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Risk Factors for Cholelithiasis

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Abstract

Gallstone disease is one of the most common public health problems in the United States. Approximately 10%–20% of the national adult populations currently carry gallstones, and gallstone prevalence is rising. In addition, nearly 750,000 cholecystectomies are performed annually in the United States; direct and indirect costs of gallbladder surgery are estimated to be $6.5 billion. Cholelithiasis is also strongly associated with gallbladder, pancreatic, and colorectal cancer occurrence. Moreover, the National Institutes of Health estimates that almost 3,000 deaths (0.12% of all deaths) per year are attributed to complications of cholelithiasis and gallbladder disease. Although extensive research has tried to identify risk factors for cholelithiasis, several studies indicate that definitive findings still remain elusive. In this review, predisposing factors for cholelithiasis are identified, the pathophysiology of gallstone disease is described, and nonsurgical preventive options are discussed. Understanding the risk factors for cholelithiasis may not only be useful in assisting nurses to provide resources and education for patients who are diagnosed with gallstones, but also in developing novel preventive measures for the disease.

Gallstones affect 10%–15% of the adult population (over 6 million men and 14 million women) (Everhart, Khare, Hill, & Maurer, 1999) in the United States (U.S.) (Schirmer, Winters, & Edlich, 2005; Shaffer, 2005; Tazuma, 2006). In 2009, gallstones accounted for over 300,000 physician visits and were the second most common gastrointestinal discharge diagnosis in U.S. hospitalizations (Peery et al., 2012). Furthermore, it is estimated there are almost 3,000 gallstone-related deaths in the U.S. annually (Everhart & Ruhl, 2009; National Institutes of Health, 2005). Traditionally, age, female gender, and obesity have been considered the major risk factors of cholesterol gallstone disease (Shaffer, 2006; Tsai, Leitzmann, Willett, & Giovannucci, 2004a). Although it is one of the most prevalent gastrointestinal disorders, the etiology and pathophysiology of gallstone disease still remain incompletely understood (Sanders & Kingsnorth, 2007). In order to better identify preventive strategies, this article reviews the literature describing the predisposing factors for gallstone disease and the impending risks for cholelithiasis, cholecystectomies, and other complications of the disease.

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Physiology and Characteristics of Cholelithiasis

Cholelithiasis is the process of gallstone formation (Venes & Taber, 2013). Cholecystitis is an acute or chronic infection of the gallbladder (Kimura et al., 2007), and may occur in association with gallstones. Although most gallstones are silent, symptomatic gallstones trigger biliary colic, a steady, sudden, severe, right upper-quadrant pain lasting for more than 30 minutes (Venes & Taber, 2013). Some accompanying features include nocturnal onset of nausea, vomiting, and pain radiating through to the back (Gracie & Ransohoff, 1982) lasting 1–4 hours. Common complications associated with gallstones include infection, perforation, or gangrene (Gracie & Ransohoff, 1982). The clinical management of gallstone disease almost exclusively eventuates in cholecystectomy and endoscopic or medical treatment of complications.

Generally, circulating cholesterol is carried by lipoproteins and taken up by the liver, metabolized, and eventually secreted into bile (Zanlungo & Rigotti, 2009). Biliary super saturation with cholesterol is an important predisposing factor for the precipitation of cholesterol gallstones (Acalovschi, 2001; Portincasa, Moschetta, & Palasciano, 2006; Zanlungo & Rigotti, 2009). Although cholesterol constitutes only 5% of bile, cholesterol or a cholesterol mix causes 75% of gallstones in the U.S. (Portincasa et al., 2006). Other gallstone types include black pigment gallstones (15%–20%) and brown pigment gallstones (0%–5%) (Cariati & Cetta, 2003).

