Prevalence of biliary lithiasis in a Sicilian population of chronic renal failure patients

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Abstract

Background. The aim of this study was to evaluate the prevalence of biliary lithiasis (BL) and associated risk factors in a population of undialysed patients with chronic renal failure (CRF), and to compare these with findings we had obtained previously in chronic haemodialysis (HD) patients and in subjects from the general population located in the same geographic region.

Methods. A total of 118 CRF patients on conservative treatment were included in the study. In all subjects, we measured several clinical and humoral parameters potentially correlated with BL. Liver and biliary tract ultrasonography was performed with a 3.5 MHz linear probe after at least 12 h of fasting.

Results. The prevalence of BL in CRF patients was 22%, which was higher than in the general population (χ² = 9.4, P < 0.002) but lower than in HD patients (χ² = 25.9, P < 0.0001). Age was similar in the three groups. Body mass index (BMI) was significantly higher in the CRF group than in both HD patients (P < 0.0001) and the general population (P < 0.0001). When the CRF group was divided into subjects with or without BL, the only difference was lower serum calcium levels in the subgroup with BL (P < 0.04).

Conclusions. The prevalence of BL in a Sicilian population of CRF patients was higher than in the general population, but lower than in patients with CRF on chronic HD. Apart from BMI, none of the risk factors traditionally associated with BL in the general population were related to BL in the CRF patients. These data suggest that other factors inherent to kidney pathology contribute to the high prevalence of BL in CRF patients.

Keywords: biliary lithiasis; chronic renal failure; epidemiology; risk factors

Introduction

In Western countries, several epidemiological studies have reported a prevalence of biliary lithiasis (BL) of >10% in the adult general population [1–3]. In a previous study, performed on a rural Sicilian population, we reported a prevalence of 11.5%, a value largely in agreement with other studies [4]. In contrast to the general population, the prevalence of BL has been reported to be higher in chronic liver and Crohn’s disease due to the presence of additional specific risk factors [5,6]. The overall objective of these studies is to identify modifiable risk factors for BL by advising changes in lifestyle for the general population and by using appropriate therapies for specific diseases.

To our knowledge, there are no studies that have investigated the frequency of BL in pre-dialysis chronic renal failure (CRF) patients. In contrast, a number of studies have examined BL rates in CRF patients in the haemodialysis (HD) phase and reported conflicting results, with BL prevalence similar to the local general population in some [7–9] but clearly higher in others [10]. In a recent study in Sicilian CRF patients on HD, we found an age- and sex-adjusted prevalence of BL that was clearly higher than in the general local population. The risk factors associated with BL were the concomitant presence of diabetes mellitus and high serum levels of phosphorus [11].

In this study, we investigated BL prevalence and its main risk factors in a group of Sicilian patients suffering from mild to severe CRF, and compared findings with those we had obtained previously in the general population from the same geographic region [4] and in haemodialysed patients with end-stage kidney disease.
Subjects and methods

We included 118 Caucasian patients (55 male, 63 female), with mean age 64.9 ± 10.8 years, who were being followed-up at our Division of Internal Medicine and Kidney Disease Centre. Diagnosis of CRF was defined as a serum creatinine level constantly >1.3 mg/dl and creatinine clearance <70 ml/min/1.73 m², calculated using the Cockcroft and Gault formula [12]. The aetiology of kidney failure was vascular kidney disease secondary to hypertenasion in 24 cases, diabetic nephropathy in 14 cases, pyelonephritis secondary to urolithiasis in 14 cases, adult-type hepatorenal polycystosis in 10 cases, biopsy-confirmed glomerulonephritis in 16 cases, nephropathy secondary to analgesics in four cases, pyelonephritis secondary to uro-vesical reflux in four cases, various pathologies (rheumatoid arthritis, tuberculosis, medullary cystic disease, non-specific renal cystic disease) in 14 cases, and unknown aetiology in 18 patients. In all patients, we recorded age, sex, body mass index (BMI), serum values of urea, creatinine, uric acid, cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, presence of diabetes mellitus, as well as parity and past or present use of oral contraceptives in the women. Moreover, we recorded serum concentrations of calcium, phosphorus and parathyroid hormone (PTH). The screening protocol also included a physical examination and an ultrasound scan of the gallbladder and biliary tract, which was performed according to previously described criteria [11]. One patient was positive for hepatitis B virus antigen (HBsAg) with normal alanine aminotransferase (ALT), and five patients were positive for anti-hepatitis C virus, two of whom had ALT levels that were over twice the normal limit. An additional five patients had ALT values above the normal limit, and 11 had γ-glutamyl transpeptidase (γ-GT) serum levels above the normal limit.

Statistical analysis

Results are given as means ± SDs, or as medians (minimum and maximum) in cases of non-Gaussian distributions. Student’s t-tests, Mann–Whitney U-tests, χ² tests and Fisher’s exact tests were used to compare means, medians and frequency values in the various population groups. Comparisons between more than two groups were performed by ANOVA, followed by post hoc analysis using Bonferroni tests. Multiple logistic regression analysis was performed to evaluate associations between the presence of BL and all the variables studied. The Mantel–Haenszel χ² test was performed to evaluate linear associations between age and BMI, and BL.

