

Natural history of asymptomatic gallstones. A prospective 18-year follow-up

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Abstract. The ready availability of abdominal ultrasonography for the investigation of a wide range of abdominal symptoms has resulted in the increased diagnosis of asymptomatic gallstones. Management of such accidentally discovered gallstones poses a dilemma as conclusive evidence of the benefits of cholecystectomy is lacking. The aim of this study was to understand the natural history of asymptomatic gallstones discovered through a routine patient care process. We followed 109 persons with asymptomatic gallstones. All were then reviewed annually for 18 years for evidence of gallstone-related problems. Results were compared with previous literature studies.

Of 109 patients, 73 were women and 36 men, with an average age of 48.2 years (21 - 70). Symptoms developed in 31 patients (28.4%) after an average latency period of 37 months (2 – 98 months). One woman had gallbladder adenocarcinoma, and ten patients underwent prophylactic cholecystectomy. Women were more likely to become symptomatic than men, but symptom development in the men was more serious because initial presentations were biliary complications. Death due to nonbiliary causes occurred in 16 (14.7%) persons. The average age at the time of death was 70 years, ranging from 62 to 83 years. 52 persons remained asymptomatic for 18 years. The yearly risk of biliary pain appears to decrease with the passage of time .

Follow-up showed that only 28.4% developed symptomatic gallstones. Most patients with asymptomatic gallstones required no treatment.

Keywords: Asymptomatic gallstones, Cholelithiasis, Gallbladder Neoplasms, Cholecystectomy, Ultrasonography

1.Introduction

Aproximatly 6-44% of the general population have gallstones, most of which are asymptomatic (1). At the beginning of 20th century, the question was: Should asymptomatic gallstones be treated prophylactically or left alone? The answer depends in part on their natural history. Whereas Sir William Osler believed that most gallstones caused no symptoms (2), William Mayo regarded "innocent" gallstones as a myth (3). In the mid 20th century, it was recommended that all gallstones be surgically removed (4). This recommendation assumed that asymptomatic gallstones would eventually become symptomatic and that elective cholecystectomy would lower

morbidity and prevent gallbladder cancer (5). While symptomatic gallbladder disease is an accepted indication for surgery, more recent studies disclose that only 10% to 18% of asymptomatic patients ever develop symptoms (6). When symptoms do develop, they usually begin as non-life-threatening biliary colic within 5 years of the original diagnosis (7). With modern surgical techniques, cholecystectomy after symptoms develop results in a mortality rate almost equivalent to elective cholecystectomy (8)

The ready availability of abdominal ultrasonography for the investigation of a wide range of abdominal symptoms has resulted in the increased diagnosis of asymptomatic gallstones (9). Management of such accidentally discovered gallstones poses a dilemma as conclusive evidence of the benefits of cholecystectomy is lacking. The objective of this study was to understand the natural history of asymptomatic gallstones discovered through a routine patient care process.

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2. Material and methods

In order to determine the incidence of gallstone disease in the Canary Islands (SPAIN), we randomly selected one thousand women and one thousand men, aged 14 to 95 years. All were studied by abdominal ultrasound. We classified the gallstones as symptomatic or asymptomatic.

Gallstone disease was considered to be asymptomatic when the information obtained before and after abdominal ultrasound examination indicated absence of biliary pain or biliary complications. Biliary pain was defined as an episode of upper-abdominal pain that was not clearly due to another cause. Symptoms of dyspepsia, such as abdominal discomfort after eating certain foods, were not regarded as biliary pain (10). An episode of acute cholecystitis, biliary obstruction, or pancreatitis was considered to be a biliary complication.

Patients with gallstones who were asymptomatic, both at the time of discovery and at the time the study began, were followed up at yearly intervals during 18 years. Each year the medical records were reviewed to see if the patients had developed symptoms, remained asymptomatic, received treatment, or had complications associated with their gallstones. Results were entered into a statistical software package (SPSS 10.0) and, where appropriate, SD was calculated and statistical significance of the means was estimated using the Student *t* test, χ^2 was used to determine statistical significance of the difference in proportions. Statistical significance was set at $P < 0.5$.

