Does Probiotic Supplementation Help Decrease Pain and Number of Tender Joints in Adults with Rheumatoid Arthritis?

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Does probiotic supplementation help decrease pain and number of tender joints in adults with rheumatoid arthritis?

Brittany Snyder, PA-S
A SELECTIVE EVIDENCE BASED MEDICINE REVIEW
In Partial Fulfillment of the Requirements For
The Degree of Master of Science
In
Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “probiotic supplementation helps decrease pain and number of tender joints in adults with rheumatoid arthritis?”

STUDY DESIGN: Review of three double-blind, randomized control trials published between 2008 and 2018. All studies were published in English in peer reviewed journals.

DATA SOURCES: Three double-blind, randomized control trials were found via PubMed.

OUTCOMES MEASURED: The outcomes measured included number of tender joints from baseline to end of study counted by an investigator, visual analog scale (VAS) for pain severity, and a Stanford Health Assessment Questionnaire visual analog scale (HAQ VAS) for pain severity.

RESULTS: Two of the three articles found a statistically significant reduction in either patient pain or number of tender joints. Alipour et al. found a mean statistical decrease in 0.72 tender joints. Mandel et al. found a 19.8% decrease in patient pain compared to a 1.6% reduction in pain in the placebo group. Zamani et al. found no statistically significant effect of probiotics on patient pain.

CONCLUSION: There is conflicting evidence as to whether probiotic supplementation improves pain and number of tender joints in adults with rheumatoid arthritis. Further research is needed to determine the true effectiveness of probiotic supplementation on pain and number of tender joints in patients with rheumatoid arthritis.
INTRODUCTION

Rheumatoid Arthritis (RA) is a complicated autoimmune disease which causes systemic inflammation, involving multiple joints throughout the body. This chronic disease leads to pain, cartilage degradation, and deformities. Rheumatoid arthritis causes a wide array of extra-articular complications such as pulmonary nodules, myocarditis and arrhythmias, renal failure, anemia, and keratoconjunctivitis. Cardiovascular disease is a major cause of mortality in those with RA. RA is the most common autoimmune inflammatory arthritis, affecting nearly 1% of people worldwide. If left untreated, RA can cause permeant disability and shorten one’s life expectancy due to the many complications of the disease.

It is estimated that treatment for articular and extra-articular complications of rheumatoid arthritis costs the US about $19 billion each year. Although an exact cost of treatment per year for each patient with RA is unknown, one study showed that Americans with RA who are being treated with disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, incur about $19,000 in treatment cost per year. Those with RA are about 10 times more likely to be on work disability compared to Americans without RA. An exact number of health care visits per year for patients with RA is unknown; however, a study with 127 patients showed a median of 7.2 office visits per year. Corticosteroids, such as prednisone, are typically used to bridge a patient to DMARDs. Corticosteroid injections, typically triamcinolone, can provide relief if one or two joints are affected. Synthetic DMARDs are the cornerstone of treatment, with methotrexate typically being first line, although leflunomide, hydroxychloroquine (antimalarial), and tofacitinib can also be used. Biologic DMARDs such as tumor necrosis factor (TNF) inhibitors like etanercept, infliximab, adalimumab and rituximab are typically added to the treatment of those not responding to methotrexate.
Since no cure for rheumatoid arthritis has been found, alternative therapies should be researched to bridge the gaps between current treatments. The cause of rheumatoid arthritis is unknown, but studies have revealed that RA patients have altered gut microbiomes, suggesting gut bacteria to be a possible etiology of RA and proposing that probiotic supplementation may have a role in RA treatment. Probiotics restore the normal flora needed in our guts for healthy digestion. Without this beneficial bacteria in our gut, pathogenic bacteria can overgrow and cause inflammation within the body. Due to the relationship between gut microbiomes and RA, probiotics are being proposed to help decrease rheumatoid arthritis symptoms as a supplemental therapy along with DMARDs, corticosteroids, and TNFs. This paper evaluates three randomized control trials (RCTs) comparing the efficacy of probiotic supplementation as an adjunctive therapy for helping to decrease pain and the number of tender joints in RA.