<table>
<thead>
<tr>
<th>CRF group</th>
<th>HD group</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All M F</td>
<td>All M F</td>
</tr>
<tr>
<td>n</td>
<td>118 55 63</td>
<td>171 83 88</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>22 14.5 28.5</td>
<td>33.3 30.1 36.4</td>
</tr>
<tr>
<td>No. of cases</td>
<td>26 (8) (18)</td>
<td>62.5 ± 14 60.8 ± 14 64.0 ± 13</td>
</tr>
<tr>
<td>Age</td>
<td>64.9 ± 10.8 58.6 ± 8.5 67.8 ± 10.8</td>
<td>23.8 ± 5.2 23.3 ± 4.2 24.4 ± 5.9</td>
</tr>
<tr>
<td>BMI</td>
<td>29.4 ± 5.9 26.6 ± 3.7 30.6 ± 6.4</td>
<td>23.3 ± 4.2 24.4 ± 5.9</td>
</tr>
</tbody>
</table>

*BMI, F = 34.6, P < 0.0001; BMI males, F = 20.8, P < 0.0001; BMI females, F = 22.4, P < 0.0001. **r = 7.8, P < 0.0001; *r = 3.8, P < 0.0001; **r = 3, P < 0.0001; ^r = 6.5, P < 0.0001; *r = 3.2, P < 0.002; ^r = 6.9, P < 0.0001; **r = 6.3, P < 0.0001; ^r = 5.5, P < 0.0001.

Results

Twenty-six patients (eight male, 18 female) were found to have BL, producing an overall prevalence of 22% (14.5% male, 28.5% female). After diagnosis of CRF, five of these patients were cholecystectomized because of recurrent colic pain. In the remaining patients with BL, the disease was asymptomatic, even though six patients (two males, four females) had been aware of their BL because of previous abdominal ultrasonographies.

A comparison of these CRF patients with HD patients and with the general population from two of our previous studies showed that the three groups were quite similar for age, although CRF subjects had a significantly higher BMI than HD patients and the general population (F = 34.6, P < 0.0001). Although male CRF patients had a higher BMI than male patients on HD (P < 0.0001), they were very similar to males in the general population. The same pattern of results was seen for females (Table 1). Prevalence of BL was higher in CRF patients than in the general population (P < 0.0001), and this difference was valid for both men and women (Table 1). In contrast, BL prevalence was lower in the CRF group (P < 0.001) than in the HD group, and this was also true for both males and females. Although females in the CRF group had a BL prevalence twice as high as their male counterparts, this difference was not significant, a result that may be due to the small number of cases. There were no differences in BL prevalence between patients having high or normal serum ALT and γ-GT values.

When patients were divided according to serum creatinine levels (Table 2), similar BL prevalences were found (χ² MH = 0.3, P = NS). The greatest number of patients with BL was found in the subgroup having serum creatinine levels between 3 and 7 mg/dl; however, a low number of patients in the subgroup having serum creatinine > 7 mg/dl may have biased this result.

Table 3 shows demographic characteristics and the mean ± SD age-adjusted concentrations of serum
urea, creatinine, uric acid, calcium, phosphorus, the product of Ca×P, cholesterol, triglycerides, HDL-cholesterol and PTH according to the gallbladder status of the CRF group. Of these, only serum calcium concentrations were significantly lower in patients having BL (P < 0.04); serum phosphorus values were higher in BL patients but this difference was not significant. In contrast, multiple logistic regression, performed using the presence or absence of BL as the dependent variable and the other parameters as independent variables, showed that only serum cholesterol was significantly associated with BL (P < 0.03; β = 0.03; odds ratio 0.97; confidence interval 0.95–0.99). The frequency of parity, the presence of diabetes mellitus and oral contraceptive use, traditionally associated with the development of BL, were not different between CRF patients with and without BL.

