

Correction of liver changes caused by alcohol rates with probiotics

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ABSTRACT

There is evidence of the beneficial effects of probiotics in fatty liver cases. This study aims to evaluate the effects of probiotic intake on several metabolic factors in people with fatty liver. Eighty patients with fatty liver with a body mass index above 25 were divided into three groups: the control group, the alcohol group, and the probiotic group. After 45 days, fasting blood samples, physical changes, and dietary intakes were measured over the experiment. Statistical analysis was performed with SPSS software, and variance analysis was done. Significant reduction in weight (4%) and BMI (5%) was observed (p -value less than 0.001). The percent changes in weight and BMI were at a rate of 4.8% compared to the control group. The waist circumference in both groups showed a significant difference after the intervention, with the probiotic group decreasing by 8% compared to the control group. The findings showed that probiotic treatment was beneficial in reducing the severity of liver damage, most likely through increasing beneficial bacteria and reducing inflammatory responses and oxidative stress, and led to weight loss and BMI.

Keywords: Fatty Liver, Adipokines, Alcohol, Probiotic.

Article type: Short Communication.

INTRODUCTION

With the increasing prevalence of obesity (Fuenzalida *et al.* 2021) around the world, obesity-related mortality complications are increasing (Kirpich *et al.* 2008). In obese people, the risk of diseases such as alcoholic and non-alcoholic fatty liver disease, cardiovascular diseases, and diabetes is higher (Gu *et al.* 2019; Moulaei *et al.* 2024). Fatty liver disease is currently the most common liver disorder and the most common cause of chronic liver disease (Kim *et al.* 2022). The simultaneous presence of visceral obesity and fatty liver in one person increases the possibility of suffering from advanced forms of liver disease (Li *et al.* 2016). Today, fatty liver causes health problems all over the world and is known as a major cause of death. It causes an increase in transaminases and is an essential factor in cryptogenic cirrhosis and liver carcinoma (Fooladi *et al.* 2013). Fat and its relationship with metabolic syndrome and genetic discussions show that the role of visceral obesity in fatty liver is significant. Studies in the population of non-alcoholic fatty liver patients showed that fatty liver has a significant relationship with the level of serum adipokines (Forsyth *et al.* 2009). The fatty liver shows a range of diseases, from simple steatosis to steatohepatitis, which leads to fibrosis and cirrhosis (Cesaro *et al.* 2011). The pathogenesis of fatty liver includes multiple processes, the first of which is the accumulation of liver fat, which is related to insulin resistance (Vidya Bernhardt *et al.* 2024). The second blow is increased beta-oxidation of fatty acids, oxidative

stress, and endotoxemia. Alcoholic fatty liver is deduced through high alcohol consumption. The liver experiences a high amount of alcohol consumed and the process of breaking down alcohol will produce harmful substances. These substances damage the liver cells and cause inflammation and a decrease in the body's defense power. The more alcohol drink, the more damage to the liver.

Probiotics and adipokines in fatty liver disease

The liver receives most of the blood flow through the portal system and is the first line of defense against gut-derived toxins. Hence, the role of gut microbiota in pathophysiology is significant. In addition to being beneficial for the metabolic pattern, these beneficial bacteria also have anti-inflammatory effects. By reducing the ratio of Firmicutes to Bacteroides in humans, a diet containing high fiber increases *Bifidobacterium*, helps limit calories, and leads to recovery (Kirpich & McClain 2012). Probiotics contain a variety of useful bacteria that can restore intestinal flora and intervene in fat metabolism by regulating intestinal flora and improving liver function. The results show that after the probiotics intervention, the liver function in patients improves significantly (also, the level of triglycerides and total cholesterol decreases; Vassallo *et al.* 2015). Liver diseases caused by alcohol can be treated using probiotics by adjusting the intestinal axis. The use of probiotics causes changes in the intestinal microbiota and reduces metabolic disorders by reducing serum lipid profiles and inflammatory biomarkers. Fatty liver happens in about 23.5% of the United States adult population (10). 46% of adults are in Western countries (Tian *et al.* 2015). Hepatic cell damage is indicated by a disproportionate increase in aspartate transaminase (AST) and alanine transaminase (ALT) compared to alkaline phosphatase (ALP). In contrast, an undue rise in ALP is shown in cholestatic damage relative to AST and ALT. Despite previous research, this article examined the effect of probiotics on improving alcoholic and non-alcoholic fatty liver. The anthropometric characteristics of the tested subjects were evaluated by fixing other variables to evaluate the direct effect of probiotics on improving the performance of fatty liver.