Gallstone Disease Epidemiology

Multiple studies indicate that up to 72% of patients with symptomatic gallstones have ongoing biliary pain or complications resulting from cholecystitis, an inflammation of the gallbladder; pancreatitis, an inflammation of the pancreas; gallstone ileus, an obstruction of bowel to impaction of gallstones; biliary tract obstruction, a blockage of the bile ducts; gallbladder emphysema, a severe form of cholecystitis resulting in disruption of the gallbladder wall; or perforation, a rupture of the gallbladder (Gupta & Shukla, 2004). Also, gallstones are considered to be the main risk factor for gallbladder (Sanders & Kingsnorth, 2007), pancreatic (Anderson, Potter, & Mack, 1996), and colorectal cancer (Schernhammer et al., 2003; Siddiqui et al., 2009). Because nearly 85% of patients with gallbladder cancer have gallstones, gallstones constitute a detrimental risk factor for gallbladder cancer (Hundal & Shaffer, 2014). Furthermore, the average survival rate for patients with gallbladder cancer is 6 months (Levy, Murakata, & Rohrmann, 2001) with a 5-year survival rate of only 5% because of its silent prognosis (Hundal & Shaffer, 2014). In a large, national, 18-year follow-up study, gallstone disease was found to be associated with overall cardiovascular disease and cancer mortality, increased mortality overall, and mortalities from cardiovascular disease and cancer (Ruhl & Everhart, 2011). Overall mortality was also found to be increased for participants with cholecystectomy.

Cholecystectomy is considered the standard treatment for a symptomatic cholelithiasis, and is one of the most common surgeries in the U.S.; over 750,000 are performed annually (Lammert & Sauerbruch, 2005). Multiple longitudinal studies have shown conflicting outcomes after gallbladder surgery that include colon cancer (Goldacre, Abisgold, Seagroatt,

& Yeates, 2005; Schernhammer et al., 2003; Shao & Yang, 2005; Siddiqui et al., 2009), tumors of the esophagus (Freedman, Ye, Naslund, & Lagergren, 2001), small bowel and proximal colon (Lagergren, Ye, & Ekbom, 2001; Nogueira et al., 2014), and advanced adenomas of the colon (Siddiqui et al., 2009). Yet other studies have reported that the incidence rate of tumors resulting from cholecystectomy surgery is low (Mercer, Reid, Harrison, & Bates, 1995; Reid, Mercer, Harrison, & Blates, 1996). In addition, complications have been observed in almost 20% of laparoscopic cholecystectomies performed on older adults (Pérez et al., 2006). Postoperative complications often include biliary leakage, hemorrhage, infection, respiratory issues, repeat surgeries, and mortality. Furthermore, an almost 0.5% incidence of bile duct injury has been found in laparoscopic cholecystectomy surgeries (Pottakkat et al., 2010; Waage & Nilsson, 2006).

In this country, the direct and indirect costs of gallbladder disease are estimated to be $6.5 billion annually (Sandler et al., 2002), an increase of more than 20% over the last three decades (Everhart & Ruhl, 2009; Sandler et al., 2002; Shaffer, 2005). Although 80% of patients with gallstones are asymptomatic (Halldestam, Enell, Kullman, & Borch, 2004), most stones are detected by chance during routine or unrelated medical examinations (Beckingham, 2001). Yet, in the general population, 10%–25% of asymptomatic gallstones may be expected to develop into cholecystitis, cholangitis, or pancreatitis at some point during a patient's lifetime (Freedman, 1993; Halldestam et al., 2004).

Risk Factors for Gallstone Disease

The traditional risk factors for gallstone disease are the four "F's: female, fat, forty, and fertile," with many studies supporting the known risk factors for gallstone disease. Being "fair skinned" has been described by some as being a fifth factor (Sherlock, 1963), although studies have indicated that Pima Indians and Mexican populations had a high prevalence of gallstones and gallstone-related diseases (Covarrubias, Valdivieso, & Nervi, 1984; Everhart et al., 1999; Hanis et al., 1993; Maurer et al., 1989; Samplinger, Bennett, Comess, Rose, & Burch, 1970). Obesity has also been considered a major risk factor for diseases resulting from cholesterol gallstones (Acalovschi, 2001; Shaffer, 2006; Tsai et al., 2004a). Although stone formations occur as a result of the complex interaction of genetic, environmental, metabolic, and related conditions, factors such as advanced age and gender are unalterable. Diet and physical activity may be modifiable risk factors.

