Prevalence and severity of non-alcoholic fatty liver disease in patients with gall stone disease

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Abstract

Introduction

Metabolic syndrome independently has a significant alliance with both non-alcoholic fatty liver disease (NAFLD) and gall stone disease (GSD). NAFLD can present variably in different individuals from simple steatosis to non-alcoholic steatohepatitis (NASH). For establishing a valid prognosis, it is essential to differentiate appropriately between the presence and absence of NASH. Hence, the present study aimed to assess the prevalence and severity of NAFLD in GSD by using Fibroscan with Controlled Attenuation Parameter (CAP).

Methods

A hundred patients of GSD who were being evaluated for cholecystectomy and were negative for HBV and HCV infection, with no history of alcohol intake or documented liver cirrhosis were evaluated prospectively. Diagnosis and severity of NAFLD were assessed by CAP. Necro-inflammation was assessed by levels of transaminases; hepatic fibrosis and cirrhosis were measured on Fibroscan.

Results

Of 100 patients, NAFLD prevalence was 77% on CAP. On fibro scan, 17 had mild fibrosis, 8 had significant fibrosis and 1 had evidence of cirrhosis. Significant necro-inflammation was present in 16 patients. Body mass index > 25kg/m2 and central abdominal obesity was a strong predictor of steatosis in GSD with NAFLD (p 0.041, 0.029 respectively). Central abdominal obesity and low levels of high-density lipoprotein were a strong predictor of fibrosis in NAFLD (p 0.040, 0.037 respectively).

Conclusions

A higher prevalence of NAFLD (77%) was observed in patients with GSD which might have bearing on the surgical management. The observations of the study recommend that health awareness and lifestyle modifications should be advised to patients with GSD as they may be having concomitant NAFLD which may in due course of time evolve into cirrhosis if ignored.

Introduction

Gallstone disease (GSD) is a common condition worldwide with variable prevalence based on geographical location and ethnicity. The reported overall prevalence of GSD in the general population is 3.29% to 15% (10-15% in the West, 3-15% in Asia and <5% in Africa) [1]. Prevalence of GSD in India is 4.3% and is the highest in Northern India [1]. Factors which are found responsible for gallstone formation are: female gender, obesity, hypertriglyceridemia, diabetes mellitus, insulin resistance and metabolic syndrome (MS) [2].

Non Alcoholic Fatty Liver Disease (NAFLD) has become the most common liver disease the world over and is considered as the hepatic manifestation of MS. Prevalence of NAFLD is variable among different countries and different regions, and is higher in the West [3]. Insulin resistance is one of the important attributes for hepatic steatosis. Incidence of obesity, diabetes, insulin resistance, hypertension and other metabolic risk factors is increasing among Indians. The reported prevalence of NAFLD in India varies between 9-53% in general population [4-6]. Asian-Indians are more at risk to have NAFLD because of a higher incidence of insulin resistance even at lower BMI [7]. The prevalence of NAFLD among physically active but economically deprived rural adults of Sri Lanka is 18% which also strengthens the existing evidence that Asians have a susceptibility of visceral fat accumulation [8].

NAFLD can present variably in different individuals, at times as a simple case of steatosis to even as a complex condition of non-alcoholic steatohepatitis (NASH) or cirrhosis. As NASH is the leading indication for liver transplantation at present, therefore for deciding on the modality of treatment it is essential to differentiate appropriately between the presence and absence of NASH. NAFLD is a multisystem disease where morbidity and mortality are not only attributed to hepatic involvement but also the involvement of cardiovascular and renal systems, or extrahepatic malignancy.
Fatty liver is usually diagnosed using routine scanning procedures such as ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). However, these investigations are limited in their ability to differentiate between the presence and absence of NASH due to their inability to detect the degree of inflammation and fibrosis [9]. The accepted gold standard for diagnosing fibrosis and severity of liver damage is a liver biopsy. However, liver biopsy is an invasive procedure and is associated with procedure-related morbidity (1-3%) and mortality (0.01%) [10]. An excellent non-invasive modality with high sensitivity for detection of hepatic fibrosis is Transient elastography (Fibroscan) which measures liver stiffness (LSM) [11]. Controlled attenuation parameter (CAP) is an attachment with Fibroscan and is a good modality for measuring hepatic steatosis [12].

