Prevalence of Non-Alcoholic Fatty Liver with Gall Stones Disease in Himalayan Population

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ABSTRACT

BACKGROUND

Non-Alcoholic Fatty Liver Disease (NAFLD) is the hepatic pandemic of the 21st century. It is the amassing of fats in the hepatic tissue without significant alcohol intake that results in hepatic steatosis. Patients with gall bladder stones may have associated NAFLD as these ailments share similar factors like obesity, hypertriglyceridemia and diabetes mellitus. However, few, if any, reports are available about the association of NAFLD with gallstones in the hilly population. Hence, this study was conducted to find out the prevalence of NAFLD in patients with gall bladder stone disease.

METHODS

This study was done in the Department of Surgery, Indira Gandhi Medical College, Shimla, from June 2017 to May 2019. A total of 300 patients of ultrasound proven gall bladder stones was studied for NAFLD by Fibroscan (transient elastography). Transient elastography (TE) is a noninvasive method that has been shown to be useful for the detection of liver steatosis and fibrosis. NAFLD was diagnosed based on the value of CAP (Controlled Attenuation Parameter) & degree of fibrosis was assessed based on liver stiffness measurement (LSM) value on TE. Steatosis was graded as S0, S1, S2, and S3 while fibrosis was graded as F0-F1, F1, F2, F3, and cirrhosis. Minimum cut-off CAP value for diagnosing NAFLD was 214 dB/m & significant fibrosis was taken with LSM value >7.5 kPa.

RESULTS

Patients of gall stone disease showed significant liver steatosis, suggestive of NAFLD in 189 patients (63%), based on CAP value; however, 111 patients (37%) did not have significant steatosis. In patients with NAFLD, 57 (30%) had mild steatosis (s1) while 39 (20.53%) & 24 (12.63%) had moderate (s2) and severe (s3) steatosis respectively. Similarly, 72 (24%) patients had significant fibrosis while 228 (76%) patients had no to insignificant fibrosis on TE, 51 (17%) patients had moderate fibrosis, while 14 (4.5%) and 8 (2.5%) patients had severe fibrosis & cirrhosis respectively.

CONCLUSIONS

High prevalence of NAFLD in patients of gall stone disease was observed. Most of the patients had mild NAFLD i.e. grade S1 steatosis & in addition, fibrosis was present in 24% patients of NAFLD with gall stone disease.

KEY WORDS

Gall Stone Disease (GSD), Non-Alcoholic Fatty Liver Disease (NAFLD), Steatosis, Fibrosis, Transient Elastography (TE)

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BACKGROUND

Gallstones constitute a significant health problem affecting 10 – 15 % of the adult population & non-alcoholic fatty liver disease (NAFLD) is the hepatic pandemic of the 21st century & is the number one cause of chronic hepatic disease.⁽¹⁾ Patients with gallstones may have associated NAFLD as these ailments share similar factors for example obesity, hypertriglyceridemia and diabetes mellitus. There is a high prevalence of gall stone disease among patients with NAFLD versus those without NAFLD & NAFLD being an independent risk factor for patients with GSD. Moreover, GSD prevalence increased with advancing fibrosis and severity of necro-inflammatory activity. Thus, NAFLD is associated with a high prevalence of GSD, which would characterise patients with more advanced liver disease. And NAFLD and GSD are significantly associated in a bidirectional fashion. Thus, although NAFLD appears to be an independent risk factor for GSD, the latter represents an independent risk factor of NAFLD.⁽²⁾

Although the gold standard for diagnosis and staging NAFLD is liver biopsy. Liver biopsy has inherent limitations because of risks and life threatening complications, sample size and sampling variability which render liver biopsy a less than ideal gold standard.⁽³⁾ Ultrasound is commonly used to screen for hepatic steatosis, but its limitations include suboptimal sensitivity as well as specificity for the detection of mild steatosis & operator dependence. Hence it is not ideal for detecting the early stages of NAFLD.⁽⁴⁾ Transient elastography (fibroscan) is a new, user friendly, noninvasive test. TE for the evaluation of cirrhosis has shown validity and excellent diagnostic accuracy in chronic hepatitis C & B, alcoholic liver disease, primary biliary cholangitis and after liver transplant. It has high sensitivity and specificity in mild to moderate steatosis and fibrosis.⁽⁵⁾

Thus, this study is possibly the first attempt to study the prevalence of NAFLD in patients with gall stone disease by using transient elastography in Himalayan population of the Indian subcontinent, which represents a distinct geographic, environmental and diet consuming entity than the rest of the Indian subcontinent.

