Silent Gallbladder Stone Associated with Nonalcoholic Fatty Liver Disease in a Scenario of Insulin Resistance in Young Adults

Samarpita Mukherjee, Arup K Banerjee, Swati Bhattacharyya, Shubhrajit Saha

Abstract

Nonalcoholic fatty liver disease (NAFLD) is considered as the hepatic expression of insulin resistance. The high occurrence of obesity and dyslipidaemia in insulin resistant condition favours NAFLD.

The hepatic effect of insulin resistance are diverse including increased hepatic cholesterol secretion, biliary cholesterol supersaturation and decreased biliary motility all of which leads to gallstone formation.

NAFLD and gallstone disease (GSD) shares common pathological factors like hyperinsulinemia, dyslipidaemia. As all the factors are common association with Insulin resistance there could be common occurrence of NAFLD and GSD in patients with insulin resistance.

During a study two patients with insulin resistance were found to have both NAFLD and GSD. Both the patients were found to be dyslipidemic and on sonography one was found to have multiple gall bladder stones and the other with a single gall bladder stone.

Keywords: BMI, Dyslipidemia, Hyperinsulinemia, Gallstone disease, Insulin resistance, Metabolic syndrome, NAFLD

Introduction

Nonalcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver conditions ranging from fatty liver, usually a benign and nonprogressive condition, to non-alcoholic steatohepatitis (NASH), which may eventually progress to cirrhosis, portal hypertension, and hepatocellular carcinoma.1-4 Insulin resistance associated with obesity and dyslipidaemia is the underlying metabolic milieu favoring the occurrence of NAFLD. 2,3 The NAFLD is nowadays considered as the hepatic expression of the metabolic syndrome. 4

Gallstone disease (GSD) is one of the most common disorders of the hepatobiliary system. The very high prevalence of both GSD and NAFLD makes it very likely a chance co-occurrence in a high number of cases; NAFLD and GSD also share common risk factors. Both diseases are associated with overweight or obesity, hypertriglyceridemia, insulin resistance, and type 2 diabetes mellitus, and their coexistence might also be pathogenically mediated. 1

Recent experimental studies report that hepatic insulin resistance may be associated with biliary cholesterol secretion, thus promoting cholesterol gallstone formation. 5 Hyperinsulinemia may increase hepatic cholesterol secretion, biliary cholesterol supersaturation, and gallbladder dysmotility, all favoring gallstone formation 5.

Case reports

Here we present two cases of two young males suffering from the fatty liver with silent gallstones in North Bengal Medical College and Hospital.

Case 1

A 29-year-old male having body mass index (BMI) of 27.8 and waist circumference—110 cm was found to have grade 1 fatty liver with distended gallbladder (GB). GB wall was mildly thickened, it showed multiple small calculi (Figs 1 and 2).

Fig. 1: Grade 1 fatty change (case 1)
sedentary lifestyle, had no history of present or past illness like hepatitis, hypertension, etc. and he was not on any medication. There was no history of diabetes, dyslipidemia, liver disorder, gallbladder disease in his family through his mother was found to be hypertensive.

- His lipid profile, liver function test (LFT) profile, fasting blood glucose, fasting insulin, insulin resistance are given in Table 1.

Case 2
A 27-year-old male having BMI of 24.9 and waist circumference–103 cm was found to have grade 2 fatty change with a single 25 mm gallstone (Figs 3 and 4).

- In his personal history, he used to take fast foods and soft beverages frequently but had no history of drug abuse or alcohol intake. He was living a sedentary lifestyle, had no history of present or past illness like hepatitis, etc. he was not on any medication and there was no history of hypertension, diabetes, dyslipidemia, liver disorder, gallbladder disease in his family.
- His lipid profile LFT profile, fasting blood glucose fasting insulin, and insulin resistance are given in Graph 1.

**Discussion**
While conducting a study on establishing a correlation between nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome using insulin resistance (HOMA–IR), LFT, Lipid profile parameters and sonological finding in young medicos (aged between 18 years and 30 years) of North Bengal Medical College, these two subjects were found to have gallstone disease with fatty changes in liver. The study was conducted after approval from Ethics committee of North Bengal Medical College and Hospital.

