Case Report

Silymarin: a benefaction to hepatobiliary system

Abstract

Fatty liver has become predominant encrypted disease of today’s modern world, affecting 20-30% of adult population presenting with varied gastrointestinal symptoms. After accurate diagnosis, hypolipidemics give unsatisfactory result. Commonest causes being metabolic diseases like diabetes mellitus, metabolic syndrome and obesity. Its silent presentation leads to diagnostic error causing under estimation in exact prevalence of fatty liver. Non-alcoholic fatty liver disease of prime concern since its pathogenesis, diagnosis and management needs further experimental results. Silymarin is an ancient herb and has been effective in the treatment of different grades of fatty liver. Experimental evidence is available done on rats. It has anti-oxidant, anti-fibrogenic, anti-cytokine effects.

Keywords: non-alcoholic steatohepatitis, metabolic syndrome, obesity, profibrotic, adipokines, milk thistle, silymarin, silibinin

Case report 1

32 years old male, married since 2 years presents with history of indigestion, burps, abdominal fullness specifically post meal hours since 8 months. Aggravation of symptoms observed after consuming fatty meal. No other significant medical history. Personal history revealed no addiction to alcohol/ smoking on physical examination the patient seemed to have apple shaped body with the following anthropometric measurements:

| Measurement      | Value  |
|------------------|--------|
| Weight           | 94 kg  |
| Height           | 165 cm |
| BMI (body mass index) | 34.5 Kg/m^2 |
| Waist circumference | 115 cm |
| Hip circumference | 95 cm  |
| Waist to hip ratio | 1.21   |

Patient underwent biochemical, hematological and radiological investigations. Reports depicted as follows:

| Test                  | Result (mg/dL) | Normal range (mg/dL) |
|-----------------------|----------------|----------------------|
| Hemoglobin            | 14.6%          | within normal limits |
| CBC                   |                |                      |
| Peripheral smear      |                | Normocytic and Normochromic Blood Picture |
| FBS                   | 88 mg%         |                      |
| PPBS                  | 134 mg%        |                      |
| RBS                   | 156 mg%        |                      |
| HbA1C                 | 5.60%          |                      |
| Liver function tests  | Serum Bilirubin 0.8 mg% |          |
| Total protein         | 7.2g%          |                      |
| Albumin               | 3.8g%          |                      |
| Globulin              | 2.9g%          |                      |
| AG ratio              | 1.8            |                      |
| SGOT levels           | 54 IU/dL       |                      |
| SGPT levels           | 58 IU/dL       |                      |
| ALP                   | 52 IU/L        |                      |

USG abdomen revealed fatty liver grade I, rest solid reveals no pathological changes

Case report 2

55 year old male, known case of Type 2 diabetes mellitus and hypertension since 8 years on regular treatment with hypoglycemic agent, anti-hypertensive and hypolipidemics, presented with the complaints of difficulty in digestion and repeated burping, notably after fatty meal. He was diagnosed to have gastro–esophageal reflex disease and treated respectively. Personal history revealed no addiction to alcohol/ smoking. He did not respond completely. He was advised to undergo ultrasound of abdomen showing echogenic liver obscuring the echogenic walls of portal vein branches. He was diagnosed as Grade 2 fatty liver. Other solid organs showed no abnormality.

Biochemical investigations

| Test               | Result (mg/dL) | Normal range (mg/dL) |
|--------------------|----------------|----------------------|
| Fasting blood sugar| 148 mg/dL      | 70-110 mg/dL         |
| Post-prandial blood sugar | 212 mg/dL | 120-160 mg/dL         |
| Total cholesterol  | 222 mg/dL      | 140-200 mg/dL        |
| LDL                | 122 mg/dL      | 80-120 mg/dL         |
| Triglycerides      | 188 mg/dL      | 70-150 mg/dL         |
| HDL                | 41             | 35-80 mg/dL          |
| ALT                | 89 IU/L        | 21-72 IU/L           |
| AST                | 67 IU/L        | 17-59 IU/L           |
| ALP                | 32 IU/L        | 30-126 IU/L          |
| Total protein      | 6.6 g/dL       | 6-8 g/dL             |
| Albumin            | 3.8 g/dL       | 3.5-5.5 g/dL         |
| Globulin           | 1.6 g/dL       | 1.5-3.0 g/dL         |
| AG ratio           | 1.7            | 1.0-1.5              |
| Total Bilirubin    | 0.7 mg/dL      | 0.2-1.0 mg/dL        |
| HbA1C              | 6.6%           | 4.5-5.6%             |