Numerous studies have observed associations between cholesterol gallstones and many predisposing factors including obesity, "westernized diet" (Acalovschi, 2001; Di Ciaula, Wang, Wang, Leonilde, & Portincasa, 2010), hyperinsulinemia, dyslipidemia (Andreotti et al., 2008; Atamanalp, Keles, Atamanalp, Acemoglu, & Laloglu, 2013; Venneman & Van Erpecum, 2010), type 2 diabetes, and metabolic syndrome (Di Ciaula et al., 2010; Portincase et al., 2006). In addition, advanced age, female gender, parity, rapid weight loss, estrogen replacement therapies, estrogen oral contraceptives, total parenteral nutrition, genetic factors, and ethnicity have also been found to be associated with increased gallstone occurrence (Carey & Paigen, 2002).

Age

Gallstones are ten times more likely in people aged 40 and more (Chen et al., 1998; Festi et al., 2008; Volzke et al., 2005) due to a decline in the activity of cholesterol 7 α -hydroxylase, the limiting enzyme for bile acid synthesis (Carulli et al., 1980; Salen, Nicolau, Shefer, & Mosbach, 1975); as this enzymatic activity decreases, and biliary cholesterol increases, the aging individual experiences cholesterol saturation and decreasing mobility of gallbladder emptying. Volzke et al. (2005) found that cholecystectomies to resolve various symptoms and complications of cholelithiasis are more common in older people.

Gender and Ethnicity

Gender is one of the most salient risk factors for gallstone disease. At all ages, women are generally at higher risk of cholelithiasis than men because of women's naturally higher estrogen levels (Attili et al., 1997; Cirillo et al., 2005), multiparty (Moghaddam, Fakheri, Abdi, Rostami, & Bari, 2013; Murray, Logan, Hannaford, & Kay, 1994), or ingestion of estrogen-based oral contraceptives (Cirillo et al., 2005; Murray et al., 1994). Studies have also demonstrated that females are more prone to undergo a cholecystectomy procedure than men at all ages (Chen et al., 1998; Everhart et al., 1999, 2002; Racine et al., 2013; Singh, Trikha, Nain, Singh, & Bose, 2001).

Cholelithiasis prevalence has been found to be higher in North American Indians, with incidence rates reaching 73% among women older than 30 years within the Pima tribe (Sampliner et al., 1970). Everhart et al. (2002) also observed an overall gallbladder disease prevalence of 29.5% in American Indian men (43.9% in men 65 years and older) and 64.1% in American Indian women, with 46.3% having undergone a cholecystectomy at some time in their lives. For American Indian women aged 65 years and more, the prevalence rate rose to 73.6%. Other studies have also found ethnicity and gender factors associated with increased incidence of gallstone disease. Covarrubias, Valdivieso, and Nervi (1984) found a gallstone incidence rate of 49.4% in women and 12.6% in men in Chile. Studies pertaining to Mexican American populations also resulted in similar findings (Hanis et al., 1993; Maurer et al., 1989). Similar study outcomes have been observed in American and European Caucasian populations. A large cross-sectional ultrasound study found that 7.9% of men and 16.6% of females develop gallstones, with progressive increases in prevalence after 20 years of age in both groups (Everhart et al., 1999). Female gender hormones appear to be the primary factor for the observed gender difference in prevalence (see Table 1, which describes factors related to the female gender and cholelithiasis risks).

Some studies have also demonstrated a correlation between prevalence of gallstone disease and gallbladder cancer (Hundal & Shaffer, 2014; Zatonski et al., 1997), which more commonly affects certain indigenous populations (particularly in South America and Northern India), especially younger populations (Dutta et al., 2005; Misra, Chaturvedi, Misra, & Sharma, 2003). American Pima Indians with gallstone disease were found to be at twice the risk of death of those with no gallstone disease (Grimaldi et al., 1993). Moreover, the risk of death from gallbladder cancer and other malignancies has been observed to be seven times higher in tribal members with gallstone disease (Grimaldi et al., 1993). Other

studies confirm high prevalent rates of gallbladder cancer in South America, particularly in Chile and Bolivia (Pandey, 2003; Strom et al., 1995).

Lipid Profile

Cholesterol, the most prevalent substance in gallstones (Schafmayer et al., 2006), is a type of lipid synthesized primarily in the liver, and excreted only through the biliary system (Poynard, Lonjon, Mathurin, Naveau, & Chaput, 1995). Cholelithiasis is difficult to treat because formation of gallstones is so complex and multifactorial. Factors associated with cholesterol gallstone formation include cholesterol hypersecretion and supersaturation, bile salt and phospholipid concentrations, crystal nucleation, gallbladder dysmotility, and gallbladder absorption and secretion functions (Atamanalp, 2012; Lee & Chen, 2009; Poynard et al., 1995; Schafmayer et al., 2006). Although studies have been conducted to clarify the relationship between lipid levels and gallstones, the findings remain controversial.

