INTRODUCTION

Gallstone disease remains one of the most common medical conditions in the United States and in developed countries in general. Among biliary tract disease, it is the leading cause for inpatient admissions for gastrointestinal problems. In the United States in 2000 alone, there were 262,411 hospitalizations for cholecystitis and 778,632 outpatient visits. The average cost per each admission was $11,584. Between 1994–1998, an estimated 20.5 million American adults were diagnosed with cholelithiasis, which equates to approximately 15% of the American population. The most accurate and noninvasive method of predicting gallstone disease was achieved with the advent of the ultrasound, which has a sensitivity/specificity of greater than 95%. However, the true prevalence of the disease remains hard to derive as the majority of patients remain asymptomatic. Recent studies indicate that only 10%–18% of patients with cholelithiasis develop symptoms such as nausea, vomiting and abdominal pain.

This paper will review the pathogenesis and epidemiology of gallstone disease, focusing on both unmodifiable and modifiable risk factors.

PATHOGENESIS

Gallstones are principally formed due to abnormal bile constituents (e.g., cholesterol, phospholipids and bile salts). Cholesterol gallstone formation can be arbitrarily divided into 3 stages: cholesterol saturation, nucleation, and stone growth (Figure 1).

Cholesterol Solubilization and Super Saturation

Cholesterol is virtually insoluble in aqueous solution and requires some vehicle to render it soluble in bile. This is overcome by secretion of phospholipids and bile salts along with cholesterol. The biliary lipids (lecithin, cholesterol, and bile salts) are secreted into the hepatic canaliculi by adenosine tri-phosphate.
(ATP)-dependent transport proteins. Soon after the excretion, cholesterol and lecithin combine to form metastable unilamellar vesicles, while the bile salts, after reaching a critical concentration, form simple micelles. The dynamic interaction of unilamellar vesicles with the simple micelles leads to the formation of mixed micelles during the passage through the biliary tract into the gallbladder. Studies have shown that vesicles are able to solubilize more cholesterol than mixed micelles. The concentration of phospholipids and bile salts relative to cholesterol is thought to be the critical factor in determining the solubilization and saturation of cholesterol in bile and thus making it more lithogenic if homeostasis is not maintained.

**Nucleation of Cholesterol Crystals**

Nucleation is the process by which cholesterol monohydrate crystals form and agglomerate. In supersaturated bile, the interaction between mixed micelles and vesicles lead to precipitation of cholesterol crystals. Video enhanced microspic studies have shown that crystals appeared to originate from aggregated vesicles. This observation is explained by the fact that when the vesicles and mixed micelles interact in the gallbladder, the micelles remove phospholipids from the vesicles in preference to cholesterol, thus making vesicles rich in cholesterol. The remaining vesicles are relatively enriched in cholesterol and prone to nucleation. After nucleation, crystallization of the cholesterol can then occur eventually leading to the formation of macroscopic gallstones. Initially super saturation was thought to be the primary pathological event leading to the formation of gallstones, however with the advent of assays to determine the nucleation time and the observation of asymptomatic super saturation of gallstones in patients, it has become evident that nucleation of the cholesterol crystals plays a vital role in the overall development of gallstones. Nucleation time can be decreased by certain pro-nucleation factors such as gallbladder mucin, heat-labile glycoprotein, immunoglobulin, phospholipase C, and most likely, calcium. Factors which slow nucleation...
ation include apolipoprotein AI and AII and a 120-kD glycoprotein.8

**Cholesterol Stone Growth**

The nucleated cholesterol monohydrate crystal serves as the nidus for the growth of cholesterol stones.8 Repeated deposition of cholesterol on the nidus leads to stone enlargement. Growth of stones is most likely a discontinuous process that is punctuated by deposition of rings of calcium bilirubinate and calcium carbonate as the daily inter-play of cholesterol, bile salts and phospholipids continues.8

