Effect of Cholecystectomy on Lipid Profile in Bangladeshi Patients with Cholelithiasis

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Abstract

Objective: As no studies were reported from Bangladesh, the present study was conducted on serum lipid profile, i.e. triglyceride (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) in Bangladeshi patients with cholelithiasis.

Patients and methods: A total of 44 adult patients with cholelithiasis and 30 healthy subjects as normal controls (NC) were included in the study. The blood samples were taken from fasting patients at diagnosis before cholecystectomy (Serum-I) and bile during cholecystectomy (Bile-I) and blood sample again after 2-3 months at follow-up (Serum-II) and from fasting NC subjects. TG, TC, LDL-C and HDL-C were quantitated in serum and bile by standard methods using research kits from reputed companies. The results were compared statistically by ANOVA and Student’s t-test using SPSS programme.

Results: TG level was elevated in Serum-I compared to controls (NC) (p<0.001). TG level was reduced in serum -II after cholecystectomy compared to Serum-I and Bile-I, although it remained significantly elevated compared to controls (NC) (p<0.001). TC level was elevated in Bile-I compared to Serum-I and Serum-II (p<0.001). Interestingly, TC was elevated in Serum-II after cholecystectomy, although no significant difference was observed between NC and patients Serum-I (p=0.835). LDL-C levels in NC, Serum-I and Serum-II were similar (p=0.126, p=0.121), although Serum-II levels was elevated compared to Serum-I (p<0.001) and it was much elevated in Bile-I (p<0.001). HDL-C levels were similar (p=0.05) among NC, Serum-I and Serum-II, but it was higher in Bile-I significantly (p<0.001).

Conclusion: Alterations in lipid profile in cholelithiasis were significant but complex and cholecystectomy had profound impact suggesting a crucial role of gall bladder. The results were discussed accordingly.

Keywords: Cholelithiasis; Cholecystectomy; Lipid profile; Triglyceride; Cholesterol; LDL-C; HDL-C

Introduction

Cholelithiasis (gallstone disease) is one of the most common gastrointestinal disorders being prevalent in about 10-15% of adults in the developing countries [1,2]. Although most of the patients are asymptomatic, about 20% of them become symptomatic. They require treatment currently involving the surgical removal of the gallbladder and gallstones, that is cholecystectomy [2,3]. It is now widely accepted that the primary event in the pathogenesis of cholesterol gallstones is an altered lipid metabolism, because of which there is a relative increase in the cholesterol levels compared to other lipids secreted by the liver into the bile [1,3]. There are three stages of gallstone formation: super saturation, nucleation and aggregation. The association of cholesterol super saturation of bile with cholesterol gallstones paved the way for the physical-chemical basis for gallstone formation [4,5]. It soon became evident that other factors including nucleation of cholesterol crystals, binding together of these crystal with mucin and hypomotility of the gallbladder also plays an equally important role in gallstone formation [1,3,4]. However, the molecular events that underlie these processes are far from clear. It is reported that an increase in biliary arachidonyl-1- lecithin may lead to increased prostanoid synthesis, which may be responsible for increased mucin secretion as well as gallbladder hypomotility [4,5].

The association between gallstones and altered lipid profile and later increase in risk of coronary artery disease and stroke and even hepatocellular carcinoma (HCC) has been shown in many studies [3,6,7]. In a recent study, 36 (80.0%) of the female patients had one or other abnormality in their lipid profile preoperatively. Plasma concentration of total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) were significantly reduced in patients on day 3 and 6 months of cholecystectomy. In another study, targeted phospholipid analysis by HPTLC and EIA showed a modified choline metabolic profile within liver, bile and serum, culminating in an increased synthesis of lysophosphatic acid (LPA) in patients with HCC. Lysophosphatidyl choline (LPC) was increased within bile, while LPA was increased and no significant changes in phosphatidyl choline (PC) in all three biological samples of HCC patients compared with controls were reported [1-3]. In other studies, apolipoprotein A1 (Apo A1), ApoE, CETP and Mucin have been implicated with cholelithiasis [3,8-10]. However, these results are variable and need confirmation by further studies. It is apparent that a large number of lipid parameters are involved and had been implicated in the pathogenesis of cholelithiasis.

