10.5005/jp-journals-10018-1226

BRIEF REPORT

Probiotic Therapy in Patients with Nonalcoholic Steatohepatitis in Zagazig University Hospitals

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ABSTRACT

Aim: Nonalcoholic fatty liver disease (NAFLD) is probably the most common liver disorder in the world. A subgroup of NAFLD patients is characterized by injury to the hepatocytes and inflammation in addition to excessive fat (steatohepatitis), the latter condition is nominated nonalcoholic steatohepatitis (NASH). This work aimed to evaluate the role of probiotics on the outcome of NASH in patients admitted to the Tropical Medicine Department, Faculty of Medicine, Zagazig University (inpatients and outpatients).

Materials and methods: This study was performed on 30 patients (17 males and 13 females), with body mass index from 30 to 35 and average age of 44 years with bright fatty liver in ultrasonography and raised alanine transaminase (ALT) and aspartate transaminase (AST) and positive liver biopsy findings. The patients were divided into group I (case group) that included 15 patients who received probiotics and group II of 15 patients as control group who did not receive probiotics; the study was conducted between November 2014 and April 2016. Clinical assessment, laboratory evaluation, pelvic-abdominal ultrasound, and liver biopsy of all cases were carried out.

Results: In this study, there was significant decrease in liver enzymes (ALT and AST) and no statistically significant other laboratory findings. Also there was relief for dyspepsia in some patients.

Conclusion: Probiotics treatment is effective, safe, well-tolerated, inexpensive, appropriate for long-term use, and optimally, works at multiple levels to downregulate inflammatory mediators, and therefore, probiotics could be an option in the treatment of NASH.

Keywords: Nonalcoholic fatty liver disease, Probiotics, Steatohepatitis.

How to cite this article: Monem SMA. Probiotic Therapy in Patients with Nonalcoholic Steatohepatitis in Zagazig University Hospitals. Euroasian J Hepato-Gastroenterol 2017;7(1):101-106.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a state defined by extreme fat accumulation in the form of triglycerides (steatosis) in the liver (more than 5% of liver cells histologically). It is considered nowadays as one of the most frequent causes of abnormal liver tests all over the world, and it ranges from simple steatosis to advanced fibrosis and cirrhosis. A subgroup of NAFLD patients were characterized by injury to the hepatocytes and inflammation in addition to excessive fat (steatohepatitis). The latter condition, nominated nonalcoholic steatohepatitis (NASH), is practically indistinguishable histologically from alcoholic steatohepatitis, and it is characterized by fatty infiltration of the liver with different degrees of inflammation, necrosis, and fibrosis, almost identical to those of alcoholic liver disease; without significant alcohol ingestion.[1]

Simple steatosis seen in NAFLD does not correspond to increased short-term morbidity or mortality, but advancement of this condition to NASH noticeably increases the risks of fibrosis, cirrhosis (cryptogenic cirrhosis), liver failure, and hepatocellular carcinoma (HCC). The prevalence of NAFLD ranges from 10 to 24% of the general population, while NASH affects about 3% of the lean population and nearly half of morbidly obese people.[2]

The term nonalcoholic steatohepatitis or NASH is expressing the clinical and pathological characters of NAFLD coupled with the pathological characters mostly present in alcoholic liver disease itself. This description is still proper as NAFLD can progress to cirrhosis with fat from simple steatosis, through NASH and fibrosis.[3]

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Nonalcoholic steatohepatitis is a chronic liver disease, i.e., earning increasing significance due to its great prevalence all over the world, the difficulty in diagnosis with noninvasive diagnostic methods, and the risk of succession to advanced fibrosis and cirrhosis, all of which make NASH difficult for doctors. Although the natural history of NASH and the causes of disease progression remain mostly unknown, more than a few data suggest that in some patients the disease may follow an indolent course until it progresses to end-stage liver disease.[4,5]

Most patients have the clinical characteristics of insulin resistance syndrome, including obesity, hypertension, glucose intolerance, and typical dyslipidemia. Insulin resistance plays a role not only in obese individuals but also in lean nondiabetic patients with hepatic steatosis.[6]

