

The effects of synbiotics on the liver steatosis, inflammation, and gut microbiome of metabolic dysfunction-associated liver disease patients – randomized trial

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Abstract

Introduction: Metabolic Dysfunction-associated Liver Disease (MASLD) represents a spectrum of conditions from simple fat accumulation to non-alcoholic steatohepatitis. The possible role of the intestinal microbiome on MASLD development has been in focus. Our study aimed to examine the effects of synbiotics on the liver steatosis, inflammation, and stool microbiome.

Methods: A double-blind, placebo-controlled study was conducted involving 84 MASLD patients, defined by an elastometric attenuation coefficient (ATT) greater than 0.63 dB/cm/MHz with an alanine aminotransferase level above 40 U/L for men and 35 U/L for women. The patients were divided into an intervention group treated with a synbiotic with 64×10^9 CFU of *Lactobacillus* and *Bifidobacterium* and 6.4g of inulin and a control group treated with a placebo.

Results: Using synbiotics for 12 weeks significantly decreased liver steatosis (Δ ATT -0.006 ± 0.023 vs -0.016 ± 0.021 dB/cm/MHz, $p=0.046$). The group of patients treated with synbiotics showed a significant decrease in the level of high-sensitive C-reactive protein (Δ hs-CRP 0 vs -0.7 mg/L, $p \leq 0.001$). Synbiotics enriched the microbiome of patients in the intervention group with the genera *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, and *Streptococcus*, by 81%, 55%, 51%, and 40%, respectively, with a reduction of *Ruminococcus* and *Enterobacterium* by 35% and 40%. Synbiotic treatment significantly shortened the gut transition time (Δ GTT -5h vs. -10h, $p=0.031$).

Conclusion: Synbiotics could be an effective and safe option that could have place in MASLD treatment.

Keywords: Inflammation, Microbiome, Fatty Liver, Synbiotics, Constipation.

What is new? What is important?

Our study aimed to examine the effects of synbiotic administration on the liver steatosis, lipid metabolism, inflammation, and stool microbiome composition of MASLD patients. What sets our study apart from others of similar design is the rigorous control of potential cofactors such as diet and antibiotic use, as well as a significantly larger number of participants. This is the only study of its kind that has analyzed the effects of synbiotics on the composition of the gut microbiome.

INTRODUCTION

Metabolic Dysfunction-associated Liver Disease (MASLD) is one of the most prevalent manifestations of the metabolic syndrome and affects about 25–45% of the population. This term includes a spectrum of conditions from simple fat accumulation to non-alcoholic steatohepatitis (NASH) characterized by inflammation and progressive fibrosis [1, 2]. Its

pathophysiology has not been explained in detail. The possible influence of the intestinal microbiome on the MASLD development has recently been in focus [3].

The intestinal microbiome represents an ecosystem of bacteria, fungi, viruses or protozoa, existing in symbiosis with host. It is closely related with the liver, anatomically and functionally. This communication is often regarded as the gut-liver

axis. A change in the composition of the intestinal microbiome may contribute to increased intestinal permeability to bacterial metabolites with an effect on liver inflammation [4].

For these reasons, the synbiotics, a combination of pre-and probiotics, could positively affect the degree of liver steatosis. So far, there have been 21 placebo-controlled studies that investigated the possible role of probiotics in MASLD treatment. The meta-analysis by Zhou, which took into account performed studies, concluded that probiotics showed potential in reducing steatosis but highlighted their shortcomings- small number of subjects, non-uniform diets, non-objectivity in liver steatosis grading, usage of different probiotics. None of the studies monitored the composition of the intestinal microbiome [5].

Our study aimed to examine the effect of the synbiotics on the liver steatosis under the conditions of a uniform diet, controlled antibiotic usage, utilizing elastometry as a method of grading steatosis, with the correlation of clinical and laboratory parameters with microbiome dynamic.