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Literature review indicated that further studies are warranted investigating several aspects of lipids and apolipoprotein profiles and their metabolism in cholelithiasis followed by cholecystectomy. However, no study had been done or reported in literature involving cholelithiasis patients from Bangladesh. Two research reports that we managed to obtain through internet, not relevant to lipid metabolism, were on day care laparoscopic cholecystectomy (LC) and intraoperative flexible choledochoscopy (IFC) in Bangladeshi patients [11,12]. We have therefore decided to investigate in phases the various aspects of lipid profile and their metabolism in cholelithiasis patients followed by cholecystectomy at Medical Research Unit (MRU), MHWTT, Uttara, Dhaka, Bangladesh. In the present case-control interventional study (phase-1), the lipid profile i.e. triglyceride (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) in serum of cholelithiasis patients before cholecystectomy (primary) and after cholecystectomy (secondary) and in normal control subjects (NC) were investigated and the results were reported.

Patients and Methods

A total of 44 adult patients (Gender: 8 males, 36 females; Age range: 25-65 years, Mean age±SD: 45.5 ± 12.2 years) with cholelithiasis (gall stone disease) and 30 healthy adult normal controls (Gender: 12 males, 18 females; Age range: 28-60 years; Mean age ± SD: 42.5 ± 10.5 years) were included in this case-control prospective interventional phase-1 study of our objectives. The patients with gallstone disease (cholelithiasis) were diagnosed as having cholelithiasis according to standard clinical and laboratory criteria as practiced in hospital. Patients on lipid lowering drugs, patients with renal failure, nephritiform syndrome, pancreatitis, cardiac failure, morbid obesity, hypothyroidism, haemoglobinopathies, pregnancy and patients with cholecdocholithiasis and obstructive jaundice in addition to cholelithiasis were excluded [13,14]. After obtaining consent, patient’s details and clinical findings were recorded as per ‘PROFORMA’ designed for each patient at diagnosis. The fasting blood samples were taken at diagnosis before cholecystectomy, serum separated were aliquoted and stored frozen at -30°C to -80°C as first degree bile sample (I°). After Cholecystectomy, treatments/medications were given as required for the patients. After 2-3 months at follow-up, fasting blood samples were taken again from the same patient, serum separated, aliquoted and stored frozen at -30°C to -80°C as second degree serum samples (II°) until analyzed for the lipid profile i.e. TG, TC, HDL-C, LDL-C and Lp(a). All quantitative estimations in serum were made by standard medical laboratory methods such as TC by enzymatic end point CHOD-PAP, TG by enzymic colorimetric GPO-PAP and HDL-C by enzymatic colorimetric phosphotungstate/magnesium method using standard diagnostics kits from internationally reputed companies and LDL-C calculated by Friedwald formula [15]. The results in patients (I°, II°) and controls (NC) were compared statistically by ANOVA and Student’s t-test with SPSS programme in computer [16,17].

Results

The lipid profile i.e. serum levels of TG, TC, LDL-C and HDL-C in controls and patients and their statistical analysis are stated in Table 1 and Table 2 respectively.

Discussion

This is the first report of case-control prospective interventional study on serum lipid profile in cholelithiasis patients from Dhaka, Bangladesh. The present study showed that serum TG level was elevated in Serum- I°, Bile- I° and Serum- II° of patients, being highest in Bile- I° compared to controls (NC) (p<0.001). Serum TG level was much reduced in serum-II° after cholecystectomy compared to Serum- I° and Bile- I°, although it remained significantly elevated compared to controls (NC) (p<0.001). Serum TC level was very much elevated in Bile- I° compared to Serum- I° and Serum- II° (p<0.001). Interestingly, TC was elevated in Serum- II° after cholecystectomy, although no significant difference was observed between NC and patients Serum- I° (p=0.835). LDL-C levels in NC, Serum- I° and Serum- II° were similar (p=0.126, p=0.138), although Serum-II° levels was elevated compared to Serum- I° (p<0.001) and it was much elevated in Bile- I° (p<0.001). HDL-C levels were also similar (p=0.05) among NC, Serum- I° and Serum- II°, but it was higher in Bile- I° significantly (p<0.001). It was evident from the results that changes in lipid profile in cholelithiasis

