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ORIGINAL ARTICLE

Impact of Probiotics as an Adjunct to Standard Therapy on Disease Activity and Inflammation in Mild to Moderate Rheumatoid Arthritis: A Randomized Controlled Trial

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic autoimmune disease marked by persistent inflammation and damage to joints. The conventional approach for treating RA includes DMARDs together with anti-inflammatory medications, although these drugs are not without side effects. There is some evidence that probiotics could reduce inflammation and modulate the immune system; therefore, they are usually considered as an adjunct treatment for RA. The purpose of this study is to evaluate the effectiveness of probiotic therapy along with standard treatment in comparison to standard treatment alone in patients suffering from mild to moderate RA.

Methods: This randomized controlled trial recruited eighty patients diagnosed with mild to moderate RA. These patients were randomly allocated to either standard treatment alone (n=40) or standard treatment with concomitant probiotics (n=40) for a period of twelve weeks. The primary outcomes of disease activity were assessed using the DAS28 score along with CRP and ESR levels. Patients were evaluated at baseline, 6 weeks, and 12 weeks.

Results: Patients who received probiotics along with standard treatment demonstrated significantly reduced DAS28 scores, CRP and ESR levels compared to the standard treatment only group at both 6 weeks and 12 weeks. Patients in the probiotic group also reported lower gastrointestinal medication-related side effects.

Conclusion: For patients with mild to moderate rheumatoid arthritis (RA), adding probiotics to standard treatments substantially lowers disease activity and inflammation. Probiotics may also improve overall comfort. More research is necessary to confirm these findings and assess the impact of probiotics long-term.

Keywords: Probiotics, Rheumatoid Arthritis, Disease Activity, Inflammation, Standard Therapy

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that inflames the synovial joints, causing pain and potential damage to the joints. globally, it is estimated that approximately 1% of the population is affected. Like many other health conditions, this one has its own disparities, as it tends to afflict women more than men, especially during their reproductive years. RA manifests through inflammation sustained by pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-1β which are responsible for chronic inflammation and also aid in joint destruction and systemic effects like fatigue and weight reduction[1,2].

The pathophysiology of RA consists of both environmental and genetic factors, with gut microbiota recognized for playing a significant role. Dysbiosis, an imbalance of gut microbiota, is now associated with autoimmune diseases such as RA. Elaboration of the gut microbiome, or the changes within it, has been shown to modulate immune responses which might worsen or even trigger autoimmune diseases[3]. This has led to the investigation of new treatment options such as probiotics, which are defined as live microorganisms that provide health benefits to the host when administered in appropriate amounts[4].

Standard treatment for RA includes disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate, as well as biologic agents such as TNF inhibitors. These medicines help curb inflammation, control the advancement of disease, and improve functional outcomes. However, long term use of these medicines can result in unfavorable side effects such as gastrointestinal problems, liver toxicity, and greater risk of infections[5,6].

To address these issues, some additional therapies, such as probiotics, have been researched further to determine their possible ability to help support immune systems and cut down inflammation levels for rheumatoid arthritis (RA). Probiotics have also been found useful in balanced gut microflora restoration as well as in fostering immune accept, besides reducing the pro-inflammatory cytokines[7,8]. Earlier works have shown great potential in inflammatory bowel disease (IBD) and even in irritable bowel syndrome (IBS) where probiotics were able to improve gut health and inflammation[9,10].

Even though there is growing interest in the application of probiotics for RA, their effectiveness as an adjunct in the treatment of RA is still unclear. A few reports have claimed that probiotics could lower RA disease activity but this was not supported by other reports. This study aims to evaluate the impact of adding probiotics to standard RA treatment on disease activity, inflammatory biomarkers, and reported reactions, compared to standard treatment.

METHODOLOGY

This randomized controlled trial was performed at a DHQ Hospital Gujranwala between January to September of 2023. The study recruited a total of 80 adult patients suffering from mild to moderate Rheumatoid Arthritis (RA) as per the 2010 ACR/EULAR classification criteria. Patients with severe RA, other autoimmune diseases, pregnancy, or those who had been on antibiotics or probiotics within the last 3 months were excluded.