MATERIAL AND METHODS

STUDY DESIGN

We designed the study as a double-blind, placebo-controlled involving MASLD patients. MASLD was defined by the following criteria – an elastometric attenuation coefficient (ATT) greater than 0.63 dB/cm/MHz with an alanine aminotransferase (ALT) level above 40 U/L for men and 35 U/L for women, at the initial visit. The exclusion criteria were the unwillingness to provide an informed consent, the use of alcohol more than 20g per day for the 6 months before enrollment, viral hepatitis, liver cancer, bowel or liver resection, previous inflammatory bowel disease (IBD), hypothyroidism. Patients who used different probiotic or antibiotic therapy in the period of two weeks before and during the study were excluded. NASH patients were defined by a liver stiffness (E median) over 5.5 kPa and high-sensitive C-reactive protein (hsCRP) over 3 mg/L. The institutional ethics committee approved the conduct of our study based on the principles of the Helsinki Declaration and classified it under the number 111512/21.

DIET

After signing the informed consent, all patients consulted with a dietician. Specific diet was started

two weeks before the treatment and maintained during the study. The diet plan stipulated that patients take 20–30 kCal per kilogram, divided into 4–5 meals, 35–40% of the intake based on fat, 20% on proteins, and 40–45% on carbohydrates. The patients were given a cookbook with 150 Mediterranean diet recipes and educated on keeping the food diary. The Food Works software was used to examine patient adherence. All patients were advised to have regular daily walks with over 8,000 steps.

RANDOMIZATION

After two weeks of the diet, the patients were randomized into two groups: the intervention group treated with synbiotics, and the control group treated with placebo. Computerized block-randomization was performed off-site by a statistician. After the randomization, the number of the therapeutic package was sent to the researchers, and the patients would be issued the appropriate package. The randomization information were disclaimed after study completion. Therapeutic packs were prepared off-site.

INTERVENTION

The intervention group patients were treated with two capsules containing 64 billion colonies of *Lactobacillus acidophilus* CBT LA1 (16×10^9), *Lactobacillus casei* CBT LC5 (16×10^9) and *Bifidobacterium lactis* CBT BL3 (32×10^9) with 6.4 g of inulin, while the control group received an identical capsules but with a total of 6.8 g of maltodextrin. The rationale behind probiotic selection was based on good acid resistency of *Bifidobacterium lactis* when combined with *Lactobacillus acidophilus*, and positive effects of *Lactobacillus casei* on constipation [6, 7]. The therapeutic package with 56 pills was issued to the patients every four weeks. The total length of treatment was 12 weeks. Patients were advised to bring all remaining capsules to their follow-up visits. Patients who did not take more than 80% of all issued pills were considered non-adherent and excluded from analysis.

OUTCOMES

The effect of the treatment on the ATT parameter dynamic measured by point Shear-Wave Elastometry (pSWE) was considered the primary outcome. Examinations were performed using a Fujifilm Arietta 850 (Tokyo, Japan) ultrasound

machine by two certified sonographers (OO and MM), blinded to randomization. During expiration, ten sequential measurements were obtained via an intercostal approach in the upper portion of the right lobe. The measurement sites were at least 2 cm below the liver capsule and at a depth of less than 6 cm below the skin. Using the reliability index, the percentage of the net amount of effective shear-wave velocity (VsN) helped us confirm whether pSWE was appropriate [8]. Examinations were performed on the first day and at the end of the study. The secondary outcomes were the effect of synbiotics on the lipid profile, HbA1c, inflammatory markers, estimated glomerular filtration rate (eGFR), and the microbiome dynamic. Stool and serum sampling was performed twice, on the day when the first therapeutic package was issued and within 48 hours after the last drug dose.

STOOL MICROBIOME ANALYSIS

All patients were asked to submit a stool sample before the start and within 48 hours of the last therapeutic dose. Genomic deoxyribonucleic acid (DNA) was isolated from samples using the ZR FecalDNA MiniPrep™ kit (Zymo Research Corp., CA USA), following the manufacturer's recommendations. After dilution to 5 ng/μl concentration, 10 μl samples were used for 16s rRNA-amplicon-sequencing targeting the V3–V4 hypervariable region. Sequencing was performed using NovaSeq 6000 PE250-Illumina platform (Novogene Co Ltd, Hong Kong). The obtained data were filtered using Trimmomatic™ software and then analyzed using Quantitative Insights Into Microbial Ecology™ software according to the protocol described by Caporaso [9]. Using the Uparse software (Uparse v7.0.1001), the composition of the microbiome was defined [10]. Using the R statistical software, the Shannon and Simpson indexes of alpha-diversity were defined. Beta-diversity was estimated using a weighted “unifrac” measurement.

