Pigment vs Cholesterol Cholelithiasis: Clinical and Epidemiological Aspects

Bruce W. Trotman, MD, and Roger D. Soloway, MD

This prospective study demonstrated that among 92 consecutive patients who underwent cholecystectomy for gallstones at an urban university hospital, 27% had pigment stones and 73% had cholesterol stones. Age, sex, and weight, but not race, were significant determinants of stone type. The mean hemoglobin, direct and total serum bilirubin, and fasting glucose concentrations were similar for each group. The presence of alcoholism, diabetes, thyroid disease, or heterozygous hemoglobinopathy did not influence stone type. The average patient with pigment stones is a lean man or woman 63 years old; in contrast, the composite patient with cholesterol stones is a modestly overweight woman 43 years old.

Previous studies on the incidence of gallstones in an American population have relied primarily upon autopsy data and infrequently have distinguished pigment from cholesterol stones (1–5). We recently reported that pigment and cholesterol gallstones differed markedly in appearance and composition (6). Typical pigment stones were black to brown and on cross section were amorphous; cholesterol stones were yellow to light tan and on cross section were crystalline and usually laminated. All stones within a given gallbladder were of a single type but two patients had stones clearly composed of two distinct layers and these were classified by the predominant component. Chemical analysis of 22 pigment and 31 cholesterol stones verified the accuracy of classifying stones by inspection (6). Pigment stones were characterized by significantly increased percent by dry weight of bile salts, bilirubin, and residue (insoluble material). Cholesterol content of pigment stones was minimal, but was the major component of cholesterol stones (6).

Biles surrounding pigment stones differed significantly from those surrounding cholesterol stones in the mean cholesterol content and the molar lipid ratio of bile salts and phospholipids to cholesterol; the mean percentages of bile salts, phospholipids, and total bilirubin were similar for the two groups (6). Thus, the abnormality leading to cholesterol stone formation was related directly to bile cholesterol content; but the pathogenesis of pigment stones remained unclear, involving mechanisms other than cholesterol precipitation. Consequently, in the present study we sought to assess prospectively the influence of clinical and biochemical characteristics on the type of stone found in patients undergoing cholecystectomy for symptomatic cholelithiasis.

MATERIALS AND METHODS

Patients and Methods

All patients who underwent cholecystectomy for symptomatic cholelithiasis from September 1, 1972, through March 6, 1973, at the Hospital of the University of Pennsylvania agreed to take part in the study. Gallstones ob-

From the Gastrointestinal Section, Department of Medicine, Hospital of the University of Pennsylvania and School of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania.

Supported in part by NIH grants AM-14543 and AM-05462. Dr. Trotman is currently a recipient of a Macy Foundation Faculty Fellowship.

Address for reprint requests: Dr. Bruce W. Trotman, Gastrointestinal Section, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

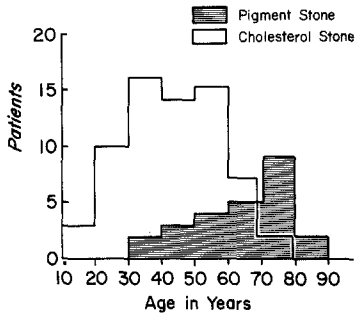

Fig 1. Incidence of pigment or cholesterol gallstones according to age of patients at cholecystectomy. The distribution shows two populations with a peak incidence of cholesterol stones in the fourth decade and pigment stones in the eighth decade.

tained at cholecystectomy were visually classified as pigment or cholesterol prior to analysis.

Age, race, and sex of each patient were recorded. Analysis of the cholecystectomized group provided relative information about the influence of age, race, or sex on stone type. To estimate the actual influence of these factors on stone type, cholecystectomized subjects were compared to a control population of noncholecystectomized patients admitted primarily for general medical and surgical services over the same interval. Age and sex bias within the control group was minimized by excluding those admitted for obstetric, anesthesia, psychiatric, pediatric, bronchologic, and oral surgical services.

Patients with pigment or cholesterol stones were compared in terms of height, actual and ideal weight and surface area, hemoglobin concentration, direct and total serum bilirubin, and fasting blood glucose values. The ideal weight was obtained from tables based on sex, height, and age (7). Ideal surface area was obtained from a nomogram based on height and ideal weight (8). Hemoglobin (normal range: males 14.0–18.0, females 12.0–16.0 g/100 ml), bilirubin (normal range: direct 0.02–0.20, total 0.7–1.0 mg/100 ml), and fasting blood glucose (normal range: 70–110 mg/100 ml) were performed in the hospital laboratories using standard techniques. Black patients were evaluated for the presence of abnormal hemoglobins by hemoglobin electrophoresis.