MATERIALS AND METHODS

This study is a controlled, double-masked, randomized clinical trial, which has been registered with the clinical trial number IRQ-34567. In the present study, 80 patients with fatty liver referred to the Baghdad Diabetes Clinic were invited according to the recommendation of a gastroenterologist who met the conditions to enter the study. Diagnosis of the disease based on liver ultrasound was done by determining the amount of fat released in the liver by a sonographer for all patients. Fat accumulates in the liver of patients with fatty liver $\geq 5\%$ of the weight of the liver. People whose disease was recently diagnosed and who had no history of taking drugs related to fatty liver disease, whose BMI was between 25 kg m⁻² and 40, and who were in the age range of 25-55 years were selected. The subjects were asked not to consume any yogurt or buttermilk containing probiotics for a week before the start of the study and during the study to avoid consuming food supplements and any other expensive probiotics outside the scope of the experiment. The sample size was based on the variable of fasting blood sugar presented in the research of Tian *et al.* (2015) and considering the confidence level of 95% in both control and control groups. Before the experiment started, the procedure was explained to the patients, and a written consent form was obtained from them, with the condition that their information be kept confidential. The patients were divided into two groups, and their information was obtained through a questionnaire. The biographical details of the patients are presented in Table 1. People in the probiotic group received 2% fat to 300 grams daily through food supplements.

Table 1. biographical details of patients.

Variables	Nonalcoholic	Alcohol	Prebiotic	
Sex	Men	14	8	22
	Women	11	6	19
Age			41.5	
Weight			84.5	
BMI			31.55	
Degree of fatty liver	1		58.5%	
	2		34.1%	
	3		7.4%	

The use of probiotics is a key factor in altering the intestinal microbiota and mitigating metabolic disorders by reducing serum lipid profiles and inflammatory biomarkers (Huang *et al.* 2019). This underscores the pivotal role of probiotics in this research. Adipokines, active biomolecules secreted from fat tissue, exert diverse effects on

various conditions. They are crucial in regulating metabolism, immunity, inflammation, cancer, and cardiovascular function (Bajaj 2019). Adipokines influence insulin sensitivity in different tissues such as the liver, muscle, pancreas, and fat tissue. They also play a significant role in liver physiology and the pathophysiology of numerous acute and chronic liver diseases, contributing to liver inflammation, cell death, and fibrosis.

Tumor necrosis factor alpha

TNF- α is a pro-inflammatory cytokine produced by lipids, macrophages, lymphocytes, natural killer cells, and neurons. Its molecular weight is 17 kilodaltons, and its main role is to regulate the function of the body's immune system (Elshagabee *et al.* 2019). High levels of TNF- α in the blood circulation are associated with obesity and insulin resistance (Hong *et al.* 2015) and play an important role in developing fatty liver and, subsequently, NASH (Gu *et al.* 2020). An increase in TNF- α causes desensitization of insulin signaling through specific phosphorylation of serine residues in the insulin receptor and insulin receptor substrate (TNF- α ; Wang *et al.* 2013). It inhibits harmful atherogenic pathways by reducing high-density lipoprotein (HDL) and increasing gene expression. Cholesterol and the increase of potentially harmful metabolites activate pro-cholesterol (TNF- α). It also stimulates the synthesis of hepatic fatty acids, increases the level of serum triglycerides, and stimulates the production of very low-density lipoprotein (LDL). TNF- α is essential in the pathogenesis of liver fibrosis in people with NASH (Gu *et al.* 2019). A prospective cross-sectional experimental study in Delhi showed a significant increase in TNF- α in NAFLD patients compared to healthy people (Kim *et al.* 2022). Similarly, another study in China showed an increase in TNF- α levels in patients with fatty liver (Lata *et al.* 2011). Studies on animals and humans have shown increased TNF- α in patients with NASH (Sung *et al.* 2016). Mice that are genetically deficient in TNF- α receptors, are resistant to NASH (Jeong *et al.* 2022), and in mice treated with TNF- α antibodies, improvement of hepatic insulin resistance and fatty liver was observed. TNF- α is an inflammatory mediator cytokine that helps and stimulates steatosis. It is the destruction of liver cells (Jeong *et al.* 2022). Studies have shown that the levels of TNF- α and IL-6 in the serum of people with a high-fat and sucrose diet have increased significantly compared to the control group. A high-fat diet causes changes in the intestinal microbiota and increases the inflammatory factors caused by the intestine (Marlicz *et al.* 2016), and probiotic adjuvant treatment reduces the level of TNF- α .

