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Prevalence of non-alcoholic fatty liver disease and hypercholesterolemia in patients with gallstone disease undergoing laparoscopic cholecystectomy

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ABSTRACT:

Background: Gallstone disease (GSD) and nonalcoholic fatty liver disease (NAFLD) are connected with a high prevalence in the general population and they share common risk factors for their occurrence. Limited literature with inconsistent results is available, suggesting a potential association between these lifestyle-induced diseases. Liver biopsy is the gold standard for diagnosing NAFLD. The aim of this study was (1) to identify the prevalence of asymptomatic NAFLD or NASH in liver biopsy; (2) to identify the association of hypercholesterolemia with NAFLD in patients undergoing laparoscopic cholecystectomy (LC).

Methods: This is a prospective observational study conducted on patients who underwent LC for symptomatic gallstones in the Department of General Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India, from 1st July 2013 to 31st December 2014. All included patients had ultrasonography (USG) and the following parameters tested: serum triglycerides (TG), cholesterol, low density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). A wedge liver biopsy was obtained from free edge of the right liver lobe during LC and all biopsy specimens were analyzed by a single pathologist.

Results: Among 101 patients included in the study, dyslipidemia was present in 49.50%. There was no association between NAFLD and serum cholesterol, TG or LDL-C (P, 0.428, 0.848, 0.371 respectively). NAFLD was confirmed in liver biopsy in 21.8% of patients but none had fibrosis or cirrhosis on biopsy. No complications were observed following liver biopsy.

Conclusions: Liver biopsy during LC gives an opportunity to diagnose the disease at an early and reversible stage. It is feasible, safe and cost effective.

KEYWORDS: dyslipidemia, gallstone disease, liver biopsy, non-alcoholic fatty liver disease (NAFLD)

ABBREVIATIONS

ALP – alkaline phosphatase
ALT – alanine transaminase
AST – aspartate transaminase
GSD – gallstone disease
HDL-C – high-density lipoprotein cholesterol
HMG – hydroxy-methylglutaryl
LC – laparoscopic cholecystectomy
LDL-C – low density lipoprotein cholesterol
NAFLD – nonalcoholic fatty liver disease
NASH – nonalcoholic steatohepatitis
TG – serum triglycerides
USG – ultrasonography

INTRODUCTION

Gallstone disease (GSD) is the most common disorder and cholecystectomy is a frequently performed surgical procedure of the hepatobiliary system. Gallstones are formed as an effect of imbalance in the bile components induced by various mechanisms causing bile to become lithogenic. In the lithogenic state, the cholesterol level can be as high as 8–10%, and the most important contributory factor is the increased biliary secretion of cholesterol [1]. This may occur in association with high-calorie, cholesterol-rich diet, obesity, drugs (Clofibrates) or increased activity of hydroxy-methylglutaryl (HMG) coenzyme A reductase, which is the enzyme limiting the rate of hepatic cholesterol synthesis, and increased hepatic uptake of cholesterol from the blood [1]. When cholesterol concentration exceeds the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.

Hypercholesterolemia is a component of the metabolic syndrome. There is a considerable association between GSD, metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) [2, 3]. NAFLD has association with obesity, dyslipidemia, insulin resistance, type II diabetes and cardiovascular diseases [3]. NAFLD was first described in 1980s in obese patients, with the liver fat accumulation exceeding 5% of hepatocytes in the absence of significant alcohol intake or other specific etiology of liver disease [4, 5]. The spectrum of NAFLD ranges from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH). NASH may occur with or without fibrosis and has the propensity to progress to cirrhosis (10–22%) [6, 7].

Both gallstones and NAFLD are associated with metabolic syndrome and sedentary lifestyle [8]. There has been a rise in the incidence of NAFLD in the last decades due to lifestyle changes [8]. Whether NAFLD causes gallstones or vise versa is not known. Limited literature with inconsistent results is available, suggesting a potential association between these lifestyle-induced diseases. Dietlen et al. [9] analyzed clinical, biochemical, and histological characteristics of NAFLD in patients with GSD and suggested

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NAFLD as a manifestation of metabolic syndrome, related to the genesis of gallstones. In another study from Turkey, NASH was found in 55% of patients with gallstones justifying the role of routine liver biopsy during cholecystectomy [2]. However, it was reported that cholecystectomy is associated with NAFLD, but not with gallstones, indicating that cholecystectomy has metabolic consequences and becomes an independent risk factor for NAFLD [10, 11]. It was again challenged in a recently published meta-analysis where Jaruvogvanich V. et al. reported a significant association between GSD and NAFLD [12].

