Lactobacillus casei and the Immune Response in Rheumatoid Arthritis

By Breanna Keller and Audrey Dickerson

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INTRODUCTION

Problem

There is considerable research done on the health benefits of pre- and probiotic supplementation in the prevention and alleviation of a wide range of infectious and inflammatory disease in both infants and adults. Some probiotic strains, such as Lactobacillus and Bifidobacterium, have been shown to regulate the secretion of inflammatory mediators, while some prebiotics such as Oligofructose may induce important immune-mediated effects (1). Lactobacillus casei, which is one of the few known lactic acid bacteria (LAB) present in probiotics, may show promise as an immune-regulatory organisms in humans (2,3,4).

The purpose of this study is to examine Lactobacillus casei, a specific strain of LAB, and its immunomodulatory effects on the prevention and alleviation of symptoms and inflammatory markers related to rheumatoid arthritis (RA). Rheumatic disease and related conditions manifest inflammation and loss of joint function. They are thought to have an autoimmune component, but there is no identifiable cause or cure known. RA affects approximately 0.5-1.0% of adults worldwide (2). Results of many human studies looking at RA show that these patients have altered gut microbiota that leads to increased permeability of the gut due to inflammation, and allows potentially harmful microorganisms to enter the bloodstream. Indeed, evidence is present that supports the theory that altered microbiota is a factor in the initiation and perpetuation of certain inflammatory disease, such as RA (5,6).
**Objective**

Determine if there is a relationship between the consumption *Lactobacillus casei* and the corresponding markers of rheumatic disease such as various inflammatory cytokines, as well as overall perception of joint pain and health in women between ages 20 and 80 years old.

**Hypothesis**

There is no relationship between supplementation of *Lactobacillus casei* and levels of inflammatory markers and perceived symptom relief in subjects with rheumatoid arthritis.

**Define Terms**

- **Probiotics** – Live organisms which, when administered in adequate amounts, confer a health benefit onto its host and help maintain the natural balance of organisms (microflora) in the intestines.
- **Rheumatoid Arthritis** – Chronic inflammatory disorder that typically affects the lining of the joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.
- **Autoimmune disorders** – Condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue.
- **Immunomodulatory** – Capable of modifying or regulating one or more immune functions.
- **Adjuvant therapy** – Treatment given in addition to the primary, main, or initial treatment.
LITERATURE REVIEW

While current research regarding the use of pro-and prebiotics to prevent or treat rheumatoid arthritis is relatively scant, research that has been done has alluded to probiotics as being an effective adjunctive therapy in RA treatment. This is done by decreasing relative symptoms of rheumatoid arthritis in patients suffering from active disease as an adjuvant therapy. While there is promising research available, more reliable research is needed.

One of the biggest limitations encountered in previous research to date is that the study population of many studies is 50 subjects or less. This limits the power of many of these studies, and makes it hard to draw significant or powerful results that will apply to the population at large, reducing external validity. Additionally, many of the research was conducted over a period of 3-6 months, not allowing a significant amount of time to elapse for adjuvant therapy to take full effect and see effective changes in the laboratory and physical findings being measured (2,7,8).

It is not clear exactly how probiotics work, but there is some evidence to suggest it reduces gut permeability and modulates the immune system by up regulating local IgA immune responses to pathogens, reducing overgrowth of harmful bacteria, or down regulating inflammatory modulators involved in the disease process (9). While many of the articles studied required subjects to take a primary pharmacological agent for the disease process, the studies did find significant difference is symptom relief between the control and primary subject groups. This suggests that pharmacological agents are not contributing to the findings seen in the studies reviewed. Probiotics may be directly impacting the disease process (2,5,7,8). This is important because perceived quality of
life is a measure of functional status and allows patients to continue their daily activities of living and enjoyment. Their perceived quality of life may not reflect physical or laboratory values.

On a similar note, some of the studies did not find any difference between the control groups and primary subject groups from baseline in cytokine levels and other physical measurements (7,8). Other studies, however, did show slight decreases in some inflammatory markers, which warrants further research with larger numbers of subjects to increase the power of results that are found (2).