SAFETY PROFILE

All adverse events were documented and reported to the institutional Ethics Committee. Unwanted symptoms and conditions that required hospitalization or threatened the subject's functioning, health, or life were considered serious adverse events. All patients were asked to complete the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire on the day of signing the informed

consent and after completing the therapy [11]. The analysis of the gut transition time was performed using the “blue stool challenge” according to the method described by Asnicar [12]. At the first and last visit, all patients were offered two muffins with blue dye, and asked to report the moment of the appearance of the blue discoloration of the stool.

STATISTICS

Statistical analyses were performed using appropriate tests within the SPSS 23.0 (IBM Corp, NY, USA). Normally distributed values were presented as mean with standard deviation, otherwise as median with 25–75% percentiles. To examine the difference between the basic characteristics and dietary profile of the two groups, the Pearson- χ^2 and Fisher test were used for categorical, or the Student's T-test for independent samples for normally distributed variables. The Delta (Δ) was calculated as an absolute change-from-baseline in parameters such as ALT, hs-CRP, lipid profile, elastometric coefficients and gut transition time. The stool microbiome dynamic was expressed as relative and presented in percentages. Their comparisons were performed using the Student's T-test for data with normal distribution or the Mann-Whitney U-test if normality was not met.

RESULTS

The research was conducted from October 2021 to February 2022. The sample size ($n=100$) was determined using Raosoft software, taking into account the level of ATT (0.63 dB/cm/MHz) in MASLD patients, as well as the expected effect of synbiotics in terms of reducing steatosis levels by 30%, with an estimation of 20% fallout [13]. After an initial interview with 146 patients, 100 who met all inclusion and exclusion criteria and provided informed consent were included. Patients were randomized into an intervention ($n=49$) and a control group ($n=51$). Three patients from the intervention group moved abroad. One patient from each intervention and control group could not be reached for unknown reasons. Two patients from the intervention group discontinued the therapy protocol due to increased bloating, while one from the control group discontinued treatment without explanation. The final analysis included 41 patients from the intervention group, after exclusion

of two patients who used antibiotic therapy for respiratory symptoms, and 43 patients from the control group, after exclusion of six patients not adhering to the recommended diet or therapeutic protocol.

There were no statistically significant differences in terms of gender and age distribution, comorbidities, BMI, and metabolic profile at the start of the study. Proportion of patients defined as having NASH was similar in both groups.