NAFLD and GSD are prevalent problems worldwide and they share common risk factors like obesity, hypertriglyceridemia, type 2 diabetes mellitus, insulin resistance and presence of the metabolic syndrome. Presence of NAFLD especially with significant fibrosis may have bearing on the surgical management of patients with GSD. Hence the present study aimed to non-invasively assess the prevalence and severity of NAFLD in patients with gall stone disease.

**Methods**

A hundred patients with GSD diagnosed on ultrasound (US) abdomen who were being evaluated for cholecystectomy were assessed prospectively for the presence and severity of NAFLD. Patients of GSD with no history of alcohol intake or intake less than 20 g/day were included. Patients with other causes of hepatic steatosis and raised transaminases (presence of hepatitis B and C infection, taking statogenic drugs, autoimmune hepatitis, Wilson's disease etc) were excluded from the study. All patients were evaluated for the presence of MS as per the adult treatment panel III (ATP III) criteria with modified waist for the Indians [13]. Patients who were also grouped into: a) Normal weight (BMI <23 kg/m2); b) Overweight (BMI 23-25 kg/m2); c) Obese (BMI >25kg/m2) as per the Indian cut-offs [13]. Patients who have known hypertensives and taking treatment or with systolic blood pressure: SBP ≥130 or DBP ≥85 mm Hg or use of medication for hypertension, 5) fasting glucose: ≥ 100 mg/dL or use of medication for hyperglycaemia.

US abdomen was performed for screening fatty liver and fatty liver was categorized as mild, moderate or severe steatosis. The severity of hepatic steatosis was assessed with CAP and categorized into S1 (215-251 db/m), S2 (252-296 db/m), and S3 (>296 db/m). The severity of necro-inflammation was assessed using ALT levels and divided into mild necro-inflammation (ALT 40-60 IU/l) and significant necro-inflammation (ALT >60 IU/l). Hepatic fibrosis was assessed non-invasively in all patients with the help of transient elastography (TE; Fibroscan). TE was carried out preoperatively in the department of Hepatology following manufacturer's instructions. The patient was made to lie down in dorsal decubitus position with maximum abduction of the arm. Liver stiffness measurement (LSM) was performed through intercostal space. The successful acquisitions were performed on each patient and minimum 10 readings were taken. The success rate was calculated as the number of successful measurements made divided by the total number of measurements. The result was expressed as the median (M) and interquartile range (IQR) in kPa (in kilopascals) and ranged from 1.5 kPa to 75 kPa. The severity of LSM was categorised as mild fibrosis (LSM 5-7.9 kPa), significant fibrosis (LSM 8-12.5 kPa) and as cirrhosis with LSM >12.5 kPa [11].

**Statistical analysis**

Statistical analysis was carried out using IBM Statistical Packages for the Social Sciences (SPSS) version 22. The categorical variables were described as a proportion. Continuous variables reported in descriptive statistics. To look for the difference in the association among variables between groups was tested by parametric test (Chi-square test, Fisher's exact test, Mann-Whitney test) and non-parametric test (student t-test). Performances of CAP and liver stiffness to assess hepatic steatosis and hepatic fibrosis were determined using Received Operating Characteristics (ROC) curve analysis. All statistical tests were performed at a significance level of alpha=0.05.

**Results**

Of 100 GSD patients, there were 76 females and 24 males with a mean age of 44.2±12.7 years. Majority of patients (n = 48) were in 3rd and 4th decade of life; 20 patients were between 21 and 30 years, 19 were between 50-60 years, 12 were between 61-70 years and only one patient was > 70 years of age.
Table 1. CAP, LSM and ALT in assessing severity of steatosis, fibrosis, and necro inflammation in NAFLD

| CAP (Steatosis) | SL (mild) | SI (moderate) | SS (severe) |
|----------------|-----------|---------------|-------------|
| LSM (Fibrosis) | Mild (5-7.9kpa) | 17 | 06 |
|                | Significant (8-11.9kpa) | 08 | 01 |
|                | Cirrhosis (>12kpa) | 01 | 01 |
| ALT (Necro-inflammation) | Mild (40-50u/l) | 10 | 15 |
|                | Significant (>60u/l) | 15 | 15 |