Several convincing studies assert a positive association between high cholesterol levels and cholesterol gallstone development (Andreotti et al., 2008; Venneman & Van Erpecum, 2010). These studies' findings are corroborated by a recent study observing a positive correlation between high cholesterol levels, high cholesterol stone rates, and high stone cholesterol concentrations (Atamanalp et al., 2013); however, Thijs, Knipschild, and Brombacher (1990) reported an inverse correlation between cholesterol levels and gallstone risk. Other detailed studies examining the relationship between low-density lipoprotein (LDL) levels and gallstone formation describe high LDL levels as a marker for increased risk of cholesterol gallstone disease (Fu, Gong, & Shao, 1995; Fu et al., 1997; Han, Jiang, Suo, & Zhang, 2000). Nevertheless, Andreotti et al. (2008) and Tang (1996) have reported an inverse correlation between LDL levels and gallstone risk (see Table 2, which describes factors related to the serum lipids and cholelithiasis risks).

Other studies have demonstrated a relationship between low high-density lipoprotein (HDL) levels and gallstone formation. For example, both Andreotti et al. (2008) and Fu et al. (1995) reported an increased risk of gallstone disease in individuals with low HDL levels, whereas Thijs et al. (1990) and Tang (1996) observed an inverse relationship between low HDL levels and gallstone disease. Moreover, Halldestam, Kullman, and Borch (2009) and Fu et al. (1997) did not observe a positive correlation between low HDL levels and gallstone development. High cholesterol, high LDL, and low HDL levels may be expected to increase cholesterol excretion with bile and cause cholesterol gallstone disease. However, serum cholesterol, LDL, HDL, and triglyceride levels present no simple correlation with cholesterol gallstone formation; rather, the relationship is multifactorial, complex, and also dependent on other individual properties.

Diet

"Westernized nutrition" (Acalovschi, 2001; Paigen & Carey, 2002; Tsai et al., 2008) has been identified as one of the strongest determinants for developing cholesterol gallstones. In Native Americans, post-World War II Europeans, and East Asians, dietary intake has been found to be a factor for gallstone incidence (Tsai et al., 2004a; Tsai, Leitzmann, Willett, & Giovannucci, 2005b; Tsunoda, Shirai, & Hatakeyama, 2004). Tsunoda and

associates (2004) reported a strong positive correlation between calories consumed and gallstone formation in a Japanese cohort of 1,264 patients. Data from two large prospective epidemiologic studies in the U.S. indicated that high intakes of carbohydrates, coupled with increased dietary glycemic load, enhanced the risk of symptomatic gallstone disease and cholecystectomy in both men and women (Tsai, Leitzmann, Willett, & Giovannucci, 2005a; Tsai et al., 2005b). In particular, refined sugar was positively correlated with increased gallstone risk (Misciagna et al., 1999; Moerman, Smeets, & Kromhout, 1994). Chronic hypernutrition, because it contributes to obesity and therefore increased cholesterol synthesis and secretion (Al-Azzawi et al., 2007; Biddinger et al., 2008), heightens the risk of gallstones (Tseng, Everhart, & Sandler, 1999). Similarly, a high-calorie, fiber-depleted diet, because it precipitates a rise in biliary cholesterol secretion and intestinal hypomobility, may result in gallstone formation (Shaffer & Small, 1977).

In general, diets high in cholesterol elevate biliary cholesterol saturation in patients with or without gallstones. The Nurses' Health Study indicates that a history of high dietary intakes of carbohydrates with an increased glycemic load and glycemic index increases the risk of cholelithiasis and resulting cholecystectomies in women (Tsai et al., 2005a). Other large epidemiologic studies have suggested that increased consumption of long-chain saturated fatty acids in the diet is associated with increased prevalence of gallstone disease in men (Tsai et al., 2008).

