Synbiotic supplementation as a treatment for nonalcoholic fatty liver disease

Mallery Knoll
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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide. It can progress to cirrhosis and hepatocellular carcinoma. There are currently no recommended pharmacologic therapies solely for the treatment of NAFLD; only weight loss and lifestyle modifications are widely agreed upon recommendations. The clinical trials reviewed here demonstrate evidence that synbiotics can be a successful form of treatment of NAFLD in addition to weight loss and lifestyle modification.

Methods: An exhaustive search of the available medical literature was performed using MEDLINE-Ovid, Web of Science, and CINAHL. Search terms included “Non-alcoholic fatty liver disease” and “synbiotics.” Eligible studies were assessed using the GRADE criteria.

Results: Three articles met the eligibility criteria. All 3 were randomized controlled trials, 2 of which were double-blind and were written by some of the same authors but were done 3 years apart using completely separate data. The results were consistent in that various elements of nonalcoholic fatty liver disease (NAFLD) significantly improved in the treatment groups compared to the control groups of all 3 studies. The quality of the outcomes is moderate to high, with a few limitations. Further studies done with the same synbiotic supplement and same duration of time can reduce these limitations and improve the quality of evidence of the effects of synbiotic supplementation on NAFLD.

Conclusion: Randomized controlled trials studying synbiotics as a treatment for NAFLD provide evidence to support their use as an adjunctive treatment to nutritional counseling and weight loss. Synbiotics are a safe and effective adjunctive treatment for all patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, synbiotics

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Keywords
nonalcoholic fatty liver disease, synbiotics, NAFLD

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Synbiotic Supplementation as a Treatment for Nonalcoholic Fatty Liver Disease

Mallery Knoll

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2018

Faculty Advisor: Brent Norris, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Mallery Knoll is a native of Montana, where she received a double major in Health Sciences and Spanish at Carroll College. After completion of her undergraduate degree, she worked as a medical scribe in St. Peter’s Emergency Department while also working as an assistant coach for the Carroll College track & field team. One year later, Mallery was accepted to Pacific University’s School of Physician Assistant Studies where she received her Master’s Degree.
Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide. It can progress to cirrhosis and hepatocellular carcinoma. There are currently no recommended pharmacologic therapies solely for the treatment of NAFLD; only weight loss and lifestyle modifications are widely agreed upon recommendations. The clinical trials reviewed here demonstrate evidence that synbiotics can be a successful form of treatment of NAFLD in addition to weight loss and lifestyle modification.

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Conclusion: Randomized controlled trials studying synbiotics as a treatment for NAFLD provide evidence to support their use as an adjunctive treatment to nutritional counseling and weight loss. Synbiotics are a safe and effective adjunctive treatment for all patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, synbiotics
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To my professors: You have all gone above and beyond in making us empathetic, caring, educated, evidence-based clinicians. Thank you so much for your time and effort.

To my family: I can’t thank you enough for your continuous love and support in all aspects of my life, especially during PA school. I couldn’t do any of it without you.
Table of Contents
Synbiotic Supplementation as a Treatment for Nonalcoholic Fatty Liver Disease .......... 1
Biography ........................................................................................................................................... 2
Abstract ............................................................................................................................................... 3
Acknowledgements ............................................................................................................................. 4
Table of Contents ................................................................................................................................. 5
List of Tables .......................................................................................................................................... 6
List of Abbreviations ........................................................................................................................... 6
Synbiotic Supplementation as a Treatment for Nonalcoholic Fatty Liver Disease .......... 7
  BACKGROUND ................................................................................................................................. 7
  METHODS ........................................................................................................................................... 8
  RESULTS ............................................................................................................................................. 8
    Mofidi et al (2017) ......................................................................................................................... 9
    Eslamparast et al (2014) ............................................................................................................... 10
    Ferolla et al (2016) ...................................................................................................................... 11
  DISCUSSION ..................................................................................................................................... 11
  CONCLUSION ................................................................................................................................... 13
References .............................................................................................................................................. 14
Table 1: Quality Assessment of Reviewed Articles ............................................................................ 16
Table 2. Summary of Findings ............................................................................................................ 17
List of Tables