Statistics

Results were evaluated by Student's t test and expressed as means ± SD. The distribution of patients was analyzed by the χ^2 test (9). A PDP-8 computer was used to retrieve and tabulate the data. Age was tabulated by decade of birth: those born before 1920 were $\geq$ 54 years and after 1920 were $\leq$ 53 years.

RESULTS

Age, Race, and Sex

Over the 6-month period, 94 patients underwent cholecystectomy for symptomatic gallstones. Of this group, 92 stone specimens were classified: 25 (27%) as pigment and 67 (73%) as cholesterol stones. When distributed by age, patients with pigment or cholesterol stones formed two populations (Figure 1). The incidence of cholesterol stones found at cholecystectomy peaked in the fourth decade; whereas the incidence of pigment stones peaked in the eighth decade. By the eighth decade, patients with pigment stones were more common than those with cholesterol stones. Sex, but not race, was a significant determinant of stone type.

Table 1. Effect of Age, Race, and Sex on the Incidence of Patients with Symptomatic Pigment (PS) or Cholesterol (CS) Gallstones Compared to Noncholecystectomized (NC) Subjects

	Age		Race		Sex	
	≤53 yr	≥54 yr	Black	White	Men	Women
PS	6(24)*	19(76)	7(28)	18(72)	10(40)	15(60)
CS	49(73)	18(27)	28(42)	39(58)	14(21)	53(79)
NC	4960(60)	3263(40)	2968(36)	5225(64)	3144(38)	5079(62)
χ^2_2	18.5		1.73		7.6	
P	<0.005		NS		< 0.025	

*Numbers in parentheses indicate percent of total patients read horizontally, grouped by age, race, or sex.

Table 2. Clinical and Biochemical Indices of Patients with Symptomatic Gallstones

Index	Pigment gallstones			Significance (pigment vs cholesterol)	Cholesterol gallstones		
	N	Mean ± SD	Range		*N**	Mean ± SD	Range
Height	25	64.7 ± 3.8	56.5-72.0	NS	66	64.9 ± 3.3	59.0-72.0
Weight (lb)	25	143 ± 31	92.0-232	$P < 0.05$	66	159 ± 41	89.0-291
% Ideal weight	25	96.1 ± 18	75.0-154	$P < 0.005$	66	112 ± 28	76.0-225
Surface area (m^2)	25	1.70 ± 0.2	1.33-2.1	NS	66	1.78 ± 0.2	1.30-2.30
% Ideal surface area	25	97.7 ± 7.5	88.0-120	$P < 0.005$	66	104 ± 11	90.0-127
Hemoglobin (g/100 ml)	25	13.1 ± 2.0	8.10-17.0	NS	66	13.3 ± 1.5	8.20-16.8
Direct (conjugated) bilirubin (mg/100 ml)	22	0.33 ± 0.9	0.02-3.60	NS	49	0.16 ± 0.4	0.02-2.60
Total bilirubin (mg/100 ml)	22	0.98 ± 1.7	0.11-7.01	NS	49	0.67 ± 0.8	0.08-4.84
Fasting blood glucose (mg/100 ml)	24	104 ± 28	75.0-220	NS	66	104 ± 23	50.0-200

*Clinical data for 1 patient were not available.

When cholecystectomized subjects were compared to the control population, age and sex, but not race, remained significant determinants of stone type, indicating that these determinants were associated with the presence of stones and were not functions of the frequency of patient admissions (Table 1). Thus, pigment stones occurred with equal frequency in men and women, but were more common in patients over rather than under age 53 (63 ± 14 years, mean ± SD). In contrast, cholesterol stones occurred twice as frequently in women as in men and more commonly in those under rather than over age 53 (43 ± 14 years, mean ± SD).

Height, Weight, and Surface Area

The mean heights and actual surface areas of patients with pigment or cholesterol stones were similar (Table 2). However, patients with cholesterol stones weighed significantly more than those with pigment stones whether expressed as actual or ideal weight. 17 subjects with pigment stones weighed less than and 8 weighed more than 100% of their ideal weight; but 27 patients with cholesterol stones weighed less than and 39 weighed more than 100% of their ideal weight ($\chi_1^2 = 5.52$, $P < 0.02$).

Clinical and Biochemical

The incidence of diabetes diagnosed prior to admission was 8%; of thyroid disease, 3%; and of alcoholism, 4%. No differences between the two groups with stones were detected for these conditions.