The "two-hit" hypothesis is the leading theory for the pathogenesis of NASH. This model suggests that the initial event or first "hit" leads to steatosis, and the second "hit" leads to necroinflammation and fibrosis. Insulin resistance has been implicated as the first "hit" and various insults, such as oxidative stress, cytokine effects, and fatty acid toxicity are suspected as potential other hits that lead to hepatocellular injury.[7] Tumor necrosis factor-alpha (TNF-α) in the liver can contribute to oxidative stress; furthermore, it may contribute to insulin resistance.[8] Additionally, TNF-α also initiates fibrosis both by direct activation of hepatic stellate cells and by stimulating production of tumor growth factor (TGF)-beta, a potent profibrogenic cytokine.[9]

A complex relationship exists between endotoxins, stellate cell activation, and release of cytokines and chemokines due to increased intestinal bacterial overgrowth, increased gut permeability, and reduced endotoxin scavenging by the reticuloendothelial system. The endotoxin releases a battery of cytokines; interleukin (IL)-1, IL-6, and TNF-α from nonparenchymal cells.[10] The general belief that intestinal bacterial overgrowth has a role in NAFLD is supported by the evidence that obesity and diabetes, which are the major risk factors for NASH, are also associated with intestinal dysmotility[11] and small bowel bacterial overgrowth.[12] Probiotics are traditionally defined as viable microorganisms that have beneficial effects in the prevention and treatment of specific pathologic conditions when they are ingested.[13] There are many proposed mechanisms by which probiotics may protect the host from intestinal disorders, including production of inhibitory substances, blocking of adhesion sites, competition for nutrients, degradation of toxin receptor, and stimulation of immunity.[13] Probiotics affect intestinal bacterial flora by increase of anaerobic bacteria and decrease of the population of potentially pathogenic microorganisms.[14]

This work aimed to evaluate the role of probiotics on the outcome of NASH in patients admitted to the Tropical Medicine Department, Faculty of Medicine, Zagazig University (inpatients and outpatients).

MATERIALS AND METHODS

This randomized controlled study was performed on 30 patients (17 males and 13 females), with body mass index (BMI) from 30 to 35 and average age of 44 with bright fatty liver in ultrasonography and raised alanine transaminase (ALT) and aspartate transaminase (AST) and positive liver biopsy findings. Patients were divided into group I (case group) that included 15 patients who received probiotics and group II that included 15 patients (control group) who did not receive probiotics and were consulting at Tropical Medicine Department, Faculty of Medicine, Zagazig University Hospitals between November 2014 and April 2016.

Inclusion Criteria

Patients with elevated liver enzymes and bright liver by ultrasonography were examined and investigated for selection of patients with NASH, which was proved by liver biopsy.

Exclusion Criteria

Patients with history of significant alcohol consumption more than 20 gm/day or under dietetic regimen; patients with positive hepatitis B and C virus markers; patients who were taking lipid-lowering medications, metformin, or thiazolidinediones; and patients with any other metabolic liver disease were excluded from the study. Kidney function tests were performed: For exclusion of cases with renal impairment. Compensated and decompensated cirrhotic patients; hepatic focal lesion; AST/ALT ratio >1 were also excluded.

All patients were subjected to the following: Full clinical history with stress on age and sex, change in appetite, dyspepsia, abdominal distension, right hypochondrial pain, and fatigue. Patients with history of medical diseases, e.g., diabetes mellitus, hypertension, bilharziasis, chronic viral hepatitis, pituitary disease, adrenal disease or pancreatic disease, history of surgical operation, e.g., gastric bypass or jejunoileal bypass were also excluded.

All patients were checked for parameters of general examinations, such as blood pressure, pulse, face complexion, hand and lower limb examination, body weight, height, and BMI that was defined by Kumar and Clark.[15]

Local examination of abdomen and liver was accomplished.

Laboratory assessment included complete blood count, hemoglobin level, white blood cells, and platelets counts. Parameters of liver function tests were also checked. Imaging of abdomen and the liver was done.

