Original Article

An observation study on the correlation between gallstone disease with non-alcoholic fatty liver disease in Iranian population as a metabolic syndrome: review of radiologic and clinical characteristics

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ABSTRACT

Background: Cholelithiasis and Non-alcoholic fatty liver disease (NAFLD) are two of the most prevalent diseases in the general population. Both diseases are associated with insulin resistance and metabolic syndrome. Objectives: The aims of this study were to evaluate the prevalence of gallstone disease in NAFLD patients and define the correlation of gallstone disease with different grades of NAFLD. Also the correlation of NAFLD and gallstone disease was evaluated regarding patient age, gender and BMI. Methods: Persons between 20 to 60 years referring to the radiology department for abdominal ultrasound participated in this study. The diagnosis of gallstone disease was made according to ultrasound criteria. Results and conclusion: 1253 patients (42% male and 58% female) participated in our study. Fatty liver was diagnosed in 59% of patients, with a significant increase in its prevalence in men (p-value 0.025). No significant difference was seen in prevalence of different grades of fatty liver in the two genders. Gallstone disease was diagnosed in 35% of men and 36% of women; no significant difference was seen in the prevalence of gallstone disease between the two genders. A weak correlation with correlation coefficient of 0.23 was detected between fatty liver and gallstone disease. Correlation was slightly more in women than in men. The prevalence of gallstone disease is higher in more severe grades of fatty liver. A weak correlation was seen between age and fatty liver and also with its grade. A weak positive correlation was seen between gallstone disease and age in women but it was not depicted in men. There was a positive correlation (p-value < 0.001) between higher BMI and existence of fatty liver. A strong correlation was identified between higher grades of fatty liver and upper values of BMI (correlation coefficient: 0.67, p-value <0.001). A weak correlation was shown between higher BMI levels and gallstone disease (correlation coefficient: 0.15, p-value <0.001). Patients with NAFLD had a higher prevalence of gallstone disease than the general population, thus gallstone disease and NAFLD are in the domain of metabolic syndrome with the same risk factors. The correlation of NAFLD and gallstone disease was stronger in women, showing that gender-specific reactions have an important role in the physiological response to insulin resistance.

Keywords: Gallstone, disease, non-alcoholic, fatty liver, metabolic syndrome, radiologic

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Introduction

Gallstone disease is one of the most prevalent diseases of the gastrointestinal tract. [1, 2] Its prevalence is approximately 10%–15% in the USA. Cholelithiasis may present with billiary colic, cholescystitis and acute pancreatitis. Obesity, female gender, ethnicity, positive family history, increasing age, type II DM, glucose intolerance, hyper triglyceridemy, decreasing cholestrolemia, child bearing, smoking and a sedantary life style are factors associated with gallstone disease [3-5].

Non-alcoholic fatty liver disease (NAFLD) is a condition ranging from a benign and non-progressive condition to non-alcoholic steatohepatitis (NASH), cirrhosis, portal hypertension and hepato cellular carcinoma [6-8].

There are common multiple risk factors between NAFLD and cholelithiasis, for example obesity, type II DM, hyper lipidemia, hyper insulinemia, pregnancy and a sedentary life style. [9-11] Recent studies in Italy, China and Japan showed that the incidence of gallstone disease increased among patients with fatty liver. Also NAFLD was identified as an independent risk factor for gallstone disease in Slovakian patients with metabolic risk factors [4].

Identifying high-risk groups and exploring the pathogenic mechanisms of gallstone formation led us to clarify the relationship between NAFLD and gallstone disease.

Ultrasound is easily available and also accurate for diagnosing NAFLD and gallstone.

The aim of this study was to:

1. Assess the prevalence of gallstone disease in unselected NAFLD patients, using ultrasound.
2. Evaluate the correlation of gallstone disease with different grades of NAFLD.
3. Investigate the correlation of NAFLD and gallstone disease adjusted for patient's age, gender and BMI.

The study was performed within Iranian population.

