Original Article

Prevalence of biopsy-proven nonalcoholic fatty liver among patients with gallstone disease

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Abstract

Background/Aim: Gallstone disease (GD) and nonalcoholic fatty liver disease (NAFLD) are associated with metabolic syndrome. Despite the benign nature of NAFLD, 10% of patients may develop advanced fibrosis and cirrhosis. We aimed to identify the prevalence and factors associated with NAFLD among GD patients in the Saudi population.

Patients and Methods: This is a single-center, observational cohort study that included patients seen in general surgery clinics at our institution from 2011 to 2017. All liver biopsies were taken at the same time as the cholecystectomy. Demographical and clinical data were prospectively collected from the study population.

Results: Of the 301 GD patients in the study, 15% had a normal body mass index (BMI), 29% were overweight, and 56% were obese. There were 143 (47.8%) patients with NAFLD, of which 125 (41.8%) showed steatosis and 18 (6%) had nonalcoholic steatohepatitis. There was a significant positive correlation between NAFLD and age ($r = 0.243$; $P < 0.0001$), and BMI ($r = 0.242$; $P < 0.0001$). Obese patients with BMI 30–40 kg/m^2 were 2.403 ($P = 0.039$) more likely to have NAFLD compared with normal BMI patients, and this value increased to 6.145 ($P = 0.002$) in patients with BMI >40 kg/m^2. Additionally, patients with T2DM were 2.839 times ($P = 0.015$) more likely to have NAFLD compared with those who did not.

Conclusions: The prevalence of NAFLD among GD patients is high. High BMI and diabetes are independent factors associated with NAFLD in GD patients. The results suggest that there may be a need for routine liver biopsy in selected patients during cholecystectomy.

Keywords: Diabetes, gallstone, NAFLD, obese, prevalence

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INTRODUCTION

Gallstone disease (GD) is one of the most common gastrointestinal disorders. The prevalence of GD is estimated to be around 15% in developed countries. Most patients are asymptomatic and the disease is usually

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detected when acute pancreatitis, cholecystitis, or biliary pain occurs as part of the complications.[1] Cholecystectomy is the standard treatment for GD.

GD is more common in females of childbearing age and is associated with age, smoking, sedentary lifestyle, central obesity, impaired glucose tolerance, diabetes mellitus type 2 (T2DM), hypertriglyceridemia, and cholesterolemia.[2] These risk factors can lead to nonalcoholic fatty liver disease (NAFLD).

NAFLD is one of the most common liver diseases encountered worldwide.[3] It is characterized by abnormal fat accumulation in the liver, leading to histological changes similar to those seen in alcoholic liver disease, but occurring in people who do not drink alcohol excessively.[4] NAFLD exists on a spectrum, starting from simple steatosis, steatohepatitis, cirrhosis, to end-stage liver failure, and hepatocellular carcinoma (HCC). Although it is benign in most patients, 10% may develop advanced fibrosis and cirrhosis. Obesity, especially central adiposity, T2DM, and dyslipidemia, which are collectively defined as the metabolic syndrome, are well-known risk factors of developing NAFLD.[5-6]

The global prevalence of NAFLD is 25.24%, with the highest prevalence in the Middle East and South America and lowest in Africa. Metabolic comorbidities associated with NAFLD include obesity, T2DM, hyperlipidemia, hypertension, and metabolic syndrome. The high prevalence of DM and obesity serves as major risk factors for nonalcoholic steatohepatitis (NASH) and significantly impact the increasing prevalence of NAFLD.[6,7] A recent meta-analysis on the prevalence of NAFLD in T2DM revealed that the pooled prevalence of NAFLD in T2DM patients, by a random-effects model, was 59.67%.[8] NAFLD shares many risk factors with GD such as obesity, T2DM, sedentary lifestyle, and hyperlipidemia. Previous studies suggest that insulin resistance and hyperinsulinemia are risk factors for both GD and NAFLD. This indicates a possible link with abdominal adiposity.[9-11] Furthermore, a recent study by Ali *et al.* demonstrated that patients who underwent cholecystectomy were more likely to gain weight significantly in a relatively short period of time.[12] These observations imply that the prevalence of NAFLD could be increased in GD patients compared to that in the general population. This was first suggested by a study by Roesch-Dietlen *et al.* whereby 54.7% of their GD patients had associated NAFLD.[13] Medina *et al.* demonstrated that 55% of patients who presented with symptoms and had been operated for GD had associated NAFLD.[14]

To date, there are no studies on the association between NAFLD and GD in the Saudi or Middle-eastern populations. Given the high prevalence of obesity and GD, it is logical to assume that NAFLD prevalence in GD patients is high. Thus, we aimed to identify the prevalence and factors associated with NAFLD among GD patients in the Saudi population. This study could be useful in developing a liver biopsy protocol during cholecystectomy in selected patients.