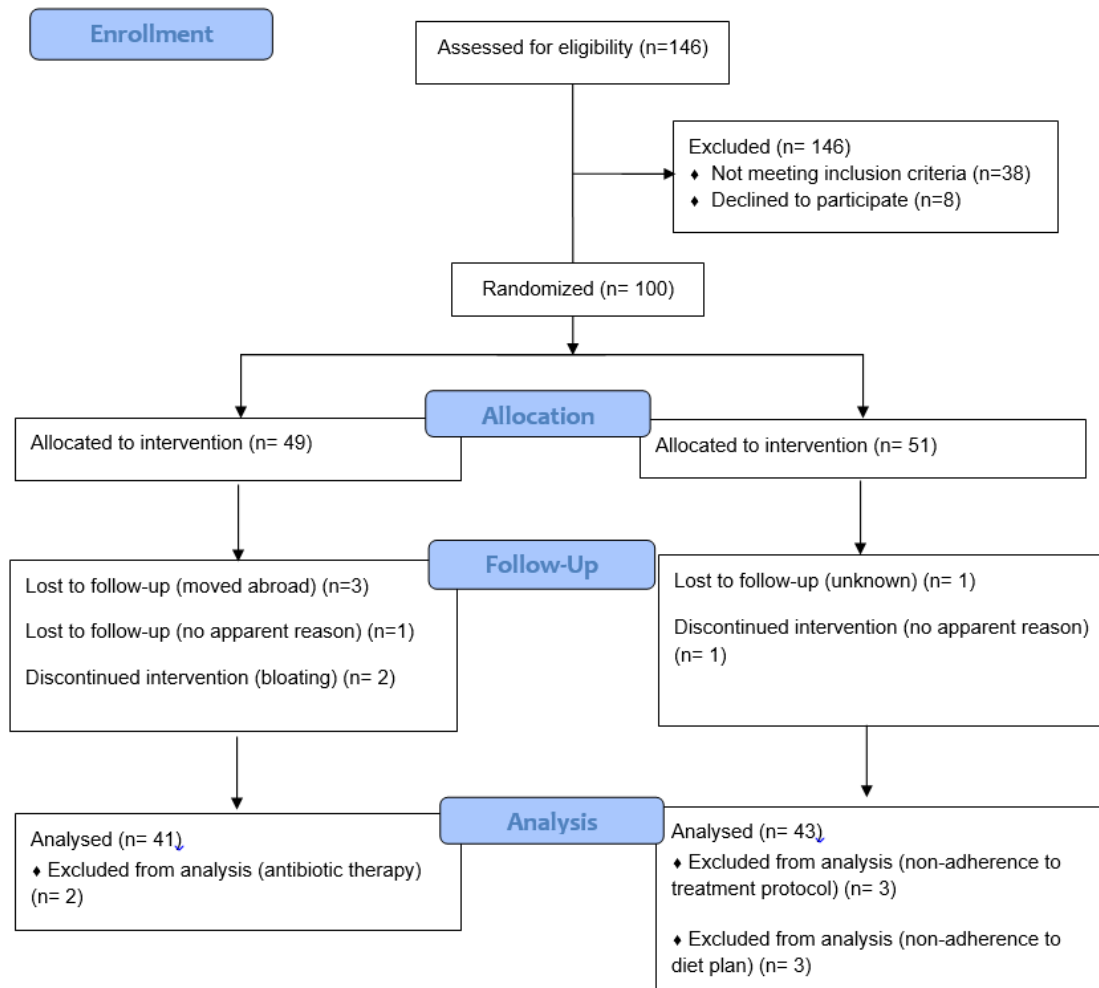


Figure 1. Patient flowchart.

Table 1

Basic characteristics of included patients

	Placebo	Treatment	p
N	43	41	
Comorbidity (Diabetes mellitus)	13	16	0.117
NASH (Yes)	11	13	0.631
Age	68±9	69±8	0.948
BMI (kg/m ²)	25.7±1.7	26.2±2	0.254
Statins (Yes)	17	15	0.825
HbA1c (%)	6±0.6	5.9±0.6	0.740
Cholesterol (mmol/L)	5.5±0.6	4.6±0.8	0.300
Tryglicerides (mmol/L)	3.8±1.2	3.5±1.2	0.123
eGFR (ml/min)	80±7	78±7	0.062

THE LIVER STEATOSIS

Synbiotic therapy significantly reduced liver steatosis (Δ ATT -0.006 ± 0.023 vs -0.016 ± 0.021 , $p=0.046$). Despite the positive impact in reducing the degree of liver stiffness, this effect (E median) did not reach statistical significance. Both groups achieved reduction in ALT levels after the therapeutic period, more pronounced in the intervention group, but not significantly.

CLINICAL AND LABORATORY PARAMETERS

The group of patients treated with synbiotics showed a statistically significant reduction in hs-CRP levels compared to the control group (Δ hs-CRP 0 vs -0.7 mg/L, $p<0.001$). Similar observations were not noted for interleukin 6 (IL-6). Regarding lipid metabolism, hemoglobin A1c values, and eGFR, their dynamic did not exhibit statistically significant differences.