Discussion

Recently, we reported that CRF patients on chronic HD [11] had a clearly higher prevalence of BL than the general population from the same geographic region [4]. However, higher BL rates did not correlate with the duration of dialysis, suggesting that other factors favouring biliary lithogenesis may have been present in the pre-dialysis phase of CRF. The present study showed that undialysed CRF patients had a BL prevalence that was midway between that of our local general population and that of our local CRF population on dialysis [4,11]. However, the pathogenetic mechanisms responsible for these effects remain to be determined. In fact, the prevalence of BL in CRF patients was not associated with age or BMI, which are two of the main risk factors classically associated with BL in epidemiological studies [2]. Although BMI was significantly higher in the CRF group than in the general population or in the HD group, this may have been due to water retention in CRF patients and was thus not a determinant of BL. In support of this, Table 3 shows that CRF patients with or without BL had similar BMI values. We found that neither sex, parity, diabetes mellitus, the use of oral contraceptives nor dyslipaemic alterations seemed to play a role in biliary lithogenesis. This finding suggests that disease-related alterations in bile composition, which begin in the early phases of CRF, may produce strong effects that mask the influence of the risk factors more classically associated with BL. One such effect could be the use of low-protein diets, which are started at very early stages in CRF and which may be applied more strictly by physicians and patients than the clinical situation actually demands. In fact, a low protein intake could be responsible for increased bile lithogenicity [13] or for a decrease in the antinucleating protein factors of the bile that may facilitate the early phase of protein precipitation and subsequent stone formation [14]. Because our patients were all on normoprotein or hypoprotein diets, confirmed by a close follow-up with the families of patients or by monthly check-ups with dieticians, this may have influenced lithogenesis. Although low fibre intakes also favour biliary lithogenesis [15], our patients followed a diet with a balanced fibre content. Other possible risk factors include the use of drugs, steroids or other immunosuppressive agents to control underlying kidney diseases but which may also favour biliary stasis. For example, four glomerulonephritis patients were taking azathioprine and/or cyclophosphamide and 16 patients with hypertension or diabetes mellitus were taking angiotensin-converting enzyme inhibitors, all of which are known to favour cholestasis [16,17]. Although half of these patients had BL, the low number did not permit us to make an appropriate statistical analysis.

Among the renal failure-associated biochemical alterations, only serum calcium levels were significantly lower in the BL group. Serum phosphorus values

### Table 2. Prevalence of biliary lithiasis in the CRF group stratified according to serum creatinine (Cr) values

<table>
<thead>
<tr>
<th>Cr (mg/dl)</th>
<th>With BL</th>
<th>Without BL</th>
<th>χ² MH P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr &lt; 3 mg/dl</td>
<td>9/46 (19.6%)</td>
<td></td>
<td>0.03; NS</td>
</tr>
<tr>
<td>Cr &gt; 3 ≤ 7 mg/dl</td>
<td>14/56 (25%)</td>
<td></td>
<td>0.8 NS</td>
</tr>
<tr>
<td>Cr &gt; 7 mg/dl</td>
<td>3/16 (18%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Demographic characteristics and serum concentrations of selected biochemical parameters according to the gallbladder status of patients with CRF

<table>
<thead>
<tr>
<th></th>
<th>With BL</th>
<th>Without BL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.6 ± 15.05</td>
<td>64.9 ± 10.8</td>
<td>t = 0.88</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 5.9</td>
<td>29.4 ± 5.9</td>
<td>t = 1.4</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>109 (34–304)</td>
<td>101 (45–385)</td>
<td>z = 0.082</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>3.5 (1.3–9.2)</td>
<td>3.7 (1.3–12)</td>
<td>z = 0.2</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.7 ± 1.1</td>
<td>9.1 ± 0.7</td>
<td>t = 2.1</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.9 ± 1.3</td>
<td>4.5 ± 0.9</td>
<td>t = 1.8</td>
</tr>
<tr>
<td>Ca×P (mg/dl)</td>
<td>42.5 ± 11.7</td>
<td>40.6 ± 7.7</td>
<td>t = 0.9</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>60 (31–540)</td>
<td>74 (7.5–732)</td>
<td>z = 0.8</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>197.2 ± 54.9</td>
<td>192.6 ± 62.4</td>
<td>t = 0.34</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>125 (57–381)</td>
<td>110 (23–382)</td>
<td>z = 1.22</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>42.7 ± 13.2</td>
<td>42.8 ± 13.6</td>
<td>t = 0.05</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.37 ± 2.3</td>
<td>7.48 ± 2.3</td>
<td>t = 0.8</td>
</tr>
</tbody>
</table>
were higher, but this difference was not significant ($P < 0.07$). Previous studies have pointed to a role for these minerals in problems related to calculi; in fact, calcium phosphate has been found in the core and outer layers of both cholesterol and pigmented gallstones [18]. In addition, anionic phosphate may easily form insoluble compounds by binding with free calcium. In kidney disease patients, ideal conditions for BL are created in the bile where there are increases in biliary calcium, in phosphate anions or in both minerals (increase in $\text{Ca} \times \text{P}$) [19]. However, in the present study, we did not find elevated phosphorus in BL ($P < 0.07$), which was probably due to the low number of cases. Furthermore, serum PTH levels, which are closely correlated with phosphorus concentrations, were not associated with higher risk for BL. This result is in agreement with our previous findings [11] and with those of Dumlu et al. [20] in HD patients.

In conclusion, we found that non-dialysed CRF patients had a BL prevalence of 22%, which was higher than in the local general population but lower than in a group of local HD patients. Thus, in our population, factors related to kidney disease may have overshadowed the classical risk factors seen in the general population. Dietary habits or metabolic changes caused by kidney disease may initiate a series of alterations in bile composition which predispose or lead to the frank development of BL, especially during high phosphorus and calcium concentrations in the biliary tract. Further investigations on a greater number of patients will be necessary to assess BL during CRF and to shed more light on the physiopathological mechanisms leading to BL. Findings from these studies will help to reduce the high percentage of BL in patients that are already disabled by CRF.

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