Prevalence of metabolic syndrome, obesity and diabetes type 2 in cryptogenic cirrhosis

Felix I Tellez-Avila, Francisco Sanchez-Avila, Mauricio Garcia-Saenz-de-Sicilia, Norberto C Chavez-Tapia, Ada M Franco-Guzman, Gustavo Lopez-Arce, Eduardo Cerda-Contreras, Misael Uribe

AIM: To evaluate the prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM) in a group of Mexican Mestizo patients with cryptogenic cirrhosis (CC) and to compare this group with patients with cirrhosis secondary to other causes (disease controls).

METHODS: Patients with CC, diagnosed between January, 1990 and April, 2005, were included in a retrospective study. Patients with cirrhosis caused by chronic hepatitis C, alcohol abuse or autoimmune hepatitis (AIH) served as disease controls.

RESULTS: A total of 134 patients with CC were analyzed. Disease controls consisted of 81 patients with chronic hepatitis C, 33 with alcohol abuse and 20 with AIH. The median age of patients with CC was 57 years (range, 16-87); 83 (61.9%) patients were male; 53 (39.6%) were Child A, 65 (48.5%) Child B, and 16 (11.9%) were Child C cirrhosis. The prevalence of MS (29.1% vs 6%; P < 0.001), obesity (16.4% vs 8.2%; P = 0.04) and T2DM (40% vs 22.4%; P = 0.013) was higher in CC patients than in disease controls. There were no differences in sex, age or liver function tests between the two groups.

CONCLUSION: The prevalence of MS, obesity and T2DM were higher in patients with CC than in patients with cirrhosis secondary to others causes. Our findings support the hypothesis that non-alcoholic steatohepatitis (NASH) plays an under-recognized role in CC.

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Key words: Cryptogenic chronic hepatitis; Metabolic syndrome; Obesity; Diabetes mellitus

INTRODUCTION

The diagnosis of “cryptogenic” cirrhosis is made after an extensive evaluation has excluded recognizable etiologies[1]. The prevalence of cryptogenic cirrhosis (CC) ranges from 5% to 30% in cirrhotic patients[2]. In Mexico, the etiology of cirrhosis remains unclear in 10% patients despite an extensive evaluation[3]. Several etiological possibilities are offered in such patients. These include occult alcohol abuse, silent autoimmune hepatitis (AIH), occult viral (non-B, non-C) hepatitis, and progression of nonalcoholic steatohepatitis (NASH)[4].

The prevalence of clinically silent autoimmune hepatitis in patients with CC is unknown; however, several studies have suggested that a significant number of patients with CC may have burnt-out AIH[5-6]. Occult virus disease (Non-B, non-C hepatitis) is considered to account for about 15% of post-transfusion hepatitis[7] and may exist in a silent form for several years[8]. Obesity and non-insulin dependent diabetes mellitus are the
two most common conditions associated with NASH\(^\text{[9]}\), which is frequently asymptomatic\(^\text{[9]}\) and can progress silently to cirrhosis with definitive histological features\(^\text{[9]}\).

The aim of the present study was to characterize the metabolic disturbances [prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM)] in a group of Mexican Mestizo patients with CC. In particular, we compared the prevalence of metabolic disturbances in the cryptogenic group with patients with cirrhosis due to other causes: hepatitis C without prior alcoholism, alcohol abuse and AIH.

**MATERIALS AND METHODS**

In a retrospective manner, we examined the medical records (paper and electronic-based records) of all patients with CC diagnosed from January, 1990 to April, 2005. We also included in a random fashion, disease controls consisting of patients with cirrhosis caused by chronic hepatitis C, alcohol abuse and AIH.

Diagnosis of CC was made after an exhaustive evaluation failed to provide a specific etiology. The data collected included the hepaticologic diagnosis, comorbid conditions, complications of portal hypertension if present, and major forms of treatment. Additional information was obtained from clinical charts, hospital records, the clinic and hospital laboratory databases, and by personal or telephone interview. Patients were included in the study if sufficient data was available and if the diagnosis was confirmed on review of all the available information.