Probiotic Therapy

The patients were kept on probiotic supplementation. Acidophilus capsule (*Lactobacillus acidophilus*, which contains 2 billion viable organism, and mixture of rice flour, gelatin, and magnesium stearate) was given to patients 30 minutes before meal three times daily for 1 month duration (Acidophilus, Swanson Health Products, USA website, www.swansonvitamins.com).

Statistical Analysis

Data were checked, entered, and analyzed using Statistical Package for the Social Sciences version 18 for Windows. Data were expressed as mean ± standard deviation for quantitative variable, number and percentage for qualitative one. Chi-squared (χ^2) or t-test and paired t-test were used when appropriate; $p < 0.05$ was considered significant; $p < 0.001$ was considered highly significant.

RESULTS AND DISCUSSION

Nonalcoholic fatty liver disease is probably the most common liver disorder in the world.[16] It is generally believed that NAFLD affects 2.8 to 24% of the general population and affects adults and children.[17]

In addition, NAFLD is the consequence of excess triglyceride accumulation in hepatocytes in the absence of significant alcohol consumption.[18] It includes a spectrum of hepatic changes from steatosis alone, to NASH, fibrosis, cirrhosis, and even HCC.[19]

Probiotics are traditionally defined as viable microorganisms that have beneficial effects in the prevention and treatment of specific pathologic conditions when they are ingested.[13] There are many proposed mechanisms by which probiotics may protect the host from intestinal disorders, including production of inhibitory substances, blocking of adhesion sites, competition for nutrients, degradation of toxin receptor, and stimulation of immunity.[13] Probiotics affect intestinal bacterial flora by increase of anaerobic bacteria and decrease of the population of potentially pathogenic microorganisms.[14]

This study is aimed to evaluate the role of probiotics on the outcome of NASH in humans.

This randomized controlled study was performed on 30 patients (17 males and 13 females), with BMI from 30 to 35 and average age of 44 with bright fatty liver in ultrasonography and raised ALT and AST and positive liver biopsy findings. Patients were divided into group I (case group) that included 15 patients who received probiotics and group II that included 15 patients (control group) who did not receive probiotics and were consulting at Tropical Medicine Department, Faculty of Medicine, Zagazig University Hospitals between November 2014 and April 2016.

In the present study of demographic, clinical, and abdominal ultrasound (U/S) findings before treatment for both groups, no significant difference was seen. Also this study showed no significant difference as regards complete blood count, liver function test, kidney function test, prothrombin time (PT), international normalized ratio (INR), lipid profile, and blood sugar. Due to all patients were complaining from nonalcoholic steatohepatitis then were divided randomly into two groups.

In the present study, patients were matched with control subject as regards posttreatment biochemical findings, which showed no significant difference (Tables 1 and 2). But there was a highly significant difference in ALT and significant difference in AST. Otherwise, other biochemical changes showed no significant difference between both groups This is in agreement with the results of Solga and Diehl,[20] Loguercio et al,[21] and Portincasa et al,[22] which found similar changes in ALT and AST. These findings denote that the use of probiotics in these patients plays some role in improving the necroinflammatory status of the liver (Tables 3 to 6).

Table 1: Comparison between groups I and II as regards demographic, clinical, and U/S findings

Variables	*Group I (n = 15)*	*Group II (n = 15)*	*p-value*
Age (years)	44.20 ± 5.51	44.33 ± 5.62	0.948
Gender			
Male	9 (60%)	8 (53.3%)	0.713
Female	6 (40%)	7 (46.7%)	
BMI (kg/m^2)	32.56 ± 1.19	33.05 ± 1.27	0.284
Clinical presentation			
Asymptomatic	8 (53.3%)	15 (100%)	0.006
Dyspepsia	4 (26.7%)	0 (0%)	0.100
Fatigue	2 (13.3%)	0 (0%)	0.483
Right hypochondrial pain	1 (6.7%)	0 (0%)	1.000
Clinical examination			
Hepatomegaly	4 (26.7%)	4 (26.7%)	1.000
Splenomegaly	0 (0%)	0 (0%)	1.000
Ascites	0 (0%)	0 (0%)	1.000
Liver in U/S			
Average	4 (26.7%)	5 (33.3%)	0.709
Enlarged	11 (73.3%)	10 (66.7%)	
Spleen in U/S			
Average	15 (100%)	15 (100%)	1.000
Splenomegaly	0 (0%)	0 (0%)	
Ascites in U/S			
Absent	15 (100%)	15 (100%)	1.000
Present	0 (0%)	0 (0%)	

