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Clinical response to probiotic supplementation in patients with osteoarthritis

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ABSTRACT

Background: Amelioration of pain and symptoms in osteoarthritis (OA) is a challenge owing to potential side effects of current medications and need of its long-term use. Probiotic supplementation has a promising profile on immunomodulation, reduction in inflammation, and beneficial effect on bone metabolism. **Aims and Objectives:** The study aimed to determine the effect of probiotic supplementation in OA patients. **Materials and Methods:** This hospital-based intervention was conducted among 58 patients with OA-knee for a period from June 2021 to August 2021, who were randomized into control and interventional groups and who were asked to consume conventional curd and probiotic curd, respectively. However, data analysis was limited to 25 and 27 participants in the control and interventional groups, respectively, after 8 weeks, owing to dropouts. Anthropometric measurements, Western Ontario and McMaster Universities OA Index (WOMAC), visual analog scale (VAS) scores, and high-sensitivity CRP (hs-CRP levels) were obtained at the beginning and end of the study period. **Results:** After 8 weeks of intervention, there was a significant improvement in WOMAC and VAS scores in the interventional group as compared to the control groups. Furthermore, hs-CRP levels were significantly reduced in interventional group than the control group. **Conclusion:** Probiotics supplementation has the potential as a disease-modifying therapeutic agent in clinical management of OA knee patients, by improving WOMAC scores and VAS scores and reducing hs-CRP levels.

Key words: Osteoarthritis knee; Inflammation; Probiotics; WOMAC scores; Visual analogue scale scores; hs-CRP levels

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INTRODUCTION

Osteoarthritis (OA), a multifaceted whole joint disease, is characterized by activated chondrocytes and synoviocytes, which causes the degradation of collagen and articular cartilage.[1] Some degree of inflammation persists in all stages of OA, evident by the detection of chemokines, cytokines, and inflammatory mediators in OA synovial fluid.[2] In OA, pro-inflammatory cytokines correlate with disease progression and pain severity.[3] OA-knee-associated morbidity and pain, not only influences functional outcome in terms of mobility and productivity, but also causes financial and emotional constrains, thus affecting the quality of life of an individual.[4]

Probiotics are living microorganisms that confer health benefits to the host.[5] They ferment nondigestible carbohydrate to release bacterial metabolites such as bile moieties, short-chain fatty acids (SCFA) which ameliorate gastrointestinal tract (GIT) epithelial integrity, and fortify intestinal barrier, thus impeding abnormal colonization of bacteria and mucosal inflammation. They also enhance calcium absorption from GIT, influence bone remodeling, and promote bone metabolism.[6] SCFAs have been shown to regulate chemotaxis and suppress the production of inflammatory cytokines, thus downscaling inflammatory responses and articular degradation in OA.[7]

Along with compressive forces and hypoxia in osteoarthritic joint, innervation and angiogenesis of articular cartilage

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as well as sensitization of nociceptors have been attributed in the pathophysiology of pain.[8,9] The current pharmacotherapy for OA revolves around corticosteroids and non-steroidal anti-inflammatory drugs which are usually symptom oriented.[10] However, these are associated with temporary alleviation and in long run, may cause adverse side effects such as disruption of gastric mucosal barrier, GIT epithelial barrier, and renal dysfunction.[11] OA has been linked with GIT mucosal inflammation, which could be either drug-induced or intestinal microbiota dysbiosis.[11,12] GIT inflammation may cause translocation of lipopolysaccharides and luminal bacterial into blood which may fuel the OA pathogenesis.[10,12]

To enhance patient safety and minimize potential side effects of analgesics, pain management in OA is challenging. Hence, alternative anti-inflammatory approaches are required to arrest progression of OA. Probiotic supplementation may change the composition of gut microbiota and its metabolic output, which can effectuate as immunomodulation, reduction in inflammation, and beneficial effect on bone metabolism.[6,7,12] Hence, we assumed probiotic supplementation might help to alleviate OA symptoms and improve the functional status of the patient.

