Comparative Study of Gallbladder Motility in Patients with Chronic HCV Hepatitis and with HCV Cirrhosis

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Aim. To compare gallbladder (GB) emptying in patients with chronic hepatitis C and in those with HCV related cirrhosis.

Method. 20 patients with HCV chronic hepatitis and 20 patients with HCV cirrhosis Child class A were enrolled in the study. The control group included 20 hospitalized patients free of liver disease. We excluded subjects with GBolithiasis or GB anomalies, and those with obesity and diabetes mellitus. In all patients, the following GB variables were measured: fasting volume (FV), minimal residual volume (RV), ejection fraction (EF), wall thickness and area under the emptying curve (AUC). The statistical analysis was performed using the Man-Whitney and Kruskal-Wallis tests and the Pearson correlation coefficient.

Results. In cirrhotic patients, the fasting GB volume (35.62 ± 4.45cm³) and the residual volume (18.46 ± 3.27cm³) were larger than in controls: 27.12 ± 5.38cm³ and 7.28 ± 3.15cm³, respectively (p < 0.00001). The GB EF was reduced in cirrhotics as compared to controls (p < 0.00001). The patients with HCV chronic hepatitis had a residual volume larger (14.18 ± 6.11cm³ vs 7.28 ± 3.15cm³; p = 0.0129), and an EF lower than controls (53.4 ± 14.15cm³ vs. 72.76 ± 9.96cm³) (p = 0.0005). The GB emptying curves showed a significantly slower emptying in cirrhotic and chronic hepatitis patients as compared to controls. We found a significant negative correlation in chronic hepatitis patients between EF, on one hand, and overweight and abdominal circumference, on the other. The GB wall was thicker in cirrhotics (5.1 ± 0.32mm) as compared to controls (2.32 ± 0.27mm) (p < 0.00001), and also in chronic hepatitis patients as compared to controls (p < 0.0001).

Conclusion. A decrease in GB motility was present both in patients with HCV related cirrhosis and in those with chronic HCV hepatitis. This may be, partly, caused by an increase in GB wall thickness, and might be a risk factor for the development of gallstones.

Key words: gallbladder volumes, motility, gallbladder wall thickness, ejection fraction, chronic HCV infection, HCV cirrhosis, abdominal ultrasound.

Gallstone (GS) disease is an important socio-economic issue, because of its high prevalence, reaching up to 10–20% in the general population [1]. Gallstones can be classified in two main types, depending on their chemical composition: cholesterol stones (predominating in industrialized countries) and pigment stones.

The risk factors for cholesterol GS are un-modifiable: female gender, older age, ethnicity and positive family history of lithiasis [2–4], and modifiable (environmental): hypercaloric, fiber-poor diet, or associated conditions: atherogenic dyslipidemia [5], type 2 diabetes mellitus [6], obesity [7], hepatic steatosis [8] and metabolic syndrome [9].

The association between liver cirrhosis (viral, alcoholic or of another etiology) and GS has been confirmed by several studies [10–11], reporting that GS are at least twice as frequent in cirrhotic patients, while the pigment GS are the predominant type. As far as chronic hepatitis C is concerned, the association with GS has more recently been acknowledged [12][13], with some studies showing that this disease might be considered as a GS risk factor in patients with positive family history, arterial hypertension, obesity or liver steatosis [14–[15].

The present study aims to assess the gallbladder motility in patients having chronic hepatitis C as compared to those having HCV related cirrhosis, in order to find a potential contractility alteration already present in the hepatitis stage, and not only in the stage of established cirrhosis with portal hypertension.

MATERIAL AND METHOD

We enrolled 60 consecutive patients admitted to the 3rd Medical Clinic, Cluj-Napoca, between
2008 and 2010, randomized into three homogeneous study groups. The groups were established as follows: 20 patients with Child A HCV related cirrhosis, 10 males and 10 females, aged between 49 and 62 years (mean age: 57.6 ± 3.1) (Cirrhosis group); 20 patients with chronic hepatitis C, aged between 45 and 69 years (mean age: 55.5 ± 5.6) (Chronic hepatitis group), and 20 controls (patients hospitalized for respiratory, cardiovascular or digestive conditions, but free of any clinical or biological signs of liver disease), with the same sex ratio and aged between 48 and 63 years (mean age: 56.2 ± 4.1) (Control group). The diagnosis of chronic HCV infection was established based on positive anti HVC antibodies, negative HBs antigen and alcohol consumption <20 g/day. In order to differentiate between chronic hepatitis and cirrhosis we analyzed the clinical, biochemical, ultrasonographical (absence of portal hypertension signs or splenomegaly), endoscopic (absence of esophageal varices or portal hypertensive gastropathy) and pathological data (if available) of each patient. In patients diagnosed with hepatopathies we measured the functional liver tests: serum transaminases (alanin aminotranspherase – ALT), cholestasis enzymes (alkaline phosphatase – ALP, gamma Glutamyl transeptidase – GGT), liver synthesis tests (prothrombin time), bilirubinemia and platelet counts (for the assessment of hypersplenism).