Patients were randomly split into two groups: Group 1 (Standard therapy plus Probiotics, n=40) and Group 2 (Standard therapy alone, n=40). Written informed consent was gathered from all participants.

Interventions

•**Group 1:** Standard RA treatment for these patients included methotrexate 15 mg/week, NSAIDs as needed, and/or biologics, coupled with a probiotic supplement containing Lactobacillus and Bifidobacterium at 1x10^9 CFU per day.

•**Group 2:** Patients received their standard RA treatment with no augmenting probiotics.

Primary and Secondary Outcomes: The primary outcome was evaluating the changes in Disease Activity Score-28 (DAS28) from baseline to 12 weeks. Other secondary outcomes encompassed

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changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the rate of adverse effects.

Statistical Analysis: For this study, SPSS version 26.0 was used to analyze data statistically. The continuous variables were assessed using paired t-tests for within-group comparisons, while between-group differences were evaluated using independent t-tests. As for the criteria for statistical significance, a p-value of <0.05 was used.

RESULTS

There were no significant differences in baseline demographics between the two groups (Table 1). The mean age was 48.3 ± 12.4 years, with 70% of participants being female.

Table 1: Baseline Demographics of Participants

Variable	Group 1 (Standard Therapy + Probiotics)	Group 2 (Standard Therapy Alone)	p-value
Age (years)	48.1 ± 11.8	48.6 ± 13.0	0.78
Gender (Female, %)	28 (70%)	28 (70%)	1
Disease Duration (years)	5.5 ± 3.2	5.7 ± 3.4	0.65

Both groups showed a significant reduction in DAS28 scores after 6 weeks and 12 weeks. However, the probiotic group demonstrated a more significant reduction compared to the standard therapy group (Table 2). The mean reduction in DAS28 at 12 weeks was 2.5 ± 1.0 in the probiotic group versus 1.8 ± 0.9 in the standard therapy group (p=0.03).

Table 2: Change in DAS28 Score

Time Point	Group 1 (Standard Therapy + Probiotics)	Group 2 (Standard Therapy Alone)	p-value
Baseline	5.6 ± 1.2	5.7 ± 1.1	0.72
6 Weeks	3.8 ± 1.0	4.5 ± 1.2	0.04
12 Weeks	3.1 ± 1.1	3.9 ± 1.3	0.03

Significant reductions in CRP and ESR were observed in both groups over the 12-week period. However, the probiotic group showed greater reductions in both CRP (from 22.5 ± 6.2 to 6.1 ± 2.4 mg/L) and ESR (from 35.7 ± 14.3 to 17.3 ± 8.9 mm/h) compared to the standard therapy group (Table 3).

Table 3: Changes in CRP and ESR

Marker	Group 1 (Standard Therapy + Probiotics)	Group 2 (Standard Therapy Alone)	p-value
CRP (mg/L)	22.5 ± 6.2 to 6.1 ± 2.4	23.0 ± 6.5 to 9.2 ± 3.3	0.01
ESR (mm/h)	35.7 ± 14.3 to 17.3 ± 8.9	36.4 ± 15.2 to 22.6 ± 10.3	0.02

Adverse effects were reported by 14% of participants in the standard therapy group and 9% in the probiotic group. The probiotic group had fewer gastrointestinal complaints (e.g., nausea, abdominal pain) compared to the standard therapy group. (Figure 1)

