Abstract. Background: The present study focused on cholecystectomized elderly patients and aimed to investigate whether inflammation in the gallbladder wall was associated with the number and size of gallstones, as well as the patients’ age. Patients and Methods: The present study included 306 cholecystectomized patients aged over 65 years. From the specimens derived from cholecystectomy, the gallstone number, the largest gallstone diameter and gallbladder wall thickness were determined. According to the histopathological examination, chronic inflammation was subdivided into mild-moderate and severe. Univariable analysis and multivariable logistic regression followed. Results: Mild-moderate inflammation characterized 63.4% of the cases and severe inflammation 36.6%. Solitary gallstones were found in 13.1% of the cases, while multiple gallstones were found in 86.9% of the cases. The largest gallstone diameter was less than 1 cm in the majority of cases (73.2%). The gallbladder wall thickness was associated with the degree of inflammation (p=0.001, Chi-square). In the univariable analysis, inflammation was positively associated with the diameter of the largest gallstone (p=0.032, Chi-square), but negatively associated with the number of gallstones (p<0.001, Chi-square) and patients’ age (p=0.008, logistic regression). The number of gallstones was negatively associated with the diameter of gallstones and positively associated with the patients’ age. The diameter of the largest gallstone was negatively associated with the patients’ age. In the multivariable logistic regression, the effect of age (OR=0.95, 95% CI: 0.91-0.99) and solitary gallstones (OR=2.66, 95% CI: 1.02-6.93) on inflammation persisted, but that of the largest gallstone diameter vanished. Conclusion: The elderly population presented mainly with multiple and small gallstones. Solitary gallstones and younger age were the most important predictors for severe inflammation.

Gallstone disease is one of the most common medical problems leading to surgery and hospitalization in the Western world. In Canada, it represents a major health hazard, accounting for about 130,000 admissions to hospital and 80,000 cholecystectomies annually. Cholecystectomy is the second most common operation in Canada and the United States, where it is performed six to seven times as often as in the United Kingdom or France (1). Although gallstones may remain silent, they frequently cause acute or chronic inflammation of the gallbladder, i.e. acute of chronic cholecystitis, respectively (2-4).

Female sex, body mass index, low serum high density lipoprotein (HDL) cholesterol levels and positive family history in a first-degree family member represent significant risk factors (5-7). Dietary habits, such as a high calorie intake, increased consumption of unrefined carbohydrate and low consumption of fiber seem also to be of importance (8). Other diseases and conditions associated with the development of gallstones include Crohn’s disease (9), hepatic cirrhosis, the metabolic syndrome and gallbladder stasis, due to spinal cord injury or drugs like somatostatin (10).

Most importantly, gallstone disease is age-associated in various, heterogeneous populations (5, 6, 11, 12). Elderly patients represent an interesting population with respect to gallstone disease. According to a recent cross-sectional survey in a neighboring Mediterranean country (Italy), the overall prevalence of gallstone disease reaches 26.7% in the elderly and multiple gallstones are particularly frequent, occurring in 62.7% of patients (13). Another recent Italian study revealed that cholecystitis-associated gallbladder and common bile duct stones are present in 16% of elderly patients undergoing cholecystectomy (14). Chronicity of gallstone disease renders this group of patients extremely interesting; it would be rational to speculate that inflammatory changes might be more obvious, since gallstones may have fully exercised their chronic effects on the gallbladder wall and vice versa.

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Key Words: Chronic cholecystitis, gallstones, gallbladder, elderly, inflammation.

Taking into account the above, the present cross-sectional prospective study focused on an elderly population. It aimed to investigate the association between the degree of inflammation in the gallbladder wall and the number and size of gallstones in cholecystectomized patients.

**Patients and Methods**

The population of the present study consisted of 306 consecutive cholecystectomized patients (130 men and 176 women) aged over 65 years. The median age was 72.6 years (ranging from 65 to 91 years). All the patients were of the same origin (Greek). Exclusion criteria were the following: diabetes, history or presence of malignancy, immunosuppressive therapy and intake of adrenal steroid derivatives. The establishment of a clinical and histological diagnosis of chronic cholecystitis, based on current and past medical history, was necessary to enroll the candidate patients in this study.