Interleukin

IL-6 is a cytokine that plays a role in the immune system and is produced by fat cells, immune cells, fibroblasts, endothelial cells, and monocytes. Circulating levels of IL-6 are increased in obese people and decrease in parallel with weight loss and insulin resistance. It disrupts insulin signaling in liver cells, increasing hepatic gluconeogenesis and creating compensatory hyperglycemia and hyperinsulinemia (Vatsalya *et al.* 2023). IL-6 increases insulin resistance by regulating the suppressor of cytokine signaling. Liver expression of IL-6 increases significantly in NASH patients and has a positive relationship with inflammation and fibrosis, and it has been reported as a predictor of steatosis and NASH. The evidence showed that serum IL-6 in people with NAFLD was significantly higher than in the control group, even after adjusting for age, gender, and BMI. The plasma level of IL-6 is directly related to the amount of fat tissue in the body, and with weight loss, the level of IL-6 decreases. Long-term exposure of the liver to IL-6 may damage the liver and cause cell death or become apoptotic (IL-6) is a pro-inflammatory and pro-oncogenic cytokine and a predictive biomarker for IR and CVD.

RESULTS

All participants completed the study. No side effects were reported due to consumption of yogurts. Table 1 shows the two groups' general, clinical, and anthropometric characteristics of patients with NAFLD. The two groups did not differ from each other in terms of distribution of average age, sex, anthropometric indices, and degree of fatty liver at the beginning of the study. In the probiotic yogurt group compared to the normal yogurt group, the average weight and BMI at the end of the study decreased significantly ($p < 0.01$). Table 2 shows the study subjects' average intake of energy and macronutrients. Other macronutrients were not statistically different between the two study groups at the beginning and the end of the eighth week. By comparing the diet of the patients in each group during the study, a significant increase in the average protein intake was observed in the two groups ($p < 0.05$). Changes in intake of energy and other macronutrients were not significant in any of the two groups. The findings of this study underscore the potential of probiotics as a potent tool in combating the onset of fatty liver disease and obesity. The use of probiotics in novel, specialized products is projected to be beneficial and

productive. Table 3 details the liver parameters. Lactobacilli, a well-known bacteria in probiotic products, have been shown to reduce plasma cholesterol concentration and shield against fat accumulation in tissues and liver cells in studies conducted on mice. Bacteria, particularly lactobacilli and bifidobacteria, play a pivotal role in the absorption and emulsion formation of fats and fat-soluble vitamins in the small intestine.

Table 2. Fat rate in various test groups.

Index	Fat rate		
	0-5%	5-10%	10-15%
Group			
Control	13	48	19
With Alcohol	6	43	31
With Prebiotic	35	31	14

Table 3. Amounts of liver parameters.

Index	ALT (pg mL ⁻¹)	IL-6 (pg mL ⁻¹)	TNF- α (pg mL ⁻¹)	p-value
Control	52.5	311.34	142.11	0.004
With Alcohol	68.9	408.66	172.50	0.001
With Prebiotic	32.3	306.78	121.87	0.001

As part of the evaluation of the prebiotic's effect, physical body parameters were measured before and after the test (see Table 4). Dysbiosis, or the imbalance of the microbial flora, coupled with increased intestinal mucosa permeability, gradually triggers inflammatory responses within and outside the liver. This process accelerates the progression of fatty liver disease, transforming it into steatohepatitis (fat accumulation in the liver with inflammation). Probiotics offer a promising avenue for addressing obesity and its associated diseases. Probiotic products control fatty liver disease and impede its progression by reducing fat absorption, lowering cholesterol levels, and managing inflammatory processes.