Hemoglobin, bilirubin, and blood glucose values are shown in Table 2. The average blood hemoglobin concentration was similar for both groups; also, the incidence of patients with hemoglobin levels below 12.0 g/100 ml was 20% for pigment and 15% for cholesterol stone patients. Direct and total serum bilirubin concentrations were similar for both groups, as was the proportion of patients (11%) with elevation of total serum bilirubin. Hyperbilirubinemia, when present, consisted of elevations of both unconjugated and conjugated fractions and usually was associated with surgical evidence of common duct stones. The mean fasting blood glucose concentration was similar for the two groups; a value of greater than 110

mg/100 ml was obtained in 21% of pigment and 24% of cholesterol stone patients. Serum calcium and cholesterol determinations were obtained so infrequently that meaningful comparisons could not be made.

Heterozygous Hemoglobinopathy

Of 50 black patients with stones (including 15 from two other hospitals), 34 had hemoglobin electrophoretic patterns determined: 26 with cholesterol stones and 8 with pigment stones. The 34 black subjects had the same proportion of pigment and cholesterol stones as white patients ($\chi_1^2 = 1.94$, $P > 0.1$). 3 of 8 subjects with pigment stones had sickle-cell trait while 3 of 26 with cholesterol stones had hemoglobin AC, AS, and SC, respectively ($\chi_1^2 = 0.95$, $P > 0.1$). Thus, among black patients with gallstones, heterozygous hemoglobinopathy did not influence stone type. However, the small number of black patients with hemoglobinopathy in this study does not allow a definitive answer to this question.

DISCUSSION

Incidence

This study demonstrated that pigment stones accounted for 27% of gallstone specimens among consecutive patients who underwent cholecystectomy for symptomatic cholelithiasis in an urban U.S. medical center. Such a high percentage of patients with pigment stones was not anticipated since it is accepted (but not documented in the U.S.) that cholesterol stones account for about 90% of the stones found in cholecystectomized patients in Western countries (10).

The only comparable study of gallbladder disease in Americans undergoing cholecystectomy for stones was the Framingham study (11). In that study, 33% of the patients had pigment and 67% had cholesterol stones as determined by description in pathology reports (11). The similar percentages of pigment and cholesterol stones removed at surgery in the present report and in the Framingham study suggest a higher incidence of pigment stones in Americans undergoing cholecystectomy than has been appreciated.

Race, Sex, and Age

Prior studies, mainly autopsy series, showed that blacks had cholelithiasis less frequently than whites (2, 4, 5), but such reports may be questioned because they reflected admission policy and autopsy selectivity. In the present study, race was not a significant determinant of stone type. Furthermore, since white and black Americans account for 98% of the U.S. population (12) and represented 62% and 38%, respectively, of the subjects in this study, it is suggested that pigment lithiasis is a significant cause of gallbladder disease in the general American population.

The predilection for women to develop cholesterol stones more frequently than men was documented previously (13). Femininity and parity were suggested as predisposing factors in the formation of cholesterol stones (14), and the present report supports this contention. Pigment lithiasis, however, affected men and women equally, suggesting that the underlying factors responsible for pigment lithiasis are unrelated to sex hormones.

The mean ages of pigment and cholesterol stone populations at cholecystectomy were markedly different. The age difference could reflect the association of cholesterol stones with the child-bearing period or the relative clinical quiescence of pigment stones. Alternatively, pigment stones may form later in life. The precise time of stone formation cannot be determined in this group of patients.

Height, Weight, and Surface Area

Although the mean heights were similar for the two groups, patients with cholesterol stones weighed significantly more than patients with pigment stones. Other studies have suggested that patients with cholesterol stones were more

obese than controls (15). A recent study suggested a causal role for obesity in the pathogenesis of cholesterol cholelithiasis by demonstrating that obese females secreted more cholesterol into their bile than controls (15). However, the majority of patients with cholesterol gallstones in this series were distributed within 20% of ideal weight, precluding obesity as a singular cause in most cases. The pathogenetic significance of less than ideal weight in the majority of these patients with pigment stones is unclear.

Clinical and Biochemical Parameters

Since the incidence of diabetes, thyroid disease, and alcoholism within the two groups was similar, these disorders do not predispose to either cholesterol or pigment gallstone formation.

The similar levels of hemoglobin and conjugated and total bilirubin in pigment and cholesterol stone patients do not support the thesis that overt hemolysis is necessary for the development of pigment stones. Furthermore, the presence of heterozygous hemoglobinopathy in black patients did not predispose to pigment stone formation. The significantly increased incidence of pigment stones found in cholecystectomized patients without overt hemolysis raises doubts concerning the classic view that pigment stones are associated primarily with hemolytic disorders (16) and alcoholic cirrhosis (17).

