

CASE REPORT

Silymarin and management of liver function in non-alcoholic steatohepatitis: a case report

Ahmed Hashem^{1,2}

¹Endemic Medicine Department, Cairo University, Giza, Egypt; ²Department of Medicine & Gastroenterology, Saudi German Hospital Jeddah, Jeddah, Kingdom of Saudi Arabia

Abstract

Non-alcoholic fatty liver disease (NAFLD) and its progressive form (non-alcoholic steatohepatitis; NASH) are the main reason for chronic liver disease in the general population, characterized by fat accumulation in hepatocytes (steatosis) and anomalies in liver biochemical analyses. To date, no pharmacological agents have been approved for NAFLD or NASH treatment. However, silymarin, the active ingredient in milk thistle, has been used in the last decades for the treatment of several liver diseases. In this case report, treatment with silymarin 140 mg three-times daily highlighted moderate efficacy and a good safety profile in the management of NASH and liver function, as it decreased serum AST and ALT levels over the treatment period with no side-effects, supporting silymarin as a promising supplemental in-

tervention that can normalize liver activity in NAFLD and NASH.

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Keywords: case report, deranged liver enzymes, liver function, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, silymarin.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of incidental elevation of liver enzymes worldwide, with a global prevalence of ~23–25% of the adult population.^{1,2} The clinical features of the disease range from simple steatosis with a benign prognosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, with an increase in mortality and morbidity. NAFLD and NASH are known to have a close and bidirectional association with obesity, diabetes and metabolic syndrome.^{2–4}

Silymarin, a milk thistle extract, has long been used for the management of liver disorders due to its assumed hepatoprotective and antioxidant properties. In particular, silymarin may counteract lipid peroxidation and radical-induced damage, which are probable mechanisms of liver injury in NASH.⁵

This case report recommends silymarin treatment in patients with diabetes, obesity and NASH to manage abnormal liver enzyme activity.

Ethics statement

This manuscript has been prepared according to CARE guidelines. No patient consent was required as no information is reported that could allow identification of the patient.

Case report

In January 2022, a 50-year-old woman was referred to our department (Department of Medicine & Gastroenterology, Saudi German Hospital Jeddah, Jeddah, Kingdom of Saudi Arabia) by an endocrinologist due to deranged liver enzyme levels accidentally discovered during check-up examinations.

The medical history was type 2 diabetes, diagnosed in 2015, high blood pressure (hypertension) and obesity, with a BMI of 39.2. For diabetes management, she was treated with a combination of metformin 1 g daily and

gliclazide 120 mg daily, whilst amlodipine 10 mg daily was prescribed for hypertension.

In January 2022, the general physical examination was unremarkable: no palmar erythema or vascular spiders were observed, whilst the abdominal examination revealed a palpable liver that was relatively soft and mild splenomegaly.

Blood and liver function tests revealed elevated liver enzymes, especially for alanine transaminase (ALT or GPT), aspartate transaminase (AST or GOT), and γ -glutamyltransferase (GGT) (Table 1). In addition, an abnormal lipid profile with high triglycerides (324 mg/dL) was observed. The fibrosis 4 index (FIB-4), a non-invasive liver fibrosis marker used in the diagnosis and management of liver disease, was elevated (6.4), indicating a high risk of liver fibrosis. Hepatitis B surface antigen, anti-hepatitis C virus antibodies and autoantibodies were negative.

An abdominal ultrasound was performed and showed bright hepatomegaly and mild splenomegaly (14 cm in length). In addition, the portal vein measured 14 mm in diameter, and no ascites were observed.

Accordingly, the patient was diagnosed with NASH and, in January 2022, she was advised to start treatment in the form of weight reduction and dyslipidaemia control. For losing weight, liraglutide with an initial dose of 0.6 mg daily was prescribed, and maintained at a dose of 3 mg daily. In addition, simvastatin 20 mg daily was prescribed to control hyperlipidaemia.

Table 1. Hepatic profile at baseline and during follow-up visits.

	Baseline	After 4 months	After 7 months
ALT (IU/L)	66	53	25
AST (IU/L)	91	67	38
GGT (IU/L)	47	45	35
ALP (IU/L)	79	102	84
Total bilirubin (μ mol/L)	19	12	14
Direct bilirubin (μ mol/L)	5	3	5
Total protein (g/L)	73	75	71
Albumin (g/L)	39	41	42

Normal ALT: 7–55 IU/L; normal AST: 8–48 IU/L; normal GGT: 5–40 U/L; normal ALP: 30–120 IU/l.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ -glutamyltransferase.

To normalize liver enzyme activity, silymarin (Legalon®) 140 mg three-times daily was recommended as it is frequently reported to have antioxidant, hepatoprotective and anti-fibrotic abilities. Moreover, silymarin is known to be well tolerated, with only a few minimal adverse events.

Four months following the start of silymarin treatment (May 2022), the follow-up visit showed a gradual decrease in ALT and AST levels and 3 months later (August 2022), normalization of liver enzyme levels was reached, with a reduction also for GGT levels (Table 1). An improvement in the lipid profile also occurred over the treatment period, with reduced blood triglyceride levels within normal limits (<150 mg/dL). In addition, treatment adherence was good, and the patient did not develop any adverse events or other drug interactions due to polytherapy.

