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Epidemiology of gallbladder stone disease

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Gallstone disease is common: >700,000 cholecystectomies and costs of ~$6.5 billion annually in the U.S. The burden of disease is epidemic in American Indians (60–70%); a corresponding decrease occurs in Hispanics of mixed Indian origin. Ten to fifteen per cent of white adults in developed countries harbour gallstones. Frequency is further reduced in Black Americans, East Asia and sub-Saharan Africa. In developed countries, cholesterol gallstones predominate; 15% are black pigment. East Asians develop brown pigment stones in bile ducts, associated with biliary infection or parasites, or in intrahepatic ducts (hepatolithiasis). Certain risk factors for gallstones are immutable: female gender, increasing age and ethnicity/family (genetic traits). Others are modifiable: obesity, the metabolic syndrome, rapid weight loss, certain diseases (cirrhosis, Crohn's disease) and gallbladder stasis (from spinal cord injury or drugs like somatostatin). The only established dietary risk is a high caloric intake. Protective factors include diets containing fibre, vegetable protein, nuts, calcium, vitamin C, coffee and alcohol, plus physical activity.

Key words: epidemiology; gallbladder disease; cholesterol gallstones; pigment stones; brown pigment stones; obesity; metabolic syndrome; weight loss; diet.

THE IMPORTANCE OF GALLSTONE DISEASE AND THE IMPACT OF ETHNICITY

Gallstones have been recognized since antiquity, being identified in autopsy studies of Egyptian mummies. Today, gallbladder disease is a frequent problem in developed countries, representing a major health burden.[1] An estimated 20–25 million adults in the U.S. are afflicted with gallstones, the most common cause of biliary tract disease in this age group. Gallstone disease is the leading cause of inpatient admissions for gastrointestinal problems.[2] Population-based statistics, based on a comprehensive survey in the U.S., shows that 262,411 hospitalizations occurred in 2000 for cholecystitis,

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while there were an estimated 778,632 outpatient visits. Each admission costs $11,584. Fortunately, cholecystitis has a relatively low mortality at 0.6%. The incidence (yearly frequency) of hospital admissions and operations for cholelithiasis has increased in developed countries since the 1950s.[3,4] The number of cholecystectomies in those times was six times higher in North America than in western Europe. The advent of laparoscopic cholecystectomy in 1989 created a further increase in gallbladder surgeries in the U.S. and the U.K.[5,6] In fact, the prevalence of gallstone disease in a population appears to have little influence on the incidence of gallbladder surgery.[7] Such variances might reflect an increased incidence of cholelithiasis, an increased frequency for gallstones to become symptomatic, improved diagnostic expertise (i.e., more readily available ultrasonography) or a lowered clinical threshold for surgery. Conversely, this could imply that therapeutic usefulness has been exceeded and eventually may lead to an excessive health-care burden and associated morbidity/mortality. The cholecystectomy rate, though increased, appears to have stabilized in the latter part of the 1990s following the introduction of the laparoscopic technique[8] and may even be on the decline in the U.S.[9]

The burden of gallstone disease in the U.S. afflicts some 6.3 million men and 14.2 million women aged 20–74 years,[10] making it a most costly digestive disorder at an estimated $6.5 billion annually.[11] Gallstone disease in Europe is similar to the U.S., with a median prevalence in large population surveys, ranging from 5.9 to 21.9%.[8]