OBJECTIVES

The objective of this selective EBM review is to determine whether or not “probiotic supplementation helps decrease pain and number of tender joints in adults with rheumatoid arthritis?”

METHODS

From searching on Pubmed with keywords “probiotics” and “rheumatoid arthritis”, three randomized control trials (RCTs) were selected based on their credibility and relevance to my question. Articles were considered credible if they were published in peer reviewed journals, controlled bias through double-blinded randomization, and were reproducible studies. The articles needed to measure patient-centered outcomes and be published within the past 10 years, from January 2008 to January 2018. All three articles were published in English and in a peer reviewed journal. Inclusion criteria comprised being double-blind, randomized control trials
about adults with rheumatoid arthritis symptoms from 2008-2018. Articles were excluded from this selective EBM if they included minors <18 years old and had patients without rheumatoid arthritis. The summary of statistics reported were through p-values, mean difference from baseline, and % change from baseline. In Table 1, the demographics and characteristics of the three double blind RCTs can be found.

Articles were also selected based on meeting the criteria for population, interventions, comparison groups, outcomes measured, and type of study. The population of studies targeted in this selective EBM review were adult patients who had been diagnosed with rheumatoid arthritis. The interventions used in each study were probiotic strains. Strains varied per study, but all are considered probiotic supplementation. These probiotic caplets contained bacteria such as Bacillus coagulans, L.casei and maltodextrin, and a mixture of lactobacillus acidophilus, lactobacillus casei, and Bifidobacterium. While the treatment groups received an oral probiotic caplet, the placebo group received a visually similar oral placebo pill. The outcomes measured that are discussed in this selective EBM include pain severity and number of tender joints.

**Table 1: Demographics & Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>#pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Alipour, 2014  | Double blind  | 60   | Between 20-80yrs | -Females with RA dx based on the American College of Rheumatology’s Criteria, for more than 1 year who had inactive to moderate levels and were under treatment with DMARDs  
-Not taking NSAIDs or cytokine inhibitors | -Pregnant or lactating, under hormone therapy, Dx of DM, thyroid disorders, kidney or hepatic diseases, Cushing’s syndrome, IBD, other inflammatory disorders, digestive tract diseases, lactose intolerance, taking antioxidants, vitamins, fiber, or omega-3 supplements 3 weeks prior to interventions, using antibiotics 1 month prior to study, being on a weight reduction diet, smoking or being exposed to cigarette smoke, using other probiotic products | 14  | Capsule containing 10^8 colony forming units of L.casei and maltodextrin taken once a day for 8 weeks |
| Mandel, 2010   | Double blind  | 45   | Between 36-82 yrs | - Adult men & women with symptoms of RA for at least 1 year from outpatient departments of Kashan University of Medical Sciences | -Pregnancy  
-Chronic IBD, kidney disease, liver disease  
-Exposure to > 10 mg/day of prednisolone | 1   | Bacillus coagulans GBI-30, 6086 caplet once a day for 60 days |
- Participants must have had 4 or more of the following symptoms: Morning stiffness lasting at least 1 hour (present for at least 6 weeks), Soft tissue swelling in 3 or more joint areas observed by physicians (present for at least 6 weeks), Swelling of the proximal interphalangeal, metacarpophalangeal, or wrist joints, Symmetric swelling (present for at least 6 weeks), Rheumatoid nodules (present for at least 6 weeks), The presence of rheumatoid factor, Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints

- Treatment with other probiotics

Zamani, 2016 (9)

| Double blind RCT | 60 | Between 25-70 | Patients with RA that met the American College of Rheumatology’s criteria. Were being treated out patiently from Kashan University of Medical Sciences from October 2015 to December 2015. Diagnosed with RA 6 months prior with moderate and severe disease activity (DAS-28 > 3.2) | Patients who had chronic renal failure, renal tubular acidosis, or pancreatitis. Patients likely to be started on biological agents. Pregnant or lactating women. Patients unlikely to come for follow up in 3 months. Patients unable to read numbers and/or unable to mark the pain scale. | 8 Daily capsule with freeze dried strains of \textit{lactobacillus acidophilus} (2 X 10^9 CFU/g), \textit{lactococcus casei} (2 X 10^9 CFU/g), and \textit{bifidobacterium} (2 X 10^9 CFU/g) for 8 weeks |

**OUTCOMES**

The outcomes measured in this selective EBM are the Stanford Health Assessment Questionnaire Visual Analog Scale (HAQ VAS) pain scale for pain severity, visual analog scale (VAS) pain scale for pain severity, as well as the number of tender joints from baseline to end of study, which were counted by a rheumatologist.

**RESULTS**

This selective EBM review evaluates the effects of probiotic supplementation on the effects of rheumatoid arthritis. All three RCTs were double blinded so that neither researchers nor participants knew who received placebo or intervention. Two studies compared adult men and women with RA while another study, Alipour et al., compared adult women with RA. Two articles evaluate patient pain while the third article discusses number of tender joints. All three articles study the effects of probiotic supplementation with other medications such as methotrexate and DMARDs, instead of probiotics as a monotherapy.
Alipour et al., assessed the number of tender joints from baseline to end of study, counted by a rheumatologist. Sixty adult females, between the ages of 20 to 80, were recruited from a rheumatology clinic associated with Sinai Hospital in Tabriz, Iran. The participants had meet the American College of Rheumatology (ACR) criteria for more than 1 year and were currently being treated with DMARDs. Patients could not be taking NSAIDs or cytokine inhibitors. The intervention was a capsule containing $10^8$ colony forming units of *L. casei* and maltodexin which was taken once a day for 8 weeks. The placebo group received identical capsules containing only maltodextrin taken once a day for 8 weeks. Adult females were randomly assigned to intervention or placebo group, with twenty-four participants being assigned to the placebo group and twenty-two in the intervention group. A capsule count was performed at the end of the study which indicated that patients had followed the protocol and only took one pill a day for 8 weeks. Baselines characteristics, such as age, height, weight, BMI, menopausal status, education, and current medications, showed no statistical significant difference between the placebo and probiotic group. Of the 60 patients, 14 were noncompliant with the study protocol and therefore not included in the final analysis.

A Wilcoxon test was used to independently compare changes within the probiotic and placebo group from baseline to end of study. An ANCOVA analysis was used to compare the differences from baseline to end of study between the probiotic and placebo group. At the conclusion of the study, the authors report a statistical mean difference of 0.72 joints (95% CI, 0.25 to 1.19) from baseline to end of study. The p-value for this measurement is 0.003 which was reported as statistically significant. This result can be interpreted as the probiotic group had a mean difference of 0.72 less tender joints than the placebo group. Although this p-value is
statistically significant, it is important to note that 0.72 is not considered a reduction in 1 full joint. The authors claim that no adverse effects were reported upon completion of the study.

Table 2. Effect of 8 weeks of probiotic supplementation on disease activity in females with RA

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean difference (95%)</th>
<th>Confidence Interval (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alipour (2014)</td>
<td>0.72</td>
<td>95% CI, 0.25 to 1.19</td>
<td>0.003</td>
</tr>
</tbody>
</table>

In a study by Mandel et al., 45 adult men and women between the ages of 36 to 82 were randomized into intervention or placebo group. The participants, a majority of which were women, had to have RA for at least one year and were recruited from the same practice. Those in the probiotic group received *Bacillus coagulans* GBI-30, 6086 strain everyday for 60 days. The intervention capsule contained green tea extract, methylsulfonylmethane, and vitamins and minerals, as well as the probiotic itself. The placebo group received a matching pill, containing microcrystalline cellulose, every day for 60 days. Twenty-two participants were analyzed in each group. One participant was not analyzed due to starting an antibiotic for an upper respiratory infection (URI) during the trial. Patients were seen at their primary investigator’s office at baseline, 30 days, and 60 days. Participants were analyzed based on their improvement from baseline to end of study from their pain scale reports which was measured through the HAQ VAS pain scale. One patient discontinued treatment due to need for antibiotics for an upper respiratory infection and was therefore not included in the final analysis.