Discussion

Worldwide, NAFLD is one of the leading causes of deranged liver enzymes and chronic liver diseases, with a prevalence of ~23–25% in the general population, increasing up to 55% in those with type 2 diabetes.⁶ Different specialists frequently encounter this intricate metabolic disorder in clinical practice, including primary care physicians, gastroenterologists, endocrinologists, gynecologists and radiologists.⁷

The clinical spectrum of NAFLD is characterized by the presence of steatosis in >5% of hepatocytes; with liver biopsy, it is possible to differentiate NAFLD from NASH.⁴ This is crucial as NAFLD generally has a benign prognosis, whereas NASH progresses histologically and can lead to cirrhosis and liver dysfunction.^{1,8}

According to previous clinical and experimental studies, oxidative stress is thought to be one of the main mechanisms involved both in hepatic damage in NAFLD and in its progression to NASH. Indeed, lipid peroxidation is induced by the abnormal synthesis of reactive oxygen species (ROS), which in turn lead to inflammation and fibrogenesis. In addition, ROS induce liver fat accumulation and activate several intracellular pathways, causing hepatocyte apoptosis.⁹

NAFLD and NASH are usually considered hepatic manifestations of metabolic syndrome. Thus, the main risk factors for its development are increased weight, diabetes, insulin resistance, hypertension and hyperlipidaemia.^{4,5} Given the close correlation between NAFLD and metabolic alterations, in 2020, an international panel of experts proposed a disease terminology change to more accurately reflect its pathogenesis.¹⁰

Hence, metabolic-associated fatty liver disease is the new naming terminology for NAFLD, identified by hepatic steatosis along with the presence of overweight or obesity, diabetes, or other metabolic dysfunctions.^{10,11}

Liver biopsy is generally recommended as the 'gold standard' method for the diagnosis and quantification of disease damage; however, it is an invasive, expensive technique with a significant sampling error.¹² As a potential alternative, the FIB-4 index is a liver fibrosis marker for the assessment of liver disease, acting as a 'red flag'.¹³ A FIB-4 cut-off of ≥ 3.25 is currently validated for metabolic-associated fatty liver disease.¹³ Our patient had a FIB-4 index of 6.4, reflecting a high risk of advanced liver fibrosis.

Although various medications and supplements have been suggested as NAFLD therapies (e.g. vitamin E for advanced fibrosis without diabetes mellitus and pioglitazone for those with NASH and diabetes¹⁴) no effective drug treatment is available for NAFLD and NASH to date.^{3,12} The milk thistle extract silymarin is a complex compound of plant-derived elements, mostly flavonolignans, flavonoids and polyphenolic molecules. The main flavonolignans identified in the silymarin complex are silibinin, silichristin, isosilibinin and silidianin, with silibinin as the most prevalent and biologically active isomer.¹⁵ Different pharmacological actions of the silymarin complex have been observed, including antioxidant properties, anti-inflammatory properties and anti-fibrotic effects.¹⁵ In particular, silymarin demonstrated antioxidant properties by protecting the hepatocyte membrane from ROS-induced damage and counteracting toxin uptake.^{12,16} Both preclinical and clinical studies reported the efficacy of silymarin in the management of NAFLD and in reducing progression to NASH.⁴ Silymarin has also been found to increase the enzymatic activity of superoxide dismutase in lymphocytes and erythrocytes,¹² and to significant-

ly decrease serum ALT and AST levels.^{12,17} Silymarin also reduced hepatic fat accumulation as demonstrated by changes in hepatorenal brightness index at ultrasonography imaging.¹²

In this case report, the use of silymarin 140 mg three-times daily has demonstrated significant hepatoprotective effects on non-alcoholic steatohepatitis as shown by decreased serum ALT, AST, and GGT levels, and ensured good treatment adherence during long-term liver function tests and follow-up (Table 1).

These outcomes are in line with those reported by other studies and support silymarin to be markedly effective as NAFLD and NASH treatment. In addition, it is crucial to promptly start silymarin therapy and consider its long-term use as needed.⁴

Conclusion

NAFLD and its progressive form (NASH) are the most common causes of chronic liver disease worldwide, identified by steatosis in the liver and alterations in liver biochemical analyses. To date, no pharmacological options have been approved for the treatment of NAFLD or NASH. However, silymarin, the active derivate of milk thistle, has long been used for the management of liver disorders due to its assumed hepatoprotective and antioxidant properties.

In this case report, treatment with silymarin 140 mg three-times daily highlighted moderate efficacy and a good safety profile in the management of NASH and liver function as it decreased serum ALT, AST, and GGT levels over the treatment period with no side-effects, supporting silymarin as a promising supplemental intervention to normalize liver activity in NAFLD and NASH.

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Correspondence: Ahmed Hashem, Endemic Medicine Department, Cairo University, Egypt; Department of Medicine & Gastroenterology, Saudi German Hospital Jeddah, Jeddah, Kingdom of Saudi Arabia. Email: amahashem@hotmail.com; endoscopy1.jed@sghgroup.net

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