The true prevalence (the number of individuals with gallstones at any point in time) has come from non-invasive and safe ultrasonography studies in defined population surveys. (see Table 1). This eliminates the bias of earlier reports: necropsy implies death and clinical diagnosis requires symptoms (of which only 20% ever develop[12]). The highest prevalence of cholelithiasis occurs in North American Indians, reaching 73% of female Pima Indians over the age of 30 years[13] and also Chippewa Indians,[14] Canadian Micmac Indians[15] and 13 American Indian tribes or communities in Arizona, Oklahoma and the Dakotas.[16] In the latter study, the overall prevalence of gallbladder disease was 64.1% in women and 29.5% in men. The Indians of South America have a similar high prevalence of gallbladder disease. In Chile, the native Mapuche Indians demonstrate a high occurrence of gallbladder disease; 49.4% in women and 12.6% in men (>60% amongst women in their fifties).[17,18] The frequency is lower in Chilean Hispanics with a lesser American Indian admixture: 36.7% of women and 13.1% in men. The prevalence of gallstones in Mexican Americans is also a direct function of the degree of Amerindian admixture.[19,20,21] White Americans have a somewhat lower prevalence: 16.6% of women and 7.9% of men.[10] Superlative ultrasound-based surveys in Europe have revealed that higher overall prevalences occur in Norway (21.9%) and the former East Germany (19.7%), whereas lower rates are evident in Italy (Sirmione 6.2% and Chlanciano 5.9%).[8] (Table 1) A fine example is the Multicentre Italian Study of Cholelithiasis (MICOL) that examined 29,739 subjects aged 30–69 years in 16 cohorts in 10 Italian regions.[22] Overall, gallstone disease was present in 18.8% of women and 9.5% of men. Similar results came from the Sirmione study of 19,030 Italians between the ages of 18 and 65 years, yielding a total prevalence of 11%.[23]

Intermediate prevalence rates occur in Asian populations (~5–20%; see Table 1) and Black Americans (13.9% of women and 13.9% of men). The lowest frequencies are in Black Africans (<5%), the best studied being the Masi tribe and the Bantu, in whom the entity is virtually non-existent.[24,25]

Ethnicity also determines the type of stone and where they reside in the biliary system. In developed countries, the majority (about 80–85%) consists predominantly of cholesterol crystals, while the remainder are of black pigment (calcium bilirubinate and mucin glycoproteins). Cholesterol and black pigment stones form in the gallbladder. When they cause symptoms, some 10% secondarily migrate from the gallbladder into the bile ducts. Brown pigment stones consist of calcium bilirubinate, calcium soaps (palmitate and stearate), mucin (predominantly from the biofilm of bacteria) and some cholesterol. Soft and greasy, they develop in bile ducts, usually in association with infection (partial biliary obstruction), but also from biliary tract infestation (from parasites like *Clinorchus sinensis*, *Opistochus vivarini*, or *Ascaris*). Brown pigment stones are the predominant type in East Asia, and may account in part for the high prevalence there of hepatolithiasis in the intrahepatic bile ducts.[26,27] In hepatolithiasis, stones are present in all bile ducts peripheral to the junction of the right and left hepatic ducts, regardless of the co-existence of stones elsewhere in the biliary system: the extrahepatic ducts and/or the gallbladder. These intrahepatic brown pigment stones have higher cholesterol content and less bilirubin than when extrahepatic, presumably due to a different basis for their formation.[27] The frequency of hepatolithiasis, as a proportion of all biliary tract stones, varies from a high of 20% in China[28] and Taiwan[29] to 2—3% in Japan, Singapore and Hong Kong.[27,28]

Such ethnic differences in the frequency of gallstones worldwide and the different stones that develop likely reflect a combination of phenotypic expression of genetic traits, predisposing to stone formation,[30,31] but elicited by exogenous and dietary factors. In fact, there is a decreasing prevalence of intrahepatic brown pigment stones in Asia, perhaps related to multiple factors including the eradication of parasites and westernization of the diet.[32—35] Conversely, marked gene defects occasionally can cause intrahepatic and gallbladder cholesterol stones in developed countries,[36] while genetic alterations and protein expression may be involved in primary intrahepatic cholelithiasis (hepatolithiasis), which is endemic in East Asia.[37]

RISK FACTORS

Gallstone formation is clearly multifactorial. For any individual, some risk factors are unalterable, such as advancing age, being female and genes/ethnicity. Other factors can be modified, such as obesity, rapid weight loss, diet, drugs and activity. Case-controlled studies (comparing those with versus those without gallstones) have identified associations between key demographic characteristics and the risk of having gallstones. Even when controlled for immutable risk factors (particularly age and sex), many of these epidemiological studies are confounded by inadequate sample size or selection bias.[38] A small sample size is open to a beta-II type error: i.e., failure to identify a true difference (false negative). Selection bias can create false differences (false positive results). More reliable studies employ screening of asymptomatic populations. Further, geographic/ethnic differences exist relative to stone type: cholesterol gallstones predominating in the Western world whereas pigment stones are more common in Asia.