Table 2: Comparison between groups I and II as regards laboratory findings before treatment

Variables	*Group I before (n = 15)*	*Group II before (n = 15)*	*p-value*
Hemoglobin (g/dL)	13.16 ± 0.88	13.57 ± 0.84	0.208
WBCs (× 10^3/mm^3)	6.78 ± 1.72	7.36 ± 1.85	0.383
Platelet count (× 10^3/mm^3)	300.60 ± 78.33	312.20 ± 75.56	0.683
Protein (g/dL)	7.47 ± 0.77	7.45 ± 0.89	0.819
Albumin (g/dL)	4.60 ± 0.44	4.64 ± 0.45	0.835
TSB (mg/dL)	0.88 ± 0.38	0.86 ± 0.41	0.950
DSB (mg/dL)	0.11 ± 0.04	0.12 ± 0.05	0.665
ALT (U/L)	81.45 ± 23.32	83.53 ± 12.01	0.962
AST (U/L)	44.05 ± 14.65	42.73 ± 9.95	0.967
PT (sec)	15.19 ± 1.72	15.86 ± 1.94	0.325
INR	1.00 ± 0.09	1.04 ± 0.10	0.336
Serum creatinine (mg/dL)	0.90 ± 0.29	1.05 ± 0.30	0.186
BUN (mg/dL)	18.06 ± 6.81	19.13 ± 7.46	0.686
Triglycerides (mg/dL)	257.80 ± 55.02	245.33 ± 70.78	0.755
Cholesterol (mg/dL)	258.60 ± 31.70	250.53 ± 45.12	0.771
LDL (mg/dL)	158.53 ± 23.67	154.73 ± 33.24	0.721
HDL (mg/dL)	48.73 ± 4.83	48.80 ± 5.00	0.971
FBS (mg/dL)	104.86 ± 21.33	107.06 ± 27.06	0.807
PBS (mg/dL)	161.13 ± 53.37	173.06 ± 73.91	0.819

WBC: While blood cell; TSB: Total serum bilirubin; DSB: Direct serum bilirubin; BUN: Blood urea nitrogen; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBS: Fasting blood sugar; PBS: Peripheral blood smear

Table 3: Comparison between groups I and II as regards laboratory findings after treatment

Variables	*Group I after (n = 15)*	*Group II after (n = 15)*	*p-value*
Hemoglobin (g/dL)	13.20 ± 0.85	13.67 ± 0.71	0.108
WBCs (× 10^3/mm^3)	6.79 ± 1.70	7.36 ± 1.67	0.366
Platelet count (×10^3/mm^3)	298.40 ± 76.37	309.26 ± 70.02	0.688
Protein (g/dL)	7.47 ± 0.77	7.42 ± 0.80	0.857
Albumin (g/dL)	4.58 ± 0.45	4.66 ± 0.41	0.493
TSB (mg/dL)	0.87 ± 0.37	0.88 ± 0.37	0.967
DSB (mg/dL)	0.11 ± 0.04	0.12 ± 0.05	0.613
ALT (U/L)	46.10 ± 20.75	82.53 ± 10.41	<0.001
AST (U/L)	38.20 ± 11.58	55.86 ± 5.11	0.03
Serum creatinine (mg/dL)	0.89 ± 0.26	0.91 ± 0.20	0.142
BUN (mg/dL)	17.73 ± 6.13	18.46 ± 6.45	0.752

WBC: While blood cell; TSB: Total serum bilirubin; DSB: Direct serum bilirubin; BUN: Blood urea nitrogen

Table 4: Comparison between before and after treatment in group I as regards clinical and U/S findings