In contrast, diets high in unsaturated fat (Tsai, Leitzmann, Hu, Willett, & Giovannucci, 2004b), coffee (Leitzmann et al., 2002), fiber (Misciagna et al., 1999), ascorbic acid (Simon & Hudes, 2000), calcium (Moerman et al., 1994), fish oil (Mendez-Sanchez et al., 2001), and fresh fruits and vegetables (Acalovschi, 2001; Tsai, Leitzmann, Willett, & Giovannucci, 2006b) have been found to reduce the risk of cholesterol gallstones. A large prospective cohort study based on the Nurses' Health Study reported that frequent nut consumption was associated with a lower risk of cholecystectomy in women (Tsai et al., 2004b). Men who consumed nuts five times or more per week appeared to have an approximately 30% lower risk of gallstone disease (Tsai et al., 2004b). Nuts are mostly unsaturated fats (Kris-Etherton, Zhao, Binkoski, Coval, & Etherton, 2001; Rajaram, Burke, Connell, Myint, & Sabate, 2001), a rich source of dietary fiber (Kris-Etherton et al., 2001), and have beneficial effects on blood cholesterol and lipoprotein profiles (Almario, Vonghavaravat, Wong, & Kasim-Karakas, 2001). However, some study findings have suggested that the role of dietary cholesterol in cholesterol gallstones formation needs more investigation (Acalovschi, 2001; Andreotti et al., 2008; Halldestam et al., 2009).

Obesity and Weight Loss

Obesity, which positively correlates with body mass index (BMI), is also a well-known risk factor for gallstones (Katsika, Tuvblad, Einarsson, Lichtensten, & Marschall, 2007; Portincasa et al., 2006; Stender, Nordestgaard, & Tybjaerg-Hansen, 2013; Volzke et al., 2005). Prospective cohort studies reported a positive association between gallstone formation and central adiposity, relative to upper and lower extremity adiposity; regional fat distribution may thus exacerbate gallstone risk even further (Attili et al., 1997; Everhart et al., 1999). A large cohort study of 77,679 patients confirmed a close association (in both

genders, but especially pronounced in women) between increasing BMI and increased risk of symptomatic gallstone disease (Stender et al., 2013).

Findings from the Nurses' Health Survey demonstrated a direct relationship between the frequency of symptomatic gallstones and BMI (Chen et al., 2006; Stampfer, Maclure, Colditz, Manson, & Willett, 1992). Compared to lean women (BMI <24 kg/m^2), obese women (BMI ≥ 30 kg/m^2) exhibited a twofold increased risk and morbidly obese women (BMI ≥ 45 kg/m^2) a sevenfold increased risk of having symptomatic gallstones. According to the study, high BMI (BMI ≥ 25 kg/m^2) appears to be a risk factor for gallbladder disease in women more than in men (Stampfer et al., 1992).

Weight loss has also been found to reduce the risk of gallstones, unless it is excessively rapid (i.e., > 1.5 kg/week). Rapid weight loss and/or loss of greater than 25% of body weight has also been found to increase the possibility of gallstone formation (Li et al., 2009). After bariatric surgery, gallstones developed in 25%–35% of the patients following a 500-kcal diet for 8 weeks (Li et al., 2009). A large cohort study found positive correlations between weight cycling and cholecystectomy risks (Syngal et al., 1999). Another large prospective study observed a 40% increase in symptomatic gallstones when male participants had weight gains or losses of more than 20 lb (Tsai, Leitzmann, Willett, & Giovannucci, 2006a) (see Table 3, which describes factors related to body weight and cholelithiasis risks).

Physical Activity

Physical activity appears to be proactive, decreasing the possibility of developing cholelithiasis (Leitzmann et al., 1999), whereas reduced physical activity increases the risk (Leitzmann et al., 1998). Two large cohort studies reported that recreational physical activity was associated with an independent reduction in risk of symptomatic gallstones and also cholecystectomies in men and women (Leitzmann et al., 1998, 1999). Leitzmann et al. (1998) suggested that 34% of symptomatic gallstones in men could be prevented with 30 minutes of endurance-type exercise (e.g., running or cycling) five times per week. Results of another study indicated that an average of 2–3 hours of recreational exercise per week appeared to reduce the risk of cholecystectomy by approximately 20% (Leitzmann et al., 1999). Improved hepatobiliary function—by increasing bile salt excretion and enhancing gut motility—may be partially responsible for the preventive effect of physical activity on gallstone formation (Philipp, Wilckens, Friess, Platte, & Pirke, 1992; Watkins, Crawford, & Sanders, 1994) (See Table 4, which describes factors related to the diet and physical activity and cholelithiasis risks). Physical activity has also been purported to have an indirect protective effect by increasing HDL (Dubrac et al., 2001) and improving plasma triglyceride levels and insulin release (Kirwan, Kohrt, Wojta, Bourey, & Holloszy, 1993), all of which lower biliary cholesterol saturation.

