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CASE REPORT

Silymarin in the management of liver enzyme activity in steatohepatitis: a case report

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Abstract

Metabolic-associated fatty liver disease (MAFLD) is the main condition of altered liver enzymes worldwide. With a constant increase in liver hospitalizations, MAFLD is the second cause of cirrhosis and soon will be the first cause of liver transplantation. Early recognition of MAFLD and a personalized approach are essential to its treatment. This case study presents personalized management of a patient with MAFLD with advanced fibrosis and severe steatosis. The impact of silymarin use, concomitant treatment with diet, exercise, insulin sensitizers and antifibrotic agents, was evaluated.

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Introduction

Metabolic-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is one of the main causes of liver cirrhosis and hepatocellular carcinoma worldwide. MAFLD has emerged as a growing public health issue due to its relation to obesity and diabetes.[1] Hence, the prevalence of MAFLD and metabolic-associated steatohepatitis (non-alcoholic steatohepatitis (NASH), the advanced inflammatory stage of MAFLD) are predicted to increase worldwide.[1]

Silymarin, a milk thistle extract, is the botanical treatment most used for liver disorders owing to its anti-inflammatory, antioxidant and antifibrotic activity, showing positive results with a good safety profile.[2,3]

In this case report, treatment with silymarin was recommended in a patient with overweight, glucose intolerance, NASH and advanced fibrosis, with the aim of managing abnormal liver activity.

Ethics statement

No information is reported that could enable the patient to be identified; therefore, patient consent to report this case was not required. This manuscript was prepared according to CARE guidelines.

Case report

A 43-year-old male with overweight (BMI, 28.1 kg/m^2; abdominal circumference of 105 cm), insulin resistance and glucose intolerance (glycaemia, 110 mg/dL; Homeostatic Model Assessment of Insulin Resistance index, 12.4) was referred to a physician for examination due to fatigue and weight gain (+6 kg in 2 years).

The patient had a parental history of diabetes mellitus, hypertension and dyslipidaemia; his father also had gastric cancer.

During the physician's examination (on 5 January 2021), visceral obesity, acanthosis nigricans in the neck, and skin tags were observed, whilst the cardiopulmonary examination was normal.

The liver function test, performed in December 2020, showed the presence of abnormal liver functions, especially for aspartate transaminase (AST), alanine transaminase (ALT) and γ-glutamyl transferase (GGT)

activities (Table 1). Furthermore, thrombocytopenia was present (blood platelet count of 132,000).

Ultrasound was also performed in January 2021, showing the presence of severe liver steatosis. However, normal portal vein diameter and flow (12 mm and 15 cm/seg, respectively), normal spleen diameter (11.8 cm), and no ascites were observed. Therefore, the presence of portal hypertension was ruled out. The patient also underwent a transient liver elastography analysis (Fibroscan) showing a liver stiffness of 18.8 kPa and a controlled attenuation parameter (CAP) of 335 db/m.

The complete clinical picture suggested MAFLD, obesity and glucose intolerance with advanced fibrosis. However, in March 2021, due to the discrepancy between ultrasound, elastography and platelet features, a liver biopsy of both hepatic lobules was performed, resulting in severe steatohepatitis with steatosis and advanced fibrosis (F3–S3).

On March 2021, the patient was prescribed weight-loss and glucose-lowering treatment, accompanied by physical exercise. Pharmacological treatment involved pirfenidone 600 mg every 12 hours for liver fibrosis management, metformin 850 mg every 8 hours for insulin resistance, and silymarin 140 mg every 8 hours, together with cholecalciferol 4000 IU/day, for an antioxidant effect.

At the first follow-up visit, in May 2021, after 2 months of treatment, an important reduction in AST and ALT levels was observed (Table 1). At the second follow-up visit, in November 2021, after 8 months of treatment, fewer acanthosis nigricans were observed, and the cardiopulmonary examinations were good. In addition, the abdominal perimeter was reduced by 3 cm, and the patient lost 5 kg of weight. The liver function test was normal, with a further reduction of AST, ALT and, even, GGT levels (Table 1), and there was a decrease in the insulin resistance index (HOMA). The treatment adherence was very good, and the patient did not develop any adverse events.

In February 2022, there were further improvements, with liver enzyme levels reaching physiological values and a further loss of abdominal perimeter by 6 cm. A new transient liver elastography analysis was performed on 6 July 2022, showing a significant improvement (liver stiffness of 5.1 kPa and a CAP of 263 db/m, with a 10% reduction of MAFLD on liver steatosis).

The patient was recommended to continue with the same pharmacological treatment, diet and physical exercise. He was then requested to repeat transient liver elastography analysis after 1 year and liver biopsy after 2 years.

Discussion

Worldwide, every year, approximately 2 million people die due to liver diseases, with cirrhosis as the most frequent cause of death in patients with liver disease.[4] The leading causes of cirrhosis and chronic liver disease are alcohol and NAFLD, with an estimated global prevalence of 25%.[4,5]

Because NAFLD is closely related to obesity, metabolic syndrome and type 2 diabetes, the increasing trend of

Table 1. Liver function test at baseline and at the various follow-ups.