Age

Gallstones are uncommon in infants and children, arising occasionally as pigment stones in a setting of hemolysis.[39] Reports of increased cholecystectomies in this age group relate mainly to girls over 16 years, being obese and/or having a Mexican—American origin.[40] Young Pima Indian women in the Southwestern United States demonstrate a spectacular increase in gallstones (usually asymptomatic) after 20 years of age, exceeding a 70% prevalence by age 30; the men have a slower rise, later in

Table 1. Prevalence of gallstones and gallbladder disease (cholecystectoly) in sonographic and ultrasound surveys[a].

Geographic population	Prevalence (%)[b]			Age range (years)	Number studied	Study	Year
	Male	Female	Total				
The Americas							
N. America							
Canada							
Montreal	65.9	51.4	61.5	55–95	117	Ratner et al[113,e]	1991
United States							
American Indians –13 tribes	29.5	64.1		47	3296	Everhart et al[16]	2002
Mexican American	8.9	26.7		20–74	4174	Everhart et al[10]	1999
Starr County, Texas	8	20.2	17.9	15–74	1004	Hanis et al[114]	1990
Hispanic	5.4	19.1	13.3	20–74	2320	Maurer et al[20]	1982
NHANES III, US (overall)	7.9	16.6	14.3	20–74	13374	Everhart et al[10]	1999
White (non-Hispanic)	8.6	16.6		20–74	5257	Everhart et al[10]	1999
Black American	5.3	13.9		20–74	4212	Everhart et al[10]	1999
S. America							
Chile							
Malpuche Indians	12.6	49.4	35.2	20–>50	182	Miquel[18]	1998
Santiago (Hispanics only)	14.5	37.4	28.5	>20	1811	Covarrubias et al[115]	1995
Hispanics	13.1	36.7	27.5	20–>50	1584	Miquel[18]	1998
Peru							
Lima, Peru	16.1	10.7	14.3	>15	1534	Moro et al[116]	2000
Easter Island							
Maoris	8.3	29.4	21.6	20–>50	225	Miquel[18]	1998
Europe							
Scandinavia							
Gothenburg, Sweden		50.5	50.5	77–78	109	Mellstrom et al[117]	1988
Malmo, Sweden		18.2–23.1	21.7	48–53	424	Janzon et al[118]	1985
Stockholm, Sweden	(4–15)	(11–25)	15	40–60	556	Muhrbeck and Ahlberg[119]	1995

