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# Effectiveness of Probiotics and Standard Therapy Versus Standard Therapy Alone in Patients of Mild to Moderate Rheumatoid Arthritis

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## ABSTRACT

Analgesics, steroids and disease modifying anti-rheumatic drugs (DMARDs) are the cornerstone of treatment in rheumatoid arthritis (RA). **Objective:** To determine effectiveness of probiotics, introduced to standard treatment, in improving Disease Activity Score 28 (DAS-28) in patients with mild to moderate rheumatoid arthritis, when given for a period of three months. **Methods:** This randomized controlled trial registered under ClinicalTrials.gov ID: NCT06594822, was conducted on diagnosed cases of rheumatoid arthritis presenting to Mayo hospital, Lahore from 24th August 2023 till 23rd February 2024. Eighty-eight patients were recruited employing simple random sampling techniques and were categorized into two groups. Group A received standard therapy along with probiotics whereas Group B received standard therapy alone. DAS-28 score was assessed at baseline, at 45 and 90 days. **Results:** Patients in Group A showed an effective reduction in DAS-28 of 22.7% compared to 6.8% in group B ($p=0.035$). DAS-28 score in group A and B at baseline was $3.67 \pm 0.61$ vs $3.63 \pm 0.52$, $p=0.708$, after 45 days was $3.15 \pm 0.63$ vs $3.49 \pm 0.56$, $p=0.010$ and after 90 days was $2.93 \pm 0.75$ vs $3.27 \pm 0.52$, $p=0.015$. During treatment at days 45 and 90, group A patients showed a greater decrease from baseline i.e., $-0.52 \pm 0.63$ vs $-0.14 \pm 0.56$, $p<0.010$ and $-0.74 \pm 0.75$ vs $0.36 \pm 0.52$, $p<0.015$ than group B patients. Group A also had a significant improvement in mean DAS-28 score at days 45 and 90 ($p<0.05$). **Conclusion:** Daily supplementation of probiotics with standard treatment is effective for the alleviation of symptoms and disease severity in patients having mild to moderate rheumatoid arthritis.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated, progressive inflammatory disorder that causes joint pain, peri-articular soft tissue swelling, morning stiffness, reduced functional status, with osteoporosis and cartilage destruction leading to profound disability [1]. The worldwide prevalence of RA ranges from a mean point prevalence of 0.56% (SD 0.51) to a mean period prevalence of 0.51% (SD 0.35). A higher point to period prevalence is reported in the urban setting (0.69% vs 0.48%) compared to 0.54% vs 0.25% in the rural settings [2]. The age group affected is 20-40 years with increased susceptibility in the 75 and older individuals [3]. Female tend to have three to four times higher preponderance compared to male [4]. Apart from synovial joint inflammation, bone and cartilage deformities, there is production of antibodies namely Rheumatoid Factor (RF) and anti-cyclic citrullinated protein/peptide (Anti- CCP) antibodies [5]. Being a systemic disorder, inflammation tends to affect the heart, lungs, skeletal tissue and bone. Higher mortality is attributed to the increased risk of diabetes, asthma, bronchogenic carcinoma, chronic obstructive pulmonary disease, hypertension, cardiac and renal problems [6]. Although the exact etiopathogenesis of RA remains obscure, there appears to be a complex interaction of genetic, environmental, socioeconomic factors, dietary influences and imbalance of gut microbiota [7]. The current treatment recommendations for RA range from the simpler non-steroidal anti-inflammatory drugs (NSAIDs),