Aims and objectives

The primary objectives were to assess the changes in Western Ontario and McMaster Universities OA Index (WOMAC) and visual analog scale (VAS) scores in patients with OA-knee after probiotic supplementation. Estimation of the changes in serum levels of high-sensitivity CRP (hs-CRP) after probiotic supplementation was the secondary objective.

MATERIALS AND METHODS

This was a hospital-based intervention conducted among patients with OA-knee for a period from June 2021 to August 2021. The study design followed the Declaration of Helsinki Guidelines. Approval for the study protocol was obtained from the Institutional Ethical Committee. Participation was voluntary. Written informed consent was obtained with confidentiality assurance. No incentives or rewards were offered for the study participation.

Initial screening of the patients was done to determine their participation in the study. The inclusion criteria were (a) age ≥18 and <80 years, (b) bilateral OA of knee as per radiographic findings and confirmed by clinician using criteria of American College of Rheumatism[13], (c) degenerative OA of mild to moderate severity, and (d) regular consumption of curd.

The exclusion criteria were (a) lactose intolerance, (b) OA secondary to trauma, inflammation, rheumatoid arthritis, and congenital deformities, (c) patient for surgical joint replacement or any other procedure, (d) consumption of probiotic supplements and/or antibiotics preceding 3 months, (e) known case of thyroid/hepatic/diabetic/renal dysfunction/immunodeficiency diseases, (f) known case of inflammatory bowel disease/malabsorption disorder, (g) physically or mentally compromised, (h) use of steroids (<10 mg/day) or intra-articular injections preceding 6 months, (i) pregnancy or lactation, (j) refusal for participation, (k) the presence of factors which may interfere with participation or compliance with the study.

Sample size calculation

The total sample size for a study capable of detecting a 0.78 standardized difference with 80% power using a cutoff for statistical significance of 0.05 was estimated using the following formula.

$$N = \frac{2}{d^2} \times C_{p,power}$$

Where "n" was the number of subjects in each group, "d" was the standardized difference, and "$C_{p,power}$" was a constant defined by the "P" value and power.

Substituting the values as d=0.78 and $C_{p,power}$ = 7.9 for P=0.05 at power 80%.

$$N = \frac{2}{(0.78)^2} \times C_{0.05,80\%}$$

$$= \frac{2}{0.6084} \times 7.9$$

$$=3.29 \times 7.9$$

$$=25.99$$

The minimum number of total participants required was approximately 52, i.e., for each group, 26 participants were required.

Randomization and group design

The OA patients were subjected to face-to-face interviews and clinical examination for the eligibility of participation. The selected patients were allocated into two groups: control (consuming conventional curd) and interventional group (on probiotic yogurt) using block randomization with age- and gender-matched subjects in each block. The control group consumed their conventional curd 150 g after breakfast as well as after dinner for 8 weeks. In the interventional group, the participants were provided with probiotic yogurt containing *Lactobacillus delbrueckii* subsp., Bulgaricus, and *Streptococcus thermophilus*. They were instructed to consume 150 g after breakfast and dinner for a period of 8 weeks.

All the participants were asked to maintain their normal lifestyle and physical activity and not to consume any fermented food or medications or supplements containing probiotics during the study period. They were assessed for their compliance with yogurt consumption twice a week by telephonic interviews. The sociodemographic data included age, gender, marital status, educational qualification, and medical history.

Anthropometric measurements

Body weight was estimated using a digital weighing machine with 0.1 kg accuracy without footwear and wearing light clothes. Height was quantified to nearest 0.1 cm using a stadiometer without footwear. Body mass index was computed by dividing weight (kg) by height squared (m^2).[14]

WOMAC score

It was a self-administered, standardized index used for OA symptom severity assessment.[15] It consisted of 24 items divided into three subscales: (a) stiffness (2 items), (b) pain (5 items), and (c) physical function (17 items). Each item was rated on a five-point Likert scale "0"–"4" which corresponded to: none (0), mild (1), moderate (2), severe (3), and extreme (4). The scores for each subscale when totaled ranged from 0 to 8, 0–20, and 0–68 for stiffness, pain, and physical function, respectively. The scores for three subscales when summed yielded total WOMAC score. Higher scores on the WOMAC indicated worse pain, stiffness, and functional limitations.[16,17]