Table 1: Quality Assessment of Reviewed Studies
Table 2: Summary of Findings

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>NASH</td>
<td>Nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>GGT</td>
<td>𝛾-glutamyltransferase</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
</tbody>
</table>
Synbiotic Supplementation as a Treatment for Nonalcoholic Fatty Liver Disease

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases worldwide.\(^1\)-\(^4\) It is the most common chronic liver disease in the Western world.\(^1\),\(^4\) NAFLD can be subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH); NAFL describes when there is hepatic steatosis, or accumulation of fat in the liver, but no evidence of significant inflammation, and NASH describes hepatic steatosis that does have evidence of hepatic inflammation.\(^5\) Thus, when a person has NAFLD, they have fat accumulation in the liver with or without inflammation of the liver. Other terms that have been used to describe NASH include pseudoalcoholic hepatitis, alcohol-like hepatitis, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis.\(^1\),\(^2\)

One of the major risk factors for NAFLD is central obesity, though lean people can be affected by NAFLD as well. Other risk factors include metabolic syndrome, diabetes mellitus type 2, and dyslipidemia.\(^6\),\(^7\) Patients are most often diagnosed with NAFLD in their 40s or 50s, and studies are inconclusive in regard to the predilection of NAFLD in men or women.\(^8\) The diagnosis has three requirements: hepatic steatosis shown on imaging or biopsy, exclusion of other causes of hepatic steatosis such as viral or autoimmune hepatitis, and exclusion of significant alcohol consumption.\(^9\) These patients may complain of pain in the right upper quadrant, fatigue, or malaise, though it is more likely that they will be asymptomatic.\(^10\) The diagnosis could be investigated further due to incidental lab findings such as elevated liver enzymes or hepatic steatosis found incidentally on abdominal imaging.\(^1\) However, it is important to note that elevated liver enzymes is not a requirement for the diagnosis, and they are in fact usually normal or only minimally elevated.

It is important to reduce risk factors and treat NAFLD because it can progress to cirrhosis and other complications including hepatocellular carcinoma. Weight loss and lifestyle modification are the only generally recommended forms of treatment for
NAFLD; pharmacologic agents have been studied, though none of them are yet recommended specifically for the treatment of hepatic steatosis. This is due to the fact that most of the trials have been too short and/or the results have conflicted.

Synbiotics were proposed as a form of treatment due to the anti-inflammatory properties of probiotics, and the concept of gut microbiota involvement in the pathogenesis of liver disorders. Synbiotics are formulas containing a combination of prebiotics and probiotics, which can have beneficial effects on various disease processes. They are a safe, simple, and inexpensive treatment option; side effects are rare, and the over-the-counter cost of synbiotics in the United States ranges between $15-$50 depending on the brand and the number of capsules or amount of powder in the container. This systemic review provides evidence that synbiotics are a safe and effective adjunctive treatment for nonalcoholic fatty liver disease.

**METHODS**

An exhaustive search of the available medical literature was performed using MEDLINE-Ovid, Web of Science, and CINAHL. Search terms included “Non-alcoholic fatty liver disease” and “synbiotics.”

The inclusion criteria were randomized controlled trials with adult humans with NAFLD, written in English. Animal studies and studies written in other languages were excluded. These eligible articles were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

**RESULTS**

The search on MEDLINE-Ovid yielded 10 results, 2 of which were duplicates. Web of science gave 5 results, and CINAHL gave 1 result. Of those results, 3 of them were randomized controlled trials that fit the inclusion criteria for this review. (See Table 1). Two of the articles were written 3 years apart by some of the same authors; the Mofidi et al study refers to their previous study (by Eslamparast et al) on the use of synbiotic supplementation in overweight and obese patients with NAFLD, so the next study was done similarly with lean patients. The third study by Ferolla et al had no requirements for BMI.
Mofidi et al (2017)

Fifty lean patients were recruited for the study, and were randomly assigned to receive either a synbiotic capsule or placebo capsule. Patients were included if they were 18 years or older, had evidence of hepatic steatosis on the FibroScan (transient elastography) with a CAP score of >260, did not have a history of alcohol consumption, had a normal or low BMI of <25, had ALT and AST concentrations >1.5 times the upper normal range, and had no evidence of any other liver disorders (ie, hepatitis B and C), biliary disease, autoimmune diseases, cancer, or inherited disorders affecting the liver. They were excluded if they were pregnant or breastfeeding, taking antibiotics or hepatotoxic medications at any point during the study, or if they lost >10% body weight during the study period.