It is clear from the studies looked at that there were no adverse effects from probiotics reported, nor any increases in creatinine levels or liver enzymes. This suggests that using probiotics are safe and may be useful in patients with liver disease or those who experience adverse side effects from other therapies (7).

**CONCLUSION**

Despite the number of effective pharmacological agents available for patients with rheumatoid arthritis, a significant number of patients still experience disease activity (7). While probiotics are well tolerated and may suppress the subjective symptomology of rheumatoid arthritis, their specific role in alleviating these symptoms is still not completely understood. It does remain possible, however, that their use as adjuvant therapy is useful and worth trying in patients who may be suffering from the debilitation effects of active disease.

Probiotics can be used to introduce missing microbial components that are known to be beneficial to the human host, while prebiotics can enhance the proliferation of these beneficial microbes in order to receive maximum sustainable changes in the human
microbiota (3,10). The use of probiotics is worthy of consideration, as novel therapeutic approaches are sought after. There is an emerging recognition in the importance of the interaction that gut microbiota has on human health.

**METHODS**

**Study Design**

In this double blind, randomized, placebo-controlled trial, at least 100 subjects (50 subjects in each test group) will be randomly assigned to a probiotic supplement group or placebo group. The target population will consist of women with rheumatoid arthritis who are referred to a rheumatologist and meet the inclusion criteria. The study will be explained to the subjects and the subjects enter the study if they are interested.

The active agent is a probiotic capsule. Subjects in the probiotic group will receive one hard gelatin capsule containing a minimum of $10^8$ colony forming units (CFU) of *Lactobacillus casei* and maltodextrin, once a day for 6 months. The participants in the placebo group will take identical capsules that contain only maltodextrin, for the same period. Subjects will be asked to keep the capsules refrigerated and to take 1 each day in the morning on an empty stomach (before eating breakfast) after drinking a glass of water. The women will be asked not to alter their dietary intake or physical activity level during the study.

**Sample**

**Inclusion Criteria**

The inclusion criteria of the study will consist of being diagnosed with RA on the basis of American College of Rheumatology criteria, for more than one year, having inactive to moderate RA, under treatment with disease-modifying anti-rheumatic drugs
(DMARDs: methotrexate, hydroxychloroquine and prednisolone < 10 mg/day) and not receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or cytokine inhibitors, following a stable medication regimen for 3 months before the intervention, having a BMI of <40 kg, being between 20 and 80 y old, and willing to participate in the study.

Exclusion Criteria

The exclusion criteria will include being pregnant or lactating, having diabetes mellitus, thyroid disorders, kidney or hepatic diseases or Cushing’s syndrome, inflammatory bowel disease or other inflammatory disorders, having digestive tract diseases or lactose intolerance, taking antioxidants, vitamins, fiber or omega-3 supplements 3 weeks prior to the interventions or using antibiotics a month prior to the study, being on a weight reduction diet, smoking or being exposed to cigarette smoke and using other probiotic products.

Data Collection

At baseline, 3 months, and at the end of the study (6 months), blood samples will be collected to evaluate inflammatory cytokines. At baseline and at the end of the study, swollen and tender joint pain will be evaluated and Physician Global Assessment of Disease activity will be assessed. Also, a 24-hour dietary recall and food frequency questionnaire will be attained. A survey will be given to the subjects at the end of the study to determine overall joint and pain relief and study compliance.

Statistical Analysis

The Two Independent Groups t test will be used to assess inflammatory cytokines and physical activity levels between the two groups both at baseline and at the end of the study. Analysis of Covariance (ANCOVA) will be used to compare the two groups for
the measures at the end of the study, adjusting for the baseline measures and confounding variables (changes of BMI and menopausal status).

**BUDGET**

- Probiotic capsules - $25/month per subject x 50 subjects x 6 months = $ 7500
- Placebo capsules - $10/month per subject x 50 subjects x 6 months = $ 3000
- Collection and evaluation of cytokine panel (baseline and after the study) - $100 per test x 2 x 100 subjects = $2000
- Questionnaire development and distribution (baseline and after the study) - $10/subject x 100 subjects = $1000
- Statistician for evaluation of results - $40/hour
REFERENCES