VAS scores

It was a continuous scale comprising a 10 cm (100 mm) horizontal line. The patient was instructed to mark the scale from "0" to "10" depending on pain perception where "0" indicated "no pain at all" and "10" indicated "maximal pain."[18] The VAS score was determined by measuring 10 mm from the left end of the line to the point where patient had marked. That score was interpreted as a perception of pain. It is a validated and subjective measure for acute and chronic pain, both in clinical and home settings.[19]

hs-CRP estimation

Under all aseptic precautions, 5 mL of non-fasting serum sample was collected for estimation of hs-CRP levels. The sample was processed in the Institutional Central Laboratory on the same day of collection. The quantitative estimation was done using the nephelometric method.

Anthropometric measurements, WOMAC scores, VAS scores, and hs-CRP levels were obtained at the beginning and end of the study period.

Data analysis

The collected data were organized into Microsoft excel sheet and Statistical Package for the Social Sciences version-24 was utilized for statistical analyses. The descriptive data were expressed as frequency (n) and percentages (%). The categorical variables were expressed in means and standard deviations and were analyzed by Chi-square and Fisher's exact test, depending on the distribution of data. The mean values of WOMAC, VAS, and hs-CRP among the case and control groups were analyzed using independent "t"-test. The mean values of WOMAC, VAS, and hs-CRP before and after the interventional period were analyzed using two-tailed dependent "t"-test. $P<0.05$ was adopted as a level of significance for all statistical analyses.

RESULTS

A total of 76 patients with OA knee were enrolled for this hospital-based interventional study for a period of 2 months. Of these, 18 patients were excluded due to the reasons cited in Figure 1. The 58 eligible patients were assigned into two groups, control (conventional curd) and interventional group (probiotic yogurt) using block randomization method with matched subjects in each block depending on their age and gender. During the interventional period of 8 weeks, there were 4 and 2 dropouts in the control and interventional group, respectively. Hence, at the end of 8 weeks, the data analysis was limited to 25 and 27 participants in the control and interventional group, respectively (Figure 1). None of the participants reported any adverse events throughout the study period.

The baseline characteristics of the patients from both groups before treatment they are compared and analyzed as per Table 1. There is no statistically significant difference between age and gender in both groups. Thus, both groups are age and gender matched.

The clinical characteristics of the participants before the intervention are described in Table 2. No significant variation was observed between the two groups considering age, gender, BMI, WOMAC scores, VAS scores, and hs-CRP value.

After the intervention period of 8 weeks, there was significant reduction in the scores for stiffness, pain, physical function, WOMAC scores, VAS scores and