Both groups were encouraged to lead a healthy lifestyle and were advised to follow an energy-balanced diet. They were also given the same physical activity recommendations. Forty-two of the patients completed all 28 weeks of treatment, but all 50 were included in the analysis. The primary outcome was reduction of hepatic steatosis, as measured by CAP scores of the FibroScan (transient elastography) test. Steatosis was reduced in both groups (Table 2), though the reduction in the synbiotic group was significantly greater.

Secondary outcomes included hepatic fibrosis, hepatic enzymes, lipid profile, and inflammatory markers. Similar to the reduction of steatosis, fibrosis was reduced in both groups but significantly greater in the synbiotic group. (See Table 2). No significant differences were observed between the synbiotic and placebo groups in reduction of hepatic enzymes, with the exception of aspartate aminotransferase (AST); both groups showed an improvement in serum enzyme levels, but the synbiotic group had a significant difference in AST improvement compared to the placebo group. (See Table 2). Also of note, the synbiotic group also demonstrated a significant difference in the improvement of fasting blood sugar (FBS) and triglycerides (TAG).

Various organizations helped with the production of this randomized, double-blind, placebo-controlled clinical trial. Members of the same organizations helped develop a similar trial 3 years prior, which will be discussed next.
**Eslamparast et al (2014)**

Fifty-two overweight or obese patients were enrolled in this study and were randomly assigned to receive either a synbiotic capsule or a placebo capsule. The synbiotic contained 7 strains of bacteria (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Lactobacillus bulgaricus*) and prebiotic (fructooligosaccharide) and probiotic cultures and a vegetable capsule; the same strains and prebiotic were used in the study by Mofidi et al.11,12

Patients were included if they were given the diagnosis of NAFLD based on the presence of hepatic fibrosis on ultrasound and transient elastography, persistently elevated liver enzymes, and they were 18 years or older. They were excluded if they had viral hepatitis, alcohol use, other causes of chronic liver disease, diabetes mellitus, untreated hypothyroidism, systemic disease, pregnancy, lactation, or lack of effective birth control if the women were of childbearing age.12

Both groups were encouraged to follow an energy-balanced diet and were given exercise recommendations. Forty-six patients completed all 28 weeks of treatment, but all 52 were included in the analysis. The primary outcome of this study was a reduction of ALT concentration, which was significant in both the synbiotic group and the placebo group. However, the mean reduction of ALT was significantly greater in the synbiotic group.12 (See Table 2).

Secondary outcomes that were measured included the FibroScan (transient elastography) score for which they evaluated hepatic fibrosis, inflammatory factor concentrations, fasting blood sugar (FBS), and serum aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP). Patients taking the synbiotic demonstrated a significant difference in the reduction of hepatic fibrosis compared to the placebo group. The synbiotic group also showed a significant difference in the reduction of AST and GGT. Both groups had a significant reduction of FBS. There was no significant different between the 2 groups in reduction of ALP. Additionally, the inflammatory factor concentrations decreased at the end of the 28 weeks in both groups, but again the mean decrease in the synbiotic group was greater.12 (See Table 2).
Ferolla et al (2016)

Fifty patients were included in this trial and were randomly assigned to the treatment group, which received a synbiotic and nutritional counseling, or the control group, which was only given nutritional counseling. The synbiotic consisted of *Lactobacillus reuteri* with guar gum and inulin.

Patients were included if they had a diagnosis of NASH that was confirmed by previous liver biopsy, and other causes of liver disease were excluded. They were excluded if they consumed >20 grams of alcohol per day (males) or >10 grams of alcohol per day (females). Other exclusion criteria included viral hepatitis infections, autoimmune hepatic disorders, Wilson disease, hemochromatosis and alpha-1-antitripsin deficiency, use of steatogenic medications within the past 6 months, exposure to hepatotoxins, history of bariatric surgery, contraindication to MRI, and evidence of decompensated liver disease.

The primary outcome of the study was significant reduction of hepatic steatosis. Steatosis was assessed at baseline and at the end of the 12-week study period using MRI-derived proton density fat fraction (PDFF). The synbiotic group demonstrated a significant reduction in steatosis (p=0.027) compared with the control group (p=0.148). (See Table 2).