The life-table method was used to determine the cumulative probability of the development of biliary pain or complications. A person was considered to be at risk from the time when asymptomatic gallstone disease was discovered until a specific end point was reached: the onset of biliary pain or complications or, if no such

Table 1

SEX	Abdominal ultrasound	Symptomatic gallstones	Asymptomatic gallstones	<i>p</i>
Females	1000	119	98	> 0.05
Males	1000	43	40	< 0.05
Total	2000	162	138	

biliary problem developed, prophylactic cholecystectomy, death, or December, 2003.

Using MEDLINE and other search tools, the literature was reviewed until 2003 for study

series of asymptomatic patients with gallstones. These studies were then compared with the patients of our study. To ensure consistency, medical record reviews each year were conducted by the same physician (the first author).

3. Results

We discovered a total of 138 persons with asymptomatic gallstones (Table 1). The mean age was 55 years (range 21 to 87). With respect to sex and type of gallstones, 51.8% of the men had symptomatic vs. 48.2% asymptomatic gallstones, with no significant differences ($p > 0.05$). However, in the women, 54.8% had symptomatic vs. 45.2% asymptomatic gallstones, with significant differences ($p < 0.05$).

Abdominal ultrasound was the only method of diagnosis. Of the 138 persons with asymptomatic gallstones, we followed the evolution of 109 persons below the age of 70 years. Mean age was 48 years (range 21 to 70), of whom 73 were women with a mean age of 49 years (range 21 to 69), and 36 were men with a mean age of 46 years (range 25 to 70). The frequency of diabetic patients (21 cases) was 19.3%. None of them had sickle cell disease, cirrhosis, colorectal cancer, none had had a transplant nor were on the waiting list for organ transplant.

Table 2
Follow-up of 109 persons with asymptomatic gallstones

Outcome	Men	Women	Total
Biliary pain	3	22	25
Acute cholecystitis	2	1	3
Acute pancreatitis	2	0	2
Obstructive jaundice	1	0	1
Total developing symptoms	8	23	31
Prophylactic cholecystectomy	6	4	10
Death due to nonbiliary causes	5	11	16
Asymptomatic after 18 years	17	35	52
Total	36	73	109

The natural history of asymptomatic gallstones is shown in Table 2. Of the 73 women; 23 (31.5%) developed symptoms, 22 of them had biliary pain (two of them during gestation) and one had cholecystitis. Of the 36 men, 8 (22.2%) developed symptoms; three of them had biliary pain, and 5 had biliary complications - acute

pancreatitis in two, cholecystitis in two, and obstructive jaundice in one. All biliary complications appeared as their initial presentation.

Cholecystectomy was performed on an emergency basis in five of these 31 persons; all five had an uneventful recovery. Of the remaining 26 persons, 24 underwent elective cholecystectomy, usually within a year of an episode of biliary pain; no postoperative complications occurred. The other two persons declined cholecystectomy.

A total of 31 patients (28.4%) developed symptoms at some point during follow-up. The average latency period from the time of discovery of gallstones until the onset of symptoms was 37 months, with a range of 2 to 98 months. One woman had a latency period as short as 2 months: the histologic study of her gallbladder revealed adenocarcinoma and she died five months later. The average age at onset of symptoms was 60 years, with a range of 30 to 73 years.

Patients who remained asymptomatic were only somewhat younger on average than those who developed symptoms (44.9 years vs. 60 years). Women were more likely to become symptomatic than men (23 women vs. 8 men; $P < .05$). However, symptom development in the men was more serious because their initial presentation was biliary complications (acute pancreatitis, obstructive jaundice and acute cholecystitis).

Ten persons underwent prophylactic cholecystectomy on the advice of a personal physician. Three of them had porcelain gallbladder, two patients had diabetes, and two gallbladder polyps larger than 10mm in diameter. Personal interviews and hospital records indicated that gallstone disease had remained asymptomatic during the years from discovery to operation.

Average age at the time of prophylactic cholecystectomy was 64.6 years, ranging from 54 to 74 years. Death due to nonbiliary causes occurred in 16 (14.7%) persons with gallstones not surgically removed. The average age at the time of death was 70 years, ranging from 62 to 83 years.

The remaining 52 persons reported in 2003 that their gallstones had remained asymptomatic for 18 years. The yearly risk of biliary pain appears to decrease with the passage of time (Figure 1).

Body mass index of these 52 persons increased throughout the years to the point of obesity in most cases.

