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CASE REPORT

Silymarin treatment and reduction of liver enzyme levels in non-alcoholic fatty liver disease: a case report

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent chronic liver disorders worldwide. It is closely associated with metabolic syndrome components, including type 2 diabetes, hyperlipidaemia and obesity. To date, no effective drug treatment is available for NAFLD but several clinical trials suggested that silymarin, the active milk thistle extract, has well-documented antioxidant and hepatoprotective properties. In this case report, silymarin 140 mg twice daily decreased liver enzyme activity with a good safety profile in a patient with NAFLD and overweight, supporting silymarin as a promising supportive intervention aimed at normalizing liver activity in NAFLD.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder worldwide, affecting up to 30% of the general population.[1,2] There is a close and bidirectional association between NAFLD and components of metabolic syndrome;[1] indeed, type 2 diabetes, insulin resistance, hyperlipidaemia and obesity are the main risk factors for developing NAFLD, which commonly affects 50% of patients with diabetes and 76% of people with obesity.[3]

International guidelines recommend that the diagnosis of NAFLD should include (1) a complete evaluation of family and personal history of NAFLD-associated diseases, (2) physical and extended blood examinations with liver function tests showing increased liver enzyme levels, (3) abdominal ultrasound as a non-invasive test to assess hepatic steatosis, (4) fibrosis index evaluations (FIB-4, transient elastography/Fibroscan), and (5) liver biopsy only if clinically indicated.[4,5] A detailed protocol for NAFLD diagnosis is presented in Box 1.

To date, though different treatment options have been shown to have potential impacts on NAFLD (such as vitamin E and pioglitazone), there is no effective drug treatment available, with a healthy lifestyle and weight reduction remaining crucial to the prevention and treatment of NAFLD.[1,6]

Silybum marianum, or milk thistle, is the most studied plant for the management of liver disease due to its possible anti-inflammatory, antioxidant and anti-fibrotic activity, showing positive results with a good safety profile.[6]

In this case report, silymarin treatment was prescribed to a patient with overweight and NAFLD, with an attempt to manage the increased liver enzyme activity levels.

Ethics statement

No information is reported that could enable the patient to be identified; therefore, no patient consent to report this case was required. This manuscript was prepared according to CARE guidelines.

Case report

A 70-year-old, non-smoker man with overweight (BMI 26.4 kg/m^2) and a medical history of hypertension and

Box 1. Protocol for a comprehensive evaluation of suspected NAFLD.

Diagnostic tests

- Personal and family history diabetes, hypertension and cardiovascular disease
- BMI, waist circumference, change in body weight
- History of steatosis-associated drugs
- Alcohol intake*: <20 g/day (women), <30 g/day (men)
- Hepatitis B virus markers (HBsAg, anti-HBC and anti-HBS)/hepatitis C virus antibody
- Total liver function test profile (alanine transaminase, aspartate transaminase, γ-glutamyltransferase), synthetic and enzymatic, International Normalized Ratio and creatinine
- Complete blood count
- Lipid profile, HDL cholesterol, triacylglycerol, uric acid
- Fasting blood glucose, HbA1c, oral glucose tolerance test
- Thyroid-stimulating hormone
- Abdominal ultrasound
- Fibroscan/acoustic radiation force impulse
- Biopsy is not necessary in standard case, only if clinically indicated

*>21 standard drinks per week in men and >14 standard drinks per week in women.
Source: Hashem et al. 2021.[4] Reproduced from MDPI under a Creative Commons (CC BY) licence (https://creativecommons.org/licenses/by/4.0/).

dyslipidaemia was referred, on 24 August 2019, to the Department of Internal Medicine, Rajavithi Hospital, Bangkok, Thailand, following the emergence of elevated levels of liver enzymes during a check-up analysis.

The patient had been on treatment with Valsartan 80 mg/day for more than 10 years to manage hypertension, but no medication for dyslipidaemia was prescribed due to a history of statin-induced myositis.

On 24 August 2019, the physician's examination was normal, except for the presence of an obese abdomen. The patient was negative for hepatitis B (negative HBsAg test) and hepatitis C (negative HCV test). The patient also underwent a transient elastography analysis (Fibroscan®), showing a liver stiffness of 4.6 kPa but a controlled attenuation parameter of 305 db/m, reflecting a severe grade of steatosis.

The liver function test, performed on 26 December 2020, showed elevated liver enzyme levels, particularly of alanine transaminase (ALT) and aspartate transaminase (AST) (Table 1). Bilirubin, glucose and cholesterol levels were normal.

Table 1. Laboratory test results at examination and follow-up.

Laboratory tests	Results on 26/12/2020	Follow-up 03/02/2021	Follow-up 04/03/2021
Albumin, g/dL	4.5	–	–
Total bilirubin, mg/dL	0.7	–	–
Direct bilirubin, mg/dL	0.29	–	–
Aspartate transaminase, U/L	53	43	33
Alanine transaminase, U/L	74	50	42
Alkaline phosphatase, U/L	44	–	–
Blood glucose, mg/dL	112	–	–
Cholesterol total, mg/dL	201	–	–
Triglyceride, mg/dL	111	–	–
HDL cholesterol, mg/dL	56	–	–
LDL cholesterol, mg/dL	127	–	–

Based on this clinical picture, the patient was diagnosed with NAFLD. On 26 December 2020, he started treatment with silymarin 280 mg/day (Legalon®, 140 mg twice a day) to control the abnormal liver activity as no other suitable treatment options were available. Silymarin is known to be well tolerated. In addition, the patient was prescribed with a weight-control diet and regular exercise.