There are several factors that favor cholesterol gallstone formation. The first is cholesterol hypersecretion, which can occur due to advanced age, obesity, hormones (eg, estrogens, progesterone, use of oral contraceptive pills), medications (eg, clofibrate), and marked weight reduction. Pro-nucleating factors (including mucus, glycoproteins, high bile salt to lecithin ratio, high cholesterol to lecithin ratio in vesicles, infections, calcium and bacterial biofilms) and gallbladder stasis (which can occur from total parenteral nutrition, octreotide use, pancreatic insufficiency, and spinal cord injury) also increase the risk of cholesterol gallstone formation. Finally, conditions causing a decrease in bile acids, such as ileal disease, bypass or resection of the ileum, primary biliary cirrhosis, congenital 12-hydroxylase deficiency, and cholestyramine can increase the chance of gallstone disease. These factors will be discussed in detail later in this review.

Pigment stones make up a small minority and account for approximately 10%–30% of gallstone cases in the United States.11,12 This review will not explore in depth the pathogenesis of pigment gallstones due to a lack of epidemiological studies. Briefly, there are 2 types of pigment gall stones: black and brown gallstones. Black pigment stones are predominantly composed of an insoluble bilirubin pigment polymer mixed with calcium phosphate and carbonate.13 Precipitation of calcium bilirubinate occurs whenever the ionic product of calcium and unconjugated bilirubin exceeds its solubility product. The major factors causing black pigment stones are hemolytic anemias, ineffective erythropoiesis, and increased production of bilirubin (caused by hereditary spherocytosis, thalassaemia, sickle cell disease, liver cirrhosis, malaria, and ineffective erythropoiesis).13 Factors causing absorption of bilirubin from gut include ileal resection or ileal disease, liver cirrhosis, total parenteral nutrition, and cystic fibrosis.13

Most of the brown pigment stones are formed in the bile ducts as a consequence of some infection and stasis of bile flow.13 Chemically they are calcium salts of long chain fatty acids and cholesterol. Bacterial B-glucuronidase deconjugates bilirubin diglucuronide into insoluble unconjugated bilirubin which precipitates in the bile duct. Any factor that interrupts normal bile flow predisposes to infection, and subsequently to brown pigment stone formation as is observed with biliary strictures, periampullary diverticulum, and Caroli syndrome. Intrahepatic brown pigment stones are seen with infestation of bile ducts with *Ascaris lumbricoides* and *Clonorchis sinensis*.13

**EPIDEMIOLOGY AND RISK FACTORS**

**Unmodifiable Risk Factors**

**Gender** Generally, gallstone disease is more prevalent in females than in males (Table 1). However, the differences in gallstone incidence between sexes decreases
with advancing age. According to the Group for Epidemiology and Prevention of Cholelithiasis (GREPCO) study, the female-to-male ratio for gallstone disease was 2.9 between 30 to 39 years of age, 1.6 between 40 to 49 years of age, and 1.2 between 50 to 59 years of age.14

Female sex hormones appear to play a role, especially between the ages of 20 and 30 years.5 Another study that researched estrogen receptors and cholesterol biosynthesis found that estrogen in particular stimulated the HMG-Co-A reductase enzyme causing increased synthesis of cholesterol and thus putting women at an increased risk of super saturation. Further supporting the link between estrogen and gallstones, it was determined that postmenopausal women on estrogen replacement therapy were found to have an increased incidence of gallstones.15 Progesterone may also contribute to gallstone disease by inhibiting gallbladder contraction and promoting hypomotility and gallbladder stasis.

Parity also appears to be a factor in the development of gallstones. Women with more pregnancies and longer lengths of fertility periods appear to have a higher likelihood of developing gallstones than those who remain nulliparous. A study in Chile found gallstones in 12.2% of multiparous women versus 1.3% of nulliparous women within the same age.16 Another study found women under the age of 25 years with ≥4 pregnancies were 4 to 12 times more likely to develop cholesterol stones compared to nulliparous women of the same age and weight. It should be noted that biliary sludge usually disappears a few weeks after the pregnancy concludes/terminates/ends.