Table 2

The impact of synbiotics on dynamic of liver elastometry parameters

	Placebo	Treatment	p
Baseline ATT (dB/cm/MHz)	0.73 $\pm$ 0.06	0.75 $\pm$ 0.06	0.168
EOT* ATT	0.73 $\pm$ 0.07	0.74 $\pm$ 0.08	0.460
Δ ATT	-0.006$\pm$0.023	-0.016$\pm$0.021	0.046
Baseline E median (kPa)	6.96 $\pm$ 2.55	6.46 $\pm$ 2.03	0.331
EOT E median	6.9 $\pm$ 2.54	6.36 $\pm$ 2.01	0.281
Δ E median	-0.055 $\pm$ 0.25	-0.1 $\pm$ 0.29	0.388
Baseline ALT (U/L)	62 $\pm$ 12	63 $\pm$ 12	0.458
EOT ALT	49 $\pm$ 12	45 $\pm$ 10	0.59
Δ ALT	-13 $\pm$ 11	-18 $\pm$ 13	0.058

*EOT-End-of-treatment

Table 3

The impact of synbiotics on laboratory parameters

	Placebo	Treatment	p
Baseline IL6 (pg/mL)	10.3 (8.2-13.2)	10.7 (9.2-12.8)	0.428
EOT* IL6	11.4 (8.8-14.1)	11.2 (8.7-12.3)	0.354
Δ IL6	0.6 (-1.5-2.5)	-0.4 (-2-1.3)	0.112
Baseline hs-CRP (mg/L)	2.6 (1.3-3.8)	2.5 (1.3-3.6)	0.823
EOT hs-CRP	2.1 (1-3.9)	1.9 (1.7-2.7)	0.143
Δ hsCRP	0 (-0.7-0.5)	-0.7 (-1.3 - -0.3)	0.001
Baseline HbA1c (%)	6 $\pm$ 0.62	6 $\pm$ 0.6	0.74
EOT HbA1c	6 $\pm$ 0.6	6 $\pm$ 0.5	0.65
Δ HbA1c	-0.01 $\pm$ 0.14	-0.02 $\pm$ 0.12	0.724
Baseline cholesterol (mmol/L)	5.6 $\pm$ 0.6	5.4 $\pm$ 0.6	0.3
EOT cholesterol	5.5 $\pm$ 0.5	5.4 $\pm$ 0.6	0.521
Δ cholesterol	0 $\pm$ 0.3	0 $\pm$ 0.04	0.5
Baseline tryglicerides (mmol/L)	3.8 $\pm$ 1.1	3.5 $\pm$ 1.2	0.262
EOT tryglicerides	3.7 $\pm$ 1.1	3.4 $\pm$ 1.2	0.18
Δ tryglicerides	-0.07 $\pm$ 0.32	-0.12 $\pm$ 0.29	0.454
Baseline eGFR (ml/min)	80.7 $\pm$ 6.9	78.3 $\pm$ 6.9	0.123
EOT eGFR	81.2 $\pm$ 7.6	79.6 $\pm$ 6.9	0.315
Δ eGFR	0.6 $\pm$ 2.9	1.3 $\pm$ 3.4	0.286

*EOT-End-of-treatment

STOOL MICROBIOME DYNAMIC

All provided stool samples were adequate. A good microbiome diversity was observed, with approximately 184,501 reads per sample. The Shannon and Simpson indices underwent statistically significant changes in the intervention group ($p=0.0174$ and $p=0.0385$). A difference in beta diversity did not reach statistical significance ($p=0.0734$).

When observing the dynamics of bacterial genera, it is noted that synbiotics significantly enriched the microbiome of treated patients with *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, and *Streptococcus* genera by 81%, 55%, 51%, and 40%, respectively, while reducing the genera *Ruminococcus* and *Enterobacterium* by 35% and 40%, respectively. As for the microbiome dynamics in the control group, a positive trend in the genera *Streptococcus* and *Faecalibacterium* was observed, increasing by 55% and 47%, respectively.

CORRELATION SUB-STUDY

In order to better understand the relation between positive effects on clinical and laboratory

parameters and changes in the composition of the intestinal microbiome, a correlation substudy was conducted. A positive correlation was observed between hs-CRP level and abundance of the *Veilonellaceae* family ($Rho=0.161$, $p=0.037$). We found negative correlation between hs-CRP and abundance of *Holdemanella* genera ($Rho=-0.161$, $p=0.037$). Regarding elastometric parameters, a positive correlation was noted for the ATT parameter with the presence of the *Methanobacteriaceae* ($Rho=0.231$, $p=0.03$) and *Clostridiaceae* ($Rho=0.197$, $p=0.01$) families.

