Table 4**, when compared with placebo, Proknee Collagen II™ and the G+C groups showed a statistically significant change at day 84 (Proknee Collagen II™: p=0.0184; G+C: p=0.0041). The WOMAC pain scored decreased by 5.16 and 6.10 in the IP and comparator group, respectively; whereas in the placebo group it decreased by only 2.67. After 12 weeks of product administration, Proknee Collagen II™ corroborated a statistically significant and clinically comparable result with G+C.

Effect of Proknee Collagen II™ on Stiffness

WOMAC stiffness scores for the three groups were identical at the baseline. 12 weeks of product administration showed that Proknee Collagen II™ significantly improved stiffness scores to assess joint health when compared with placebo (p=0.0011) [Proknee Collagen II™: 2.33 (1.78) vs. placebo 0.72 (1.32)] **(Table 4).** This change was clinically relevant with the comparator group as evident in **Table 4**.

Effect of Proknee Collagen II™ on Physical Function

WOMAC physical function scores for the three groups were identical at baseline. Day 84 demonstrated a substantial decrease in the physical function scores in the Proknee Collagen II™ and G+C groups (**Table 4**). The scores decreased by 23.95, 28.102.94 and 9.11 in the IP, comparator and placebo groups, respectively. After 12 weeks of product administration, it was found that Proknee Collagen II™ showed a statistically significant and clinically comparable result with G+C when compared with the placebo as stated in **Table 4**.

Table 4: Change in the WOMAC scores at week 12 from baseline (mITT population).

	Mean (SD)				
	Proknee Collagen II™ (n = 18)	**G+C (n= 19)**	**Placebo (n = 18)**	**p***	**p#**
WOMAC – Total	-31.44 (18.52)	-36.84 (25.66)	-12.50 (15.30)	0.0021	0.0002
WOMAC – Pain	-5.16 (3.38)	-6.10 (4.29)	-2.67 (3.31)	0.0184	0.0041
WOMAC – Stiffness	-2.33 (1.78)	-2.63 (2.11)	-0.72 (1.32)	0.0011	0.0009
WOMAC – Physical function	-23.95 (14.47)	-28.10 (19.94)	-9.11 (11.54)	0.0022	0.0001
Notes: *p-value was calculated using ANCOVA for Proknee Collagen II™ with treatment and visit as factor and baseline as covariate vs. placebo #p-value was calculated using ANCOVA for G+C with treatment and visit as factor and Baseline as covariate vs. Placebo					

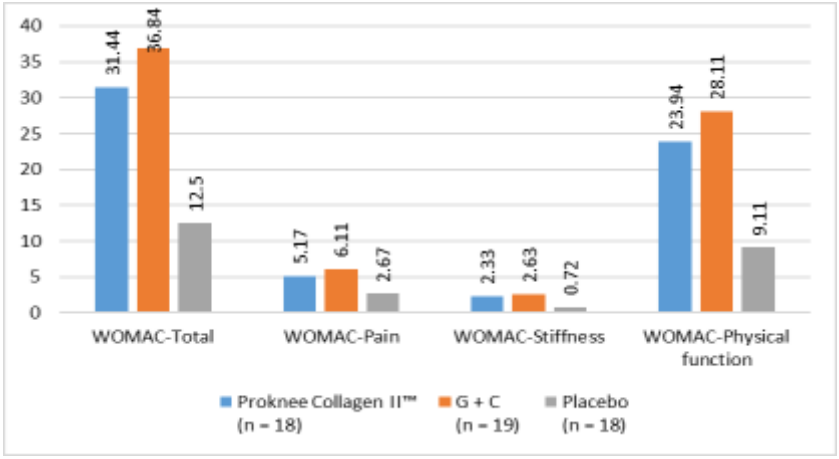

Figure 2: Change in WOMAC scores.

Effect of Proknee Collagen II™ on Quality of Life

During the baseline visit, the scores for each of the 5 domains from the total EQ-5D score were comparable between all the study groups (p>0.05). Visit-wise EQ-5D domain scores and EQ-5D VAS scores are depicted in **Figure 3** and **Table 4,** respectively. After 12 weeks of product administration, a significant difference was observed within all the five EQ-5D questionnaire domains (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Furthermore, Proknee Collagen II™ demonstrated a statistically significant change in the "usual activities" domain than in the G+C group when compared to placebo (p=0.0392 & p=0.1491, respectively). Also, a statistically significant change was observed in the Proknee Collagen II™ in the "pain or discomfort" domain than in the G + C group domain when compared to placebo (p=0.0274 & p=0.0478, respectively). As compared to placebo, a statistically significant change was noted for the EQ-5D VAS scores in the Proknee Collagen II™ group (p=0.0081) and it was clinically comparable to G+C (p=0.0042).