In all patients, we recorded the following variables: sex, age, parity in females, family history of GS, sedentary life style (appreciated by the mean duration of physical activity: patients performing less than 30 minutes of physical effort daily were considered sedentary), abdominal circumference (AC) (normal values: ± 80 cm in women and ± 94 cm in men), body mass index (BMI), the presence of hypertension, atherogenic dyslipidemia (cholesterol, HDL-cholesterol, triglycerides) or hepatic steatosis. We excluded the patients diagnosed with GS, gallbladder malformations, obesity (BMI > 30 kg/m²), diabetes mellitus, gastric or ileal resections.

The assessment of gallbladder motility was achieved in each patient by ultrasonographic evaluation, performed by the same operator (C.B.) after a 12-hour fasting and after discontinuation of any medication with potential influence on gallbladder motility for at least 24 hours.

The gallbladder volume was calculated using the ellipsoid method, involving the three diameters of the gallbladder obtained in two planes. The gallbladder wall thickness was appreciated on the anterior gallbladder wall and expressed in millimeters. The fasting volume was calculated after fasting as the mean of three consecutive measurements. Afterwards, the patients ingested a test meal: 14 g of lipids (equivalent of 425 kcal), containing 39 g bread, 1 boiled egg, 10 g butter and 300 ml tea sweetened with 20 g sugar (baseline moment). Subsequently, the gallbladder volume was measured for 90 minutes at regular 15-minute intervals. The volumes were expressed in cm³ or milliliters and also as percentages of the fasting volume at each time interval.

We determined the residual volume (RV) = the smallest gallbladder postprandial volume; the ejection fraction (EF) = the ratio between (fasting volume-residual volume)/fasting volume, expressed as percentage; ΑUC = the percentage of the fasting volume at 90 minutes. The gallbladder evacuation and refilling curve was obtained by projecting on a diagram the gallbladder volume as a function of time.

**Statistical analysis**

The differences between groups were analyzed using the Man-Whitney, Kruskal-Wallis tests and the Pearson correlation coefficient. The p value < 0.05 was considered statistically significant. The statistical analysis was performed using the SPSS 17.0 program (SPSS Inc, Chicago, IL, SUA).

**RESULTS**

The characteristics of the patients included are presented in Table I. The majority of cirrhotic patients had cytolisis or hepatic synthesis deficit (prolonged PT), 7 patients (35%) had hypersplenism (thrombocytopenia) and 6 (30%) had hyperbilirubinemia, particularly unconjugated type.

In cirrhotic patients, the fasting was greater than in controls (35.62 ± 4.45 cm³ vs 27.12 ± 5.38 cm³), with a very high statistical significance (p < 0.00001). The residual volume was reached in all groups 60 minutes postprandially and was greater in cirrhotics as compared to controls (18.46 ± 3.27 cm³ vs 7.28 ± 3.15 cm³) (p < 0.00001). The ejection fraction was decreased in cirrhotics (47.24 ± 5.17 %) as compared to controls (72.76 ± 9.96 %) (p < 0.00001). The GB wall thickness was greater in cirrhotics (5.10 ± 0.32 mm) as compared to controls (2.32 ± 0.27 mm) (p < 0.00001) (Table II).
The GB emptying curves were compared between cirrhotic patients and controls (Fig. 1). A much impaired gallbladder emptying was observed in cirrhotic patients at all the measurement moments (p < 0.00001 for all).

With regard to the emptying parameters in the *Chronic hepatitis* group, we noticed that these patients had a greater residual volume (p = 0.0013) and a lower maximal emptying rate than in controls (p = 0.005). The gallbladder wall thickness was greater in patients with chronic viral hepatitis C (p < 0.0001) (Table III). Fig. 2 shows the significantly decreased motility in patients with chronic hepatitis C as compared to controls.