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corticosteroids mainly glucocorticoids like prednisone, conventional disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, to more advanced biologic agents like infliximab, anakinra, abatacept, adalimumab to name a few and newer targeted synthetic DMARDs like baricitinib, tofacitinib etc. All these drugs mainly work my reducing inflammation and pain thereby leading to a reduction in tissue degradation and cellular damage and slowing the advancement of the disease [8]. The pathogenesis of RA involves cellular activation leading to autoimmunity in joints and other organs manifesting as synovial inflammation and joint injury with fibroblast-like synoviocytes (FLS) playing a key role in the inflammatory process [9-11]. People with RA have intestinal inflammation leading to changes in the gastrointestinal homeostasis and enhanced gut permeability causing leakage of harmful bacteria from the gut to the rest of the body [12]. Cytokines are released due to proinflammatory responses generated by the increased number of bacterial lipopolysaccharides present in the bloodstream as well as their build-up in the synovial joints [13]. A normal gut bacteria *Prevotella* spp. which is an anaerobic, non-spore forming bacteria, also constitutes an etiological factor for RA. By activating Toll-Like Receptors-2 (TLR-2) receptors in the intestinal epithelium and stimulating the secretion of proinflammatory cytokines like Interleukin-1β (IL-1β), IL-6 and IL-23, it produces inflammation and initiates RA by causing cartilage destruction and bone damage attributed to increased TNF-α [14]. Probiotics, the living organisms responsible for improving host microbiota and imparting health benefit when taken orally, have the potential to treat immune-mediated forms of arthritis by preserving equilibrium between beneficial and pathogenic bacteria in the body [15]. Numerous clinical trials have demonstrated the anti-inflammatory effects of probiotics supplementation in alleviating the symptoms of RA [16]. Various species of probiotics namely Lactobacillus spp. and Bifidobacterium spp. have been widely investigated. Owing to their anti-inflammatory effects on the intestines, probiotics mixture reduces IL-6 and TNF-α levels, nitric oxide metabolites and improved total antioxidant capacity thereby leading to alleviation of the symptoms of RA [17]. *Lactobacillus casei* 01 has been used in several randomized clinical trials and has shown to decrease proinflammatory cytokines, reduce global wellness score (gauged by visual analogue scale VAS), improve DAS-28 score and tender and swollen joint counts [18]. The addition of *Lactobacillus* and *Bifidobacterium* to diet produces anti-inflammatory short-chain fatty acids (SCFAs) which are beneficial to the gut [19].

This study aims to utilize *Bacillus clausii* in addition to DMARDs in patients having mild to moderate RA. The objective was to document symptom improvement in terms of reduction in DAS-28 score of ≥0.6 from baseline by recording symptoms on basis of European League Against Rheumatism (EULAR) response rates.

## METHODS

This randomized controlled trial recruited patients presenting to the Rheumatology out-patients department of the Department of Medicine, King Edward Medical University, Mayo hospital, Lahore from 24th August 2023 till 23rd February 2024. The study was registered with ClinicalTrials.gov Identifier as NCT06594822, and approval was taken from Institutional Review Board (IRB) of King Edward Medical University vide No. 169/RC/KEMU. A sample size of 88 (44 in each group) was calculated by taking confidence level of 95%, absolute precision as 10% and expected percentage of efficacy in probiotic group as 20.11% and in standard therapy as 7.22% [20]. A total of 88 patients of both genders, between the age range of 18 to 70 years and having an established diagnosis of rheumatoid arthritis (proven on history, X-rays and biologic markers like RF and Anti-CCP antibodies, ESR) and having mild to moderate disease activity (DAS-28 score between 2.6 to <5.1) were selected via simple random sampling. Patients treated previously for RA with probiotics and those with a history of allergy to probiotics, patients with mixed connective tissue disorder and overlap syndrome as per history and labs, those with a history of gastrectomy, renal failure and liver cirrhosis, patients with recent or current use of antibiotics, pregnant patients and lactating mothers were excluded from the study. After approval, all patients conforming to the selection criteria were registered for the study. Informed written and verbal consent was obtained from all the participants. Patient's demographic data were obtained and recorded in a predesigned proforma. Patients were divided into two groups by computer generated method. Group A comprised 44 patients who received standard therapy (analgesics mainly diclofenac sodium 50mg thrice a day, glucocorticoids i.e., prednisone 10mg daily, DMARD mainly methotrexate 10mg weekly but sulfasalazine 1g twice a day in child- bearing age female) along with probiotic (*Bacillus clausii* in ampoule form containing 2 billion per 5ml once daily), whereas Group B also comprising 44 patients received standard therapy alone. Lab investigations like complete blood counts (CBC), Erythrocyte Sedimentation Rate (ESR), liver function tests (LFTs) and renal function tests (RFTs) were done at baseline and on follow up visits at 45 and 90 days. Disease activity score (DAS-28) consisting of 28 tender joint count (range 0-28), 28 swollen joint count (range 0-28), ESR and patient global assessment based on a visual analog scale (range 0-100) was assessed at baseline then on each subsequent visit to monitor response to treatment. Effectiveness was

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defined in terms of reduction of DAS-28 score of ≥0.6 from the baseline based on European League against Rheumatism(EULAR)response rates as given in Table 1.