From the specimens derived from cholecystectomy, the number and diameter of the encased stones, as well as the gallbladder wall thickness were determined. Gallbladder wall thickness of less than or equal to 0.3 cm was classified as thin, between 0.3 cm and 0.6 cm as moderate and equal to or more than 0.6 cm as thick. When multiple stones coexisted, the diameter of the largest stone was noted. Afterwards, the gallbladder specimens were fixed in 10% neutral buffered formaldehyde, embedded in paraffin, and 5 µm thin slices were cut and stained with haematoxylin-eosin.

The present study involved only patients suffering from chronic cholecystitis, involving inflammation in the gallbladder wall is mainly characterized by lymphocytic and plasma cell infiltration, of variable degree. Chronic inflammation was subdivided into two categories, mild / moderate and severe, according to the severity and extent of the inflammatory reaction of the gallbladder wall. Mild to moderate inflammatory reaction included mainly lymphocytes primarily confined to the mucosa and submucosa. Severe inflammation was defined as intense transmural infiltration by inflammatory cells.

Statistical analysis included firstly non-parametric tests and univariable logistic regression. Subsequently, multivariable logistic regression modeling was performed to evaluate the independence of the documented (in the univariable analysis) effects. The degree of inflammation was set as the dependent variable, and the patients’ age, the number of gallstones and diameter of the largest gallstone were set as the independent variables. The statistic performed is indicated in the text in parentheses. The analysis was performed with STATA 8.0 statistical software (Statacorp, Texas, USA).

Written informed consent was obtained from all patients. The study was approved by the Local Institutional Ethics Committee.

**Results**

Among the 306 specimens studied, 194 (63.4%) were characterized by mild / moderate inflammation and 112 (36.6%) by severe inflammation. Forty cases involved solitary gallstones (13.1%), while 266 (86.9%) multiple (up to 26) gallstones. The largest gallstone diameter was less than 1 cm in the majority of cases (224 cases, 73.2%).

Thickness of the gallbladder wall was ≤0.3 cm in 49.4% of cases (151 out of 306), between 0.3 and 0.6 cm in 34.3% of cases (105 out of 306), and ≥0.6 cm in the remaining 16.3% (50 cases). The pathological correlation between degree of inflammation and thickness of the gallbladder wall is shown in Table I.

In the univariable analysis, the degree of inflammation was positively associated with the diameter of the largest gallstone, but negatively associated with the number of gallstones and patients’ age (Table II). There was no association between sex and degree of inflammation. The number of gallstones was negatively associated with the diameter of gallstones (Spearman’s ρ = -0.676, p < 0.001), and positively associated with the patients’ age (Spearman’s ρ = 0.163, p = 0.004). The diameter of the gallstones was negatively associated with the patients’ age (Spearman’s ρ = -0.194, p < 0.001).

The results of the multivariable logistic regression are shown in Table III. Of notice, the statistical significance concerning the diameter of the largest gallstone disappeared after the adjustment for the other predictors.

**Discussion**

The elderly population enrolled in this study presented mainly with multiple and small gallstones (less than 1 cm in diameter, Table I). Our results were in line with the Silea study, which also reported the predominance of the above profile (13). At the univariable analysis, the present study documented interesting associations between the severity of gallbladder wall inflammation and gallstone features, i.e. positive associations with solitary gallstones and the diameter of the largest gallstone.

The overall association between gallstones and chronic gallbladder inflammation is established (15), intriguing and has many aspects. From a mechanical point of view, the physical presence of stones within the gallbladder might impede the viscus evacuation and cause inflammatory changes of the gallbladder wall, such as fibrosis and muscular atrophy (16). However, contradictory findings exist, for instance, the addition of prosthetic gallstones in an animal (guinea pig) model, resulted only in moderate changes (17).

Besides the mechanical notions, another important parameter linking gallstones and the inflammatory changes in the gallbladder wall is gallbladder contractility. In line with our findings, large gallstone volume has been associated with reduced contractility of the gallbladder (16), a hypocontractile gallbladder favors cholecystostasis, which is in turn a favorable environment for crystal growth and gallstone formation (18). Indeed, in our study, though lacking functional tests, the highly significant association between gallbladder wall thickness and inflammation...
pointed to the existence of a thick, dysfunctional, inflamed gallbladder with impaired contractility.