STUDY POPULATION AND METHODS

The study population consisted of all gallstone patients seen in general surgery clinics at King Saud University Medical City (KSUM) from 2011 to 2017. There were 301 patients scheduled for cholecystectomy enrolled in the study. Informed consent was obtained from all patients at the point of recruitment for the study while an additional, standard, institutional consent was obtained for the liver biopsy. The study was approved by the institutional review board.

Adult male and female, nonalcohol-consuming patients aged between 18 and 70 years age, having ultrasound evidence of gallstones such as echogenicity, distal shadowing, and movable structures inside the gallbladder were included in the study. Patients were excluded if they fulfilled any of the following criteria: (1) history of alcohol intake; (2) chronic liver disease of any other etiology; (3) presence of secondary causes of NAFLD; (4) history of neoplastic disease of the liver and gallbladder; (5) hemolytic disorders; (6) evidence or history of severe systemic illness; (7) prior liver biopsy confirming the diagnosis of NAFLD.

During the preoperative visit, patients provided informed consent to participate and study procedures were carried out according to the Declaration of Helsinki. A panel of laboratory tests was requested, which included a complete blood count, serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, albumin, fasting glucose levels, hemoglobin A1c (HbA1c), and a lipid profile. Additionally, all participants received a complete assessment of metabolic and autoimmune liver disease. All laboratory tests were performed at the central laboratory of KSUM.

All liver biopsies were taken at the time of the cholecystectomy surgery using a biopsy gun (18 × 20 cm, BARD, Max-Core, Arizona, USA) from the right lobe. Biopsies were placed in 10% formalin, transferred to the histopathology laboratory,

and stained using routine hematoxylin and eosin stain. All biopsies were reviewed and interpreted by one experienced hepatopathologist who was blinded to the clinical data. Grading for steatotic hepatocytes was as follows: grade 0: <5%; grade 1: 5–33%; grade 2: >33–66%; and grade 3: >66%. Normal patients were in grade 0 for steatosis and stage 0–1 for fibrosis with no or mild inflammation. Fatty liver was defined as the presence of at least 5% steatotic hepatocytes with or without mild lobular or portal inflammation and stage 0–1 fibrosis. All liver biopsies contained at least 10 portal tracts.

Histological diagnosis of NASH was based on the NAFLD Activity Score (5 or more) which is a combination of steatosis grade, hepatocyte ballooning, and lobular inflammation with or without fibrosis.

Statistical analysis

Frequencies are expressed as absolute (number, n) and relative (percentage, %) values for categorical variables. Central tendency (median) and dispersion (first, third quartiles) are used to present continuous variables that were not normally distributed. Variables that were normally distributed are presented as mean ± standard deviation. Data between groups were compared by Pearson's Chi-squared test or Fisher's exact test as appropriate. Pearson's correlation coefficient, r, was used to measure the correlation between continuous variables. Binary logistic regression analysis was performed to identify independent factors associated with NAFLD in the entire study population.

A two-tailed *P* value of <0.05 was used to determine statistical significance. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 41 ± 12 years, and the majority were females (76.1%). Overall, 15% had normal BMI, 29% were overweight, and 56% were obese. When subclassified, there were 32.6% with BMI 30–34.9 kg/m^2, 15% with BMI 35–39.9 kg/m^2, and 8% with BMI more than >40 kg/m^2. Most (85.2%) were not diabetic and the mean glucose and HbA1c levels were within the normal range, 5.74 ± 2.32 mmol/L and 5.78 ± 1.08%, respectively. In addition, the following parameters fell within their respective normal range: ALT 48.54 ± 65.53 U/L, AST 25.77 ± 59.16 U/L, ALP 110.61 ± 70.63 U/L, GGT 76.18 ± 139.96 U/L, total bilirubin 8.68 ± 11.28 μmol/L, albumin 37.00 ± 4.16 g/L, cholesterol 4.78 ± 1.03 mmol/L, triglycerides 1.35 ± 1.07 mmol/L, hemoglobin 129.00 ± 16.33 g/L, white blood cell count 7.35 ± 2.00 × 10^9/L, platelet count 273.53 ± 71.20 × 10^9/L, and international normalized ratio (INR) 1.05 ± 0.39 [Table 1].