Age Age also appears to have an effect on the incidence of gallstone disease. Gallstone disease before 20 years of age is a rare occurrence.5 In infants and children, the most common stones are pigment stones, which are related to hemolysis or chronic diseases such as cystic fibrosis, thalassemia major, and sickle cell anemia.5 Typically, only 0.15% to 0.22% of children will have gallstones, and children account for less than 5% of all cholecystectomies. The increased incidence of gallstones with age is seen across all ethnic groups.5,17 A study in Taiwan confirmed that increasing age had a direct relationship with the development of gallstones simply due to the long-term exposure to other risk factors irrespective of locality or standard of living.17 A Danish study also showed that an increased incidence of gallstone disease in patients ≥45 years compared with those aged ≤35 years, while the differences in gallstone incidence between sexes decreased with advancing age.18 From a biochemical standpoint, age itself may increase cholesterol saturation of bile with enhanced hepatic secretion of cholesterol secondary to increased levels of HMG co-A reductase, the rate-limiting enzyme of cholesterol synthesis. Decreased synthesis of bile acids may occur secondary to decreased cholesterol 7 a-hydroxylase enzyme activity, the rate-limiting enzyme in bile acid synthesis, as age advances.19,20

Genetics It remains to be determined the exact role of genetics in the occurrence of gallstones that would account for the different prevalence rates among the different ethnic groups. However, genetic make-up appears to contribute to the prevalence of cholelithiasis as there is wide variation in incidence between different ethnicities (Table 2).1,21–24 For example, the Pima tribe of Arizona has the highest prevalence of

Table 2. Worldwide Prevalence1,21–24

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Americas</td>
<td></td>
</tr>
<tr>
<td>Pima Indians (Arizona)</td>
<td>73 (women &gt;25 years)</td>
</tr>
<tr>
<td></td>
<td>90 (women &gt;65 years)</td>
</tr>
<tr>
<td>Mupache Indians (Chile)</td>
<td>49 (women); 13 (men)</td>
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<tr>
<td>Europe</td>
<td></td>
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<tr>
<td>Norway</td>
<td>21</td>
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<tr>
<td>Former East Germany</td>
<td>19</td>
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<tr>
<td>France</td>
<td>14</td>
</tr>
<tr>
<td>England</td>
<td>8</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
</tr>
<tr>
<td>Bantu Tribe</td>
<td>5</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
</tr>
<tr>
<td>Northern India</td>
<td>6</td>
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<td>China</td>
<td>4</td>
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<td>Japan</td>
<td>3</td>
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(continued on page 17)
gallstone disease in the world, where an estimated 73% of women >25 years have cholelithiasis, with the prevalence rising to 90% by ≥65 years. In South America, the prevalence of gallbladder disease among Mapuche Indians of Chile is 49% in women and 13% in men. In the United States, the NHANES III survey showed a higher prevalence of gallstones in Mexican-Americans compared to non-Hispanic whites, while American blacks had the lowest prevalence. In Europe, the highest prevalence of gallstone disease was found in Norway (21%) and the former East Germany (19%), while the lowest incidence was found in Italy (6%). In Asian countries, the prevalence of cholesterol gallstones is relatively low. These countries and populations are being more commonly associated with pigment stones. In northern India, for example, the prevalence of cholelithiasis is about 6%. However, with the increased expansion of the Western diet throughout the world, the number of stones attributed to cholesterol is expected to increase.

In individuals, studies have shown that genetic factors are responsible for at least 30% of symptomatic gallstone disease. It has been found that monozygotic twins have been shown to have a higher cholesterol saturation index than dizygotic twins. Furthermore, a study in Europe found linked a mutation in the ABCG8-gene with the occurrence of gallstones as this mutation was carried in 21% of 178 men and women with gallstones. It was found that this mutated gene was responsible for the “pump” which transported blood lipid cholesterol from the liver into the bile ducts, therefore, increasing the formation of cholesterol gallstones.

Modifiable Risk Factors

**Obesity** Obesity is an important risk factor for the development of gallstone disease. Obese women, defined as a body mass index (BMI) >30 kg/m² are at twice the risk of gallbladder disease than women with a normal BMI (<25 kg/m²). Women with extreme obesity or a BMI >40 kg/m² have a 7-fold increased risk of gallstones. The reason for the increased risk of gallstones in obese patients is due to an increased hepatic secretion of cholesterol. Additionally, the correlation between gallstone disease and obesity is greater with those patients with central obesity and those who developed obesity at an early age rather than in the later years of life.