Methods:

The study included persons referred to radiology department for abdominal ultrasound in one year, aged between 20 to 60 years.

Participants with a history of cholecystectomy, chronic disease, hepatitis, hemolytic anemia, chemotherapy, previous abdominal surgery or alcohol abuse were excluded from the study. For each patient, liver and gallbladder ultrasound were performed with the same ultrasound machine (TOSHIBA, USDI – A500A, TOKYO, Japan) using 3.5 MHz transducer.

NAFLD and gallstone disease were diagnosed according to the ultrasound criteria listed below.

Diffuse steatosis appears as increased liver echogenicity in ultrasound. Severity of fatty infiltration of liver in ultrasound is divided into three subtypes: mild, moderate, and severe.

In mild fatty liver, minimal diffuse increase in liver echogenicity is seen. Moderate type is characterized by increase in liver echogenicity with slight impaired visualization of hepatic vessels and diaphragm. Severe fatty liver shows a marked increase in hepatic echogenicity with poor or no visualization of hepatic vessels and diaphragm, and poor penetration of posterior liver [11]. Ultrasound is highly sensitive in detecting gallstones.

The sonographic criteria for diagnosing gallstone disease are visualization of one or more echogenic, mobile, distally shadowing structures in gallbladder, or echogenic material with constant shadowing in gallbladder with little or no visualization of gallbladder [12].

Demographic data recorded were age, gender, and BMI.

Statistical analysis:

Data were analyzed with SPSS version 22.0.0.

Frequencies were compared with chi-square test.

Binary variables were correlated with Spearman test and p-values ≤0.001 were considered statistically significant.

Results:

1253 patients (525 men: 42% and 727 women: 58%) with age range between 20 to 60 years and a mean of 40 years, participated in the study.

In ultrasound evaluation, fatty liver was diagnosed in 745 patients (59%): 332 men (63%) and 413 women (57%). There was significant difference in the prevalence of fatty liver between men and women (p-value 0.025), thus fatty liver is more prevalent in men than in women.

Of the 745 patients diagnosed with fatty liver, 447 had grade I (mild), 238 had grade II (moderate), and 60 patients had grade III (severe) fatty liver. Of the male participants 60% had mild, 32% moderate, and 7% severe fatty liver, while for the females 59% had mild, 31% moderate, and 8% severe.

Table 1 shows the frequency of different grades of fatty liver in the two genders.

Table 1: Frequency of different grades of fatty liver in two genders

Fatty liver grade	Male	Female
Mild	200 (60%)	247(59%)
Moderate	107 (32%)	131(31%)
Severe	25 (7%)	35 (8%)

Statistical analysis showed no significant difference in the grades of fatty liver disease between the two genders.

Ultrasound exam of patients revealed that 184 (33%) men and 262 (36%) women had gallstones.

In patients with fatty liver (745 patients), gallstone was diagnosed in 334 patients (137 men; 197 women). No significant difference was seen in prevalence of gallstone disease between the two genders.

A weak correlation was detected between fatty liver and gallstone with correlation coefficient of 0.23 (p-value <0.01). Correlation between fatty liver and gallstone was slightly higher in women than in men (0.28 versus 0.17).

Of the patients with mild fatty liver, 161(36%) had gallstones. Gallstone was present in 136 (57%) patients with moderate and 37 (61%) patients with severe fatty liver, showing the prevalence of gallstone is higher in more severe grades of fatty liver.

Table 2 shows the prevalence of fatty liver in both genders and different age groups.

Table 2: the prevalence of fatty liver in both genders and different age groups

Fatty liver (total)	Yes	No	Age
56	17		

189	100		
169	120		
112	95		
	Men		
Fatty liver (total)	Yes	No	Age
108	30	78	20-29
350	117	133	30-39
240	172	68	40-49
128	94	34	50-60
	Women		

The prevalence of fatty liver increased with age in both genders (p-value < 0.01) although the correlation was weak (correlation coefficient: 0.3).