The diagnosis of NAFLD is primarily made by preoperative ultrasonography (USG). The sensitivity of USG to detect steatosis depends upon the degree of hepatic fat infiltration and it decreases if hepatic fat infiltration is less than 30% [13]. The sensitivity of USG decreases further if the patient is very obese; it is also observer-dependent [13]. NAFLD/NASH has characteristic histological criteria; therefore, liver biopsy is the gold standard for detecting fat in the liver [5].

There are no guidelines for screening patients with gall stone disease for NAFLD/NASH. Laparoscopic cholecystectomy (LC) is a commonly performed surgical procedure for GSD and liver biopsy can be done safely during the procedure. The aim of this study was (1) to identify the prevalence of asymptomatic NAFLD or NASH in liver biopsy; (2) to identify the association of hypercholesterolemia with NAFLD in patients with symptomatic GSD undergoing LC.

MATERIAL AND METHODS

This is a prospective observational study conducted on patients who underwent LC for symptomatic gallstones in the Department of General Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh from 1 July 2013 to 31 December 2014. Ethical approval was obtained from the institutional ethical committee for obtaining liver biopsy during LC. Patients positive for HBV or HCV serology, with a history of alcohol intake, diagnosed with cirrhosis or autoimmune liver disease, or pregnant were not included in this observational study. A written informed consent was taken from all included patients.

Demographic profile and history of diabetes and hypertension were recorded for all patients. All included patients had various blood investigations, including fasting blood sugar, liver function tests [total protein, albumin, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP)], prothrombin time, and lipid profile [triglycerides (TG), cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]. Preoperatively all patients had USG for documentation of gall stones and presence of fatty liver (NAFLD) or cirrhosis.

A wedge liver biopsy was obtained from free edge of the right liver lobe during LC. Hemostasis was assured after obtaining liver biopsy. All liver biopsy samples were examined microscopically after tissue was fixed in 10% buffered formalin and was processed for hematoxylin and eosin stain. The histochemical staining (Silver stain) for reticulin fibers and Masson's Trichrome staining for the degree of fibrosis were carried out. All liver biopsy specimens were analyzed by one pathologist.

STATISTICAL ANALYSIS

Descriptive analysis was used to describe the basic parameters of the included patients in this study. Independent variables (determinants) evaluated were triglycerides, total cholesterol, HDL-C, LDL-C, AST, ALT, ALP, and presence of fatty changes in liver biopsy. These determinants were also studied individually, and the prevalence of the desired variables was calculated and analyzed further to establish any correlation or association. The data were analyzed using the statistical software (SPSS 20.0 [Statistical Package for the Social Sciences] for Windows, Chicago, Illinois, USA). The difference between the two means was studied with the Student's t-test (if data were normally distributed) or Mann-Whitney U test (if data were not normally distributed). Correlations were examined using the Spearman's rank correlation test. The Chisquare test was used to assess differences in the proportion between qualitative data. Measurable data were tested for their normality using the Kolmogorv-Smirnov test. The level of significance for all comparisons was kept at 5%.

RESULTS

A total of 101 patients were included in this study over a period of 18 months. Twenty-five (24.7%) of them were men and 76 (75.22%) were women. The mean age of the study population was 42.37 ± 13.21 (range: 18–70) years. The mean age of male patients was 42.96 ± 12.58 (range: 18–67) years and that of female patients was 42.17 ± 13.48 (range: 18–70) years. Seven patients had diabetes and 11 were hypertensive.

The biochemical profile including serum protein, albumin, AST, ALT and ALP was normal in this study population. Hypercholesterolemia was present in 14 patients (13.86%) (mean 215.58 ± 16.47 mg%, range: 201–267 mg%). Serum TG was raised (mean 241.57 ± 55.45 mg%, range: 208–374 mg%) in seven patients (6.93%). LDL-C was raised (mean 156.01 ± 13.94 mg%, range: 137–175 mg%) in four patients (3.96%). HDL-C abnormal levels were present in 25 patients (24.8%). Therefore, risk factors (diabetes, arterial hypertension and dyslipidemia) were present in 43 (42.58%) patients (Tab. I.).