Urinalysis: normal
Both the above mentioned cases are diagnosed as having different grade of fatty liver secondary to metabolic syndrome and type 2 diabetes mellitus. Both the patients were advised to consume active principle of Silymarin of about 167mg (available in the form of tablet from Nutrilite, per serving) at night for 6months along with a routine of brisk walk for minimum of 40 minutes per day. At the end of 6 weeks both patients showed symptomatic improvement, though the patient with metabolic syndrome showed much earlier response than the patient with type 2 diabetes mellitus. By the end of 6months, radiological imaging studies were re-investigated with background of previous report. Gross difference was noted in the echotexture of hepatocytes and portal vessel walls were no longer obscured. Thus improvement in the grading the fatty liver was reported. Maintenance therapy was suggested with Silymarin along with dietary changes and physical exercise for 6months more. Repeat ultrasonography of abdomen was advised at the end of one year.

Non-alcoholic fatty liver disease

NAFLD is the commonest liver disorder in the developed world affecting 20-30% of adults. It comprises a spectrum of disease ranging from simple steatosis through non-alcoholic steatohepatitis (NASH) to fatty fibrosis and ultimately cirrhosis. It’s a disease of affluent societies which increases in prevalence in proportion to rise in obesity. Dietary & genetic factors determine susceptibility to the disease and its progression.¹

Epidemiology

The prevalence is much higher in obesity and type 2 diabetes. It has become the most common cause of chronic liver disease after Hepatitis B, Hepatitis C & alcohol.¹

Natural history of NAFLD

The long term hepatic prognosis of patients with NAFLD depends on the histological stage of the disease at presentation. Among the patients with simple steatosis 12-40% will develop NASH with early fibrosis after 8-13years follow up. Among the patients with NASH 15% will develop cirrhosis and hepatic decompensation over the period of time. About 7% of patients with compensated cirrhosis associated with NAFLD will develop hepatocellular carcinoma within 10years.¹²

It can be classified into

i. simple fatty liver disease (NAFL, non-alcoholic fatty liver) &
ii. non-alcoholic steatohepatitis (NASH)

The former has a benign prognosis, but the latter is associated with fibrosis & progression to cirrhosis.

NAFLD is considered to be a liver complication of metabolic syndrome, hypertriglyceridemia, hypertension, diabetes mellitus, an elevated body mass index (BMI) >25 & especially truncal obesity. NAFLD affects about 3% of population. The prevalence is higher in those with diabetes & those with the metabolic syndrome. Rare causes of NAFLD include tamoxifen, amiodarone & exposure to certain petrochemicals. NAFLD has been reported post weight reducing jejuna bypass surgery. Many causes of cirrhosis that were previously labeled cryptogenic (unknown cause) are now thought to be due to NAFLD.¹

Pathophysiology

Most individuals with NAFLD have insulin resistance, but not necessarily overt glucose intolerance. The current two hit hypothesis explains why not everyone with fatty liver disease develops hepatic fibrosis.

I. The “first hit” results in steatosis which is only complicated by inflammation if second hit occurs.

II. Leptin which is as well reducing appetite, is fibrogenic in vitro, is probably then needed to cause hepatic fibrosis. The components of first hit include release of fatty acids from central adipose tissue, which, along with adipokines, drain into portal vein as well as causing insulin resistance. These processes result in reduced hepatic fatty acid oxidation & increased fatty acid synthesis (Figure 1).²

![Figure 1](https://via.placeholder.com/150)

Figure 1 pathophysiology of NAFLD.