Bergen, Norway	(4.9–37.0) 17.7[c]	(6.0–41.3) 21.2[c]	21.9	20–70	1371	Glambek et al[120]	1993
Copenhagen, Denmark	(1.8–12.9)	(4.8–22.4)	8.8	30–60	3608	Jorgensen[57]	1987
Copenhagen, Denmark	18.8	30.2	24	>70	374	Jorgensen et al[121]	1990
Italy							
Padua, Italy	17	35	26.8	>60	1065	Lirussi et al[122]	1995
Silicy, Italy			18.6	>65	328	Montalto et al[123]	1991
Sezze and Rome, Italy		(2.2–27.5)	17	20–69	399	DISCO and GREPCO[124]	1987
Italy (10 regions)	(2.3–19.4)	(7.4–31.6)	13.8	30–69	29739	Attili et al (MICOL)[22]	1984
Padua, Italy	6.2	14.7	10.5	30–64	2530	Okolicsanyi et al[125]	1995
Castellana, Italy	(1.5–10.7)	(4.5–19.6)	9.2	30–69	2461	Misciagna et al[126]	1994
Sirmione, Italy	6.7 (1.1–11.0)	14.4 (2.9–27.0)	6.9	18–65	1911	Barbara et al[23]	1987
Rural pop, central Italy		6.3		20–69	426	Angelico et al (GREPCO)[127]	1997
Rome, Italy	8.2 (2.3–14.4)			20–69		GREPCO[43]	1988
Chianciano, Italy	(0–16.6)	(0–24.5)	5.9	15–65	1804	Loria et al[128]	1994
Bari, Italy	0	0.3	0.1	6 to 19	1570	Palasciano et al[129]	1989
Other European countries							
Oberperfuss, Austria	16.4	32.6	25.5	55–69	153	Rhomberg et al[130]	1984
Schwedt, Germany	(0–36.2)	(0–63.6)	19.7	20–70	3226	Berndt et al[131]	1989
Szczecin, Poland		19.5	19.5	20–70	1314	Marlicz et al[132]	1988
Oxford, England		21.7	21.7	40–69	762	Pixley et al[133]	1985
Bristol, England	(4.7–11.5)	(3.9–22.4)	7.5	25–69	1896	Heaton et al[134]	1991
Vidauban, France	12.5	17.8	15.7	>30	831	Caroli-Bosc et al[135]	1996
Timisoara, Romania	6.1	12.8	10.9	>20	1323	Sporea et al[136]	1993
Asia							
Chandigarh, India	6.2[d]	21.6[d]	15.6[d]	>15	248	Singh et al[137]	2001
Srinagar, Kashmir (India)	3.1(0–8.1)	9.6 (2.0–29.1)	6.1	15–65	1104	Khuroo et al[138]	1989
Taipei, Taiwan	10.7	11.5	10.7	>20	3647	Chen CY[41]	1998
Chiayi (Taiwan)	4.5	4.6	4.6	30–70	923	Lu et al[139]	1990

(*continued on next page*)

Table 1 (*continued*).

Geographic population	Prevalence (%)[b]			Age range (years)	Number studied	Study	Year
	Male	Female	Total				
Jiaotong (China)	2.3	4.7	3.5	7–70	15856	Zhao et al[140]	1990
Okinawa (Japan)	2.4	4	3.2	0–75	2584	Nomura et al[141]	1988
Chiang Mai (Thailand)	2.5	3.7	3.1	20–70	6146	Prathnadi et al[142]	1992
Africa							
Soweta (South Africa)	0	10	10	55–85	100	Walker et al[143]	1989
Khartoum (Sudan)	5.6	5.1	5.2	22–70	252	Bagi Abdel et al[144]	1991

[a] For previous reports see: Kraztzer W et al. *J Clin Ultrasound* 1999; **27:** 1–7,[112] Alcalovschi M et al. *Postgrad Med J* 2001; **77:** 221–229,[38] and Shaffer E. Current Gastroenterology Reports 2005; **7:** 132–140.[1]

[b] Any range given represents the age differrences:(young to older). The overall average follows.

[c] Age-adjusted prevalence.

[d] Calculated from sum of cholecystectomies + stones detected on ultrasound.

[e] For very old, institutianized people.

life.[13] The risk of gallstones increases with age in all ethnic groups (See Table 1).[41] For example, in Italian surveys, gallstone/gallbladder disease can be found in 5–8% of young women but then increases to 25–30% in women above 50 years.[23] In later years, stones generally tend to be composed of pigment material rather than cholesterol despite findings that age may correlate positively with an increased cholesterol secretion and saturation.[42]

Gender, parity and female sex hormones

Gender is a prominent risk factor: women have a greater risk of gallstone disease (and undergoing cholecystectomy) than men at all ages and in the majority of studies. (Table 1) Women predominate, particularly when young (20–30 years of age), with a range of female-to-male ratio from 10:1 in Pima Indians to 2–3:1 in Europeans women; this ratio declines after the fifth decade.[13,43] The difference between the sexes narrows with increasing age, particularly after the menopause. Female predominance is evident in the Americas and Western Europe, presumably linked to the basis for cholesterol gallstone formation, but becomes less pronounced in Asia where pigment stones are more common (Table 1).