Although bilirubin extracted from pigment stones was > 95% unconjugated (6), the mechanism whereby it is incorporated into stone is unknown. Hydrolysis of conjugated bilirubin by bacterial β-glucuronidase has been postulated as the pathogenesis of bile pigment calcium stones found in Japanese subjects (18). The etiological role of bacterial infection in pigment stone formation in American patients was questioned by a recent report which demonstrated no significant association between bacterial infection and excessive hydrolysis of conjugated bilirubin in surgically obtained gallbladder biles incubated *in vitro* (19). Furthermore, the same report suggested that hydrolysis of conjugated bilirubin in bile may be intermittent or that other mechanisms may engender pigment stone formation.

This present prospective study confirms that femininity and obesity are strongly associated with cholesterol stone formation presumably due to excess cholesterol in bile which eventuates in cholecystectomy at a mean age of 43 years. In contrast, the significance of lean body weight, lack of sex predominance, and advanced age at the time of cholecystectomy in patients with pigment stones is unclear.

ACKNOWLEDGMENTS

The authors are grateful to Mr. Charles Hayward of the Hospital's Data Processing Center and Mr. Michael Lee of the Medical School Computer Facility (supported by NIH grant RR-1512) for retrieving and tabulating patient data, to Dr. J. Donald Ostrow for his many helpful suggestions, and to Mrs. Christine Dauber for secretarial assistance.

REFERENCES

1. Ludlow AI: Autopsy incidence of cholelithiasis. Am J Med Sci 193:481–482, 1937
2. Jaffe RH: Cholelithiasis: Statistical study with special reference to its frequency in colored race. J Lab Clin Med 18:1220–1226, 1933
3. Lieber MM: The incidence of gallstones and their correlation with other diseases. Ann Surg 135:394–405, 1952
4. Cunningham JA, Hardenburg FE: Comparative incidence of cholelithiasis in the Negro and white races. Arch Int Med 97:68–72, 1956
5. Kozoll OD, Dwyer G, Meyer KA: Pathologic correlation of gallstones. A review of 1874 autopsies of patients with gallstones. Arch Surg 79:514–536, 1959
6. Trotman BW, Ostrow JD, Soloway RD: Pigment vs cholesterol cholelithiasis: Comparison of stone and bile composition. Am J Dig Dis 19:585–590, 1974
7. Boothby WM, Berkson J: Food nomogram, MC-702. Mayo Association, Mayo Clinic, Rochester, Minnesota, 1959
8. Metropolitan Life Insurance Bulletin 40: New Weight standards for men and women. New York, November–December, 1959

9. Croxton E: Elementary Statistics with Application in Medicine and the Biological Sciences. New York, Dover Publications Inc., 1959, Chapters 9, 11
10. van der Linden W, Nakayama F: Gallstone disease in Sweden versus Japan. Clinical and etiological aspects. Am J Surg 125:267–272, 1973
11. Friedman GD, Kannel WB, Dawler TR: The epidemiology of gallbladder disease: observations in the Framingham study. J Chronic Dis 19:273–292, 1966
12. U.S. Bureau of the Census: Statistical abstract of the United States: 1973 (94th ed), Washington, D.C., 1973
13. Heaton KW: The epidemiology of gallstones and suggested aetiology. Clin Gastroenterol 2:67–83, 1973
14. Glenn F, McSherry CK: Gallstones and pregnancy among 300 young women treated by cholecystectomy. Surg Gynecol Obstet 127: 1067–1072, 1968
15. Grundy SM, Duane WC, Adler RD, Aron JM, Metzger AL: Biliary lipid outputs in young women with cholesterol gallstones. Metabolism 23:67–74, 1974
16. Hauter A, Wintrobe MM: Hemolytic anemias. Harrison's Principles of Internal Medicine, 7th ed, MM Wintrobe, GW Thorn, RD Adams, E Baunwald, KJ Isselbacher, and PG Petersdorf (eds), New York, McGraw-Hill, Inc., 1974, p 1597
17. Nicholas P, Rinaudo PA, Conn HO: Increased incidence of cholelithiasis in Laennec's cirrhosis. A post mortem evaluation of pathogenesis. Gastroenterology 63:112–121, 1972
18. Maki T: Pathogenesis of calcium bilirubinate gallstones. Ann Surg 164:90–100, 1966
19. Boonyapisit ST, Trotman BW, Ostrow JD: Unconjugated bilirubin (UCB) and hydrolysis of conjugated bilirubin (CB) in gallbladder bile of patients with pigment or cholesterol gallstones. Gastroenterology 67:781, 1974 (Abstract)