<table>
<thead>
<tr>
<th>Controls &amp; Patients</th>
<th>Lipid Profile*</th>
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<tbody>
<tr>
<td></td>
<td>TG (mg/dl)</td>
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<tr>
<td><strong>Normal Control (NC)</strong></td>
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<tr>
<td>N=30 (M:12, F:18)</td>
<td>93.67 ± 18.92 (3.45)</td>
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<tr>
<td>Mean±SD (SE)</td>
<td>65.01-127.02</td>
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<tr>
<td>Observed Range</td>
<td>86.61-100.73</td>
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<tr>
<td><strong>Patients (Serum-I°)</strong></td>
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</tr>
<tr>
<td>N=44 (M:8, F:36)</td>
<td>188.18 ± 48.92 (7.37)</td>
</tr>
<tr>
<td>Mean±SD (SE)</td>
<td>95.01-303.01</td>
</tr>
<tr>
<td>Observed Range</td>
<td>173.31-293.05</td>
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<tr>
<td><strong>Patients (Bile-I°)</strong></td>
<td></td>
</tr>
<tr>
<td>N=30 (M:8, F:22)</td>
<td>324.87 ± 154.23 (28.16)</td>
</tr>
<tr>
<td>Mean±SD (SE)</td>
<td>121.01-688.01</td>
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<tr>
<td>Observed Range</td>
<td>267.29-582.46</td>
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<tr>
<td><strong>Patients (Serum-II°)</strong></td>
<td></td>
</tr>
<tr>
<td>N=34 (M:4, F:30)</td>
<td>139.61 ± 46.01 (7.89)</td>
</tr>
<tr>
<td>Mean±SD (SE)</td>
<td>55.01-236.21</td>
</tr>
<tr>
<td>Observed Range</td>
<td>123.56-155.67</td>
</tr>
</tbody>
</table>

*TG (mg/dl): Triglyceride, TC (mg/dl): Total Cholesterol, HDL-C (mg/dl): High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol; N: Number of subjects, M: Male, F: Female; SD: Standard deviation, SE: Standard error, 95% CI: 95% Confidence Interval of mean.

Table 1: Serum levels of TG, TC, LDL-C, HDL-C and Lp(a) in controls and patients.
were significant and interesting, but a very complex one and cholecystectomy did have significant impact on them.

Individuals are predisposed to cholesterol gallstones if their bile has an increased proportion of cholesterol, relative to its two more hydrophilic lipids, i.e. bile acids (salts) and phospholipids. Patients with gallstones may have defects resulting in the production of abnormally supersaturated bile because of an increase in the secretory rate of biliary cholesterol or decrease in the secretory rate of biliary bile salts, lecithin and phospholipids. Changes in the concentration of one of the key promoters of crystallization, mucus glycoprotein, are mediated by mucosal prostaglandins (PGs). Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) prevent microcrystal and gallstone formation by decreasing PG synthesis, especially in obese people on weight-reduction diets. Gallbladder motor dysfunction and stasis also contribute to gallstone formation [18]. Intrahepatic cholestasis is associated with dyslipidemia, which might also contribute to the pathogenesis of the disease. The major risk factors for cholesterol gallstone disease are age, female gender and parity. However, there are several other risk factors involved too, such as postpartum, estrogen replacement therapy, oral-contraceptive use and rapid weight loss. The risk of cholesterol gallstone disease increases with age, obesity, type 2 diabetes, dyslipidemia (hypertriglyceridemia) and low HDL levels), hyperinsulinemia, and sedentary lifestyle, similar to atherosclerosis [19-21]. In this respect, our findings of lower HDL-C level in Serum-I0 but higher in Serum-II0 (not significantly) and very high HDL-C level in Bile-I0 (significantly) are of considerable interest. Possibly, high levels of HDL-C in Serum-I0 and Bile-I0 may have protective role in gall bladder against cholelithiasis.

The results of the present study indicated a higher incidence of cholesterol gallstones in this population with females comprising about 82.0% of the study population. The incidence of cholesterol gallstones, although less in the male population, was probably related to sedentary lifestyle and consumption of diet particularly rich in animal fats, refined sugars and poor in vegetable fats and fibers, all of which are significant risk factors for gallstone formation [21,22].

In the West, consumption of a high calorie diet is more common and is clearly an important factor in the formation of cholesterol gallstones. This wave has gradually spread even to the East Asian countries, with dietary habits becoming unhealthier [22-24].