GASTROINTESTINAL SYMPTOMS AND THE GUT TRANSITION TIME

Except for one patient, all other participants complained of at least one gastrointestinal symptom during the initial GSRS interview, most commonly constipation (87%) and indigestion (76%). The use of synbiotics in patients with constipation significantly reduced the intensity of the symptoms. Similar findings were observed in the analysis of the gut transition time, which was considerably shorter in the intervention group.

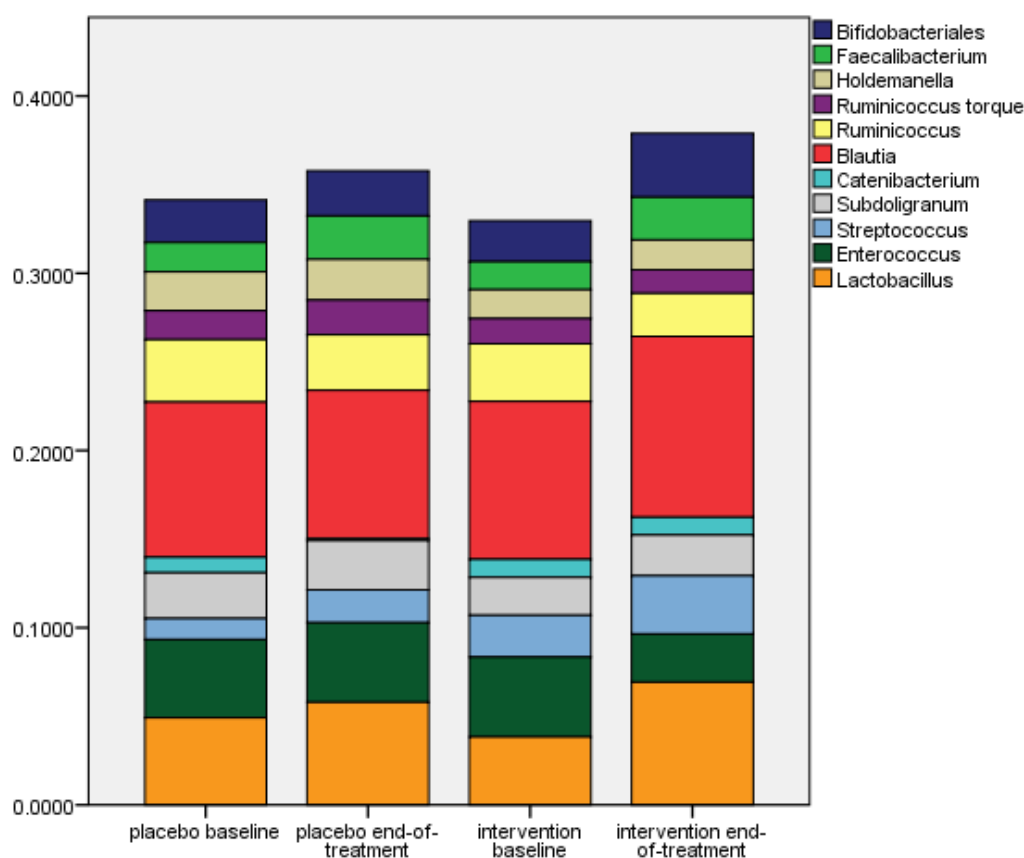


Figure 2. The microbiome dynamics.