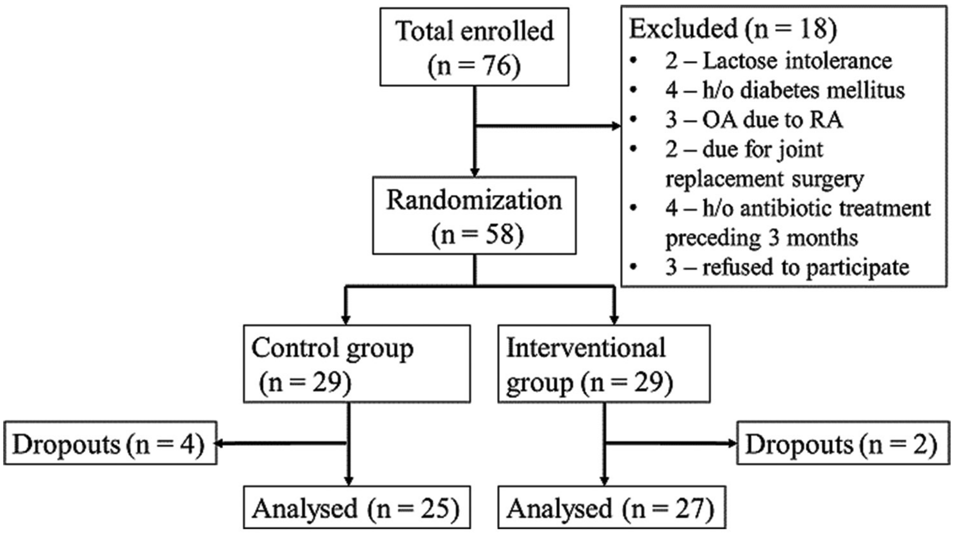

Figure 1: Flowchart showing recruitment of participants for the study. *h/o:* History *of OA: Osteoarthritis,* RA*:* Rheumatoid arthritis, *Control group – consuming conventional curd,* Interventional group – consuming probiotic curd

Table 1: Demographic characteristics of the participants

Variable	Categories	Interventional (n=27)	Control (n=25)	P-value
Age (in years)	40–50	1	3	0.6641
	51–60	7	7	
	61–70	14	12	
	>70	5	3	
Gender	Males	13	12	0.99
	Females	14	13	
Educational qualification	Illiterate	9	9	0.5588
	Primary grade	4	6	
	Matriculation	7	7	
	Intermediate	5	1	
	Graduation	2	2	
Duration of OA (in years)	0–≤	7	4	0.505
	1>1 and≤2	5	8	
	>2 and≤3	10	4	
	>3 and≤4	3	2	
	>4 and≤5	2	1	
Average BMI (kg\m^2)	-	24.40±3.40	24.51±3.35	0.844
Physical activity	Present	26	23	0.6029
	Absent	1	2	

OA: Osteoarthritis, BMI: Body mass index

hs-CRP values in the interventional group who consumed probiotic yogurt (Table 3).

However, in the controls (on conventional curd), only pain and VAS scores exhibited significant reduction after 8 weeks, whereas changes in scores for stiffness, physical function, WOMAC, and hs-CRP values remained non-significant in the control group as per Table 4.

DISCUSSION

Although previously regarded as a quintessential degenerative joint ailment, inflammation has proven its pivotal role in the pathophysiology of OA.[3] Progressive inflammation triggers cartilage destruction and osteophyte formation, resulting in synovitis, joint dysfunction, and nociception.[9,20] Intestinal dysbiosis has a critical association with inflammatory and metabolic diseases, though the exact mechanism still needs to be defined. However, dietary intervention favorable for gut microbiome environment may ameliorate symptoms, especially as alleviation of pain and stiffness.[21]

In the present study, hs-CRP levels were raised in both groups.[22] This finding correlates with several studies substantiating the link between inflammation and OA.[2,20] Punzi et al., highlighted the potential role of hs-CRP as clinical biomarker to assess disease severity, especially in erosive OA.[23] hs-CRP levels were significantly higher in erosive OA as compared to non-erosive OA, thus reflecting

Table 2: Clinical characteristics of participants before the intervention

Variable	Interventional (n=27)	Control (n=25)	P-value
WOMAC score			
Stiffness	9±1.71	7.12±1.64	<0.0001*
Pain	3.923±0.828	3.76±1.128	0.5531
Physical function	30.37±4.226	29.48±4.840	0.4824
Total	42.296±5.29	39.28±5.726	0.0539
VAS score	6.481±0.57	6.32±0.690	0.3642
hs-CRP values	9.926±1.517	9.36±1.604	0.1969

WOMAC: Western ontaria and Mcmaster universities osteoarthritis index, VAS: Visual analogue scale, hs-CRP: High sensitivity C-reactive protein, * - statistically significant, *P*<0.05

Table 3: Clinical characteristics of interventional group (n=27) before and after intervention