The above flow chart shows the pathogenesis of non-alcoholic fatty liver disease: the two-hit hypothesis. Fatty liver occurs as a result of increased fat import into hepatocytes and reduced fat export. Insulin resistance causes hepatic steatosis, which also perpetuates insulin resistance. Subsequent activation of TNF-α, oxidative stress through the production of reactive oxygen species & production of endotoxin then result in inflammation and eventually fibrosis. Factors including leptin are probably needed for fibrosis.⁷

Clinical features

NAFLD is largely asymptomatic condition. Right upper quadrant discomfort, fatigue & lethargy have been reported in up to 50% of patients but are uncommon modes of presentation. NAFLD is the commonest cause of incidental abnormal liver blood tests, accounting for between 60-90% of such cases. NAFLD should therefore be suspected and sought in all patients with established risk factors, regardless of liver blood tests. These risk factors include the presence of polycystic ovary syndrome, obstructive sleep apnea, both of which have been associated with NAFLD. History is based on determining the presence /absence of conditions associated with NAFLD and excluding alternative causes of steatosis including excess alcohol.
intake, previous abdominal surgery & drugs such as amiodarone & tamoxifen. Most patients present with asymptomatic abnormal LFT’s particularly elevation of the transaminases or isolated elevation of GGT. Occasionally, the condition presents with a of cirrhosis, variceal hemorrhage, carcmona liver. It is usually diagnosed in patients with mild to moderate elevations in transaminases, no alcohol abuse & negative chronic liver disease screening.¹

Investigation

Currently available imaging modalities, including ultrasound, CT, and MRI are all excellent at detecting steatosis but none can reliably detect NASH and fibrosis. Newer imaging techniques, including proton magnetic resonance spectroscopy and transient elastography, show promise but require further study prior to routine use for disease staging. Liver biopsy is not required for diagnosis in a typical patient with classical risk factors and compatible imaging although may be required when other blood tests suggest an alternative or coexistent diagnosis.¹ The definition of nonalcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders. Clinical or laboratory features associated with advanced disease include advanced age >45years, body mass index (BMI) >30Kg/m², type 2 diabetes, serum aspartate aminotransferase / alanine aminotransferase (AST/ALT) ratio >1, hyperferritinaemia and positive autoantibodies.²

Management

Almost no large randomized control trials have been published on NAFLD to establish evidence based treatment recommendations. The rationale for NAFLD therapies is based on a growing understanding of disease pathogenesis with a particular focus on reducing insulin resistance, hepatic free fatty acid levels and oxidative stress, endoplasmic reticulum and cytokine mediated stress. Also influencing the balance and effects of profibrotic, proinflammatory and antifibrotic, anti-inflammatory adipokines released from adipose tissue. With respect to treatments directed primarily at the liver, there have been encouraging pilot studies with antioxidants and anticytokine agents.³

Obesity is a common and well documented risk factor for NAFLD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and up to 5% of patients may have unsuspected cirrhosis. There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus (T2DM).³ An ultrasonographic study of patients with T2DM showed a 69% prevalence of NAFLD. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50%. Simple steatosis doesn’t cause morbidity, while NASH is linked to progressive fibrosis, liver cirrhosis and liver cancer. NAFLD is strongly related to obesity, dyslipidemia, insulin resistance and type 2 diabetes mellitus.⁴ The prevalence of NAFLD in individuals with type 2 diabetes mellitus is >45% and it is estimated to be 50%. Most patients present with asymptomatic abnormal LFT, particularly elevation of transaminases or isolated elevation of GGT. Occasionally disease presents with complications of cirrhosis, variceal bleeding.

Risk factors include:

a. Age >45years
b. Type 2 diabetes mellitus
c. Obesity (BMI >30Kg/m²)

d. Hypertension
e. hyperlipidemia,
f. Diabetes.
g. Genetic inheritance.
h. Rapid weight loss.
i. Drugs like aspirin, steroids, tamoxifen, and tetracycline.

I. Macrovesicular steatosis:

a. Excessive alcohol consumption
b. Hepatitis C (genotype 3)
c. Wilson’s disease
d. Lipodystrophy
e. Starvation
f. Parenteral nutrition
g. Abetalipoproteinemia
h. Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

II. Microvesicular steatosis:

a. Reye’s syndrome
b. Medications (valproate, anti-retroviral medicines)
c. Acute fatty liver of pregnancy
d. HELLP syndrome
e. Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease).