There were 51.8% (155) patients with normal liver histology, 41.8% (125) patients with simple steatosis, and 6% (18) with steatohepatitis, of which 1.7% (5) had fibrosis and 0.3% (1) had cirrhosis [Figure 1].

There was a positive correlation between NAFLD and age (r = 0.243; *P* < 0.0001) and BMI (r = 0.242; *P* < 0.0001), and a significant weak correlation with glucose level (r = 0.149; *P* < 0.012).

There was no significant correlation between NAFLD and nationality, hemoglobin, white blood cell count, ALT, AST, GGT, and total bilirubin [Table 2].

Multivariate results showed that increase in age carries a risk of 1.027 (*P* = 0.021) times and that patients with BMI 30–40 kg/m^2 were 2.403 (*P* = 0.039) times more likely to have NAFLD compared with normal BMI patients, and this value increased to 6.145 (*P* = 0.002) times in patients with BMI >40 kg/m^2. Although the overweight group (BMI 25–29.9 kg/m^2) had an OR of 2.030, it was

Table 1: Sociodemographic and clinical characteristics of gallstone disease patients

Variables	Percentage (*n*) or Mean±SD
Age (years)	40.5±12.2
Male	23.9% (72)
Female	76.1% (229)
Body mass index (kg/m^2)	
Underweight (<18.5)	0.7% (2)
Normal (18.5-24.9)	14.3% (43)
Overweight (25.0-29.9)	29.2% (88)
Obese 1 (30.0-34.9)	32.6% (98)
Obese 2 (35.0-39.9)	15% (45)
Obese 3 (≥40.0)	8.3% (25)
Diabetes	
Diabetics	14.8% (40)
Nondiabetic	85.2% (230)
Laboratory parameters	
Glucose	5.74±2.32 mmol/L
HbA1c	5.78±1.08%
Hemoglobin	129.00±16.33 g/L
White blood cell count	7.35±2.00 x 10^9/L
Platelet count	273.53±71.20 x 10^9/L
INR	1.05±0.39
ALT	48.54±65.53 U/L
AST	25.77±59.16 U/L
ALP	110.61±70.63 U/L
GGT	76.18±139.96 U/L
Total bilirubin	8.68±11.28 μmol/L
Albumin	37±4.16 g/L
Cholesterol	4.78±1.03 mmol/L
Triglyceride	1.35±1.07 mmol/L

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio

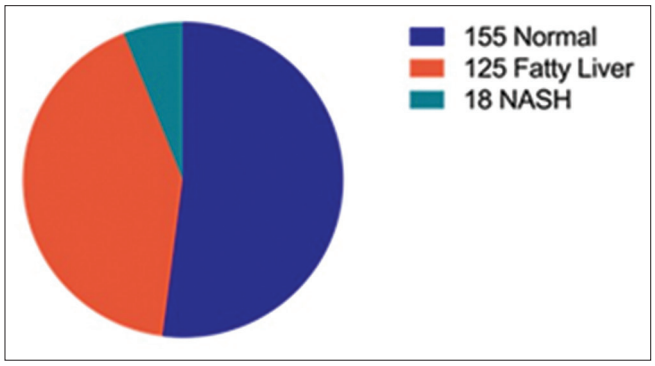

Figure 1: Frequency of nonalcoholic fatty liver disease (NAFLD) among gallstone disease patients

statistically insignificant ($P = 0.116$). In addition, patients with T2DM were 2.839 times ($P = 0.015$) more likely to have NAFLD compared with those who did not [Table 3 and Figure 2]. There was no difference in liver enzyme levels between patients with NAFLD and normal liver histology [Table 4].

DISCUSSION

NAFLD is one of the most prevalent liver diseases in many developed countries. To our knowledge, this is the first study in our region that evaluates the association between NAFLD and GD.