The diagnosis of cirrhosis was made on the basis of clinical, laboratory and imaging data. In addition, histological findings were available in 56 (42%) CC patients. Biopsy was not performed in 78 patients, either because of refusal by the patient or their in-charge physician. Data collected included gender, age at diagnosis of cirrhosis, presenting symptoms, potential occupational exposure to hepatotoxins, family history of liver disease, and family or personal history of autoimmune diseases. Risk assessment for viral hepatitis included history of exposure to intravenous drugs, blood transfusions, tattoos, other known percutaneous needle exposures, and high-risk sexual behavior. All patients underwent extensive serological testing including hepatitis B and C screening [hepatitis B surface antibody, surface antigen, and anticoore antibody, and hepatitis C enzyme-linked immunosorbent assay (Abbott Laboratories, Abbott Park, IL)], iron studies (ferritin, iron, iron binding capacity, and tissue assessment if the diagnosis was questionable), ceruloplasmin, antinuclear antibody, surface antigen, and anticore antibody, and hepatitis C enzyme-linked immunosorbent assay (Abbott Laboratories, Abbott Park, IL, USA).

**RESULTS**

After careful review of the medical records, 50 patients who were originally classified as CC in the hospital registry were found to have other causes of liver disease. The main reason for this discrepancy was incomplete investigation or erroneous interpretation of the test results when the patients were referred to our center. These patients were initially listed as CC, but the diagnosis was not corrected in the registry when the new information became available. Other less common reasons for patient exclusion were incomplete medical information and indeterminate test results. For the final analysis, a total of 134 patients with CC were included in the study. In addition, EIGHTY ONE patients with chronic hepatitis C, thirty-three with alcohol abuse and twenty with AIH were evaluated as disease controls. The demographic, clinical, and laboratory characteristics of the study subjects are summarized in Table 1. In patients with CC, the median age was 57 years (range 16-87); 83 (61.9%) were female; and 53 (39.6%) had Child A cirrhosis, 65 (48.5%) were Child B and 16 (11.9%) were Child C.

Five patients were determined to have moderate alcohol consumption (< 2 drinks/d), but this was not considered to be the cause of their liver disease, either by the hepatologist or their primary care physician. None of the patients had a history of intravenous drug
The present study shows a high prevalence of MS, obesity, and T2DM in Mexican Mestizo population with CC. The relationship between T2DM, obesity, and cirrhosis has been much debated. To our knowledge, this is the first study that shows an association between MS and CC. There is less controversy regarding an association between MS, obesity, T2DM, and NASH, and several previous studies have shown a relationship between components of MS and NASH as well as the severity of liver fibrosis. MS is a worldwide problem with a high prevalence rate, and in agreement with our data this abnormality, along with some of its components, is more frequent in CC than in patients with cirrhosis caused by other etiologies. This finding is very important because it provides further evidence to support the theory that NAFLD/NASH can progress to cirrhosis in some patients.

The prevalence of MS was 500% higher in patients with CC compared to patients without CC. When the prevalence of each of the MS components in patients with and without CC was analyzed, only abnormal glucose values and dyslipidaemia showed statistically significant differences between the two groups (Table 1). There was no difference between the two groups with respect to the prevalence of HBP and being overweight. This may be related to the hemodynamic changes and malnutrition, seen commonly in cirrhotic patients. The mean ± SD of HDL and triglyceride levels in CC patients were similar in women (43.4 ± 10.9 mg/dL and 92.4 ± 49 mg/dL) and men (39.5 ± 8.5 mg/dL and 111.3 ± 59 mg/dL). Both of these test values were abnormal when the NCEP guidelines were taken into consideration (abnormal HDL serum levels < 50 mg/dL for women and < 40 mg/dL for men); prevalence of low HDL levels was seen in 76.7% women and 41.5% men. An observation not previously reported is the finding of higher prevalence (statistically significant) of hyperuricemia in CC compared to disease controls. Hyperuricemia is not accepted as