(CAP- Controlled Attenuation Parameter, LSM- Liver Stiffness Measurement, ALT-Alanine Amino Transferase)

Table 2. Comparison of demographic features, anthropometry and MS components in patients of GSD with NAFLD

| GSD (n=100) | NAFLD (n=77) | NO NAFLD (n=23) | p value |
|-------------|--------------|-----------------|---------|
| AGE (years) | 44 ±12.8     | 43.7±12.7       | 0.815   |
| BMI         |              |                 |         |
| Normal weight [<23kg/m2] | 26±4.6 | 24.5±4.3 | 0.041 |
| Overweight [23-24.9kg/m2] |              |                 |         |
| Obese [>25kg/m2] |              |                 |         |
| Waist circumference |              |                 |         |
| Male [> 90CM] | 96.8±10.5 | 91.3±10.5 | 0.029 |
| Female [> 80CM] |              |                 |         |
| SBP [>130 mm Hg] | 127±15.2 | 123±7.4 | 0.255 |
| DBP [>85mm Hg ] | 77.8±10 | 77.9±8 | 0.977 |
| FBS [> 100 mg/dl] | 92.3±9.1 | 94.7±11.5 | 0.308 |
| Cholesterol [>150mg/dl] | 171.2±44.1 | 167.2±36.7 | 0.692 |
| Triglycerides [>150mg/dl] | 153.2±84 | 26.5±56.5 | 0.085 |
| HDL |              |                 |         |
| Male [<40 mg/dl] | 44.9±3.6 | 46.0±9.2 | 0.689 |
| Female [<50mg/dl] |              |                 |         |

(SBP- systolic blood pressure, DBP-diastolic blood pressure, FBS-fasting blood sugar, HDL- high density lipoprotein)

Table 3. Comparison of demographic features, anthropometry, MS components in patients of GSD with NASH

| GSD (n=100) | NASH (n=0) | NO NASH (n=1) | p value |
|-------------|-------------|---------------|---------|
| AGE (years) | 49.2±10.5 | 43.8±12.9 | 0.227 |
| BMI         | 27.9±9 | 26±4.6 | 0.308 |
| Normal weight [<23kg/m2] |              |                 |         |
| Overweight [23-24.9kg/m2] |              |                 |         |
| Obese [>25kg/m2] |              |                 |         |
| Waist circumference |              |                 |         |
| Male [> 90CM] | 101.5±8.7 | 94.9±9 | 0.040 |
| Female [> 80CM] |              |                 |         |
| SBP [>130 mm Hg] | 131.5±15.7 | 125.6±14.5 | 0.313 |
| DBP [>85mm Hg ] | 78.3±9.2 | 77.6±10.08 | 0.748 |
| FBS [> 100 mg/dl] | 95.3±8.9 | 77.6±10.08 | 0.442 |
| Cholesterol [>150mg/dl] | 184±45 | 168±41.9 | 0.282 |
| Triglycerides [>150 mg/dl] | 190±71.8 | 142±79 | 0.089 |
| HDL |              |                 |         |
| Male [<40 mg/dl] | 39.4±9.5 | 45.7±8.4 | 0.037 |

(SBP- systolic blood pressure, DBP-diastolic blood pressure, FBS-fasting blood sugar, HDL- high density lipoprotein)
Association of BMI, Waist Circumference and Metabolic Syndrome components with GSD

Of 76 females in this study, 46 (60.5%) were obese, 13 (17.1%) were overweight and 17 (22.4%) had BMI <23kg/m2. Of 24 males, 11 (46.9%) were obese, nine (37.5%) were overweight and four (16.7%) had BMI <23kg/m2; with no significant difference between females and males, p=0.11). Abdominal obesity was significantly more common in females [68 (89.4%)] in comparison to males [17 (70.8%)](p=0.008).