**Table 1:** : Improvement in DAS-28 Score among study participants

| Present DAS-28 Score | Improvement in DAS-28 Score | | |
|---|---|---|---|
| | >1.2 | >0.6 and ≤1.2 | ≤0.6 |
| ≤3.2 | Good Response | Good Response | No Response |
| >3.2 and ≤5.1 | Moderate Response | Moderate Response | No Response |

Pancytopenia, derangement in LFTs and RFTs twice from the baseline because of treatment resulted in exclusion from the study. Data were interpreted using computer software Statistical Package for Social Sciences (SPSS) version 26.0. Mean ± SD were used for the calculation of quantitative variables including age and DAS-28 score. Qualitative variables including gender were expressed in the form of frequency and percentages. Chi- square test was employed to compare response between the two groups. p-value≤0.05 was considered statistically significant.

## RESULTS

Out of a total of 88 enrolled patients, 44 were assigned to each group. The mean age of patients in group A was 56.64 ± 6.80 years and in group B, 58.07 ± 7.40 years with a p-value of 0.348. A female preponderance was observed in both the study groups. In group A, male comprised 15(34.1%) of the patients whereas 29(65.9%) of the patients were female and in group B, male patients constituted 13(29.5%) and female 31(70.5%) with a p-value of 0.647. The male to female ratio in group A was 1:1.93 and in group B it was 1:2.39. The mean DAS-28 score in group A and B at baseline was 3.67 ± 0.61 and 3.63 ± 0.52 with a p-value of 0.708. During follow-up at 45 days, it was reported to be 3.15 ± 0.63 and 3.49 ± 0.56 in Group A and B respectively with a p-value of 0.010 and at the end of treatment at 90 days, mean DAS-28 scores were 2.93 ± 0.75 in Group A and 3.27 ± 0.52 in Group B with a p-value of 0.015. The p-values calculated during follow-up and end of treatment were both found to be statistically significant indicating effective treatment response in the probiotic group, i.e., Group A as depicted in Table 2.

**Table 3:** Results of DAS-28 Score in Study Groups

| DAS-28 scores | Group | N | Mean ± SD | Mean Difference | p-value |
|---|---|---|---|---|---|
| At Baseline | Group A | 44 | 3.67 ± 0.61 | - | 0.708 |
| | Group B | 44 | 3.63 ± 0.52 | - | |
| After 45 Days | Group A | 44 | 3.15 ± 0.63 | -0.52 | 0.010 |
| | Group B | 44 | 3.49 ± 0.56 | -0.14 | |
| After 90 Days | Group A | 44 | 2.93 ± 0.75 | -0.74 | 0.015 |
| | Group B | 44 | 3.27 ± 0.52 | -0.36 | |

Group A: Standard treatment plus probiotic; Group B: Standard treatment alone

Effectiveness monitored in terms of a reduction in DAS-28 score of ≥0.6 was noted in 10 (22.7%) patients in Group A while it was observed in only 3 (6.8%) patients in Group B. This is given in a tabulated form in Table 3. A graphical representation of treatment response in both the groups is given in Figure 1.

**Table 3:** Effectiveness of Treatment in Study Groups

| Effectiveness | Groups | | Total | p-value |
|---|---|---|---|---|
| | Group A (Standard Therapy Plus Probiotic) | Group B (Standard Therapy) | | |
| Yes | 10 | 3 | 13 | 0.035 |
| | 22.7% | 6.8% | 14.8% | |
| No | 34 | 41 | 75 | |
| | 77.3% | 93.2% | 85.2% | |
| **Total** | 44 | 44 | 75 | |
| | 100.0% | 100.0% | 100.0% | |