The comparison between chronic hepatitis and cirrhotic groups showed an alteration of GB motility (Table IV) and a slower emptying rate in cirrhotic patients, with statistical significance for every recorded moment (Fig. 3).

The comparison of emptying curves in all three groups suggested a GB emptying in inverse proportion to the severity of the liver disease (Fig. 3).

### Table I
Characteristics of the patients with chronic HCV hepatitis, HCV cirrhosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Chronic hepatitis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.2 ± 4.10</td>
<td>55.5 ± 5.60</td>
<td>57.6 ± 3.14</td>
</tr>
<tr>
<td>Family history of GD</td>
<td>3 (15%)</td>
<td>6 (30%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Females with ≥ 2 child births</td>
<td>6 (60%)</td>
<td>6 (60%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Sedentarity</td>
<td>12 (60%)</td>
<td>7 (35%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>HTA</td>
<td>7 (35%)</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Cholesterol ↑ (mg/dl)</td>
<td>8 (40%)</td>
<td>5 (25%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Triglycerids ↑ (mg/dl)</td>
<td>8 (40%)</td>
<td>11 (55%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>BMI (≥ 25 kg/m²)</td>
<td>9 (45%)</td>
<td>10 (50%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>11 (55%)</td>
<td>9 (45%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>12 (60%)</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>ALT ↑ (UI/ml)</td>
<td>0</td>
<td>6 (30%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Bilirubin ↑ (mg/dl)</td>
<td>0</td>
<td>0</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Prolonged PT (seconds)</td>
<td>0</td>
<td>0</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>0</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>

### Table II
Gallbladder emptying parameters in controls as compared with patients with HCV cirrhosis

<table>
<thead>
<tr>
<th>Group</th>
<th>FV (ml)</th>
<th>RV (ml)</th>
<th>EF (%)</th>
<th>AUC (%)</th>
<th>GB wall (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>27.12 ± 5.38</td>
<td>7.28 ± 3.16</td>
<td>72.76 ± 9.96</td>
<td>38.12 ± 14.26</td>
<td>2.35 ± 0.28</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>35.63 ± 4.45</td>
<td>18.46 ± 3.28</td>
<td>47.24 ± 5.17</td>
<td>61.74 ± 5.53</td>
<td>5.10 ± 0.33</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.00001</td>
<td>&lt; 0.00001</td>
<td>&lt; 0.00001</td>
<td>&lt; 0.00001</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

### Table III
Gallbladder emptying parameters in controls as compared with patients with chronic HCV hepatitis

<table>
<thead>
<tr>
<th>Group</th>
<th>FV (ml)</th>
<th>RV (ml)</th>
<th>EF (%)</th>
<th>AUC (%)</th>
<th>GB wall (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>27.12 ± 5.38</td>
<td>7.28 ± 3.16</td>
<td>72.76 ± 9.96</td>
<td>38.12 ± 14.26</td>
<td>2.35 ± 0.28</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>30.99 ± 7.32</td>
<td>14.18 ± 6.11</td>
<td>53.40 ± 14.16</td>
<td>54.99 ± 15.81</td>
<td>3.20 ± 0.22</td>
</tr>
<tr>
<td>P</td>
<td>0.05827</td>
<td>0.00129</td>
<td>0.00054</td>
<td>0.00490</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table IV
Gallbladder emptying parameters in chronic HCV hepatitis as compared with patients with HCV cirrhosis

<table>
<thead>
<tr>
<th>Group</th>
<th>FV (ml)</th>
<th>RV (ml)</th>
<th>EF (%)</th>
<th>AUC (%)</th>
<th>GB wall (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis</td>
<td>30.99 ± 7.32</td>
<td>14.18 ± 6.11</td>
<td>53.40 ± 14.16</td>
<td>54.99 ± 15.81</td>
<td>3.20 ± 0.22</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>35.63 ± 4.45</td>
<td>18.46 ± 3.28</td>
<td>47.24 ± 5.17</td>
<td>61.74 ± 5.53</td>
<td>5.10 ± 0.33</td>
</tr>
<tr>
<td>p</td>
<td>0.01187</td>
<td>0.00178</td>
<td>0.00106</td>
<td>0.02655</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
The univariate analysis using the Pearson correlation coefficient demonstrated a very good negative correlation between ejection fraction and overweight ($r = -0.719; p = 0.00035$) and abdominal circumference, respectively ($r = -0.736; p = 0.00012$) in chronic hepatitis C patients. In all the patients included in the study, a very good negative correlation was found between the ejection fraction and the residual volume (controls: $r = -0.931; p < 0.0001$, chronic hepatitis C patients: $r = -0.827; p < 0.0001$, cirrhotic patients: $r = -0.608; p = 0.004$), and also a significant negative correlation between ejection fraction and gallbladder wall thickness ($r = -0.701; p < 0.00001$).
**DISCUSSION**