Personal history was taken along with clinical and drug history. Waist circumference, BMI, LFT, lipid profile and fasting blood glucose were measured in those two subjects using standard laboratory procedures and fasting Insulin had been measured by a commercially available ELISA kit. ELISA test for insulin assay is a very sensitive easily doable and yet cost-effective method. Blood for fasting insulin assay was drawn by single prick. Serum was separated and stored in a cold refrigerator (-20° C) for 15 days. Then ELISA for Insulin assay was performed in a lot after thawing the stored serum samples to room temperature. Insulin resistance was evaluated using the HOMA calculator. Ultrasonography had been performed per protocol for the evaluation of steatosis at the time of biochemical evaluation. The GSD was diagnosed in the presence of sonographic evidence of gallstones (one or more echogenic, distally shadowing, possibly movable structures in the gallbladder).

For diagnosis of metabolic syndrome presence of 3 of the revised adult treatment panel III (ATPIII) criteria namely waist circumference, serum triglyceride level and serum HDL-C were used.

**Table 1:** Biochemical profiles of two cases under the present study with appropriate reference ranges and methods

<table>
<thead>
<tr>
<th>Name of the parameter</th>
<th>Test result found</th>
<th>Reference range *</th>
<th>Name of the test method and kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose</td>
<td>94 mg/dL</td>
<td>74–100 mg/dL</td>
<td>Glucose oxidase–peroxidase method. (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>17.6 µIU/mL</td>
<td>2–19 µIU/mL</td>
<td>ELISA method. (INS- EASIA, Dia-Source.)</td>
</tr>
<tr>
<td>Insulin Resistance (HOMA IR)</td>
<td>2.3</td>
<td>Cut off value of IR in</td>
<td>Receiver operating characteristics curve.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the study population</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>found to be 2**.</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>198 mg/dL</td>
<td>&lt;200 mg/dL</td>
<td>CHOD-PAP method. (Erba Mannheim XL Syspack.) Triglyceride</td>
</tr>
<tr>
<td></td>
<td>163 mg/dL</td>
<td>&lt;150 mg/dL</td>
<td>Glycerol phosphate oxidase method. (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>High density lipoprotein (HDL-C)</td>
<td>29 mg/dL</td>
<td>Adult male–35.3–79.5 mg/dL Adult female-42–88 mg/dL</td>
<td>Modified polyvinyl sulfonic acid (PVS) and polyethylene –glycol-methyl ether (PEGME) coupled classic precipitation method. (Erba Mannheim XL Syspack)</td>
</tr>
</tbody>
</table>

(Contd...)
Silent Gallbladder Stone Associated with Nonalcoholic Fatty Liver Disease

**Table 1.**

<table>
<thead>
<tr>
<th>Name of the parameter</th>
<th>Test result found CASE 1</th>
<th>Test result found CASE 2</th>
<th>Reference range *</th>
<th>Name of the test method and kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein (LDL-C)</td>
<td>136 mg/dL</td>
<td>62 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>Modified polyvinyl sulfonic acid (PVS) and polyethylene–glycol-methyl ether (PEGME) coupled classic precipitation method (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Very low-density lipoprotein (VLDL-C)</td>
<td>33 mg/dL</td>
<td>54 mg/dL</td>
<td>2–30 mg/dL</td>
<td>Friedewald formula.</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>1.3 mg/dL</td>
<td>0.8 mg/dL</td>
<td>0.3–2 mg/dL</td>
<td>Walter and gerade method (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0.8 mg/dL</td>
<td>0.45 mg/dL</td>
<td>0–0.3 mg/dL</td>
<td>Walter and gerade method.</td>
</tr>
<tr>
<td>Total protein</td>
<td>8.1 g/dL</td>
<td>7.67 g/dL</td>
<td>6–8 g/dL</td>
<td>Biuret method (Erba mannheim XL Syspack)</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1 g/dL</td>
<td>4 g/dL</td>
<td>Adult (20–60 years): 3.5–5.2 gm/dL.</td>
<td>BCG method (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Alanine transaminase(ALT)</td>
<td>61 IU/l</td>
<td>69 IU/l</td>
<td>Adult male up to 45 IU/L. Adult female up to 34 IU/L.</td>
<td>Modified IFCC method (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td>32 IU/l</td>
<td>41 IU/l</td>
<td>Adult male up to 35 IU/L. Adult female up to 31 IU/L.</td>
<td>Modified IFCC method. (Erba Mannheim XL Syspack)</td>
</tr>
<tr>
<td>Alkaline phosphatase(ALP)</td>
<td>111 IU/L</td>
<td>94 IU/L</td>
<td>Male (20–50 years)–53–128 IU/L. Female (20–50 years)–42–98 IU/L.</td>
<td>ALP–MP method (Erba Mannheim XL Syspack)</td>
</tr>
</tbody>
</table>

*All the reference ranges are as per kit literature of Erba Mannheim XL Syspack of respective parameters.