4. Discussion

This study differs from previous follow-up investigation (11) in that our study population was randomly selected and asymptomatic gallstone disease was identified by abdominal ultrasound. Criteria for inclusion included persons <70 years who consented to annual revision until the study end point.

The widely held belief that asymptomatic gallstones commonly cause problems originates from several sources^(3, 5, 12, 13, 14). Other follow-up studies (11) however, indicate a lower incidence of biliary symptoms. Current opinion holds that dyspepsia occurs as often in persons without gallstones as in persons with gallstones and should therefore not be attributed specifically to gallstone disease (10). We excluded dyspepsia secondary to gallstone disease.

Many health problems have been associated with gallbladder disease, including old age, obesity, diabetes mellitus, alcoholism, smoking, and estrogen replacement therapy (15). These situations do lead to greater physician contact and more diagnostic testing. The discovery that 28.4% of the patients became symptomatic is at the high end of the 10% to 33% range reported in series of the general population (1, 14-17) and suggests that patients of the Canary Island (SPAIN) may be somewhat more likely to develop symptoms.

Clinicians also questioned whether there was a typical symptom latency period for these patients. In this series, the average latency period for the 31 cases (28.4%) of the 109 patients who became symptomatic was 37 months, but the range was wide (2 months to 98 months). Even though other studies have suggested that a large number of affected individuals will remain asymptomatic throughout life; only 1-4% per year will develop symptoms or complications of gallstone disease^(16, 18). Only 10% will develop symptoms in the first five years after diagnosis and approximately 20% after 20 years; fewer complications developing in later years than in the early years after gallstone diagnosis (18). Other studies have suggested that most patients who develop symptoms do so within a short period (1).

We had one case of gallbladder carcinoma with latency of 2 months. The literature suggests that carcinoma of the gallbladder is rare enough to warrant no specific follow-up recommendations (1). A few patients with porcelain gallbladder or gallbladder polyps larger than 10mm in diameter and with large gallstones were at high risk of cancer (19, 20) and, hence, prophylactic cholecystectomy was advocated in such patients