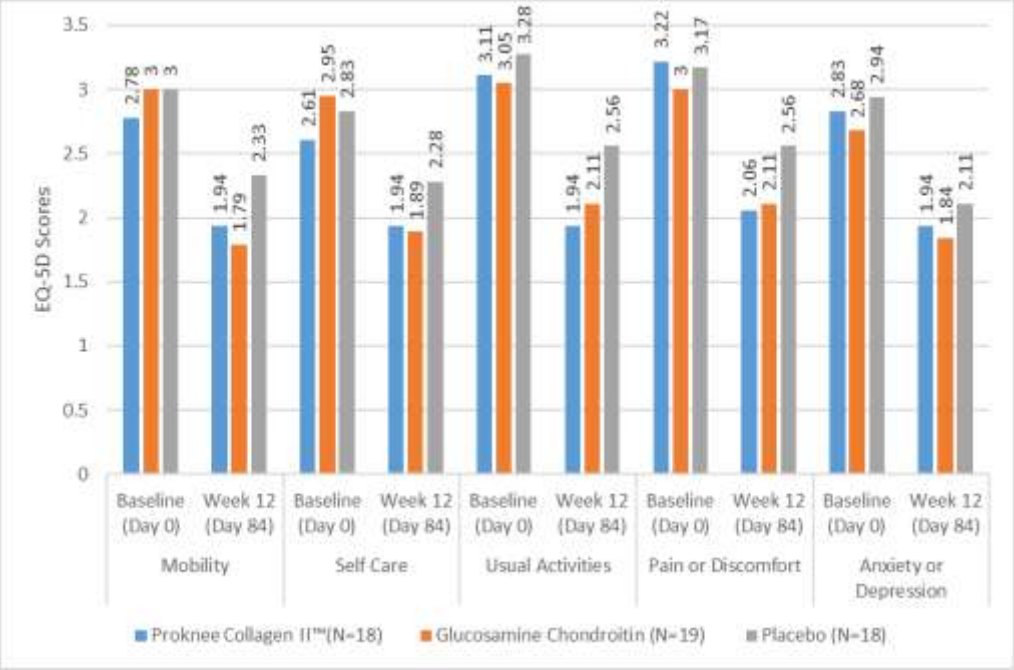

Figure 3: Visit-wise EQ-5D Domain Scores.

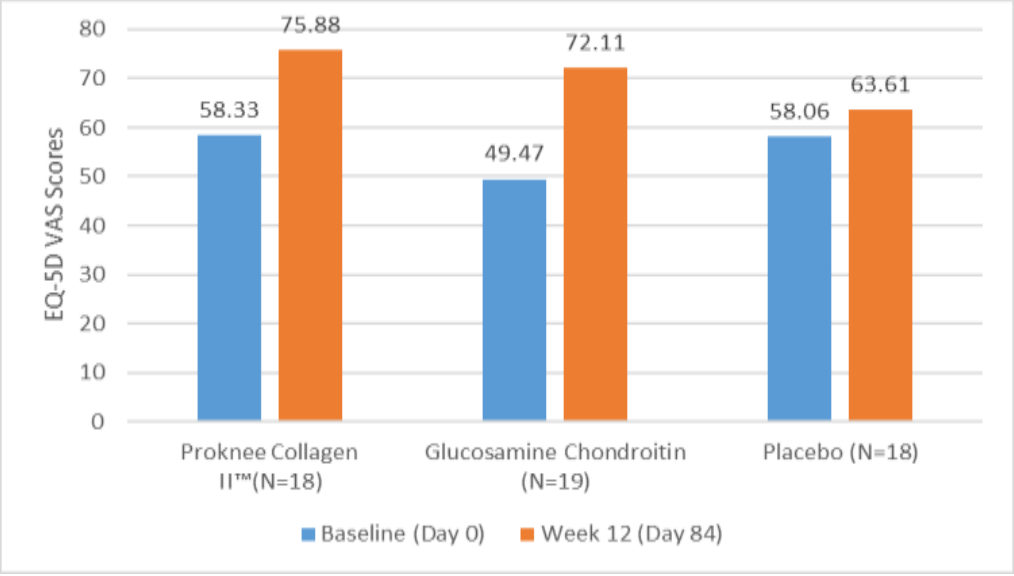

Figure 4: Visit-wise EQ-5D VAS Scores.