The adjustment of all factors revealed that the two major predictors for severe inflammation in the elderly may be the presence of a solitary gallstone and younger age. The effect of age should be interpreted in the context of the age range, and may imply that either more elderly patients present with a less intense inflammatory response or that patients with severe inflammation select themselves out for earlier cholecystectomy.

With respect to the importance of the solitary gallstones, their association with more intense inflammation may once again point to the aforementioned hypocontractile gallbladder, harboring or promoting one sole gallstone. It is tempting to speculate that the presence of solitary or multiple gallstones implies differences in the contractility patterns of the gallbladder. In any case, the environment of multiple versus solitary gallstones presents differences concerning bile composition and nucleation time (19). It should be mentioned, however, that a recent study did not detect any association between gallstone number and degree of inflammation; nevertheless, that negative finding may not have been definitive, since the power of the study due to its sample size and statistics adopted was limited (20).

Keeping all the above in mind, an interesting question emerges concerning causality in the gallstones-gallbladder relationship, do gallstones lead to the gallbladder wall inflammation (16), or do they represent the final result in a predisposed gallbladder? According to recent studies, the gallbladder is not directly involved in the formation of gallstones (21). Studies dating back to the 1980s on animal models, have shown that changes in the gallbladder affecting its contractility (22) or associated with inflammation (23) appear very early, even before gallstone formation. Since then, data on animal models have underlined the importance of molecular mechanisms-

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### Table I. Correlation between degree of inflammation and thickness of the gallbladder wall.

<table>
<thead>
<tr>
<th>Degree of inflammation</th>
<th>Mild/moderate (88.1%)</th>
<th>Severe (11.9%)</th>
<th>Total</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness of gallbladder wall</td>
<td>≤0.3 cm</td>
<td>133 (88.1%)</td>
<td>18 (11.9%)</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>0.3-0.6 cm</td>
<td>51 (48.6%)</td>
<td>54 (51.4%)</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>≥0.6 cm</td>
<td>10 (20%)</td>
<td>40 (80%)</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>112</td>
<td>306</td>
<td></td>
</tr>
</tbody>
</table>

*Pearson’s Chi-square.

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### Table II. Factors predicting the severity of inflammation in the gallbladder wall, univariable approach.

<table>
<thead>
<tr>
<th>Degree of inflammation</th>
<th>Mild/moderate (67.3%)</th>
<th>Severe (32.7%)</th>
<th>Total</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of gallstones</td>
<td>Solitary (37.5%)</td>
<td>15 (37.5%)</td>
<td>25 (62.5%)</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Multiple (67.3%)</td>
<td>179 (67.3%)</td>
<td>87 (32.7%)</td>
<td>266</td>
</tr>
<tr>
<td>Diameter of the largest gallstone</td>
<td>&lt;1 cm</td>
<td>150 (67.0%)</td>
<td>74 (33.0%)</td>
<td>224</td>
</tr>
<tr>
<td></td>
<td>≥1 cm</td>
<td>44 (53.6%)</td>
<td>38 (46.3%)</td>
<td>82</td>
</tr>
<tr>
<td>Age</td>
<td>Odds ratio (OR)=0.94</td>
<td>95% CI: 0.90-0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>112</td>
<td>306</td>
<td></td>
</tr>
</tbody>
</table>

*Pearson’s Chi-square; ^b univariable logistic regression.

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### Table III. Results of the multivariable logistic regression analysis.

<table>
<thead>
<tr>
<th>Degree of inflammation</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.91-0.99</td>
<td>0.039</td>
</tr>
<tr>
<td>Diameter of the largest gallstone^a</td>
<td>1.10</td>
<td>0.71-1.70</td>
<td>0.68</td>
</tr>
<tr>
<td>Solitary gallstone^b</td>
<td>2.66</td>
<td>1.02-6.93</td>
<td>0.046</td>
</tr>
</tbody>
</table>

^a Treated as continuous variable; ^b vs. multiple gallstones.
References