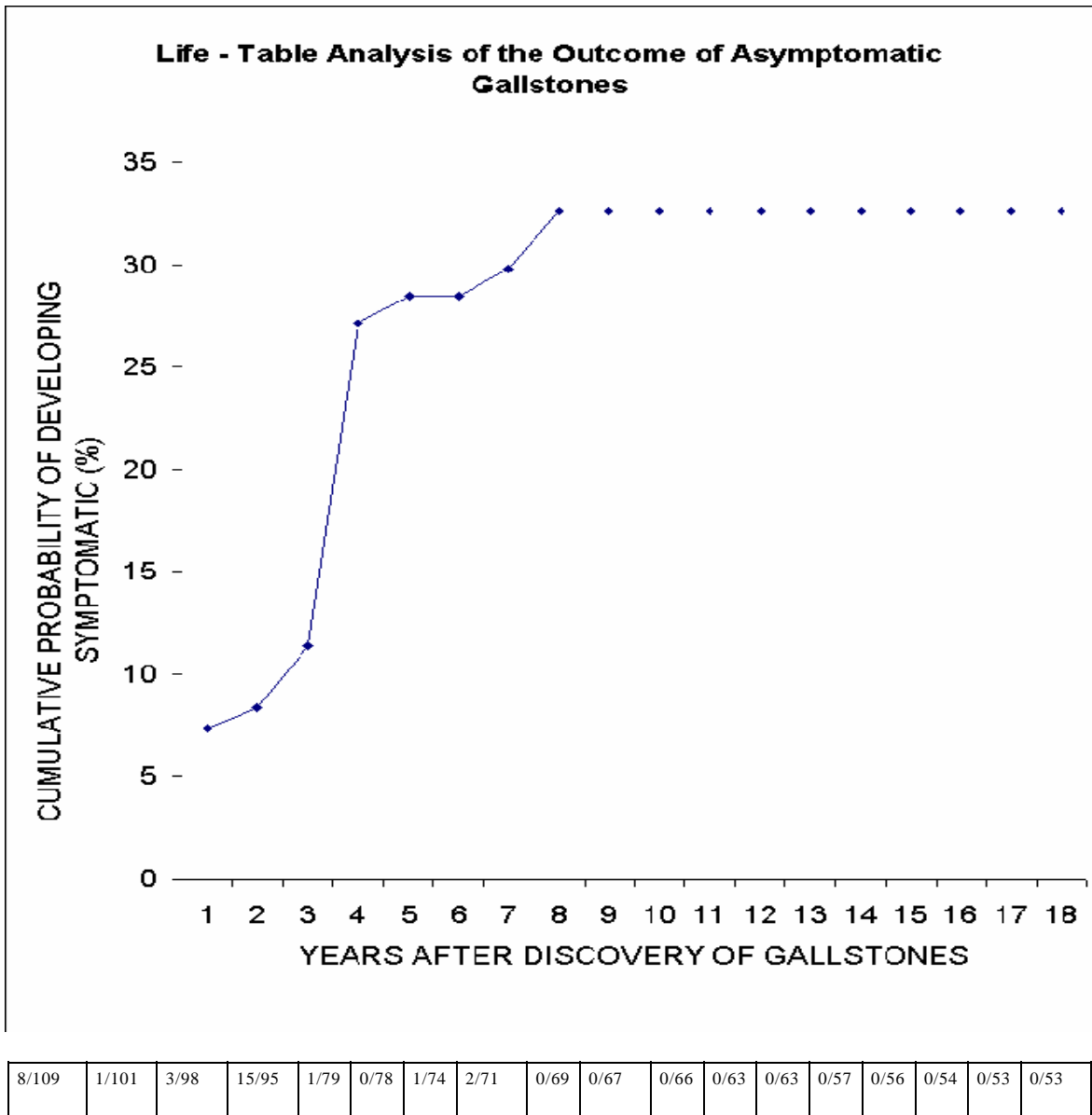


Figure 1 The fractions show the number of people developing symptomatic over the number at risk

in areas where there is a high incidence of gallbladder cancer.

We had 3 cases of acute cholecystitis, of whom only one was diabetic. Other reports found the risk of acute cholecystitis and perioperative morbidity and mortality for treatment of diabetics with acute cholecystitis to be significant enough to warrant the performance of an early cholecystectomy (21-23). Therefore, surgeons were urged to consider diabetics as a high-risk group and prophylactic cholecystectomy was recommended until the natural history of gallstones in diabetics had been better defined (23). Recent evidence, however, has shown that the rates of operative morbidity and mortality for

biliary surgery in diabetics are comparable with rates in non-diabetics (24) Diabetics have an increased morbidity primarily as a result of older age and concomitant medical diseases such as cardiovascular and renal diseases (25). The frequency of asymptomatic gallstones is less common in diabetic than in non-diabetics (26). In this series the frequency of diabetics was only 19.3 %.

In view of this recent evidence adult diabetics with asymptomatic or incidental gallstones should be managed expectantly and preemptive surgery should not be routinely recommended (24). However, early elective laparoscopic

cholecystectomy is advocated once symptoms develop (27).

Ultrasonography has added considerably to our awareness of gallstones in otherwise well patients and has increased the need to understand the natural history of this disease in all populations. Prior knowledge of the presence of gallstones may lead to timely diagnosis and is consistent with other studies that have found no significant difference between elective and emergency surgery (28). The risk of treatment can, on occasion, exceed the risk of waiting, especially for conditions that require invasive surgical procedures (29). This article describes a longitudinal attempt to understand our patient population relative to published data. The similarity of results increases the confidence with which physicians can recommend watchful waiting to the asymptomatic patient.

Why gallstones produce pain or complications in some persons and not in others is unknown (30). Do characteristics of the gallstones or of the biliary tree have predictive value? Do demographic characteristics affect prognosis? Additional cohort studies are needed to answer these important questions.

We believe that routine prophylactic operation for asymptomatic gallstone disease, is neither necessary nor advisable.

5. Conclusion

The management of most patients with asymptomatic gallstones should be expectant, although it is still a controversial issue. In the era of laparoscopic cholecystectomy, although most of the guidelines for surgery are the same as they were in the prelaparoscopic era, a consensus appears to be emerging regarding laparoscopic cholecystectomy in selected groups of patients with asymptomatic gallstones. Laparoscopic cholecystectomy is recommended for asymptomatic gallstones in areas where gallbladder cancer is prevalent and in patients with porcelain gallbladders due to its association with cancer. The indication for surgery remains an individual decision.

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