Liver function test	December 2020 (baseline)	May 2021	November 2021	February 2021	July 2021
AST (U/L)	64	28	30	28	27
ALT (U/L)	110	36	33	20	32
GGT (U/L)	123	52	14	12	12
Albumin (g/dL)	4.3	4.2	4.7	4.7	4.6
TB (µmol/L)	19	10	15	14	9
Globulin (g/dL)	3	2.9	2.4	2.5	2.5
LDH (U/L)	173	154	145	156	113
Glucose (mmol/L)	6.1	5	4.7	4.4	4.3
HOMA	12.4	7.6	3.3	1.5	1.3

ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase; TB, total bilirubin.

these metabolic diseases is also expected to increase NAFLD incidence. In 2020, an international expert panel suggested a change in the disease terminology to reflect its pathogenesis more accurately.[6] Hence, MAFLD is a new designation of NAFLD, and is characterized by hepatic steatosis in addition to the presence of overweight or obesity, diabetes mellitus, or other metabolic dysfunctions.[5–7]

MAFLD usually initiates an accumulation of triglycerides and other lipids in liver hepatocytes. This can progress from simple steatosis to steatohepatitis (NASH), cirrhosis, or even liver cancer, with oxidative stress considered the key pathogenic feature involved in this progression.[4]

Liver enzyme concentrations are commonly used (e.g. AST, ALT and GGT) to assess and monitor patients with liver diseases in clinical settings, whilst liver biopsy is typically used to specify and assess steatosis and histological features of fibrosis.[8] A proposed alternative is to measure liver stiffness by ultrasound-based elastography and, amongst all methods, transient elastography is the most extensively evaluated and available point-of-care test. At the same time, evaluating hepatic steatosis by CAP measurement is possible.[8,9] In this setting, different liver stiffness cut-off values have been suggested by different authors, and the cut-off values suggested by Eddowes et al., defined as ≤8.1 kPa for no or mild fibrosis, ≥8.2 kPa for moderate fibrosis, ≥9.7 kPa for severe fibrosis and ≥13.6 kPa for cirrhosis,[10] are most frequently used for NAFLD staging.

Several clinical studies have tried to find an effective therapy for NAFLD or MAFLD, but there is no effective drug treatment available to date, with a healthy lifestyle and weight reduction remaining crucial to their prevention and treatment.[8]

In the last decades, the use of natural components as therapeutic options has received significant attention. Silymarin, derived from the milk thistle plant, has long been used as a botanical treatment for liver diseases due to its chemical constituents (flavonolignans, flavonoids and polyphenols) and has demonstrated antioxidant, antifibrotic and hepatoprotective properties in several preclinical and clinical studies, in addition to being well tolerated and clinically safe.[4,11] Its phenolic structure and pharmacological properties allow silymarin to protect against cellular damage and stabilize the cell membrane by suppressing lipid peroxidation, inhibiting the formation of free radicals, and stimulating the synthesis of proteins and phospholipids within hepatocytes.[11]

Moreover, silymarin efficiently reduced AST and ALT levels in patients with NAFLD with respect to placebo treatment,[3,12] and reduced hepatic fat accumulation as demonstrated by changes in hepatorenal brightness index at ultrasonography imaging.[12]

In this case report, because no other treatment-suitable options were available, and based on the promising beneficial effects of silymarin therapy on liver diseases, the patient was recommended silymarin 140 mg three-times daily together with cholecalciferol 4000 IU/day for an antioxidant effect aimed at managing the increased liver enzyme activity and normalizing liver function test outcomes. The patient was also recommended to start a weight-loss and glucose-lowering treatment accompanied by physical exercise. Other pharmacological treatments involved pirfenidone 600 mg every 12 hours for liver fibrosis control and metformin 850 mg every 8 hours for insulin resistance.

After 2 months of treatment, it was possible to observe a progressive decrease in liver enzyme levels. On follow-up in November 2021, after 8 months of treatment, the liver parameters were normal, with an important reduction of AST, ALT and GGT levels (Table 1), and a decrease in blood glucose and insulin resistance index (HOMA). Treatment adherence was very good, and the patient did not develop any adverse events. He was therefore recommended to continue with the same treatment, diet and exercise. In this case, we know that the silymarin effect will be synergistic and additive to diet and exercise.

On February 2022 and July 2022, liver enzyme levels were comparable to physiological levels, and new transient liver elastography analysis showed a significant improvement in liver stiffness and CAP (5.1 kPa and 263 db/m, respectively).

These results are in accordance with those obtained by several authors and confirmed that silymarin treatment might be significantly effective in liver biochemical improvement, decreasing transaminase levels in patients with non-alcoholic steatohepatitis.[13] In addition, silymarin may be accepted as a safe herbal product because no health hazards or side-effects have been documented following the proper administration of advised therapeutic dosages.[13]

The success of the treatment for each patient must be personalized. We must identify the MAFLD phenotype, degree of fibrosis and steatosis as well as inflammation to establish a basal treatment with diet and exercise and to treat underlying metabolic conditions (obesity, diabetes, hypertension, dyslipidaemia), indicate antifibrotic agents (if applicable), modify intrahepatic steatosis, and at the same time, start long-term silymarin treatment as a powerful antioxidant and to decrease inflammation and progression of fibrosis.

Conclusion

MAFLD, formerly known as NAFLD, is one of the leading causes of liver cirrhosis and hepatocellular carcinoma worldwide, marked by fat accumulation in the liver and alterations in liver biochemical tests. In this case report, silymarin treatment (140 mg three-times/day) showed moderate efficacy and good safety profile in managing NASH (the advanced inflammatory stage of MAFLD), as it decreased serum AST, ALT and GGT levels over treatment, with no side-effects development. Hence, silymarin may be considered a promising supportive intervention to manage liver activity in fatty liver diseases.

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