Female sex hormones are the obvious basis for this gender difference. It is therefore not surprising to find that parity is a risk factor.[44] During pregnancy, biliary sludge (consisting of cholesterol crystals, calcium bilirubinate and mucin) develops in up to 30%,[45] while gallstones form in 1–3%.[46] The link may be biliary sludge, a potential precursor to cholesterol gallstone formation. Following delivery, sludge disappears in over half, even as 30% of small stones ($<$10 mm diameter) vanish.[45] Such a return to normal, likely accounts for parity being only a modest risk factor.

Estrogen is the culprit.[47] The current use of low-dose (compared to high-dose $>$50 μg) oral contraceptives presents quite a modest risk that may even decrease with time.[48] In contrast, postmenopausal women on oestrogen replacement therapy have a definitely increased risk.[49]

Obesity, diabetes mellitus, the metabolic syndrome and rapid weight loss

Overweight and obesity are best defined by the body mass index (BMI): the body weight (in kg) divided by the square of the height (in meters).[50,51] A normal weight is a BMI of less than 25 kg/m^2. Overweight is a BMI from 25 to 30 kg/m^2, whereas obesity implies a BMI that exceeds 30 kg/m^2. Obesity may be further classified as: class I [BMI 30–34.9 kg/m^2], (severe) obesity class II [BMI 35–39.2 kg/m^2] and (extreme) obesity class III [BMI over 40 or a BMI $>$ 35 kg/m^2 with co-morbid condition like diabetes and cardiovascular disease]. In the U.S., over 60% of adults are overweight, 30% obese, while 4.7% extremely obese (BMI $\geq$ 40 kg/m^2, or in previous terms $>$170% above their ideal body weight or $>$100 lb overweight).[52,53] Obesity is an increasing health hazard that is rising to epidemic proportions in the U.S.[54] Obesity is a well-established, major risk factor for developing gallstones,[55] the basis being an increased hepatic secretion of cholesterol.[56] The risk is particularly high in women[43,57] and rises linearly with increasing obesity.[58] Women with extreme obesity can expect a sevenfold increase in their risk compared to those at a normal weight, yielding up to a 2% annual incidence of their developing gallstones. The risk is especially high if obesity onsets in youth (late teens) and continues. In men, obesity per se is a weaker risk.[59] Rather gallstone disease is more closely related to abdominal (central) obesity, diabetes mellitus and insulin resistance.[60–62]

Diabetes mellitus may be linked to gallstone formation,[33,61] but the apparent relation is frequently confounded by co-factors like age, body mass index and a family history of gallstone disease.[63] Further, there is no obvious biological basis for cholesterol gallstone formation. Instead, diabetes, abdominal obesity and gallstones appear linked through the metabolic syndrome.[64] The *metabolic syndrome* (also known as syndrome X and the insulin-resistance syndrome) represents a specific body phenotype (abdominal obesity) plus insulin resistance (hyperinsulinemia, impaired glucose tolerance and defective insulin-mediated glucose disposal, and hence type 2 diabetes). Other features are dyslipidemia (hypertriglyceridemia, low HDL-cholesterol and a preponderance of small dense LDL particles), abnormalities in fibrinolysis and coagulation. All represent risk factors for cardiovascular disease,[65] hypertension, cholelithiasis[64] and non-alcoholic fatty liver disease (NAFLD).[66] The major determinant of this syndrome is the intra-abdominal fat rather than subcutaneous fat.[67] Indeed, obesity itself is not the sole prerequisite for the metabolic syndrome: normal-weight individuals (normal BMI), who are metabolically 'obese', presumably have increased intra-abdominal fat.[68] With obesity escalating worldwide, this metabolic syndrome also may reach epidemic proportions.[69] Unknown is the impact of this increase in obesity and with it, the metabolic syndrome, on the frequency of gallstone disease.