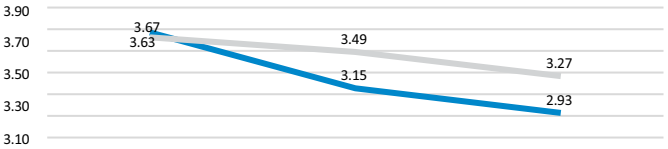


**Figure 1:** Comparison of DAS-28 Scores in Response to Treatment

## DISCUSSION

Rheumatoid arthritis, a disease that not only affects the joints leading to bone and cartilage destruction, it also markedly reduces the overall functional capacity. A higher mortality rate in RA patients is attributed to an increased likelihood of other co-morbidities like diabetes, hypertension, lung, kidney diseases, psychological problems and cancer [6]. Keeping the complex pathogenesis in mind involving the genetic, immunologic and environmental factors, research has continuously been searching for novel therapeutic options [7]. Although the early initiation of DMARDs as soon as the diagnosis of RA is established has proven beneficial, but the variable progressive nature of the disease warrants a more aggressive treatment approach that not only controls the symptoms but also decelerates the advancement of the disease. Biologic agents like TNF inhibitors, IL-6 inhibitors, Janus kinase inhibitors, all specifically target the molecules implicated in the inflammatory cascade. These agents have demonstrated significant effectiveness but at the expense of being very costly and having numerous side effects that demand careful observation and hematological tests. This high cost and adverse effect profile has intrigued the researchers to utilize a more comprehensive and holistic approach and devise supplementary therapies that are both cost-effective and have a better safety profile. As RA causes significant alterations in the gut microbiota, the use of probiotics as complementary therapy emerged. Literature search

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revealed various studies mainly conducted on laboratory rats and demonstrated the beneficial role of probiotics in rheumatoid arthritis. Rudbane *et al.*, conducted a systematic review and meta-analysis and demonstrated the role of *L. caseii* when given as an adjuvant to standard therapy in patients of active RA and showed a considerable improvement in CRP levels in these patients [20]. No effect on improvement in DAS-28 score was reported in this meta-analysis. A study conducted in Brazil on 42 patients used a combination of probiotics namely *Lactobacillus casei, Lactobacillus acidophilus, Lactococcus lactis, Bifidobacterium lactis* and *Bifidobacterium bifidum* for a period of 60 days. They concluded that probiotic combination led to a significant reduction in white cell count, TNF-α, IL-6 and NO metabolites and an increase in antioxidant parameters [21]. Alipour *et al* showed a significant improvement in DAS-28 score as well as EULAR response rates in patients who received probiotics [22]. A study undertaken by Zamani *et al*. administered 3 different strains of probiotics namely *Lactobacillus acidophilus, Lactobacillus caseii* and *Bifidobacterium bifidum* to a group of 30 RA patients and compared it with a placebo. After 8 weeks of intervention, he observed a significant improvement in DAS-28 score (-0.3 ± 0.4 vs -0.1 ± 0.4, p=0.01) and high sensitivity C- reactive protein (hsCRP) concentrations (-6.66 ± 2.56 vs. +3.07 ± 5.53mg/L, p<0.001) [23]. The results of this study were congruent with current results as 22.7% of patients taking a probiotic with standard therapy showed an improvement in DAS-28 score compared to only 6.8% of the patients taking standard therapy alone. The effectiveness of probiotics in treating RA was also shown by Yuan *et al* [9]. According to their research, probiotics improve DAS-28 score in RA patients but have limited impact on IL-6, IL-10, and ESR. All these studies, systematic reviews and meta-analyses have not yet provided sufficient data that can help the healthcare policy makers to formulate recommendations for regular use of probiotics in RA patients. Selection of the probiotic, using the optimal dose and appropriate treatment duration are all crucial and case-specific and demand extensive workup when considering their role in the management of RA. To gauge and assess treatment response, we also recommend easy availability and routine monitoring of immunologic markers like cytokines. Although probiotics cannot replace the standard treatment for RA but if proved effective on a large scale, they can be recommended as an adjunct to standard therapy in treating RA patients. There were certain limitations of current study like small sample size, use of only one type of probiotic, shorter duration of therapy and no use of assays for cytokine measurements.

## CONCLUSIONS

It was concluded that the addition of probiotics to standard therapy in the treatment of mild to moderate RA patients is effective in terms of improving DAS-28 score, reducing pain, swelling and tenderness of joints. Therefore, it leads to improved quality of life and functional status.

## Authors Contribution

Conceptualization: GI
Methodology: TN
Formal analysis: BA, YI
Writing review and editing: TN, TF, AI

All authors have read and agreed to the published version of the manuscript

## Conflicts of Interest

The authors declare no conflict of interest.

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