	Group I		
Variables	*Before treatment (n = 15)*	*After treatment (n = 15)*	*p-value*
Clinical presentation			
Asymptomatic	8 (53.3%)	12 (80%)	0.125
Dyspepsia	4 (26.7%)	1 (6.7%)	0.250
Fatigue	2 (13.3%)	1 (6.7%)	1.000
Right hypochondrial pain	1 (6.7%)	1 (6.7%)	1.000
Clinical examination			
Hepatomegaly	4 (26.7%)	4 (26.7%)	1.000
Splenomegaly	0 (0%)	0 (0%)	1.000
Ascites	0 (0%)	0 (0%)	1.000
Liver in U/S			
Average	4 (26.7%)	4 (33.3%)	0.135
Enlarged	11 (73.3%)	11 (73.3%)	
Spleen in U/S			
Average	15 (100%)	15 (100%)	1.000
Splenomegaly	0 (0%)	0 (0%)	
Ascites in U/S			
Absent	15 (100%)	15 (100%)	1.000
Present	0 (0%)	0 (0%)	

Table 5: Comparison between before and after treatment in group I as regards laboratory findings

	Group I		
Variables	*Before treatment (n = 15)*	*After treatment (n = 15)*	*p-value*
Hemoglobin (g/dL)	13.16 ± 0.88	13.20 ± 0.85	0.334
WBCs (× 10^3/mm^3)	6.78 ± 1.72	6.79 ± 1.70	0.806
Platelet count (× 10^3/mm^3)	300.60 ± 78.33	298.40 ± 76.37	0.021
Protein (g/dL)	7.47 ± 0.77	7.47 ± 0.77	1.000
Albumin (g/dL)	4.60 ± 0.44	4.58 ± 0.45	0.208
TSB (mg/dL)	0.88 ± 0.38	0.87 ± 0.37	0.144
DSB (mg/dL)	0.11 ± 0.04	0.11 ± 0.04	0.334
ALT (U/L)	83.33 ± 10.96	46.10 ± 20.75	<0.001
AST (U/L)	57.06 ± 7.86	38.20 ± 11.58	0.03
Serum creatinine (mg/dL)	0.90 ± 0.29	0.89 ± 0.26	0.414
BUN (mg/dL)	18.06 ± 6.81	17.73 ± 6.13	0.173

WBC: While blood cell; TSB: Total serum bilirubin; DSB: Direct serum bilirubin; BUN: Blood urea nitrogen

Table 6: Comparison between before and after treatment in group II as regards laboratory findings

	Group II		
Variables	*Before treatment (n = 15)*	*After treatment (n = 15)*	*p-value*
Hemoglobin (g/dL)	13.57 ± 0.84	13.67 ± 0.71	0.355
WBCs (× 10^3/mm^3)	7.36 ± 1.85	7.36 ± 1.67	0.937
Platelet count (× 10^3/mm^3)	312.20 ± 75.56	309.26 ± 70.02	0.366
Protein (g/dL)	7.45 ± 0.89	7.42 ± 0.80	0.362
Albumin (g/dL)	4.64 ± 0.45	4.66 ± 0.41	0.519
TSB (mg/dL)	0.86 ± 0.41	0.88 ± 0.37	0.340
DSB (mg/dL)	0.12 ± 0.05	0.12 ± 0.05	0.582
ALT (U/L)	83.53 ± 12.01	82.53 ± 10.41	0.096
AST (U/L)	58.73 ± 9.95	55.86 ± 5.11	0.048
Serum creatinine (mg/dL)	1.05 ± 0.30	1.07 ± 0.20	0.638
BUN (mg/dL)	19.13 ± 7.46	18.46 ± 6.45	0.329

WBC: While blood cell; TSB: Total serum bilirubin; DSB: Direct serum bilirubin; BUN: Blood urea nitrogen

This study showed improvement of dyspepsia in group I posttreatment; otherwise, there were no significant change in other symptoms and in abdominal U/S findings.

This study also showed significant decrease in ALT and AST in group I posttreatment in comparison to pre-treatment; otherwise, there was no significant change in other laboratory findings, and these were in agreement with the findings of Loguercio et al[21] and Wong et al.[23]

CONCLUSION

Probiotics treatment is effective, safe, well-tolerated, inexpensive, appropriate for long-term use, and optimally works at multiple levels to downregulate inflammatory mediators, and therefore, probiotics could be an option in the treatment of NASH.

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