Despite gallstones being predominantly comprised of cholesterol in Western countries, there is no conclusive evidence linking elevated serum cholesterol and gallstone disease.[70] LDL cholesterol has at best a weak correlation with gallstones.[71] Low HDL cholesterol and high triglycerides are positively associated with gallstones.[72] Similarly, plasma total homocysteine levels correlate with gallstones (stone type not identified), at least in middle-aged Japanese men.[73] The relation may be through homocysteine, a pro-oxidant, and oxidative stress that facilitate cholesterol gallstone formation.[74] Hyperhomocysteinemia thus presents a further risk connecting gallstones to coronary heart disease.

Rapid weight loss on low caloric diets or following bariatric surgery, paradoxically, is also a major risk factor for cholesterol gallstone formation.[75] Sludge and gallstones develop as frequently as 25–35% following bariatric surgery in the extremely obese,[76] usually during the first 6 weeks post-operatively when weight loss is most profound.[77] Weight loss above 1.5 kg/week dramatically heightens the risk for stone formation.[78] Though stones can produce symptoms, sludge in the gallbladder often disappears. Even less extreme weight fluctuations are a risk for stone formation,[79] as is a history of dieting.[80]

Physical activity, also a feature of weight status, appears protective, decreasing the possibility of developing cholelithiasis.[81] Reduced activity increases the risk.[82]

Diet

Nutrition intuitively should represent a key environmental exposure contributing to gallstone formation. Other than energy intake as calories leading to obesity, the importance of dietary content is not clear.[80] Those with gallstones consume a higher caloric intake.[83] In addition, the changes in diet and lifestyle in the past century have been linked to the increased prevalence of gallstones as exemplified by postwar Japan. The frequency of gallstones doubled in the late 1940s in association with a change in stone composition from pigment to cholesterol and a reversal of the sex ratio to one in which women predominated.[84] The culprit was attributed to westernization of the traditional Japanese diet: increased fat and decreased fibre. Detrimental are diets with a high caloric intake and refined carbohydrates. Beneficial are diets high in fibre, vegetable protein, nuts, calcium, vitamin C (ascorbic acid), caffeinated coffee, and alcohol in moderation.[38,85–89] Dietary fat is controversial, but a high intake of polyunsaturated and monounsaturated fats appears to reduce gallstone disease in the context of an energy-balanced diet.[90]

Total parenteral nutrition (TPN) is associated with the development of sludge (microlithiasis) and gallstones, as well as acalculous cholecystitis in an intensive care setting. Critically ill patients can develop biliary sludge only after 5–10 days of fasting.[91,92] After 3–4 months of TPN, some 45% of adults and children will develop gallstones. Sludge tends to persist while patients are receiving TPN but resolves once therapy is discontinued, a pattern similar to sludge appearing during pregnancy and rapid weight loss, only to disappear after the inciting event resolves. Some go on to form gallstones, which can become symptomatic and require cholecystectomy.[93]

Six per cent of those receiving total parenteral nutrition (TPN) exhibit sludge after 3 weeks, 50% after 4–6 weeks, and 100% after 6 weeks of therapy.[91,92] The basis is the gallbladder hypomotility that results from fasting with hepatic bile being altered in the gallbladder.[94] Gallbladder stasis from prolonged TPN and low-calorie diets with prolonged fasting are associated with sludge and stone formation but also as an aftermath of major abdominal surgery,[95,96] and solid organ and bone marrow transplantations.[97–99] The origin may be multifactorial, including critical illness, weight loss, TPN, drugs that impair gallbladder motility, and perhaps cyclosporine.