Hepatic fibrosis was a secondary outcome and was measured using elastography. No significant difference in reduction of fibrosis was observed between the treatment and the control groups. Other secondary outcomes included the reduction of ALT, AST, GGT, and ALP. Unlike the previous 2 studies reviewed, there was no significant reduction of any of these liver enzymes. (See Table 2).

**DISCUSSION**

NAFLD is a widespread disease, and with the exception of lifestyle modifications, there is little known about how to treat it. After integrating the data from the 3 studies reviewed here, it is clear that synbiotics have some utility in treating nonalcoholic fatty liver disease as they appear to be effective, inexpensive, and harmless.
None of the patients in any of the studies complained of any serious side effects from the synbiotics, and only 2 minor side effects were reported in the Eslamparast et al study, which were moderate headaches and abdominal pain. These side effects resolved without recurrence. Moreover, clinicians can consider recommending synbiotics to patients regardless of weight, as 2 of the studies involved overweight or obese patients, while the other study involved patients with a normal or low BMI.

The studies by Mofidi et al and Eslamparast et al were both randomized, double-blind, placebo-controlled clinical trials. The study by Ferolla et al was a randomized controlled trial, though the extent to which it was blinded is uncertain, and there was no placebo used. The most serious limitation was in the Ferolla et al study; the control group did not receive a placebo pill, but instead was only given nutritional counseling. However, the measurements of the various outcomes are standardized, objective measurements, which strengthens the study. Additionally, it is stated in the Mofidi et al and Eslamparast et al studies that none of the participants had received treatment yet for their diagnosis of NAFLD. It is unclear if this was the case in the Ferolla et al study. This could be viewed as a limitation as well.

A quality assessment was performed on the outcomes reviewed here, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria shown in Table 1. The criteria deemed the Mofidi et al and Eslamparast et al studies high quality and the Ferolla et al study moderate quality. Thus, the overall quality of evidence is high. Specifically, reduction of hepatic fibrosis demonstrates high quality of evidence, though it did have one inconsistency; the Ferolla et al study did not find a significant reduction of hepatic fibrosis while the other 2 studies did. However, the Ferolla et al study was 16 weeks shorter in duration than the other 2 studies. Additionally, the Mofidi et al study used elastography to measure steatosis, while the Ferolla et al study used MRI PDFF. The Eslamparast et al study used elastography to measure fibrosis but did not mention a value for measuring steatosis.

Further randomized controlled trials should be done using the same synbiotic capsules, the same duration, and similar diet and exercise recommendations. It is important to have multiple studies with the same controlled variables in order to obtain
more accurate results. However, there is nearly no risk of harm in taking synbiotics. Thus, due to the low cost and the few side effects in addition to the positive effects shown in the studies\textsuperscript{11-13} reviewed here, it seems as though synbiotics should be a regular part of the treatment regimen for all patients with nonalcoholic fatty liver disease.

**CONCLUSION**

All three studies concluded that synbiotic supplementation in addition to lifestyle modification is superior to lifestyle modification alone in the treatment of NAFLD. Two of the studies involved overweight/obese patients, while the other study involved patients with a normal or low BMI. This is important given that the majority of patients with NAFLD will be overweight; however, it is not limited to overweight patients. The fact that the studies found improvement among overweight and non-overweight patients strengthens the results. No serious adverse effects were observed, and all 3 randomized controlled trials showed some form of improvement in patients with NAFLD. All of this information provides strong enough evidence for clinicians to begin giving synbiotics as an adjunctive treatment for nonalcoholic fatty liver disease.
References


### Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Mofidi et al11</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Eslamparast et</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>al12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferolla et al13</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious</td>
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<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

a Blinding is uncertain in the Ferolla et al study but no downgrade was applied due to objectivity of outcomes.
b The Ferolla et al study did not show a significant difference in reduction of liver fibrosis and didn’t declare whether or not patients were treatment naive.