**Rapid Weight Loss** Rapid weight loss is another risk factor for gallbladder disease, as demonstrated by the Nurses Health Study, which followed close to 90,000 women. This study found that women who lost 4 kg to 10 kg of weight over a 2-year interval had a 44% increase in the risk for gallstone disease as compared with women whose weight change was <4 kg over the same time period. Furthermore, women who lost >10 kg of weight had a 94% increase in the risk for gallstone disease as compared with women whose weight change was <4 kg when controlling for BMI and other risk factors for gallstones. Another study demonstrated that a weight loss >1.5 kg/week led to a dramatic increase in the risk of gallstone formation. It has also been shown that sludge and gallstones develop in 25%–35% of extremely obese patients with weight loss secondary to bariatric surgery, usually during the first 6 weeks following surgery when weight loss is most profound.

**Diet and Activity** Closely related to obesity and rapid weight loss are diet and physical activity. Diets that encompass Vitamin C, moderate alcohol intake, coffee, and nut consumption lower the incidence of gallstone disease. Conversely, increased cholesterol intake and low fiber diet, typical of Western diets, are predisposing risk factors for the development of gallstone disease. This is best exemplified by a study, conducted in Japan after World War II and the

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**Table 3**

**Diet**

*Increases Risk of Gallstones*

- High cholesterol/ Low fiber (western diet)
- Total parenteral nutrition

*Lowers Risk of Gallstones*

- Vitamin C
- Moderate alcohol intake
- Coffee
- Nut consumption
ensuing Westernization of the Japanese diet. That study found that the prevalence of gallstones doubled in Tokyo after the late 1940s with a corresponding increase in pigment-to-cholesterol gallstones. Similar increases in gallstone disease have also been seen in other countries, such as Saudi Arabia, where the Western diet has become more widespread.

Total parenteral nutrition (TPN) also increases the risk of gallstone occurrence as demonstrated by a study that found that the incidence of cholelithiasis was 6.2%, 21.2%, and 38.7% at 6, 12, and 24 months of receiving TPN, respectively.

With regard to physical activity, decreased activity increases the risk of gallstones, while many forms of activity, including vigorous or brisk walking, protect against gallstone disease.

**Smoking, Medications, Hyperlipidemia, Diabetes Mellitus II**

There also appears to be a very weak relationship between gallstones and other common medical conditions such as chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD). Paradoxically, hyperlipidemia is only tenuously linked to gallstones. Although low levels of high-density lipoprotein (HDL) cholesterol and high triglycerides are associated with gallstone disease, the extent to which the risk is increased has not clearly been defined by any major study. Other diseases such as diabetes mellitus seem to facilitate the development of gallstone formation secondary to increased triglyceride levels associated obesity as well as promoting gallbladder hypomotility and stasis. A study in Japan showed a moderate increase in the risk of gallstones in patients with diabetes mellitus; however, there is no conclusive link between these two conditions.

A multitude of various medications have been linked to the development of gallstones. These include thiazides, oral contraceptives, and ceftriaxone. Somatostatin is also associated with gallstone development because of its effect on impaired gallbladder emptying.

**CONCLUSION**

In summary, gallstone disease is common among developed countries. Approximately 15% of Americans display symptoms and an even greater number remain asymptomatic, thereby making the true prevalence difficult to determine. The underlying pathogenesis appears to be the interaction between cholesterol, phospholipids, and bile salts and the other factors which promote lithogenic bile. It is important to remember that both super saturation of cholesterol in bile and nucleation of cholesterol crystals are needed for the formation of macroscopic gallstones. Risk factors for gallstones which are unmodifiable include female gender through increased estrogen, cholesterol synthesis, age, and genetics. Other risk factors include obesity, rapid weight loss, parity, and diet. Protective factors include vitamin C intake, moderate alcohol intake, coffee, nut consumption, and exercise.

**References**