Family history and genetics

Familial and population studies have indicated a nearly 30% genetic component to cholesterol gallstone disease (in contrast to environmental or modifiable factors).[18,30,31] Familial studies indicating an increased frequency in families, twins and relatives of gallstone patients.[100–102] No mode of inheritance, however, exactly fits a Mendelian pattern. More compelling evidence is beginning to appear with the definition of those genes responsible for biliary lipid transport across the canaliculus[31] and for lipid metabolism like apolipoprotein E4.[103]

Diseases, drugs and other conditions

Cirrhosis

Cirrhosis is a well-established risk factor for pigment (rather than cholesterol) gallstone disease.[104] The prevalence reaches 30%, being more common in those with a worse Child class (2 or 3), and with a high BMI. The biological basis is unclear but may relate to altered pigment secretion, increased oestrogen levels and/or abnormal gallbladder motility in cirrhosis.

Crohn's disease

Crohn's disease with fairly extensive ileal disease or resection has a two–threefold increased risk of developing gallstones.[105] This would appear to result from bile salt malabsorption leading to bile salts depletion and the hepatic secretion of bile overly saturated with cholesterol, and hence cholesterol gallstone formation.[106] Other reports, implicating an increased frequency of pigment stones, suggest that the escaped bile salts may solubilize unconjugated bilirubin pigment and so enhancing bilirubin absorption in the colon and its enterohepatic cycling. The resultant increase of bilirubin concentration in bile might then promote pigment stone formation.[107]

Irritable bowel syndrome

Cholecystectomy may be more common in the irritable bowel syndrome, likely because the symptoms of IBS may cause diagnostic confusion.[108]

Gallbladder stasis

Impaired gallbladder emptying occurs in several conditions such as: prolonged total parenteral nutrition,[91] rapid weight loss on very restricted diets and following bariatric and other surgeries,[77,95,96] spinal cord injury[109] and the use of somatostatin or its analogue, octreotide.[110] Gallbladder stasis predisposes to biliary sludge, a forerunner of gallstones.[91]

Drugs

Ceftriazone is avidly (∼40% of its elimination) secreted into bile and can precipitate with calcium to form biliary sludge and stones.[111] The HMG-CoA inhibitors ('statins') would be expected to not only depress cholesterol synthesis but also its secretion into bile, hence lessening any tendency to saturation. Any benefit from such agents is not clear.

Smoking

Smoking is unclear as a risk factor.

Socioeconomic status

There is unlikely any association for socioeconomic status as an independent factor.

SUMMARY

The prevalence of gallstone disease has advanced dramatically from the early days of clinical and necropsy studies, with their inherent biases, with the landmark cholecystography survey of Pima Indians in 1970[13] to the excellent ultrasonographic surveys (accurate, safe and non-invasive) that began predominantly in Europe, especially Italy, in the late 1980s.[23,43–45] Not only did these studies identify the true frequency of cholelithiasis at any point of time (i.e., prevalence), but have better defined ethnic differences and identified the important risk factors.[10,22,38,72,112] Ethnic differences, for example, particularly among American Indians who have an extraordinarily high prevalence and Hispanics with a mixture of Spanish–Indian background foster the concept of a genetic basis for the racial differences.

Such descriptive epidemiology indicates two types of risk factors: (1) those that are immutable (ethnic background and family history indicating a genetic basis, female gender and ageing), and (2) others that can be modified (obesity, the metabolic syndrome, rapid weight loss and certain dietary factors). The spectra of obesity as an epidemic in developed countries and the recent recognition of the metabolic syndrome with its links to gallstone formation gives emphasis for vigil: expect a rise in the frequency of cholesterol cholelithiasis. What the future holds for the prevalence of gallstone disease if the trend to increasing obesity and its bariatric surgical treatment for the extremely obese continues will only be discerned through carefully performed epidemiological studies. As important, identifying risk factors that can be altered provides the opportunity for preventing gallstones.

Practice points

- The best epidemiology studies have used ultrasonography to screen for gallstones in large populations.
- Ethnic differences vary from a high of 60–70% in American Indians to prevalences of 20% in Northern Europe and 6–17% overall in Europe and North American white adults. Very lowest rates occur in Black Africans.
- Some risk factors are unchangeable: ethnic background, age and gender.
- Other risk factors can be altered: obesity, rapid weight loss and certain dietary factors. These are preventable.

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