Variable	Before	After	P-value
WOMAC score			
Stiffness	9±1.71	7.481±1.22	0.004*
Pain	3.923±0.828	2.26±0.446	0.001*
Physical function	30.37±4.226	24.815±4.59	0.001*
Total	42.296±5.29	30.556±3.964	<0.0001*
VAS score	6.481±0.57	4.936±0.518	<0.0001*
hs-CRP values	9.926±1.517	6.815±1.86	<0.0001*

WOMAC: Western Ontaria and McMaster universities osteoarthritis index, VAS: Visual analog scale, hs-CRP: high sensitivity C-reactive protein, * - statistically significant, P<0.05

Table 4: Clinical characteristics of control group (n=25) before and after intervention

Variable	Before	After	P-value
WOMAC score			
Stiffness	7.12±1.64	6.76±1.69	0.4484
Pain	3.76±1.128	2.92±0.49	0.0013*
Physical function	29.48±4.840	27.5±5.172	0.1687
Total	39.28±5.726	38.08±6.56	0.4941
VAS score	6.32±0.690	5.9±0.6377	0.0301*
hs-CRP values	9.36±1.604	8.64±1.497	0.1074

WOMAC: Western Ontaria and McMaster universities osteoarthritis index, VAS: Visual analog scale, hs-CRP: high sensitivity C-reactive protein, * - statistically significant, P<0.05

the disease activity. However, the meta-analysis by Jin et al., emphasized more on the association of hs-CRP levels with symptoms such as pain and reduced physical functions rather than radiographic features of OA.[3]

In our current clinical response to probiotic supplementation in patients with OA knee, results showed that daily consumption of suggested probiotic yogurt for 8 weeks exhibited a beneficial effect on the values of WOMAC and VAS score among the patients with OA. Similar improvement in OA knee symptoms was observed after probiotic supplementation of *Lactobacillus casei* Shirota and *Streptococcus thermophilus* by Lei et al.,[24] and Lyu et al.,[25] in their respective clinical studies.

The present study revealed that probiotic yogurt treatment also significantly reduced the serum levels of hs-CRP in patients with OA as compared to control group, similar to findings by Lei et al.[24] Thus, administration of probiotics has shown clinical and biochemical improvement in patients with OA. Animal model studies by Korotkyi et al.,[26] Amdekar et al.,[27] and So et al.,[28] presented convincing evidence that probiotic supplementation had the prospect of arthritis modulation by downregulating the expressions of pro-inflammatory cytokines and matrix metalloproteinases production, synovial infiltration, cartilage destruction, and pannus formation. In addition, several studies have shown the beneficial effects of probiotics in articular manifestations in rheumatoid arthritis and intestinal bowel diseases as well.[29,30]

The present study demonstrated the potential of probiotics as a disease-modifying therapeutic agent in OA patients, by improving WOMAC scores and VAS scores and reducing hs-CRP levels. Although the exact mechanism of reduction of hs-CRP is still under quest, several hypothesis have been proposed to explicate the influence of probiotics on inflammation. These include increase in ratio of Lactobacilli and Bifidobacterium species to pathogenic microbes, reduced translocation of gut microbes and their toxic metabolites, SCFAs-induced reduction in hepatic synthesis of CRP, increase in glutathione levels which scavenges free radicals, restoration of GIT epithelial barrier, modulation of mucosal innate immunity, etc.[31-34]

Limitations of the study

The findings of the study need to be interpreted with the consideration of few limitations. WOMAC scores and VAS scores were self-reported, hence were subjective endpoints. The sample size was small, hence prone for larger effect sizes and overestimation of treatment effects.[35] Furthermore, it may not be representative of large population. The results were, however, significant enough to show a substantial positive deviation in the study. Increase in the sample size as well as study duration would facilitate generation of replicable and evaluable data which can be extrapolated to entire population.

CONCLUSION

Based on the observations and results in the study of clinical response to probiotic supplementation in patients with knee OA conducted for 2 months, the supplementation of probiotics reduced the OA symptoms to a noteworthy amount. The differences in WOMAC, VAS, and hs-CRP results for before and after the supplementation were noticeable. Thus, probiotics have a promising profile to reduce inflammation and improve functional outcomes in OA patients.

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