Also, a weak correlation was seen between age and fatty liver grade (correlation coefficient: 0.28) (p-value < 0.01)

An evaluation of patients with gallstone disease showed that no correlation was present between gallstone disease and age in men, but a weak correlation with coefficient of 0.14 was seen in women (p-value <0.01).

There was a positive correlation between higher BMI and existence of fatty liver (p-value < 0.001).

Also, a strong correlation was seen between higher grades of fatty liver and upper values of BMI (correlation coefficient: 0.67, p-value <0.001) (Table 3).

Table 3: Correlation between grade fatty liver and upper values of BMI

BMI group	Mild fatty liver	Moderate fatty liver	Severe fatty liver
15–18	67	3	0
18–25	239	36	1
25–30	109	198	32
30–35	0	0	22
35–42	0	0	4

A weak correlation was seen between higher BMI levels and gallstone disease (CC: 0.15, p-value <0.001)

Discussion:

Gallstone disease is a multifactorial disorder. Multiple genetic and environmental factors are known to have a role in forming gallstones. Bile super saturation, lower gallbladder motility and enucleation of cholesterol crystals are mechanisms leading to stone formation [13].

The incidence of gallstone increases with age, obesity, hypertriglyceridemia, diabetes, pregnancy and sedentary life style.

These factors are also known risk factors of NAFLD [2, 3, 8, 9]. Obesity, diabetes, hyper triglyceridemia and sedentary life style cause insulin resistance, which has a role in forming gallstones and NAFLD, as both belong to the domain of metabolic syndrome [6, 14]. Insulin activates LDL receptors in the liver, which leads to cholesterol excretion in the bile; thus hyper insulinemia can cause gallstones with two mechanisms: 1) cholesterol excretion in bile and forming supersaturated bile with cholesterol, and 2) decreasing gallbladder motility. [15]

Obesity is involved by changing gallbladder motility and increasing billiary cholesterol secretion.

Diabetes is associated with altered gallbladder motility and hyper hypertriglyceridemia affects both bile composition and gallbladder emptying [16].

Bacterial overgrowth is seen in gastro intestinal (GI) tract in NAFLD patients because of reduced fiber intake. This phenomenon reduces transit time in the bowel, leading to increased billiary deoxycholic acid. As a result, bile supersaturation and gallstone formation occur.

These are additional mechanisms for NAFLD and gallstone disease (GD) association [17-19].

Our results revealed a weak correlation between GD and NAFLD. The prevalence

of GD is 10%–15% in the normal population in the USA [1] while it was higher in our patients

population (35%), which is may be due to the participation of a higher percentage of the female population in our study. [20]

The incidence of GD in patients with fatty liver is two times higher than in patients without fatty liver (44% versus 22%). The same results are seen in studies accomplished in China, Italy and Japan. [4]

These results revealed that GD and NAFLD are in the domain of metabolic syndrome with the same risk factors.

In our study the prevalence of fatty liver is higher in men, which is shown by previous other studies. [4]

An increase in a patient's BMI correlates with higher incidence and higher grades of fatty liver. Also higher BMI values are associated with increased incidence of GD, but this correlation was weaker in our study. This phenomenon is depicted in multiple studies that show obesity is a risk factor for both NAFLD and GD. [2, 4, 5]

The correlation between NAFLD and GD is stronger in women than in men in our population, which shows that gender-specific reactions have an important role in the physiological response to insulin resistance states. In a study performed in China, NAFLD is shown as an independent risk factor for GD, especially in women.

The incidence of GD is two times more in women with NAFLD than in women without. This phenomenon is not seen in men. Estrogen causes lipoapoptosis in females with NAFLD, leading to increased cholesterol secretion in bile and formation of gallstone. [4]

In conclusion, the prevalence of gallstone disease is higher in NAFLD patients than in the general population, which supports the fact that GD and NAFLD both belong to one pathophysiologic mechanism: insulin resistance in metabolic syndrome.

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