On 3 February 2021, after 2 months of treatment, liver enzyme values had significantly improved (Table 1), with no body weight changes observed. Hence, the patient was recommended to continue with the same therapies and stop alcohol consumption (he normally consumed ~10 drinks per day prior to the treatment). After 1 month

(4 March 2021), liver enzyme values were further reduced. Treatment adherence was good, and the patient did not report any adverse events.

Discussion

Given its high prevalence, NAFLD is now the main cause of liver-related mortality worldwide, with a substantial health economic burden.[1] NAFLD is typically defined by the presence of steatosis in more than 5% of hepatocytes in association with metabolic syndrome components and without an alcohol consumption history or other chronic liver diseases,[1] with a spectrum ranging from simple steatosis to steatohepatitis (non-alcoholic steatohepatitis; NASH), liver cirrhosis and hepatocellular carcinoma.[6]

In clinical settings, liver enzyme concentrations are commonly used (e.g. ALT, AST) to assess and monitor patients with liver diseases.[1] Usually, liver biopsy is used to specify and assess steatosis and histological features of fibrosis, but this is an invasive procedure and is not recommended for the evaluation of disease stage or therapy response.[1] A proposed alternative is to measure liver stiffness by ultrasound-based elastography; amongst the available methods, transient elastography has been the most extensively evaluated and available point-of-care test. At the same time, evaluating hepatic steatosis by controlled attenuation parameter measurement is possible.[1]

Several clinical studies have been conducted to find a pharmacological therapeutic option for control of NAFLD, but a healthy lifestyle and weight reduction remain pivotal to the prevention and treatment of NAFLD.[1,4] Pharmacological treatments aiming primarily at improving liver disease should generally be limited to patients with biopsy-proven NASH and fibrosis. The American Association for the Study of Liver Diseases guidelines recommend vitamin E for patients with advanced fibrosis and without diabetes mellitus and pioglitazone in patients with NASH and diabetes.[5]

For centuries, silymarin, obtained from the milk thistle plant, has been extensively used as a herbal option for the management of liver disease.[6] Both preclinical and clinical studies have demonstrated the antioxidant, anti-inflammatory and anti-fibrotic properties of silymarin, suggesting it as a useful NAFLD therapy with a good safety profile.[2,4] Indeed, abnormal ALT and AST levels have been reduced by silymarin treatment in patients with NAFLD with respect to placebo treatment.[6–10] In addition, silymarin significantly reduced hepatic fat accumulation as demonstrated by changes in hepatorenal brightness index at ultrasonography imaging.[8]

AST and ALT levels are typically used as the primary outcomes because these are general hepatocellular injury markers. Indeed, elevated transaminase levels increase the risk of end-stage liver disease development; hence, these are an important general prognostic factor in patients with NAFLD.[6]

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 prescribed treatment with silymarin 140 mg twice daily to manage the increased liver enzyme activity and normalize the liver function test outcomes. The patient was also recommended to start a weight-control diet and physical activity.

At the follow-up visits (03/02/2021 and 04/03/2021), after 2 and 3 months of silymarin treatment, respectively, an improvement in liver function was observed. In particular, serum AST and ALT levels were notably decreased (Table 1) with no significant adverse effects, supporting the efficacy of long-term maintenance and safety of silymarin in fatty liver disease.

These findings are in agreement with those obtained by other authors in similar trials,[6–10] and support silymarin as a promising intervention to normalize liver activity during NAFLD, to be initiated as early as possible given the decreasing regenerative potential of the liver.[11]

However, this study still has some limitations. As a case report, there are still several uncontrolled factors that might impact the change in liver enzymes, such as the effect of exercise, weight control, diet modification and alcohol abstinence. Further studies to evaluate the role of silymarin in NAFLD treatment are warranted.

Conclusion

NAFLD is the most common chronic liver disorder worldwide, marked by fat accumulation in the liver and alterations in liver biochemical tests. Several clinical studies have been conducted to find a pharmacological therapy option for NAFLD management. Silymarin, the active ingredient in milk thistle, may be useful for NAFLD treatment given its antioxidant, anti-inflammatory and anti-fibrotic properties.

In this case report, a 70-year-old man with overweight and a medical history of hypertension and dyslipidaemia was diagnosed with elevated liver enzyme levels during a check-up analysis. Following proper physical, diagnostic and haematological examinations, the patient was diagnosed with NAFLD and prescribed therapy with silymarin.

Over the course of treatment, silymarin 140 mg twice daily showed moderate efficacy and a good safety profile

in the management of NAFLD by decreasing serum AST and ALT levels with no side-effect development, supporting silymarin as a promising supportive intervention aimed at normalizing liver activity in NAFLD.

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