Table 4. Amount of physical body parameters.

Index	Weight (kg)	BMI (kg m ²)	waist circumference (cm)	p-value
Control	84.50	31.15	97.55	0.000
With Alcohol	85.98	32.12	98.87	0.001
With Prebiotic	82.49	30.01	95.65	0.000

DISCUSSION

Research has shown that probiotic and prebiotic supplements have favorable effects on glycemic factors. Serum concentrations of leptin, fasting blood sugar, and insulin were significantly reduced in the groups consuming probiotics and prebiotics compared to the control group. The quantitative insulin sensitivity index (QUICKI) was notably increased in the probiotic and prebiotic groups compared to the control group. Other researchers observed the effect of *Bifidobacterium* and *Lactobacillus plantarum* in reducing leptin in animal studies (Wang *et al.* 2012). A study also demonstrated that administering probiotics and prebiotics among patients with fatty liver for 12 weeks had beneficial effects on insulin and serum leptin metabolism. Therefore, the administration of probiotics can improve insulin resistance and fatty liver (Ram *et al.* 2024). However, recent studies have reported conflicting results regarding the relationship between probiotics and leptin levels (Gratz *et al.* 2010). Hence, further studies on a larger scale are necessary to investigate the relationship between leptin and probiotics in the context of fatty liver. In studies (Hsieh *et al.* 2021) in which *L. acidophilus* was controlled four times daily for adult fatty liver cases, AST and ALT were sharply reduced. This indicated that *Lactobacillus* helps to enhance the inflammatory status of the cases. In a study by Raff and colleagues, they showed that the consumption of probiotic yogurt increased the levels of liver enzymes, total cholesterol, and high-density lipoproteins. The bottom in the samples affected by fatty liver improved, which can be helpful in the management of fatty liver. It is consistent with our study in terms of reducing liver enzymes. A study by Sun *et al.* (2021) on mice suffering from liver damage found that *Bacillus* SC06 caused liver damage by oxidative stress reduces the intestines by optimizing the composition, metabolic pathways, and proliferation of pathogenic microbiota. These findings shed light on the mechanisms of probiotics in reducing oxidative stress and provide a promising strategy for preventing liver diseases by reducing intestinal microbiota to reduce liver enzymes. This study's AST, ALT, and ALP can be aligned with our research. A study by Manzhali *et al.* (2017) observed that the consumption of probiotic tablets containing *Streptococcus thermophilus* and *Lactobacillus bulgarius* for three months caused a significant decrease in ALT and AST, which is consistent with the results of our study. In a study (Stadlbauer *et al.* 2008), it was observed that the level of the

enzyme AST decreased in people suffering from NASH by consuming *Bifidobacterium longum* and fructo-oligosaccharide for 24 weeks, which can be consistent with our study. In a study (Tian *et al.* 2015) on infected people in NASH, people taking metformin and protoxin decreased the amount of ALT and AST enzymes. Still, only the AST enzyme decreased in people taking metformin along with placebo. It is the same as ours.

CONCLUSION

Fatty liver disease is one of the most common cases seen worldwide. This disease is caused by excessive accumulation of fat particles in liver cells. If not diagnosed and treated, it will progress to cirrhosis and death. In addition to fat storage, adipose tissue synthesizes and secretes hormones called adipokines, which play an essential role in fatty liver disease. Results indicated that probiotics can enhance fat metabolism and decrease inflammation by regulating gut flora. Studies have shown the relationship between the microbiome and the pathogenesis of fatty liver. The compounds obtained from microbiomes can affect the liver through biomarkers and lead to liver inflammation and fibrosis. Changing the lifestyle, following the diet, and increasing the consumption of dietary fiber, probiotics, prebiotics, and calorie restriction will improve the fatty liver. Therefore, probiotics can be used as a potential treatment in the medical treatment of non-alcoholic fatty liver disease. In this study, we learned more about adipokines, the effects of probiotics on adipokines, and their relationship with fatty liver disease, so it is a suitable research field for future studies.

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