In view of the growing evidence indicating that NAFLD and GD share the same risk factors, a meta-analysis to assess the relationship between GD and NAFLD was conducted. The meta-analysis found that the pooled prevalence of GD in cases with NAFLD was 17%. NAFLD was significantly correlated with GD compared with the non-NAFLD group.[15] The prevalence of NAFLD in Asia generally ranges from 20 to 33%. The prevalence in China is estimated to be 11.8–24.4% whereas it is 30% in Japan. Korea and Taiwan have the lowest prevalence in Asia at 16.1% and 11.5%, respectively.[16] The prevalence in the United States is 24%.[17,18] In Saudi Arabia, earlier studies estimated the prevalence of NAFLD to be between 10 and 16.6% based on radiological studies.[19-21] Because of the obesity and metabolic syndrome epidemic,[22] models were used to estimate NAFLD and NASH disease progression, primarily based on changes in adult prevalence rates of adult obesity and T2DM. In a recently published study, estimates and expert interviews were used to build and validate a model projection for NAFLD. By 2030, the projected NAFLD prevalence is estimated to be around 25–30% in Saudi Arabia.[23]

In this study, we assessed the prevalence of NAFLD based on histological examination of the liver among GD patients. There were 47.8% with NAFLD, of which 41.8% showed simple steatosis, and 6% had NASH. This is in agreement with previously published studies demonstrating a high prevalence of NAFLD in patients with GD. García-Monzón *et al.* evaluated the prevalence of biopsy-proven NAFLD and NASH among patients with gallstones. They demonstrated that the prevalence of NASH was 10.2% whereas that of simple steatosis was 41.4%. They also demonstrated that NASH was more

Table 2: Correlation of factors associated with nonalcoholic fatty liver disease (NAFLD) in gallstone disease patients

Variables	Pearson correlation	*P*
Nationality	0.000	1.000
Age	0.243	0.000
Gender	−0.095	0.100
BMI	0.242	0.000
Glucose	0.149	0.012
Hemoglobin	0.036	0.538
White blood cell count	0.075	0.195
ALT	0.063	0.281
ALP	−0.023	0.697
AST	0.004	0.939
GGT	0.064	0.363
Total bilirubin	0.006	0.911
Albumin	−0.038	0.513
INR	−0.016	0.786
Platelet count	−0.012	0.841

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase: AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio

Table 3: Predictors of NAFLD in gallstone disease patients

Variables	Odds ratio	95% CI (Lower, Upper)	*P*
Univariate analysis			
Saudi Nationality	1.00	0.427, 2.343	1.00
Age	1.042	1.022, 1.063	0.000
Male gender	1.566	0.916, 2.678	0.101
Body mass index (BMI)	1.092	1.047, 1.140	0.000
Normal (Reference)			
BMI 25.0-29.9 kg/m^2	2.681	1.176, 6.113	0.019
BMI 30.0-40 kg/m^2	3.8	1.741, 8.294	0.001
BMI >40 kg/m^2	8.486	2.758, 26.104	0.000
Diabetes mellitus	4.048	1.884, 8.699	0.000
Hemoglobin	1.004	0.991, 1.018	0.536
White blood cell count	1.079	0.962, 1.209	0.195
Platelet count	1	0.996, 1.003	0.841
ALT	1.002	0.998, 1.006	0.292
ALP	0.999	0.996, 1.003	0.698
AST	1	0.996, 1.004	0.939
GGT	1.001	0.999, 1.003	0.370
Total bilirubin	1.001	0.981, 1.021	0.911
Albumin	0.982	0.929, 1.037	0.512
INR	0.919	0.497, 1.697	0.786
Multivariate analysis			
Age	1.027	1.004, 1.051	0.021
Normal (Reference)			
BMI 25.0-29.9 kg/m^2	2.030	0.841, 4.904	0.116
BMI 30.0-40 kg/m^2	2.403	1.047, 5.513	0.039
BMI >40 kg/m^2	6.145	1.894, 19.936	0.002
Diabetes mellitus	2.839	1.225, 6.580	0.015

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio

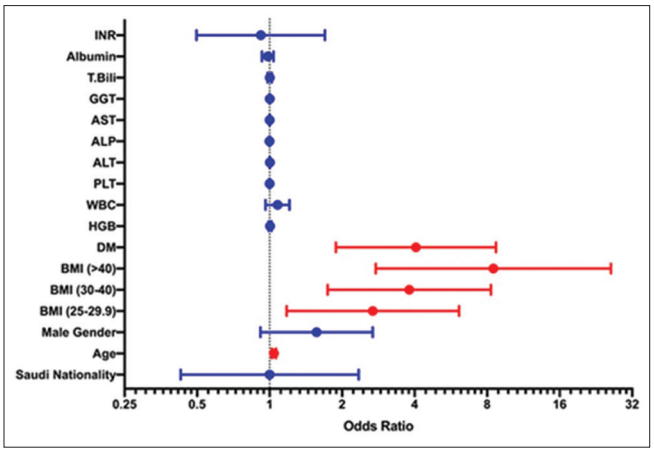

Figure 2: Predictors of NAFLD in gallstone disease patients

Table 4: A comparison of liver enzymes level between NAFLD positive patients and healthy subjects