Several studies have demonstrated a high GS prevalence in patients with liver cirrhosis, especially for pigment GS [10–11]. It was also found that the more advanced the cirrhosis, independent of its etiology, the higher the GS incidence; GS incidence was also higher in patients with HCV related cirrhosis [11]. The mechanisms involved in GS formation in cirrhotic patients are: the decreased liver synthesis and transport of the bile acids, the decreased cholesterol synthesis, decreased apolipoprotein A1 and A2 levels, high estrogen levels, hypersplenism leading to chronic hemolysis and also gallbladder hypomotility [16–19]. Our study has confirmed that both gallbladder fasting and residual volumes were significantly greater in cirrhotic patients. In addition, we found a lower ejection fraction and a higher AUC in patients with cirrhosis, suggesting impaired gallbladder emptying in these patients. These results are similar to other studies [18–19].

Recent studies have also found an association between chronic HCV hepatitis and gallbladder lithiasis [14–15]. Indeed, some histological characteristics of chronic HVC infection are the small bile duct inflammation/destruction and hepatic steatosis [20], both leading to changes in bile composition. Hepatitis C virus was isolated in the gallbladder epithelial cells, while the HCV-RNA concentration was found to be the same in serum and in bile and cultures of gallbladder epithelial cells [21]. These findings suggest that chronic HVC infection may alter gallbladder mucosal function, favoring lithogenesis. The gallbladder epithelial cells are known to be involved in bile secretion and water absorption via aquaporins and may therefore favor biliary lithogenesis [22–24]. Deficient lipid absorption through the gallbladder epithelium can alter both bile composition and smooth muscle contractility, playing a potential part in cholesterol GS formation [25–26].

There are no clear data regarding the GS type (either cholesterol or pigment) encountered in patients with chronic HCV hepatitis. The study reporting the increased lithogenic risk in chronic hepatitis C patients having a positive family history, arterial hypertension, obesity or hepatic steatosis [15] suggesting the presence of cholesterol GS in these patients.

The pathogenesis of cholesterol GS is a multifactorial process. Cholesterol supersaturation of bile is the indispensable condition, leading to bile destabilization by alteration of the proportion of biliary lipids, and finally leading to cholesterol crystallization (accelerated nucleation) [27–28]. This phenomenon is favored by pronucleating agents, especially mucin, acting as a viscous gel for the deposition of cholesterol crystals [29]. Gallbladder hypomotility prolongs the time of bile stagnation in the gallbladder, thus favoring GS formation [30–31]. It can be induced by excess cholesterol in the bile, acting upon GB smooth muscle and affecting its contractility by incorporation into the sarcolemma and by uncoupling signal transmission to smooth muscle cells [31].

Intestinal hypomotility is the most recently demonstrated lithogenic factor (32). In this context, an alteration of the enterohepatic circulation increases the bile concentration of deoxycholic acid, an inhibitor of bile acid synthesis through a negative feedback mechanism, and also increases the cholesterol concentration and biliary cholesterol saturation.

Gallbladder hypomotility is an important risk factor not only for the formation of cholesterol GS, but also for the formation of pigment stones [10–11][16][19]. An impaired gallbladder contractility was documented in cirrhotics by ultrasonographic and scintigraphic methods, and was found to be in direct proportion with the severity of liver disease [18–19]. A series of studies have found decreased gallbladder motility in patients with cirrhosis, further decreased by GS presence [33–34]. The serum cholecystokinin levels are higher in cirrhotics than in healthy individuals, most probably due to its impaired hepatic degradation [35]. The GB resistance to the action of cholecystokinin may also be generated by the high serum levels (due to the same mechanism) of some intestinal peptides: somatostatin, glucagon, VIP, PP, FGF19, which induce relaxation of GB smooth muscle [36–37].

The present study aimed to assess whether gallbladder motility is also impaired in the chronic hepatitis stage, not only in the cirrhosis stage, and may therefore contribute to the increased formation of GS in that particular stage. Indeed, Bini et al found that in HCV-infected patients, the relative risk of GS increased alongside the severity of liver disease, with consequent alteration of bilirubin and albumin levels and also of platelet numbers [12]. In the present study, we also found that the more advanced the stage of HCV infection, the more severe the decrease in GB contractility.