Table 4
The effect of synbiotics on gut transition time (GTT) and constipation

	Placebo	Treatment	p value
Baseline constipation score	2 (0-8)	1 (0-10)	0.119
EOT* constipation score	2 (0-9)	1 (0-5)	0.428
Δ Constipation	0 (-2-3)	-2 (-6-1)	<0.001
Baseline GTT (h)	44±9	46±9	0.396
EOT GTT (h)	38±7	35±8	0.074
Δ GTT (h)	-5±9	-10±10	0.031

*EOT-End-of-treatment

SEPARATE ANALYSIS OF NASH PATIENTS

If we separately analyze patients with possible NASH, we observed that the treatment with synbiotics significantly reduced the levels of hs-CRP (Δ hs-CRP -1.3 vs 0.3 mg/L, $p=0.029$), ALT (Δ ALT -20 vs -11 IU/L, $p=0.049$), and liver stiffness (Δ E median -2.3 vs -0.5 kPa, $p=0.036$). Elastometric measurements did not show a significant effect on the liver steatosis (Δ ATT -0.0155 vs -0.0154, $p=0.96$).

DIET

Dietary plan adherence was high 90% in the intervention and 91% in the control group. There were no significant differences in calorie, carbohydrate, fat, or protein intake between the groups, and the treatment itself did not significantly affect BMI dynamics (Δ BMI -0.5±0.6 control vs -1.5±0.6 intervention, $p=0.478$).

SAFETY PROFILE

Except for increased flatulence in two patients, where the treatment was discontinued, no other adverse events were reported.

DISCUSSION

Compared to the placebo, the synbiotics led to a significant reduction in liver steatosis, a substantial decrease in hs-CRP levels, a shortening of gut transit time, and a reduction in constipation. All positive effects of the therapy were associated with a significant change in the composition of the patient's stool microbiome.

Good adherence to a Mediterranean dietary plan in both groups of patients might explain positive overall ALT dynamic. This also might be the reason why the effect of synbiotics on ALT levels did not stand out in intervention group. In his meta-analysis concerning the subject, Zhou also noted that the length of synbiotic treatment over 12 weeks yielded better results in correcting serum levels of liver enzymes, so hypothetically, this effect could be expected if we prolonged our treatment [5].

Only four studies analyzed the effect of synbiotics on the levels of inflammatory markers in MASLD patients, but the results were mixed [14–17]. Zhou's meta-analysis of the studies showed that pro- and synbiotic therapy could even slightly increase inflammation markers such as IL-6, TNF- α , lipopolysaccharides, and hs-CRP [5]. One of the differences between our study and these studies was that we included patients with mild chronic kidney insufficiency (eGFR placebo 81 ml/min vs. eGFR treatment 78 ml/min). This might be the reason of the observed positive effects on therapy, if we take into account the positive experience with synbiotics in population of chronic kidney disease patients [18].

While a definitive diagnosis of NASH typically requires a biopsy, we attempted to identify it by combining liver elastometry and laboratory parameters. Notably, our analysis of this subset of patients revealed intriguing findings- synbiotic treatment led to a significant reduction in inflammatory markers and liver stiffness without a significant impact on liver steatosis. The rationale behind this effect may be explained in an experimental study on mice with NASH, conducted

by Arai. The study revealed that probiotics initially reduced the levels of lobular inflammation and hepatocyte ballooning, with a potential impact on liver steatosis later in the course of the treatment [19].

One of the greatest strengths of our study compared to studies of a similar design is that it included intestinal microbiome analysis. The treatment in the intervention arm enriched the intestinal microbiome with the genera *Bifidobacterium* and *Lactobacillus*, but also reduced the prevalence of *Ruminococcus* and *Enterobacterium*. The positive impact of *Bifidobacterium* and *Lactobacillus* has been known for some time. However, in the case of MASLD, their essential role is in preserving intestinal integrity and forming a specific intestinal milieu unfavorable for protein-fermenting bacteria, such as *Ruminococcus* and *Enterobacterium*. The role of the *Ruminococcus*, especially *Ruminococcus gnavus*, is particularly highlighted in the pathogenesis of IBD, given the possibility that its metabolic products stimulate local T-lymphocytes [20]. The increased prevalence of *Enterobacterium* is one of the characteristics of dysbiosis in IBD patients, and it contributes to the pathogenesis by affecting the production of short-chain fatty acids, vital for the integrity of mucosal barrier [21]. The significant enrichment of the microbiome with the genera *Faecalibacterium* and *Streptococcus* in both arms could probably be explained by the Mediterranean diet [22].