**DISCUSSION**

The present study shows a high prevalence of MS,
Table 3  Comparison of patients with cryptogenic cirrhosis and disease controls separated by the etiology of cirrhosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cryptogenic (n = 134, %)</th>
<th>CHC (n = 81, %)</th>
<th>Alcohol (n = 33, %)</th>
<th>AIH (n = 20, %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>83 (62)</td>
<td>54 (66.7)</td>
<td>7 (21.2)</td>
<td>14 (70)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DM</td>
<td>53 (40)</td>
<td>17 (21)</td>
<td>10 (30.3)</td>
<td>3 (15)</td>
<td>0.013</td>
</tr>
<tr>
<td>HBP</td>
<td>24 (18)</td>
<td>8 (10)</td>
<td>4 (12.1)</td>
<td>2 (10)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13 (10)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.027</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>72 (54)</td>
<td>5 (6)</td>
<td>1 (3)</td>
<td>2 (10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overweight (BMI &gt; 25)</td>
<td>103 (77)</td>
<td>63 (78)</td>
<td>27 (81.8)</td>
<td>16 (80)</td>
<td>0.93</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>22 (16.4)</td>
<td>5 (6.2)</td>
<td>5 (15.2)</td>
<td>1 (5)</td>
<td>0.10</td>
</tr>
<tr>
<td>MS</td>
<td>39 (29.1)</td>
<td>5 (6.2)</td>
<td>2 (6)</td>
<td>1 (5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>54.6 ± 14.3</td>
<td>56.8 ± 11.4</td>
<td>58 ± 12.6</td>
<td>55.6 ± 14.1</td>
<td>0.48</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27 ± 4.6</td>
<td>26 ± 4</td>
<td>26.4 ± 3.5</td>
<td>26.1 ± 5.1</td>
<td>0.65</td>
</tr>
<tr>
<td>ALT (U/L, mean ± SD)</td>
<td>52.5 ± 39</td>
<td>57.5 ± 33</td>
<td>52.6 ± 47.9</td>
<td>46.2 ± 27.7</td>
<td>0.79</td>
</tr>
<tr>
<td>AST (U/L, mean ± SD)</td>
<td>67.1 ± 60</td>
<td>77.8 ± 46</td>
<td>73.1 ± 52</td>
<td>73.5 ± 69</td>
<td>0.59</td>
</tr>
</tbody>
</table>

CHC: Cirrhosis by hepatitis C virus; AIH: Autoimmune hepatitis; DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patients’ body weight divided by the square of the height expressed in kg/m²); MS: Metabolic syndrome.

In 1999, Caldwell et al. described the prevalence of obesity and T2DM in 70 patients with CC, and compared the findings with three patient groups: NASH, cirrhosis with hepatitis C, and primary biliary cirrhosis (PBC). The prevalence of these risk factors (obesity and T2DM) were similar between patients with NASH and patients with CC, both of which had a higher prevalence compared to patients with hepatitis C and PBC. In another study by Poonavala et al., the prevalence of obesity and T2DM in patients with CC was compared with the prevalence in control patients. The various causes of cirrhosis in the control group were alcohol, chronic hepatitis, AIH, PBC and primary sclerosing cholangitis. Similar to the findings by Caldwell et al., the prevalence of obesity (55% vs 24%) and T2DM (47% vs 22%) were significantly higher in patients with CC compared with disease controls. Both authors concluded that their data supported the hypothesis that NASH may be an etiological factor in some of the patients with CC. We obtained similar results, but in a different population (Mexican Mestizo) and with a bigger sample size. When we classified the patients as CHC vs no CC, important differences in the prevalence of obesity and T2DM were observed (16.4% vs 8.2% and 40% vs 22.4%, respectively). However, when patients without CC were classified by etiology, only the prevalence of T2DM was statistically significant (Table 3). With respect to obesity, the prevalence between CC and patients with cirrhosis secondary to alcohol abuse was both similar, and both showed a higher frequency than patients with cirrhosis due to hepatitis C and AIH.

An interesting finding in the present study was that patients with CC without a liver biopsy had a greater prevalence of MS, obesity and T2DM compared with patients with CC who had a liver biopsy, despite similar liver function tests. This finding may be related to the presence of metabolic disturbances, suggesting to the physician the diagnosis of CC secondary to NASH; thus creating a different situation from patients with CC without metabolic disturbances.

The present study suffered from some limitations. First, the study design. Second, we did not record the waist circumference for the diagnosis of MS, but used BMI as a substitute for waist circumference. The use of BMI may have had a small impact on the number of cases diagnosed with MS, since there is a strong correlation between these parameters (r = 0.8) in the present study imply that non-alcoholic steatohepatitis is frequently associated with cryptogenic cirrhosis. This paper is well written and the results suggest an under-recognized role of NASH in patients with cryptogenic cirrhosis.
REFERENCES