Biology of milk thistle

Milk thistle (Silybum marianum) is a flowering herb belonging to asteraceae family, which also includes sunflowers and daisies. The less well known plant is native to Mediterranean countries. It has been used since 2000years as a natural treatment for liver disorders. Also named as Mary thistle or holy thistle. It has been used since thousands of years to support liver, kidney and gall bladder health. The parts above the ground and seeds are used for preparing medicine. The plant itself grows as a stout thistle in rocky soils with large purple flowering heads. Milk thistle gets its name from the milky sap that comes out of the leaves when they are broken. The leaves also have unique white markings that, according to legend, were the Virgin Mary’s milk. It is a member of the asteraceae family, which also includes sunflowers and daisies. It is now found throughout the world. This stout thistle usually grows in dry, sunny areas. Spiny stems branch at the top and reach heights of 5 to 10 feet. The leaves are wide with white blotches or veins. Milk thistle gets its name from the milky white sap that comes from the leaves when they are crushed. The flowers are red purple. The small, hard-skinned fruit is brown, spotted, and shiny. Milk thistle spreads quickly (it is considered a weed in some parts of the world), and it matures in less than a year. Milk thistle leaves and flowers are eaten as a vegetable for salads and a substitute for spinach. The seeds are roasted for use as a coffee substitute. Milk thistle’s anti-inflammatory effects are among its greatest achievements and many researches suggest that it is accomplished. The proposed mechanisms for the above are targeting endoplasmic reticulum and gene suppression.⁶

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Silymarin contains flavonoid and its structural components silybin. Silymarin is a complex mixture of four flavonolignan isomers, namely silybin, isosilybin, silydianin and silychristin. Flavonoids belong to the family of the benzo gamma-pyrones. More than 4000 different flavonoids are currently known; they are ubiquitous not only in the plant kingdom, where they are particularly abundant in the photosynthetic cells of higher plants, but also in the animal kingdom. For centuries they have been attributed numerous therapeutic properties and many have been used as popular therapeutic remedies. Compounds such as quercetin, taxifolin and silymarin have been used as active ingredients, both alone and as components of complex chemical preparations. Silymarin is orally absorbed and is excreted mainly through bile as sulphates and conjugates. The active constituents of the plant are obtained from the dried seeds and consist of four flavonolignans which are collectively known as Silymarin. The active principle was first isolated and chemically characterized during 1968-1974.4

SILYMARIN, a mixture of bioflavonoids, has hepatoprotective properties. The various mechanism of action is described below. It acts on the liver.10-12

- By stabilizing the cell membrane of hepatocytes, thereby preventing liver toxins and poisons from entering the interior cell. Silymarin can also interact directly with cell membrane components to prevent any abnormalities in the content of lipid fraction responsible for maintaining normal fluidity.10
- By stimulating DNA and RNA synthesis and in yrn protein synthesis thus facilitating hepatic regeneration without causing malignant changes.
- By inhibiting the enzyme lipoygenase, which forms leukotrienes from oxidized polyunsaturated fatty acids (PUFA) that damage the liver.
- By acting as an antioxidant (Silymarin is at least ten times more powerful than vitamin E). The cytoprotective effects of Silymarin are mainly attributable to its antioxidant and free radical scavenging properties.
- By increasing the glutathione (GSE) content of the liver.
- The Silymarin exerts membrane-stabilizing and antioxidant activity, it promotes hepatocyte regeneration; furthermore it reduces the inflammatory reaction, and inhibits the fibrogenesis in the liver.
- Antifibrotic action: Liver fibrosis can result in remodeling of liver architecture leading to hepatic insufficiency, portal hypertension and hepatic encephalopathy. These processes involve complex interplay of cells and mediators.46 In the initial phase there will be proliferation of hepatic parenchymal cells. The conversion of hepatic stellate cells (HSC) into Myofibroblast is considered as the central event in fibrogenesis. Silymarin inhibits NF- and also retards HSC activation. It also inhibits protein kinases and other kinases involved in signal transduction and may interact with intracellular signaling pathways.13
- Silymarin has a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against xenobiotic injury. It can prevent the absorption of toxins into the hepatocytes by occupying the binding sites as well as inhibiting many transport proteins at the membrane. These actions along with antiperoxidative property make Silymarin a suitable candidate for the treatment of iatrogenic and toxic liver diseases.14,15
- Immunomodulatory properties via inhibition of NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), as demonstrated in vitro.16
- Studies of Silymarin in the HCV replicon system also suggest an effect on HCV core and NS5A expression, although at high concentrations. These same pathways, implicated in the pathogenesis of chronic liver disease, provide the rationale to investigate silymarin as a potential treatment for chronic HCV infection.17