METHODS

This cross-sectional study was done in the department of surgery from June 2017 to May 2019 in Tertiary care medical college hospital in hill state of Himachal Pradesh which is a part of western Himalaya. And patients from all over the state are being referred & treated in this hospital. A total of 300 patients of ultrasound proven cholelithiasis admitted in hospital for cholecystectomy, underwent Fibroscan in the department of Gastroenterology and were evaluated to establish relationship between cholelithiasis and NAFLD.

Inclusion Criteria

Were aged 18 years or above, diagnosed gall bladder stone disease on screening ultrasonography for right hypochondriac pain or biliary pain who underwent cholecystectomy.

Exclusion Criteria

Were clinical, radiological or biochemical evidence of choledocholithiasis, evidence of gall stone induced pancreatitis, pregnancy, patients with significant alcohol addiction >25 g/day, patients not willing to participate or on hepatotoxic drugs.

Data Collection

Data was recorded and baseline demographic data of all study patients including - Age, Sex, height, weight, BMI (body mass index), blood pressure were recorded. GPE (general physical examination) and systemic examination was done. All routine and relevant investigations to exclude secondary causes of fatty liver including estimation of blood glucose, HbA1c, complete hemogram, renal function tests, ALT, AST, total and direct bilirubin, CRP, thyroid function tests, total protein and albumin and lipid profile, Hep B, Hep C, HIV serology, serum ceruloplasmin and ANA were done. The patients with investigations suggestive of alternative diagnosis were excluded.

The lab. investigations included estimation of blood glucose, HbA1c, complete hemogram, renal function tests, SGOT, SGPT, total and direct bilirubin, CRP, thyroid function tests, total serum proteins, serum albumin and lipid profile. Abdominal USG examination of the subjects was performed using a 3.5 MHz transducer and the presence of gallstones was determined.

NAFLD was diagnosed based on value of CAP (controlled attenuation parameter) on transient elastography (fibroscan), simultaneously degree of fibrosis was assessed based on liver stiffness measurement (LSM) value on transient elastography. Based on CAP value steatosis was graded as S0, S1, S2, S3 and fibrosis was graded as, F0-F1, F2, F3 and cirrhosis. Minimum cut-off value for diagnosing NAFLD was 214 dB/m. Minimum fibrosis significant was taken as F2 or more i.e. LSM value >7.5 kPa.

The finding of Fibroscan were interpreted as: S0 (no fatty liver), S $\geq$ 1 ($\geq$ 10% of hepatocytes with fat), the CAP cut-off values ranged from 214 to 289 dB/m, with a 64%-91% sensitivity and 64%-94% specificity; for S $\geq$ 2 ($\geq$ 33% hepatocytes with fat), the CAP cut-off values ranged from 255 to 311 dB/m, with a 57%-96% sensitivity and 62%-94% specificity; finally, for S3 ($\geq$ 66% hepatocytes with fat), the CAP cut-off values ranged from 281 to 310 dB/m with a 64%-100% sensitivity and 53%-92% specificity. S1, S2, S3 were graded as mild, moderate and severe NAFLD respectively. The adjusted values were taken as: S0, if CAP score is <214, S1, if CAP score is (215-255), S2, if CAP score is (256-312), and S3, if CAP score is > 312 dB/m. And F0-F1 i.e. no to mild fibrosis if LSM score was between 2.5 and 7.5 kPa, F2 i.e. moderate fibrosis if LSM score was between 7.5- 10 kPa, F3 i.e. severe fibrosis if LSM score was between 10-14 kPa and F4 i.e. cirrhosis if LSM score is >14 kPa. Significant fibrosis was taken as F2 and above.

Statistical Analysis

All numerical data were expressed as mean with standard deviation (SD). All the statistical tests were done using Excel/SPSS software. Discrete and continuous variables were compared using Pearson's coefficient, Chi square test and Student t-test as appropriate. Multiple comparisons were

made using ANOVA. A p value <0.05 was taken as statistically significant.