**Fig. 3:** showing grade 2 fatty liver (case 2)

**Fig. 4:** single calculi with in gallbladder (case 2)

Taken. In case 1 and case 2 waist circumference found to be 110 cm and 103 cm (>102 cm), both having elevated serum triglyceride 163 mg/dL and 271 mg/dL (>150 mg/dL) respectively and low serum HDL-C 29 mg/dL (<40 mg/dL).

Both the subjects having dyslipidemia, elevated ALT with AST: ALT ratio <1 with suggestive sonological findings of hepatic steatosis which favors the diagnosis of NAFLD. Both had insulin resistance (2.3 and 3, respectively with HOMA–IR cut off the value of 2 found by ROC curve (Graph 1) and other studies.

Insulin resistance and compensatory hyperinsulinemia have central etiologic roles in the development of MetS. Insulin resistance decreased the ability of insulin to act effectively on target tissues (especially muscle, adipose tissue, liver) is a prominent feature of metabolic syndrome.

Insulin resistance is also the key pathogenic factor for the development of hepatic steatosis. Both peripheral and hepatic insulin resistance is present in patients with NAFLD, irrespective of the coexistence of impaired glucose tolerance or obesity. The common causes of insulin resistance in these two subjects been increased BMI [both the subjects were having BMI of pre-obese group (27.8 and 24.9, respectively)] and sedentary lifestyle with lack of exercise. Both had no impaired glucose tolerance.
Silent Gallbladder Stone Associated with Nonalcoholic Fatty Liver Disease

But both can be prevented early, simply by changing life style, resulting in an increase in biliary cholesterol secretion.

Nearly 60–80% of liver triacylglycerol is derived from circulating FFAs. Insulin resistance decreases the inhibitory effects of insulin on peripheral lipolysis, increasing the availability of FFAs. A total of 25% of liver triacylglycerol is derived from De novo Lipogenesis (DNL). Insulin resistance and compensatory hyperinsulinemia also increases the conversion of glucose to Glucose–6–Phosphate to Acetyl CoA. Excess Acetyl CoA leads to increased fatty acid synthesis. Excess hepatic fatty acids are not only oxidized, but also they are converted to diacyl– and triacylglycerols and are stored in the hepatocyte cytoplasm leading to steatosis. DNL mediating enzymes are under the transcriptional regulation of sterol regulatory element binding protein-1c (SREBP-1c), which is also upregulated by insulin and is likely to be activated by hyperinsulinemia.

An association of GD with insulin resistance has been found in both the cases here. A few papers have already suggested the existence of an association between GD and NAFLD. This association might stem from the pathogenic factors shared by both GD and NAFLD, given that the risk for GD is especially high in patients with obesity and insulin resistance.

From a pathogenic perspective, insulin has been shown to augment the activity of hydroxymethyl glutaryl coenzyme A reductase (the rate-limiting step in cholesterol synthesis) and increases cholesterol synthesis. Hepatic insulin resistance, the metabolic milieu of steatosis, is associated with increased biliary cholesterol secretion, a mechanism to explain cholesterol gallstone formation. Disinhibition of the forkhead transcription factor FoxO, increases expression of the biliary cholesterol transporters Abcg5 and Abcg8, resulting in an increase in biliary cholesterol secretion. Hepatic insulin resistance also decreases expression of the bile acid synthetic enzymes, particularly Cyp7b1, and produces partial resistance to the farnesoid X receptor, leading to a lithogenic bile salt profile.

**APPLIED CLINICAL IMPORTANCE**

Young adults who are living a sedentary life style with improper dietary habits, having high BMI, dyslipidemia and insulin resistance might suffer from both NAFLD and gallstone disease. Co-occurrence of these two conditions may lead to more severe complications later on. But both can be prevented early, simply by changing life style, regular exercise, weight reduction.

**REFERENCES**

5. Bae JC, Suh S, Park SE, et al. Regular Exercise Is Associated with a Reduction in the Risk of NAFLD and Decreased Liver Enzymes in Young adults who are living a sedentary life style with improper exercise, weight reduction.
11. Day CP. Non-alcoholic steatohepatitis (NASH): where are we now and where are we going?. Gut. 2002 May 1;50(5):585-588.