Gallbladder hypomotility was found already in the chronic hepatitis stage. Chronic HCV hepatitis patients presented a very good negative correlation between the gallbladder ejection fraction and the...
presence of overweight (obese patients were not included in the study) and abdominal obesity. A series of studies have proven the association between chronic hepatitis C and a high BMI, obesity, hepatic steatosis or the metabolic syndrome [38–40]. Since the high BMI and abdominal obesity are known risk factors for cholesterol GS, we conclude that the GS accompanying chronic hepatitis might be cholesterol stones and that gallbladder hypomotility might contribute to the lithogenic risk.

Finally, gallbladder wall thickening, due to edema induced by portal hypertension, occurs frequently in patients with liver cirrhosis [33]. We also found wall thickening in chronic HCV hepatitis patients, but less advanced than in the cirrhosis stage. The negative correlation between the ejection fraction and gallbladder wall thickness \((r = -0.701; p < 0.00001)\) suggest that this is yet another cause of gallbladder hypomotility. Further studies are required in order to establish the type of GS occurring in patients with chronic HCV hepatitis and the mechanisms involved in their increased risk for lithogenesis.

**In conclusion,** gallbladder motility is diminished in patients with chronic HCV infection while still in their chronic hepatitis stage, and decreases progressively alongside the increase in liver disease severity. Gallbladder hypomotility may represent a contributive factor to the increased risk of gallstone formation in these patients.

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**Scopul studiului.** Evaluarea comparativă a golirii veziculei biliare (VB) la pacienții cu hepatită cronică virală C și la cei cu ciroză hepatică virală C.

**Metoda.** Au fost incluși în studiu 20 de pacienți cu hepatită cronică virală C și 20 pacienți cu ciroză hepatică virală C clasa Child A. Grupul Martor a fost alcătuit din pacienți spitalizați fără afecțiuni hepatice. Au fost excluși din studiu subiecții cu litiază biliară sau anomalii ale VB. La toți pacienții au fost evaluate următoarele variabile: volumul bazal (VB) al colecistului, volumul rezidual (VR), fracția de ejeție (FE), grosimea peretelui veziculei biliare și aria de sub curba (AUC) a golirii veziculare. Analiza statistică s-a realizat utilizând testele Man-Whitney, Kruskal-Wallis și coeficientul de corelație Pearson.

**Rezultate.** La cirotici, volumul bazal \((35.62 ± 4.45 \text{ cm}^3)\) și cel rezidual \((18.46 ± 3.27 \text{ cm}^3)\) au fost mai mari decât la martori: 27.12 ± 5.38 cm³, respectiv 7.28 ± 3.15 cm³ \((p < 0.00001)\). Franța de ejeție a veziculei biliare a fost semnificativ mai redusă la cirotici comparativ cu martorii \((p < 0.00001)\). Pacienții cu hepatită cronică avut volum rezidual semnificativ mai mare decât martorii \((14.18 ± 6.11 \text{ cm}^3 \text{ versus } 7.28 ± 3.15 \text{ cm}^3; p = 0.0129)\). Franța de ejeție a fost de asemenea mai redusă la pacienții cu hepatită \((53.4 ± 14.15 \text{ cm}^3 \text{ față de } 72.76 ± 9.96 \text{ cm}^3; p = 0.0005)\). Analiza curbelor de golire a indicat o golire semnificativ reduși la pacienții cirotici și la cei cu hepatită cronică virală C comparativ cu Martorii, pentru toate momentele de timp urmărite. S-a constatat o corelație negativă semnificativă la pacienții cu hepatită cronică într-un FE și suprapondere, respectiv circumferința abdominală. Grosimea peretelui VB a fost mai mare la cirotici \((5.1 ± 0.32 \text{ mm})\) comparativ cu Martorii \((2.32 ± 0.27 \text{ mm})\) \((p < 0.00001)\), și de asemenea, la pacienții cu hepatită cronică comparativ cu Martorii \((p < 0.0001)\).

**Concluzie.** Atât pacienții cu ciroză hepatică virală C cât și cei cu hepatită cronică virală C prezintă o reducere a motilității veziculei biliare. Aceasta ar putea fi datorată, în parte, creșterii grosimii peretelui vezicular, și ar putea fi un factor favorizant pentru formarea calculilor veziculare.

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