Thirty-five patients (34.7%) had NAFLD on USG, 12 (34.3%) of them were males and 23 (65.7%) were females. The mean age of the population with NAFLD on abdominal USG was 45.8 ± 12.2 years, 46.8 ± 11.6 in males and 45.3 ± 12.7 in females. No patient had evidence of cirrhosis on USG examination. The grades of NAFLD on USG were shown in Tab. II.

NAFLD was confirmed in liver biopsy specimen in 22 (21.8%) patients. Eight (36.4%) of them were males and 14 (63.6%) were females. The degree of steatosis was not assessed further. Fibrosis and cirrhosis were not found in any patient in this study group. The mean age of the patients with NAFLD was 44.5 ± 11.9 (range: 21–67) years; 47.5 ± 14.25 (range: 21–67) years in males and 42.7 ± 10.5 (range: 26–65) years in females. In two patients, the liver biopsy was inconclusive and 77 (76.23%) patients had normal liver biopsy. Thirteen patients had NAFLD, both on USG and liver biopsy, while 22 patients who had NAFLD on USG were found to have normal liver biopsy (P, 0.006). Nine patients who had NAFLD on liver biopsy had normal liver on USG. Three of seven diabetic patients and four of 11 hypertensive patients had NAFLD on liver biopsy.

Hypercholesterolemia was present in 14 patients; five of them had fatty changes on liver biopsy. Serum TG was raised in seven patients and two of them had fatty changes on liver biopsy. LDL-C was raised in four patients and two of them had features of NAFLD on liver biopsy. There was no significant association observed between NAFLD and raised serum cholesterol, TG and LDL-C levels (P, 0.428, 0.848, 0.371 respectively).

DISCUSSION

Gallstone disease is a consequence of excessive production of cholesterol by the liver and its concentration in the gall bladder which is influenced by both genetic and environmental factors [9]. The major source of cholesterol in gallstones is diet and only 20% is de novo hepatic synthesis [14]. This emphasizes the importance of high-calorie diet and sedentary lifestyle as risk factors for the development of gallstones. Therefore, obesity is a risk factor for the development of gallstones and also is the part of metabolic syndrome and NAFLD [2, 8, 15]. The existing epidemic of obesity and diabetes suggests that the prevalence of NAFLD is on the rise at present, affecting 30–35% of the general population in developed nations and is expected to increase more in the future [9]. This incidence increases further to 55 to 70% when body mass index (BMI) is above 30 kg/m^2 [9].

Various components of metabolic syndrome are type 2 diabetes mellitus secondary to insulin resistance, dyslipidemia, increased waist circumference and hypertension. Insulin resistance is the key to the pathogenesis of both gallstones and NAFLD [9, 10, 16]. Therefore, metabolic syndrome maintains in a close relationship with the genesis of both gallstones and NAFLD by increasing the synthesis of cholesterol in the liver and subsequent formation of gallstones. The spectrum of NAFLD ranges from simple hepatic steatosis to NASH to cirrhosis (10–22%) [2, 6, 7]. Absence of signs and symptoms, and a lack of sensitive and specific diagnostic tests (biochemical and imaging) limit the ability to estimate the exact prevalence of NAFLD. NAFLD is a common cause of chronic liver disease and liver transplantation in western countries, and an increasing incidence of NAFLD has also been documented from Japan and China [17]. The reported incidence of GSD in NAFLD patients is 20% and the occurrence of NAFLD in GSD is 55–77% [16, 18]. There is insufficient data from India showing the frequency of NAFLD in patients with cholelithiasis.

Koller et al. in their study of 482 patients reported higher prevalence of GSD in patients with NAFLD than without NAFLD (47% vs. 26%), with 52% having more than two metabolic risk factors (obesity, type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol) [19]. However, the prevalence of NAFLD was reported to be as high as 68% in a US population-based study and 35% in an Asian population-based cross-sectional study in patients who had cholecystectomy before [10, 11]. They suggested an increase in the circulation of bile acid pool following cholecystectomy which exposes the liver to a great flux of bile acids. It was opposed in a recently published meta-analysis where a significant association between GSD and NAFLD was found [12].