At the conclusion of the study, improvement of pain severity from baseline to end of study was documented through the HAQ VAS pain scale with a p-value of 0.046 which was statistically significant. The p-value was calculated using a Student t-test which measured the
differences from baseline to end of study between the placebo and intervention group. It was also noted that the intervention group had a reduction of 19.8% in patient pain from baseline to end of study. Placebo group only had a 1.6% reduction in patient pain. It was determined that the 19.8% reduction in patient pain was just shy of the ≥20% reduction needed by the American College of Rheumatology (ACR) to meet ACR20 criteria. ACR20 criteria helps determine the effectiveness of a therapy due to intervention compared to placebo and is defined as having a ≥20% improvement. Although these results are statistically significant, it is hard to determine if the improvement seen with Bacillus coagulans is based solely off the probiotic itself since there were other elements in the intervention group’s capsule, such as vitamins.

The authors report no serious adverse effects although minor adverse events in the intervention group, such as shingles, poison ivy, upper respiratory infection (URI), and leg edema were documented. However, it was stipulated that these minor adverse events are unlikely related to the probiotics. The placebo group also had documented minor adverse events such as gastroesophageal reflux, URI, and urinary tract infection (UTI) which were also decided to be unrelated by the investigator.

Table 3. Reduction in patient pain from baseline to end of study

<table>
<thead>
<tr>
<th>Study</th>
<th>% change in patient pain from baseline to end of study</th>
<th>Confidence Interval (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandel (2010)</td>
<td>19.8% reduction</td>
<td>95% CI (0.01 to 0.91)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Zamani et al., randomly divided 60 study participants, recruited from an outpatient practice, into intervention group or placebo group to determine the effects or probiotics on VAS pain severity. Study participants were adult men and women with RA between the ages of 25-70
years old. The visual analog scale for pain severity is a horizontal line 100 mm long that has points along the line representing different intensities of pain such as no pain to unbearable pain. The intervention group received probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium* while the placebo group received a visually indistinguishable pill that contained starch instead of the probiotic strains. Participants took the placebo or probiotic pill every day for 8 weeks.

Patients were assessed at baseline and at the end of the 8 week study and pain was evaluated by the VAS pain scale. Eight patients withdrew from the study for personal reasons; however, they were still included in the final analysis. At the conclusion of the study, it was determined that the effects of probiotic supplementation on VAS pain were not significant. A 5mm difference was reported when comparing the change from baseline to end of study between the placebo and probiotic group. The study concluded with a decrease in VAS pain of 16.7mm for the probiotic group while the placebo group saw a decrease of 11.7mm. A repeated ANOVA was used to compare the change in pain from baseline to end of study between the probiotic group and placebo group. The repeated ANOVA produced a p-value of 0.25 which was determined to not be statistically significant. A CI was not given. The study reports that no side effects were encountered following probiotic supplementation.

**Table 4. Mean change from baseline to end of study for VAS pain**

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (± SD) change for placebo group</th>
<th>Mean (± SD) for probiotic group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamani (2016)</td>
<td>-11.7 ±15.5</td>
<td>-16.7±18.1</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**DISCUSSION**
Rheumatoid arthritis is a systemic lifelong disease for which there is no cure, supporting the need for new medications and supplements. Since there is evidence that those with RA have altered gut microbiomes and impaired immune systems, the idea of probiotic supplementation in these patients is a plausible one. According to the Food and Agriculture Organization of the World Health Organization, probiotics can be beneficial to patients when given in correct doses. Some studies suggest that probiotics, once ingested, can help fight the pathogens in the gut that are responsible for intestinal inflammation. Probiotics, since classified as supplements, do not need FDA approval before marketing. Manufacturers of probiotic supplements do, however, have to notify the FDA before promoting their product.