RCT = randomized controlled trial
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mofidi et al\textsuperscript{11}</th>
<th>Eslamparast et al\textsuperscript{12}</th>
<th>Ferolla et al\textsuperscript{13}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean change from baseline (SE)</td>
<td>mean change from baseline (95% CIs)</td>
<td>reduction of median value from baseline to post treatment (95% CIs)</td>
</tr>
<tr>
<td></td>
<td>Synbiotic group</td>
<td>Placebo group</td>
<td>Synbiotic group</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>-1.71 (0.25) via FibroScan in kPa</td>
<td>-0.71 (0.18) via FibroScan in kPa</td>
<td>9.36 + 1.9 to 6.38 + 1.5 via elastography*</td>
</tr>
<tr>
<td>ALT - IU/l</td>
<td>-11.61 (0.63)</td>
<td>-5.04 (0.13)</td>
<td>-25.1 (-26.2, -24.0)</td>
</tr>
<tr>
<td>AST - IU/l</td>
<td>-10.8 (0.50)</td>
<td>-1.98 (0.09)</td>
<td>-31.3 (-32.1, -30.5)</td>
</tr>
<tr>
<td>GGT - IU/l</td>
<td>-28.65 (1.88)</td>
<td>-3.20 (0.22)</td>
<td>-15.08 (-15.5, -14.7)</td>
</tr>
<tr>
<td>FBS - mg/dl</td>
<td>-17.33 (4.98)</td>
<td>-2.47 (0.52)</td>
<td>-7.96 (no CIs given)</td>
</tr>
<tr>
<td>Insulin - mU/l</td>
<td>0.26 (0.78)</td>
<td>-0.38 (0.14)</td>
<td>2.02 (no CIs given)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.10 (0.22)</td>
<td>-1.32 (0.03)</td>
<td>-0.68 (-0.8, -0.5)</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.02 (0.01)</td>
<td>0.07 (0.00)</td>
<td>--</td>
</tr>
<tr>
<td>TAG - mg/dl</td>
<td>-32.32 (10.04)</td>
<td>-9.80 (2.35)</td>
<td>--</td>
</tr>
<tr>
<td>HDL - mg/dl</td>
<td>3.69 (1.64)</td>
<td>0.95 (0.75)</td>
<td>--</td>
</tr>
<tr>
<td>LDL - mg/dl</td>
<td>-24.85 (11.71)</td>
<td>-13.42 (2.39)</td>
<td>--</td>
</tr>
<tr>
<td>Total C - mg/dl</td>
<td>-46.09 (12.04)</td>
<td>-16.00 (4.67)</td>
<td>--</td>
</tr>
<tr>
<td>hs-CRP - ng/ml</td>
<td>-1162.61 (437.65)</td>
<td>-426.57 (132.41)</td>
<td>-2.30 (-3.0, -1.5)</td>
</tr>
<tr>
<td>TNF-α - pg/ml</td>
<td>-1.22 (0.82)</td>
<td>-0.30 (0.22)</td>
<td>-1.40 (-1.7, -1.1)</td>
</tr>
<tr>
<td>NF-κB p65</td>
<td>-0.01 (0.00)</td>
<td>-0.01 (0.00)</td>
<td>-0.016 (-0.022, -0.011)</td>
</tr>
</tbody>
</table>

P values <0.05; P values < 0.0001
In the synbiotic group, 95% of patients showed some improvement in their fibrosis score, whereas the scores of 5% remained unchanged. Of those with improvements, 8% had a 1-level reduction in their fibrosis score, whereas 36% and 56% had 2- and 3-level reductions, respectively. Fibrosis scores also decreased in the placebo group, but less than in the synbiotic group. Only 36% of the patients in this group had one or more levels of reduction in their fibrosis scores.\textsuperscript{2}

In line with this result, 40.7% of the patients in the study group were classified as having moderate/severe steatosis (grades 2–3) in MRI at baseline; and, after the synbiotic supplementation, this proportion fell to 18.5% (p = 0.031). Therefore, the proportion of patients initially with mild steatosis (grades 0–1) increased from 59.2% to 81.5% (p = 0.031). In the control group, they did not observe improvement in the grade of steatosis (p = 1.00).\textsuperscript{3}

Abbreviations: CIs, confidence intervals; MRI: magnetic resonance imaging; PDFF: hepatic proton density fat fraction; kPa: kiloPascal; NAFLD: nonalcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; C, cholesterol; hs-CRP, high-sensitive C-reactive protein.