Safety outcomes

During the course of the study, there were no serious adverse events reported in any of the study groups. Proknee Collagen II™ was found to be safe, the product being well tolerated by the study participants.

DISCUSSION

The current study successfully demonstrated that undenatured type II collagen reduces joint pain and the elevated joint symptoms compared to placebo and also improves the quality of life. The results for the study were comparable with the G+C study group.

Our results agree with the previous findings from other studies,[15] reporting a statistically significant reduction in WOMAC total score by Proknee Collagen II™ as compared to placebo. The total mean WOMAC score in Proknee Collagen II™ reduced considerably at the end of the 12th week and can be considered as an impressive result in patients suffering from joint pain.

Past studies have shown that G+C is an effective treatment option for joint pain and other associated symptoms. Many of the studies reported that these products reduced symptoms of OA after a 12-week treatment period. Despite these findings, certain clinical trials did not show the same degree of efficacy toward OA management. These compounds were inconsistently effective individually but were seen to be effective when taken together.[21] However, despite all these trials, there were comparable results obtained for studies with Proknee Collagen II™ and the G+C combination. Based on the brief duration of action in this trial, the author believes that this finding was made. Proknee Collagen II™ group participants experienced a greater degree of reduction in WOMAC scores and thus showed an improved joint health. Further, efficacy gap between the two groups narrowed progressively with timeline. The results obtained suggest that if the study duration is extended from 3 months to 6 months, Proknee Collagen II™ may show a more superior effectiveness in the reduction of elevated symptoms associated with joint health. Moreover, a different six-month randomized trial performed by another group of researchers showed similar results. The change in the total WOMAC score was statistically significant for the undenatured type II collagen after being compared with a combination of glucosamine plus chondroitin -551 vs. -454; p=0.04).

For four months, 27 healthy subjects took undenatured type II collagen at a dose of 40 mg daily, which significantly improved knee extension when compared with placebo (81.0±1.3 vs. 74.0±2.2; p=0.011).[15] In the current study, the total mean WOMAC score was reduced by 31.44 (18.52) at 12th week in Proknee Collagen II™ group in the span of 3 months in comparison to placebo group with a mean reduction of 12.50 (15.30) (p=0.0021). This is considered a great degree of improvement in patients suffering from joint health. Proknee Collagen II™ depicted statistically significant and clinically comparable results with G+C in all the WOMAC subscales – pain, stiffness and physical function. These results suggest that undenatured type II collagen can significantly reduce symptoms associated with joint health in three months. The dosage of Proknee Collagen II™ was 40 mg/day, demonstrated much higher efficacy than the G+C combination, which was 2700 mg/day.

Severe joint pain affects a person's quality of life (QoL) because it limits their ability to perform everyday functions.[22] In the present study, an EQ-5D questionnaire was used to measure the QoL in study participants. At the end of the study, of the participants in the Proknee Collagen II™ group observed an improvement in QoL, as evident by the improvement in all the five EQ-5D questionnaire domains (mobility, self-care, usual activity, pain/discomfort, and anxiety/ depression). Thus, the present study showed that Proknee Collagen II™ provided a better improvement in QoL, which in turn increased the study participants' treatment satisfaction over placebo. These findings demonstrate that Proknee Collagen II™ was not only significantly improving knee pain, stiffness, and physical function, but was also very effective in improving patient QoL.

The study had a few limitations. The 40 mg/day dosage of Proknee Collagen II™ was compared with the G+C dose of 2700 mg/day. The study size for the present trial was also relatively smaller (n = 55). A larger population size and longer treatment duration study may help to provide a better conclusion. Even so, the present study was able to demonstrate a greater reduction of joint pain and an improved quality of life in patients with compromised joint health.

CONCLUSION

This study found that Proknee Collagen II™ was able to significantly improve the joint health and quality of life of participants, compared to placebo and to G+C, and was well-tolerated. We believe that additional studies may confirm these findings.

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Disclosure

The study was funded by the Amnutra (China) Co., Ltd., Jiaxing, Zhejaing, China. There were no conflicts of interest reported for this study.

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