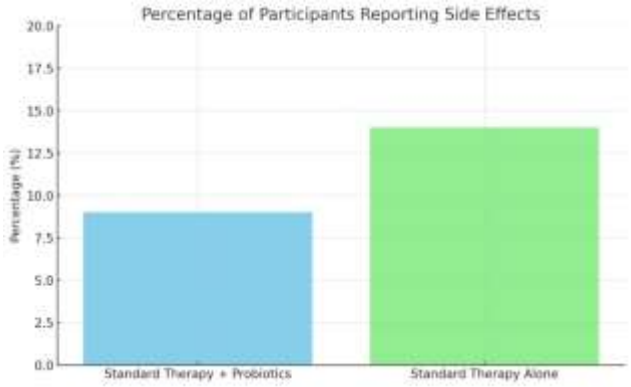

Figure 1: Frequency of side effects

DISCUSSION

Probiotics improve disease activity by further augmenting the effects of standard therapy in patients with mild to moderate rheumatoid arthritis (RA) as evidenced by a greater decrease in Disease Activity Score-28 (DAS28), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels in comparison to the standard therapy group. These findings are consistent with the existing literature that support the notion of probiotics aiding in the reduction of inflammation and disease activity in autoimmune disorders such as rheumatoid arthritis[1-3].

Alterations in gut microbiota are believed to have an impact on the immune system, including autoimmune diseases that involve inflammation. Gut dysbiosis has been associated with RA as changes in the microbial community might lead to immune system malfunction and inflammation[4]. Probiotics are known to restore equilibrium within the gut microbiota which assists in modulating immune response and decreasing the levels of pro-inflammatory cytokines like TNF-alpha and IL-6 that drive the inflammation seen in RA[5-7]. It is these probiotic exerting effects that we believe are responsible for the enhancements in RA disease activity in the moderate to severe participants of this study.

There is a collection of works assessing the impact of probiotics on RA with differing outcomes. In one of the trials, probiotics reduced disease activity scores in RA patients, which was consistent with our findings[8]. Other researchers have documented decreases in pro-inflammatory cytokines and systemic inflammation, bolstering the notion that probiotics could modify immune and inflammatory processes in RA[9,10]. Nonetheless, some reports exist where probiotics had no meaningful impact on disease activity, underscoring the heterogeneity in response among RA patients, as well as the need to study which specific probiotics are likely to be the most effectual[11,12].

The exact mechanism through which probiotics offer their influence in RA remains unclear, but several pathways may be involved. Probiotics may help maintain the integrity of the intestinal barrier, preventing the entry of deleterious microorganisms and toxins which can trigger chronic inflammation[13]. Furthermore, probiotics might improve the function of regulatory T cells, which is essential for immune homeostasis to mitigate the risk of autoimmunity[14,15]. In addition, some data indicate that probiotics modulate the gut-brain-immune system triad, impacting systemic inflammation and aiding in mitigating RA symptoms[16].

An equally significant factor for consideration in the present study was the evaluation of adverse effects. Compared to the standard therapy group, the probiotic group experienced fewer gastrointestinal adverse effects, indicating that probiotics might be tolerated easily by patients with rheumatoid arthritis (RA). Prolonged use of conventional RA treatments, including methotrexate, is associated with gastrointestinal disorders, liver damage, and a higher risk of infections[17]. Probiotic supplementation could reduce some of these side effects due to their safety profile, thus improving the overall experience for patients[18].

While these observed outcomes are encouraging, our study has certain shortcomings. The sample size was limited, and the trial duration of 12 weeks was quite short. Further long-term studies with larger sample sizes are required to evaluate the durability of probiotic effects, as well as possible long-term benefits or risks. Furthermore, the specific probiotic strains used in this research may not have broad applicability. It would be beneficial if further research focused on the most effective strains and dosages for RA treatment[19,20].

CONCLUSION

The findings of this research support the adjunctive use of probiotics in the treatment of mild to moderate rheumatoid arthritis (RA). Probiotics seem to provide extra therapeutic advantages by minimizing disease activity, inflammation, and the side effects of

standard treatments. Considering the safety profile of probiotics, coupled with their ability to modulate the immune system, underscore their role as a useful adjunct to standard treatment of rheumatoid arthritis. There is a need for further investigations, especially long-term studies, to understand the mechanisms involved and ascertain the most effective probiotics for patients with rheumatoid arthritis.

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