RESULTS

This study, was conducted from 1st of June 2017 to May 31st 2019, included 300 patients who came to surgery or gastroenterology OPD with ultrasonography proven cholelithiasis (gall stone disease). Out of 300 patients in the study 240 (80%) patients were females and 60 (20%) were male respectively. Patient's ranged from 22 to 80 years of age with an average age of 44.3 yrs. (SD-11.9). Maximum numbers of patients were in the age group of 31-50 yrs. constituting 57.5% of the total study population. Age wise distribution showed 43 patients (14.3%) in age group 18-30 years, 76 (25.3%) patients in age group 31-40 yrs., 96 (32%) patients in age group 41-50 yrs., 51 (17%) patients in age group 51-60 yrs., 30 (10%) patients in age group 61-70 yrs., and 4 (1.4%) patients in age group >70 years.

The mean BMI of the study population was 25.7(SD-3.7), with a range from 16.5 to 36.3. Mean LFT's of the study population were found to be within normal limits, in which, mean total bilirubin of the study population was 0.77 mg % (SD-0.5), with a range from 0.1 mg% to 4.8 mg%, and mean conjugated bilirubin was 0.24 mg% (SD 0.20), with a range from 0.01 mg% to 0.96 mg%. Mean ALT of the study population was 34.9 U/L (SD-16.7), with a range from 10 U/L to 111 U/L. Mean AST of the study population was 33.5 U/L (SD-20.1), with a range from 15 U/L to 205 U/L. Mean ALP of the study population was 103.4 U/L (SD-45.5) with a range from 43 U/L to 370 U/L.

Mean total cholesterol of the study population was 179.3 mg/dL (SD-40.5) with a range from 100 mg/dL to 287 mg/dL. Mean triglycerides of the study population were 71.6 mg/dL (SD-71.6), with a range from 32 mg/dL to 474 mg/dL. Mean HDL of the study population was 48.8 mg/dL (SD-13.1), with a range from 24 mg/dL to 119 mg/dL. (table-1) In this study, significant liver steatosis, suggestive of NAFLD was found in 189 patients, i.e. 63%, however 111 patients i.e. 37% did not have significant steatosis suggestive of NAFLD, calculated on the basis of CAP value. Those with significant steatosis suggestive of NAFLD were graded as 90(30%) mild steatosis (S1), 62(20.6%) moderate steatosis (S2) and 37 (12.4%) severe steatosis (S3). Similarly, fibrosis was calculated on the basis of LSM score and it was found that 79 patients, i.e. 26.3% had significant fibrosis (basic cut-off value for significant fibrosis was taken as >7.5 kPa) and 221 patients did not have significant fibrosis.

Variable	GSD without NAFLD (Mean)	GSD with NAFLD (Mean)	p-Value
Age	43.5	44.8	0.43
TOT. Bilirubin	0.76	0.77	0.538
Conj. Bilirubin	0.27	0.22	0.335
ALT	31.4	37.0	0.018
AST	30.3	35.5	0.143
ALP	105.0	102.4	0.431
TG	139.2	180.0	<0.001
HDL	49.6	48.3	0.499
LDL	97.6	105.7	0.086
Total Cholesterol	169.2	185.4	0.005
Steatosis	175.3	271.5	<0.001
Fibrosis	4.3	7.8	<0.001

Table 1. Comparison of Various Parameters in Gall Stones Patients with and without NAFLD

Figure 1. Comparison of Mean Value (CAP dB/m) of Steatosis in Patients of Gall Stone Disease with and without NAFLD

Figure 2. Comparison of Mean Value (kPa) of Fibrosis in Patients of Gall Stone Disease with and without NAFLD

Figure 3. Grades of Steatosis in Patients of NAFLD with Gall Stone Disease

Fibrosis was graded as F0-F1, F2, F3 and cirrhosis i.e. no to insignificant fibrosis, moderate fibrosis, severe fibrosis and cirrhosis, based on the cut-off values and out of 300 patients, 221 (73.7%) patients had no to insignificant fibrosis (f0-f1), 51 (17%) patients had moderate fibrosis, 14 (4.6%) patients had severe fibrosis and 7 (2.4%) patients had cirrhosis on TE (fibrosan). In this study, patients of gall stone disease with NAFLD and patients without NAFLD were compared and it was found that: Mean age of patients with NAFLD was found to be 44.8 yrs., and without NAFLD was 43.5 yrs. with a p-value of 0.43. Thus, no significant association was found between age and NAFLD in patients with gall stone disease. Mean number of male patients, with NAFLD were 80.7 and without NAFLD were 79.0. Similarly, the mean number of females with NAFLD were 19.3 and without NAFLD were 21.0, with a p-value of 0.771. Thus, no significant association

was found between sex and NAFLD in patients with gall stone disease.