Diseases

Metabolic syndrome, dyslipidemia, diabetes, and insulin resistance/hyperinsulinemia frequently co-occur in gallstone disease (Ahmed, Barakat, & Almobarak, 2014; Tsai et al., 2008; Volzke et al., 2005). Ruhl and Everhart (2000) reported a two- to threefold higher prevalence of gallstone disease in insulin-resistant subjects with type 2 diabetes.

Additionally, increased hepatic cholesterol secretion, supersaturation of bile, and gallbladder dysmotility exacerbate the conditions of metabolic syndrome, providing the ideal setting for the development of gallstones (Al-Azzawi et al., 2007).

Chronic hepatitis C virus (HCV) infection may also increase the risk of gallstones. In the U.S. National Health and Nutrition Examination Survey of 456 participants, men with HCV infections were found to have an increased risk of gallstones and resulting cholecystectomies compared to HCV-negative men (Bini & McGready, 2005). Although in this study the HCV association was not reported in women, other studies have found that the presence of HCV in both genders is associated with an increased risk of gallstones (Acalovschi, Buzas, & Grigorescu, 2009; Stroffolini, Sagnelli, Mele, Cottone, & Almasic, 2007). In patients with HCV, Acalovschi et al. (2009) reported central obesity and liver steatosis as significant risk factors, both of which have been linked to insulin resistance (Cua, Hui, Kench, & George, 2008; Eguchi et al., 2009). Insulin resistance, because of its ability to increase bile cholesterol saturation, has been suggested as a causal link in the development of gallstones (Acalovschi et al., 2009).

Liver cirrhosis and Crohn disease are risk factors for gallstones, in particular black pigment gallstones (Lammert & Miquel, 2008; Lapidus, Akerlund, & Elnarsson, 2006; Stinton, Myers, & Shaffer, 2010). Studies have shown a 25%–30% increased prevalence rate in advanced cirrhosis resulting from abnormal gallbladder motility, malabsorption of bile salts, and decreased bile salt synthesis (Buzas, Chira, Mocan, & Acalovschi, 2011; Vitek & Carey, 2003).

Alcohol and Smoking

Alcohol consumption has been found to be inversely associated with risk of gallstone disease (Katsika et al., 2007; Leitzmann et al., 2003; Volzke et al., 2005). Moderate alcohol intake may lower risk of cholesterol gallstone disease by reducing bile cholesterol saturation and raising HDL-cholesterol levels (Pixley & Mann, 1988). However, several other studies have failed to find any such association (Kratzer et al., 1997; Walcher et al., 2010). Volzke et al. (2005) reported that incidence rate of cholelithiasis is higher in men consuming 0–20 g of alcohol per day, but lower with a daily intake of 20–60 g of alcohol. Other studies have indicated that severe alcohol abuse increases the risk of (pigment) gallstone synthesis, with alcoholic cirrhosis being a strong independent risk factor for gallstones (Sahi, Paffenbarger, Hsieh, & Lee, 1998).

Studies examining the association between smoking habits and gallstone formation are also controversial. Stampfer et al. (1992) found that heavy smoking (more than 35 cigarettes per day) is a strong risk factor among women for gallstones. A large population-based study also confirmed that smoking is an important risk factor for developing symptomatic gallstones among women (Murray et al., 1994). Nevertheless, some studies find no relationship between smoking and gallstone development (Katsika et al., 2007; Shaffer, 2006; Walcher et al., 2010).