In some studies, apolipoprotein A1 (Apo A1), ApoE, CETP and Mucin have been implicated with cholelithiasis [3,8-10]. However, these results were variable and need confirmation by further studies. It is apparent therefore that a large proportion of lipid parameters are involved and had been implicated in the pathogenesis of cholelithiasis. Abnormalities in lipids and apolipoproteins metabolism may, however, arise from a combination of various factors such as excess dietary cholesterol/fat, obesity, diabetes and genetic factors [2-4]. A number of studies have implicated HDL-C, VLDL-C, Low density lipoprotein-cholesterol; NC: Normal control subjects, Serum-I0: Patients (Serum-I0), Serum-II0: Patients (Serum-II0), Bile-I0: Patients (Bile-I0), p<0.05: Significant, p> 0.05: Not significant (NS)

<table>
<thead>
<tr>
<th>Statistical Test (Groups Compared)</th>
<th>TG (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
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<tbody>
<tr>
<td>ANOVA (NC, Serum-I0, Bile-I0, Serum-II0)</td>
<td>df=3,134, F=46.44, p&lt;0.001</td>
<td>df=3,134, F=52.79, p&lt;0.001</td>
<td>df=3,134, F=13.51, p&lt;0.001</td>
<td>df=3,134, F=173.94, p&lt;0.001</td>
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<tr>
<td>Student’s t – test (Groups Compared)</td>
<td>NC vs Serum-I0</td>
<td>df=72, t=-10.1, p&lt;0.001</td>
<td>df=72, t=0.209, p=0.835 (NS)</td>
<td>df=72, t=1.381, p=0.12</td>
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<td>NC vs Serum-II0</td>
<td>df=62, t=5.09, p&lt;0.001</td>
<td>df=62, t=-5.43, p&lt;0.001</td>
<td>df=62, t=-1.55, p=0.126 (NS)</td>
</tr>
<tr>
<td></td>
<td>NC vs Bile-I0</td>
<td>df=58, t=8.15, p&lt;0.001</td>
<td>df=58, t=-7.48, p&lt;0.001</td>
<td>df=58, t=-3.51, p=0.001</td>
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<td>Bile-I0 vs Serum-I0</td>
<td>df=72, t=8.50, p&lt;0.001</td>
<td>df=72, t=8.93, p&lt;0.001</td>
<td>df=72, t=5.38, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Bile-I0 vs Serum-II0</td>
<td>df=62, t=6.68, p&lt;0.001</td>
<td>df=62, t=5.89, p&lt;0.001</td>
<td>df=62, t=2.45, p=0.017</td>
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<tr>
<td></td>
<td>Serum-I0 vs Serum-II0</td>
<td>df=76, t=4.46, p&lt;0.001</td>
<td>df=76, t=5.72, p&lt;0.001</td>
<td>df=76, t=3.73, p&lt;0.001</td>
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</table>

Table 2: Statistical analysis by ANOVA and Student’s t-test of the results of lipid profile (from Table 1).

Conclusion

It was evident from our results that changes in lipid profile in cholelithiasis were significant and interesting, but a complex one and cholecystectomy did have significant impact on them. The perturbation in the delicate balance among components of lipid profile is of crucial importance and the gallbladder may have a definitive role in it leading to development of gall stone disease i.e. cholelithiasis. Further studies are warranted in Bangladeshi patients investigating several aspects of lipids, apolipoproteins, Lp(a) and their metabolism and MDA and paraoxonase activities in cholelithiasis followed by cholecystectomy.

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5. Portincasa P, Di Ciula A, Vendemiale G, Palmieri V, Moschetta A, et al. (2000) Intrahepatic cholestasis is associated with dyslipidemia, which might also contribute to the pathogenesis of the disease. The major risk factors for cholesterol gallstone disease are age, female gender and parity. However, there are several other risk factors involved, too, such as postpartum, estrogen replacement therapy, oral-contraceptive use and rapid weight loss. The risk of cholesterol gallstone disease increases with age, obesity, type 2 diabetes, dyslipidemia (hypertriglyceridemia) and low HDL levels), hyperinsulinemia, and sedentary lifestyle, similar to atherosclerosis [19-21]. In this respect, our findings of lower HDL-C level in Serum-I0 but higher in Serum-II0 (not significantly) and very high HDL-C level in Bile-I0 (significantly) are of considerable interest. Possibly, high levels of HDL-C in Serum-I0 and Bile-I0 may have protective role in gall bladder against cholelithiasis.

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