Probiotics can be found in nearly all grocery and vitamin stores in the United States. Probiotic supplements are not considered standard treatment for most diseases and therefore are considered experimental and not covered by most commercial insurances. Some insurances may cover probiotics if ordered by a healthcare professional, but the probiotics will likely not contain the strength needed for those with autoimmune diseases. All this information considered, probiotics are immensely cheaper than standard RA medications such as DMARDs.

The three randomized control trials in this review have conflicting results. Alipour et al. supports probiotic supplementation; however, this result is not considered clinically significant since it concluded an average decrease of less than one tender joint. While probiotics are fairly inexpensive with a manageable dosing regime, the minor reduction observed in number of tender joints does not justify regular dosing. However, for patients with advanced RA, the chance of a small improvement in number of tender joints may make a difference in the quality of life for these patients. It is important to note participants who violated protocol procedures were excluded from this study’s analyses, making the results very precise. However, these results may
not be feasible in real life as not every patient will not be fully compliant. If those 14 who violated protocol had not been excluded in the analyses, the study may not have achieved statistically significant evidence. Mandel et al., provides a statistically significant p-value for patient pain, but this evidence does not meet ACR criteria by having less than a 20% reduction in pain, making this study not clinically applicable. Zamani et al. shows no statistically significant correlation between the use of probiotics and decrease in pain severity. All three of the studies had limitations, mainly based off of sample size, length of study and compliance.

Although all articles studied adults with RA, their age intervals varied from 25-70, 36-82, and 20-80. It is unknown if probiotics have more of an impact at specific ages. Alipour et al. only discusses the effectiveness of probiotics on only adult females with RA, indicating less generalizability to the US population. Although RA is more prevalent in women, Mandel et al. showed a statistically significant reduction in patient pain in both men and women. All three articles studied different strains of probiotic supplementation- Bacillus Coagulans, L. Casei, and Lactobacillus. Alipour is the only article which doesn’t evaluate patient pain through VAS and instead looks at tender joints. Two of the studies took place in Iran which may question the applicability of the results to different patient populations in different countries. The intervention pill in Mandel et al. contained vitamins and green tea extract in addition to the probiotic strain which may have confounded the results. Each of the three studies were approximately 2 months in length. Mandel et al. stated that 60 days was long enough to determine the effects of probiotics since NSAIDs relief can usually be determined within 60 days. Nevertheless, 60 days is not sufficient when monitoring disease involvement in a chronic disease or the long term side effects of probiotics.

**CONCLUSION**
There is conflicting information on whether probiotic supplementation improves pain and number of tender joints in rheumatoid arthritis patients. Alipour et al. showed a statistically significant average decrease in 0.72 tender joints with probiotic supplementation, however this is not considered clinically significant as it is not a full joint. Mandel et al. concludes statistical significance of probiotic supplementation on reduction in pain severity with a p-value of 0.046, but a reduction in 19.8% pain does not meet ACR criteria and is therefore not clinically significant. Zamani et al. showed no statistically significant effect on patient pain.

To determine a more concrete answer to whether probiotics have a significant effect on rheumatoid arthritis symptoms, there needs to be studies with increased sample sizes and for a period of time longer than two months.\textsuperscript{1,8,9} Rheumatoid arthritis is a chronic disease that patients suffer with for years and with studies only conducted for two months, it is difficult to determine the long term efficacy of probiotic supplementation as well as any long term side effects. An ongoing study over a year or more should be conducted. Each of the three articles in this review used different strains of probiotics. A study with multiple intervention groups, comparing the effectiveness of different strains of probiotic groups to each other and a placebo group could provide even more information. It is also important to note that each of the three studies took places overseas so future studies should be conducted in different countries around the world to determine the generalizability of the treatment effects to the global population. Future studies should also compare the effects of probiotic supplementation on women with RA to men with RA to determine if there are any differences between genders.
References