Even though correlations between the dynamics of the microbiome and findings are statistically significant, they are weak. However, they could be meaningful, especially if we observe consistency in such findings with those of studies of a similar nature. We have shown a positive association between hs-CRP levels and the prevalence of the bacterial family *Veilonellaceae* and a negative one with the bacterial genus *Holdemanella*. Lee in his study highlighted possible role of the *Veilonellaceae* family in the progression of fibrosis in MASLD [23]. Although there is not much literature data on

the function of the bacterial genus *Holdemanella* in the human microbiome, during the examination of the effect of glucagon-like receptor 1 (GLP1) agonists on mice, it was shown that individuals with a higher prevalence of the *Holdemanella* had a better therapeutic response [24]. GLP1 have proved themselves more efficient than placebo in resolving NASH, during phase IIa trials [25].

The dynamic of ATT elastometric parameter correlated positively with the prevalence of *Methanobacteriaceae* and *Clostridiaceae*. In his meta-analysis, Gudan highlighted the direct relationship between syndrome of intestinal bacterial overgrowth (SIBO) and NASH [26]. *Methanobacteriaceae* and *Clostridiaceae* strains are often considered to be in the basis of the pathophysiological process of SIBO [27]. Up to 87% of MASLD patients in study complained of constipation, and the average intestinal transit time was 45 hours. This provides a sound basis for the proliferation of protein-fermenting and methanogenic strains such as *Methanobacteriaceae* and *Clostridiaceae*. The use of synbiotics led to a significant shortening of intestinal transit time and a reduction in constipation. Schattenberg in his study spoke about intestinal motility as an important therapeutic target in MASLD patients [28]. Kessoku even showed that the laxative effects of lubiprostone in MASLD patients were paralleled with resolution of steatosis [29].

Despite a single center design and the treatment lasting for a shorter period, the thing that gives strength to our study is the randomized, double-blind, placebo-controlled design with strict control of the diet and antibiotic usage, along with the analysis of stool microbiome composition.

CONCLUSION

Synbiotics represent an effective, safe and available therapeutic option that could have an important place in MASLD treatment.

Introducere: Boala ficatului asociată disfuncției metabolice (MASLD) reprezintă un spectru de afecțiuni ce poate lua forma de la simpla acumulare de grăsime până la steatohepatita non-alcoolică. Posibilul rol al microbiomului intestinal asupra dezvoltării MASLD este încă dezbatut. Studiul nostru și-a propus să examineze efectele sinbiotice asupra steatozei hepatice, a inflamației și a microbiomului.

Metode: A fost realizat un studiu dublu-orb, controlat placebo, care a implicat 84 de pacienți cu MASLD, definit printr-un coeficient de atenuare elastometric (ATT) mai mare de 0,63 dB/cm/MHz cu un nivel al alanin aminotransferazei peste 40 U/L pentru bărbați și 35 U/L pentru femei. Pacienții au fost împărțiți într-un grup de intervenție tratat

cu un simbiotic cu 64×10^9 CFU de *Lactobacillus* și *Bifidobacterium* și 6,4 g de inulină și un grup de control tratat cu placebo.

Rezultate: Utilizarea sinbioticeilor timp de 12 săptămâni a scăzut semnificativ steatoza hepatică (Δ ATT $-0,006 \pm 0,023$ vs $-0,016 \pm 0,021$ dB/cm/MHz, $p=0,046$). Grupul de pacienți tratați cu sinbiotice a prezentat o scădere semnificativă a nivelului de proteină C-reactivă (Δ hs-CRP 0 vs $-0,7$ mg/L, $p \leq 0,001$). Sinbioticele au îmbogățit microbiomul pacienților din grupul de intervenție cu genurile *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium* și *Streptococcus*, cu 81%, 55%, 51% și, respectiv, 40%, cu o reducere a *Ruminococcus* și *Enterobacterium* cu 35% și 40%. Tratamentul cu sinbiotic a scurtat semnificativ timpul de tranzit intestinal (Δ GTT -5 h vs. -10 h, $p=0,031$).

Concluzie: Sinbioticele ar putea fi o opțiune eficientă și sigură în tratamentul MASLD.

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