Ultrasonography is the commonly performed investigation to diagnose NAFLD, but liver biopsy is the gold standard to confirm the clinical suspicion of NAFLD and to determine its severity [2, 5].

Tab. I. Risk factors for NAFLD in patients with gallstones.

RISK FACTORS	NUMBER	%
Diabetes Mellitus	07	06.93
Hypertension	11	10.90
Dyslipidemia	50	49.50
Total	68	67.33

Tab. II. Grades of NAFLD on abdominal USG.

GRADE	NO.	MEAN AGE (YEARS)	SEVERITY
No NAFLD	66 (65.3%)	40.53	-
Grade 1	18 (17.8%)	47.33	Mild
Grade 2	12 (11.9%)	44.67	Moderate
Grade 3	05 (5%)	43.20	Severe

About 15% of normal and 70–80% of obese patients were recognized to have fatty liver [2]. Routine liver biopsy to screen for NAFLD during cholecystectomy for GSD was first advocated by Ramos-De Ia Medina et al. in 95 patients, where 55% of biopsies were compatible with NAFLD although only 13% of subjects had a preoperative suspicion of NAFLD [18]. It was also observed by Dietlen et al. [9] who performed liver biopsy in 95 patients after cholecystectomy and found NAFLD in 54.74% (grade I in 51.93%, grade II in 28.84% and grade III in 19.23%, cirrhosis in 3.15%). Female predominance (4.3:1), dyslipidemia (76.92%), arterial hypertension (36.53%), BMI >30 kg/m^2 (67.30%), and diabetes mellitus (17.30%) were other observations in their study. In another observational study, 55% of symptomatic GSD patients had NAFLD on liver biopsy taken during surgery [2]. In the present study, 34.7% had NAFLD on abdominal USG; 21.8% on liver biopsy. Thirteen patients had NAFLD both on USG and liver biopsy (P-value of 0.006). Fibrosis and cirrhosis were not seen in any patient on USG or liver biopsy in our study. This low incidence of NAFLD, as compared to Western literature, may be attributed to a lower number of obese patients in India being a developing nation. Another reason could be the prevalence of pigmented stones in Asia (80%) as compared to cholesterol gallstones in western countries (80%) [20]. In this study we also observed female predominance in GSD (3:1), in NAFLD (2.7:1) and in hypercholesterolemia (2.5:1).

Knowledge of the association of GSD with NAFLD may result in an earlier diagnosis of NAFLD. Liver biopsy is currently the only available investigation which is highly specific to confirm the diagnosis and also to assess its severity. There are presently no guidelines for screening patients with gall stone disease for NAFLD/NASH by doing intraoperative liver biopsy. Although intraoperative liver biopsy is both safe and feasible, but it is still a controversial issue in terms of safety. None of the patients in the present study or reports from the literature showed any complication due to an added procedure of liver biopsy. Critics say wedge biopsy results may be fallacious and this may overestimate the stage of liver disease. In a recent study it has been reported that both needle biopsy and wedge biopsy are equally effective in determining the degree of steatosis [21]. Therefore, in patients with symptomatic GSD, who are also at increased risk of having NAFLD, liver biopsy can be used as a screening procedure, and early diagnosis of NAFLD/NASH provides information for an underlying disease.

Dyslipidemia has been observed in patients with NAFLD [22–25]. In cross-sectional studies from USA and Brazil it was found that

patients with NAFLD had high serum triglyceride levels [22, 23]. A high level of serum cholesterol was found in 63% of patients with NAFLD in a study from Mexico [24]. Another retrospective observational study from North India in patients who had NAFLD on USG also observed a significant association between dyslipidemia and NAFLD [25]. In the present study, the observed prevalence of dyslipidemia was 49.50% but there was no significant association found between NAFLD and dyslipidemia. Present study shows an association of these two entities in the general population.

There were a few limitations of this study, as BMI and waist circumference were not recorded. Therefore, the correlation of obesity with GSD and NAFLD could not be assessed. Another weakness of this study was that the diagnosis of diabetes was made only on the basis of raised blood sugar levels. Insulin resistance was not studied in these patients.

CONCLUSIONS

GSD and NAFLD share common risk factors and there is a high prevalence of NAFLD in GSD. Liver biopsy during laparoscopic cholecystectomy gives an opportunity to diagnose the disease at an early and reversible stage. It is feasible, safe and cost effective.

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