NAFLD status	Negative		Positive		*P*
	Mean	SD	Mean	SD	
ALT	44.26	57.67	52.47	73.07	0.281
AST	25.46	70.33	25.98	44.64	0.939
ALP	111.81	87.30	108.62	46.38	0.697
GGT	65.06	117.08	82.82	154.66	0.363
Total bilirubin	8.64	13.38	8.79	8.65	0.911
Albumin	37.18	4.41	36.86	3.91	0.513
INR	1.05	0.36	1.04	0.41	0.786
Platelets	274.26	71.41	272.60	71.42	0.841

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio

frequent in patients with metabolic syndrome.[24] Yener *et al.* evaluated the histological prevalence of NASH in patients with symptomatic gallstones undergoing cholecystectomy. Similarly, they demonstrated that 55% of patients with gallbladder stones had associated NAFLD.[25] A large cross-sectional study enrolled 7,583 Chinese individuals aimed at determining the association between NAFLD and asymptomatic gallstones. The prevalence of NAFLD was significantly higher in patients with asymptomatic gallstones than in those without gallstones (59.0% vs 46.6%, respectively; $P < 0.0001$). They concluded that asymptomatic gallstones are strongly associated with NAFLD in the Chinese study population.[26]

Only 6% of our GD study population had NASH which is lower than the reported numbers in previous GD studies.[24-26] This can be explained by the lack of alcohol intake in our population and the higher prevalence of diabetes and metabolic syndrome in the previously reported studies. Furthermore, Yalmiz *et al.* examined whether the presence of GD in patients with biopsy-proven NAFLD is associated with liver fibrosis and histological NASH score. They concluded that the presence of GD is not independently associated with advanced fibrosis and definite NASH in patients with biopsy-proven NAFLD.[27]

The risk factors of developing NAFLD and GD are overlapping; obesity, T2DM, and dyslipidemia are among the most known risk factors for both diseases. In this study, we found that age and NAFLD were positively correlated, in agreement with other reports.[25,26] The association of gender and NAFLD is controversial as many authors have found that NAFLD is more common among men,[21,24] while others have reported 3.5 times higher risk in women.[26] In our study, gender did not have a correlation with NAFLD. T2DM in our study was found to be an independent predictor for NAFLD with an OR of 2.839 ($P < 0.015$).

In the current study, we assessed the correlation between different BMI groups and NAFLD among our GD patients and found significant positive correlations. More than half of our population were obese with the highest risk in the morbidly obese category (BMI >40 kg/m^2), with 6.145 times ($P = 0.002$) greater likelihood to develop NAFLD compared with normal BMI patients. Interestingly, 10 patients with normal BMI were positive for NAFLD and seven who were morbidly obese were negative for simple steatosis. This raises the question of whether there are other factors involved that need further investigation.

Abnormal liver enzymes have been reported as a screening tool for NAFLD. In our study, there was no difference in liver enzyme levels between patients with NAFLD and normal liver histology. Other studies demonstrated higher liver enzyme levels in NAFLD patients with GD compared with patients with no GD. Although patients with NAFLD commonly come to medical attention because of elevated liver enzymes, normal liver enzyme level does not exclude NAFLD. Furthermore, elevated liver enzymes do not necessarily correlate with histological liver injury.[28,29]

One of the limitations of this study is that it is cross-sectional in nature, hence, causality cannot be determined. Nevertheless, the study population is a good representation of the Saudi population with GD and highlights some of the factors that are associated with NAFLD in GD patients.

CONCLUSION

The prevalence of NAFLD among our GD population was 47.8%, with 41.8% showing steatosis and 6% with proven NASH. Age, high BMI, and diabetes were independent factors associated with NALFD. Given the high prevalence of NAFLD in our GD population, it may be useful to

perform a routine liver biopsy during cholecystectomy in selected patients. Transient elastography (FibroScan) with a controlled attenuation parameter has demonstrated good accuracy in quantifying the levels of liver steatosis and fibrosis in patients with NAFLD and could be an alternative assessment tool.[30]

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Conflicts of interest

There are no conflicts of interest.

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