Forty-nine out of 100 patients with GSD had evidence of MS with higher prevalence in females [42 (55.3%)] in comparison to males [7 (29.2%)](p=0.026). Of various components of MS, increased waist circumference was present in 85% (mean 95.59±10.68 cm); hypertension in 44% (mean SBP 126±14.6 mmHg and mean DBP 77±9.9 mmHg), type 2 diabetes mellitus in 22% (mean FBS 92.04±12.7 mg%), hypertriglyceridemia in 39% (mean 147±79.3 mg %) and low HDL in 61% of patients (mean 45.2±8.7 mg %).

Of 100 patients, at least one MS component was present in all but one patient (99%). Twelve patients had the presence of 1 component, 38 patients had 2 components, 33 patients had 3 components, 13 patients had 4 components and 3 patients had all 5 components of MS.

GSD and NAFLD

Prevalence of NAFLD was 31% on USG and it was 77% based on CAP in 100 GSD patients. On USG abdomen, 24 (77.42%) had mild steatosis, 7 (22.58%) had moderate steatosis and none of the patients had severe steatosis. On CAP, 28 had mild steatosis (S1), 24 had moderate steatosis (S2) and 25 had severe steatosis (S3). CAP is an objective assessment, subsequent analysis and correlations of hepatic steatosis with various parameters were done based on CAP assessment rather than on ultrasound [12].

Of 61 females of NAFLD; 40 (65.6%) were obese, 10 (16.4%) were overweight and 11 had BMI < 23 (18%). Of 16 male patients with NAFLD; 6 (37.5%) were obese, 8 (50%) were overweight and 2 had BMI <23 kg/m2. There was a statistically significant difference in the incidence of obesity between male and female patients with NAFLD (p 0.018). Prevalence of increased waist circumference in males was 87.5% (n=14) and in females was 91.8% (n=56) (p=0.594).

Severity of steatosis, fibrosis and necro inflammation in NAFLD patients

Of 77 NAFLD patients, 25 had severe steatosis based on CAP; 8 patients had significant fibrosis and 1 patient had cirrhosis based on LSM (Table 1). Necro-inflammation was diagnosed based upon serum ALT levels; 10 patients had mild necro-inflammation and 16 patients had significant necro-inflammation (Table 1).

Prevalence of metabolic syndrome components in NAFLD

Prevalence of MS in NAFLD was 54.5% (n 42). MS was present in 6 (37.5%) of 16 males and 36 (51%) of 61 females with NAFLD (p 0.124). Increased waist circumference was present in 90.9% (n 70, mean 96.86±10.5 cm); hypertension in 49.4% (n 38, mean SBP 123±12.3 mm Hg and DBP 77.9±10 mmHg), type 2 diabetes mellitus in 22% (mean FBS 92.3±9.1 mg%), hypertriglyceridemia in 44.15% (n 34, mean 153.2±84.2 mg %) and low HDL in 63.6% (n 49, mean 44.97±8.6 mg %).

Comparison of metabolic syndrome components in patients of GSD with or without NAFLD and with and without significant fibrosis

Comparison of demographic profile, anthropometry and metabolic syndrome components showed that BMI and waist circumference were only two factors which reached a significant level in patients of GSD who were having NAFLD when compared to patients of GSD without NAFLD (Table 2). Nine patients had evidence of significant fibrosis (LSM >8 kpa). Patients with significant fibrosis had higher waist circumference (102.5±8.7vs 94.9±9, p 0.040) and lower HDL (39.4±9.6vs45.7±8.4, p 0.037) in comparison to those without significant fibrosis (Table 3).

Discussion

Prevalence of NAFLD has increased with the improvement of living standards and lifestyle changes in the population. Incidence of NAFLD varies among different countries affecting up to one-fourth of the population in Asian countries and reported incidence from USA and Europe varies from 25% to 46% [3,14,15]. This variation in the reported incidence of NAFLD in different countries and different regions can also be attributed to awareness to look for its presence and also that which modality has been used for detection. USG and MRS have commonly used tools for detection of NAFLD worldwide. In this study prevalence of NAFLD was 31% when USG was used for assessment; but when the same study population was assessed by CAP, 77% of patients had NAFLD.
There is limited available literature reporting the true prevalence of NAFLD in India. The reported prevalence of NAFLD from West Bengal is 9% while it is 32% from south India with a higher prevalence of 53% in north India [4-6]. In the majority of these patients, NAFLD was detected incidentally on imaging which was performed for some other ailment in a patient. These patients were asymptomatic with normal liver functions. In the present study, 77% of patients of GSD had evidence of NAFLD based upon CAP. This high prevalence of NAFLD could be attributed to the presence of MS which was present in 49% of the study population, and 99% of these had the presence of at least one MS component.