Silymarin when compared with various polyhedral formulations in Carbon tetrachloride induced hepatotoxicity in rats has led to complete normalization of elevated transaminases levels. 21 Rats with chronic Carbon tetrachloride induced liver damage were treated with oral silymarin, 50mg/Kg administered for 5days. Collagen content in livers of animals pre-treated with Carbon tetrachloride was increased approximately four-fold in comparison to control. It prevented the cirrhotic changes in rats. It also reduced liver collagen content by 55%.18

The hepatoprotection provided by silymarin appears to rest on four properties:

1. activity against lipid peroxidation as a result of free radical scavenging and the ability to increase the cellular content of GSH19
2. ability to regulate membrane permeability and to increase membrane stability in the presence of xenobiotic damage;
3. capacity to regulate nuclear expression by means of a steroid-like effect; and
4. Inhibition of the transformation of stellate hepatocytes into myofibroblasts, which are responsible for the deposition of collagen fibres leading to cirrhosis.20
5. Silymarin and silibinin inhibit the absorption of toxins, such as phallolidin or amanitin, preventing them from binding to the cell surface and inhibiting membrane transport systems. Furthermore, silymarin and silibinin, by interacting with the lipid component of cell membranes, can influence their chemical and physical properties. Studies in erythrocytes, mast cells, leucocytes, macrophages and hepatocytes have shown that silymarin renders cell membranes more resistant to lesions. Furthermore, the well documented scavenging activity of silymarin and silibinin can explain the protection afforded by these substances against hepatotoxic agents.21 Silymarin and silibinin may exert their action by acting as free radical scavengers and interrupting the lipid peroxidation processes involved in the hepatic injury produced by toxic agents. Silymarin and silibinin are probably able to antagonize the depletion of the two main detoxifying mechanisms, GSH and superoxide dismutase (SOD), by reducing the free radical load, increasing GSH levels and stimulating SOD activity. Furthermore, silibinin probably acts not only on the cell membrane, but also on the nucleus, where it appears to increase ribosomal protein synthesis by stimulating RNA polymerase I and the transcription of tRNA. The stimulation of protein synthesis is an important step in the repair of hepatic injury and is essential for restoring structural proteins and enzymes damaged by hepatotoxins.22-24
Possibly effective for
a. Seasonal allergies (allergic rhinitis). Some research shows that people who take milk thistle extract in combination with a conventional antihistamine have reduced symptoms compared to people who just use an antihistamine.
b. Diabetes: Some research shows that taking Silymarin, a chemical found in milk thistle, along with conventional treatment can decrease blood sugar, total cholesterol, low-density lipoprotein (LDL or “bad”) cholesterol, and triglycerides in people with diabetes.
c. Heartburn (dyspepsia). When used daily for 4 weeks, seems to reduce the severity of acid reflux, gastritis, cramping, nausea, and vomiting.
d. Menopausal symptoms. Research in women suggests that taking a specific product containing milk thistle, black cohosh, dong quai, red clover, American ginseng, and chasteberry (Phyto-Female) twice daily for 3 months reduces menopausal symptoms, including hot flashes and night sweats.
e. Skin damage caused by radiation treatment. Silymarin, a chemical found in milk thistle, to the skin reduces skin damage caused by radiation treatment in women with breast cancer. Most studies of milk thistle’s effectiveness have used a specific extract standardized to 70% to 80% Silymarin.

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None.

Conflict of interest
The author declares no conflict of interest.

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