Figure 4. Grades of Fibrosis in Studied Patients

DISCUSSION

In our study, most of the patients were females (80%), with male: female = 4:1, most of the patients belonged to age group 41 to 50yrs (37%), with mean age of 44.3yrs. Other studies have also shown the same trend and reported more prevalence of gall stone disease in females as compared to males. Shaffer et al.^[1] And Tsai et al.^[6] have concluded that age >40, and the female sex are regarded as major risk factors for the development of cholesterol cholelithiasis. A nationwide survey conducted in America revealed a very high prevalence of cholelithiasis i.e. 13.9%–26.7% in women and 5.3%–8.9% in men under the domain of third National Health and Nutrition Examination Survey.^[7] However in India, prevalence of gall stones is 5.59% in women and 1.99% in males. There is a general conjecture that sex hormones and cholesterol metabolism have possible interrelation.^[3] This makes a point to ruminate on how sex is implicated in cholesterol stones formation. Most of the studies suggest female predominance when it comes to the prevalence of gallstones along with it the likelihood of being at risk for stone formation.^[1,2]

Non-alcoholic fatty liver disease (NAFLD) has a prevalence of 15%–20% in the general population.^[6] In our study NAFLD as detected by CAP value on TE, was present in 63% patients of GSD. The higher prevalence of NAFLD in our patients than the general population, suggest a possible association between NAFLD and gall stone disease. Similar higher prevalence of NAFLD has been reported in other studies which are in consonance with this study. Koller et al.^[8] found higher prevalence of GSD among patients with NAFLD versus those without NAFLD (47% vs. 26%, respectively). While, Farah et al from Pakistan reported the prevalence of NAFLD in 62.5% patients with gall stones disease.^[9] Higher prevalence of NAFLD in patients with gall stone disease is due to sharing of common risk factors like body mass index, gender, raised lipid levels, use of contraceptives, alcohol and having diabetes, physical inactiveness, multiparous women, water with excessive iron content & metabolic syndrome.^[10]

Most of the patients in our study population had mild severity of steatosis (S1 i.e. 30%), this is in contrast to other studies which found that there is a greater degree of steatosis

among patients with NAFLD and gallstones. Francazani et al.^[12] including 524 Italian patients with biopsy-proven NAFLD found a GSD prevalence of 20% with NASH prevalence being significantly higher in patients with GSD, as compared to patients without GSD (77% vs. 56%).

In our study, we found that fibrosis was present in 26.5% of patients and the mean fibrosis score was higher (7.8 kPa) in patients with NAFLD than those without NAFLD (4.3 kPa) with a significant p-value of <0.001. Thus, we come to a result that fibrosis present in GSD with NAFLD is severe as compared to gall stone disease patients without NAFLD. The result of one series showed about 10% of the gallstone patients at the time of diagnosis had NAFLD progression to fibrosis which was biopsy proven. NAFLD contributes as the commonest cause that leads to cirrhosis, portal hypertension and hepatic cancer and it has been estimated that approximately 22% of NAFLD progresses to cirrhosis^[10, 11]. One of the studies justified for performing liver biopsy for the detection of NAFLD during cholecystectomy and that series captured more NAFLD in patients who undergone biopsies than those with simple ultrasound findings and liver function tests.^[12]

CONCLUSIONS

There is a high prevalence of NAFLD in patients of gall stone disease in Himalayan population. Most of the patients of NAFLD with gall stones had mild degrees of steatosis. Fibrosis was present in 27% patients of NAFLD with gall stone disease. Patients of gall stone disease with NAFLD had a higher mean BMI, TG, T. Ch, steatosis and fibrosis levels than gall-stone disease patients without NAFLD.

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