Association between GSD and NAFLD is of considerable importance as both share common risk factors like DM, hypertension, dyslipidaemia, and increased waist circumference. All of these are also the components of MS. Hence, GSD, NAFLD and MS are related to each other. There is now evidence supporting that NAFLD may be the hepatic manifestation of MS [16]. Prevalence of MS in patients with NAFLD in this study was 54.5%. Majority of patients with NAFLD were in 3rd and 4th decade of life. Incidence of hypertension was more in this study when it was compared with the reported prevalence of hypertension in NAFLD patients from India [17,18]. Incidence of DM, hypertriglyceridemia and abnormal HDL levels were similar to the earlier reported high prevalence of abnormal TG and HDL in patients with NAFLD [17,18]. Comparison of demographic profile, anthropometry and MS components demonstrated that BMI and waist circumference were only two factors which reached a significant level in this study when patients with NAFLD were compared to patients without NAFLD.

Patients with NAFLD may progress to NASH, fibrosis or cirrhosis. The reported prevalence of advanced fibrosis was 17.5% by transient elastography in a multi-ethnic population-based study from Malaysia [19]. While the prevalence of advanced liver fibrosis by MRS and transient elastography in a population-based study from Hong Kong was only 3.7% [20]. In this study, 8 patients had significant fibrosis and 1 patient had cirrhosis based on LSM value. This comparatively high prevalence of fibrosis in our study may be secondary to the selected cut-off value of 8 kPa by LSM for the diagnosis of hepatic fibrosis. When these patients of NAFLD with or without significant fibrosis were compared, only waist circumference and HDL levels were significantly different between these two groups.

Limitation of this study was that details about the socioeconomic status and dietary habits were not obtained.

Conclusion

The prevalence of NAFLD and hepatic fibrosis was significantly high in this study which indirectly gives the information about the disease burden which patients of GSD are harbouring while they were still asymptomatic for NAFLD. This may have surgical implications regarding their fitness for surgery and the use of various hepatotoxic drugs and anaesthetic agents. This study also showed the possible association between GSD, NAFLD and MS indicating a common pathophysiological mechanism. Therefore, we recommend health education which includes dietary advice and lifestyle modification in patients of GSD requiring cholecystectomy. The CAP and LSM are reliable non-invasive method in the evaluation of significant hepatic steatosis and advanced fibrosis.

All authors disclose no conflict of interest. The study was conducted in accordance with the ethical standards of the relevant institutional or national ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

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| Abbreviations | Definition                                      |
|---------------|-----------------------------------------------|
| ALT           | Alanine Aminotransferase                       |
| BMI           | Body Mass Index                                |
| CAP           | Controlled Attenuation Parameter               |
| CT            | Computed Tomography                            |
| DBP           | Diastolic Blood Pressure                       |
| DM            | Diabetes Mellitus                              |
| FBS           | Fasting Blood Glucose                          |
| GSD           | Gall Stone Disease                             |
| HDL           | Serum High Density Lipoprotein                 |
| IQR           | Interquartile range                            |
| LDL           | Serum Low Density Lipoprotein                  |
| LSM           | Liver Stiffness Measurement                    |

| Abbreviations | Definition                                      |
|---------------|-----------------------------------------------|
| M             | Median                                        |
| NAFLD         | Non-Alcoholic Fatty Liver Disease             |
| MRS           | Magnetic Resonance Spectroscopy               |
| MS            | Metabolic Syndrome                            |
| NASH          | Non-Alcoholic Steatohepatitis                 |
| OPD           | Outpatient Department                         |
| ROC           | Received Operating characteristics            |
| SBP           | Systolic Blood Pressure                       |
| TC            | Serum Total Cholesterol                       |
| TE            | Transient Elastography                        |
| TG            | Serum Triglyceride                             |
| USG           | Ultrasonography                                |