Discussion

Gallstone formation is multifactorial (Marschall & Einarsson, 2007; Portincasa et al., 2006), resulting from an intricate interaction between multiple genetic, environmental, and life style determinants (Krawczyk et al., 2010; Stokes, Krawczyk, & Lammert, 2011). For example, a high prevalence of gallstones has been observed in societies who consumed predominantly "westernized nutrition." "Westernized" dietary habits have been causally linked to metabolic syndrome (Abete, Astrup, Martinez, Thorsdottir, & Zulet, 2010). Reflecting upon the impact of "westernized" societies' increasing life expectancy and changes in life style, Lammert and Sauerbruch (2005) have described gallstone disease as a disorder with a changing prevalence.

More than 80% of gallstones are cholesterol-based. Although it is known that the pathophysiology of gallstone formation involves a combination of cholesterol interactions, the relationship between lipid profile and gallstone occurrence in gallstone development still remains unclear. A recent retrospective study of females with cholelithiasis identified a significant relationship between higher levels of LDL and increased risks of gallstones but did not observe statistical significance in the association of gallstones with total cholesterol, triglycerides, HDL, and very low-density lipoprotein (Batajoo & Hazra, 2013). Therefore, it is necessary to further investigate the effects of serum cholesterol, LDL, HDL, and triglyceride levels on the cholesterol concentration of gallstones in patients with cholelithiasis and examine whether abnormal serum cholesterol is an indicator for cholelithiasis.

The major risk factors for cholesterol gallstones have been associated with aging, the female gender, ethnicity, obesity, hyperinsulinemia, dyslipidemia, and the westernized diet (Acalovschi, 2001; Carey & Paigen, 2002). Although age, female gender, ethnicity, and genetic factors are not alterable factors, obesity, comorbidities, nutrition, and physical activity are modifiable, and may precipitate a decline in gallstone occurrence.

Many studies have identified effective treatments for the prevention of gallstone diseases. For example, ascorbic acid supplementation has been recommended as a means of reducing bile lithogenicity, thereby reducing gallstone formation (Gustafesson et al., 1997). Another study indicated that treating iron deficiency prevented gallstone development (Johnston et al., 1997). Several observational studies found higher intakes of polyunsaturated or monounsaturated fatty acids were associated with the decreased risk of gallstones (Almario et al., 2001; Rajaram et al., 2001; Tsai et al., 2004a). Other studies recommended increased nut consumption to decrease the risk of gallstone occurrence (Almario et al., 2001; Tsai et al., 2004b). An increased consumption of vegetable protein (Tsai et al., 2004b), dietary magnesium (Humphries, Kushner, & Falkner, 1999), and Vitamin E (Kris-Etherton et al., 2001; Worthington, Hunt, McCloy, Maclennan, & Braganza et al., 1997) has also been associated with decreased gallstone occurrence.

Summary

In summary, cholelithiasis is a significant health problem in westernized countries. Increasing incidence of cholelithiasis in the U.S. makes it a burdensome and costly digestive

disorder (Everhart & Ruhl, 2009; Sandler et al., 2002). It seems crucial to affect behavioral changes aimed at reducing chronic cholelithiasis complications—for example, controlling intakes of dietary cholesterol, reducing body weight, and increasing physical activity. Understanding the epidemiology of gallstone disease is an asset in managing the disorder when planning preventive programs and identifying optimal therapeutic strategies (Festi et al., 2008).

Although much work has been completed to identify the risk factors for cholelithiasis, several studies have indicated that definitive answers remain elusive (Halldestam et al., 2009; Johansson, Sundstrom, Marcus, Hemmingsson, & Neovius, 2014; Singh et al., 2001). Gallstone prevalence varies among countries (Bateson, 2000; Massarrat, 2001; Reshetnikov, Ryabikov, Shakhmatov, & Malyutina, 2002) and ethnic populations (Everhart et al., 1999), and it is therefore not possible to transpose changes in prevalence from one community to another. Studies that defined specific population with the consideration of multidimensional factors should be employed during the screening of populations with cholelithiasis. Understanding the pathology of gallstone disease can help nurses provide the resources and education to those patients who were diagnosed for symptomatic gallstones and may also assist in the prevention of cholelithiasis. Big data studies are also needed to give researchers a more comprehensive picture of cholelithiasis.

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TABLE 1.

Factors Related to Female Gender and Cholelithiasis Risks

Reference	Year	Study Design	Sample Size	Results Related to Cholelithiasis Risk	Implications for Practice
Cirillo et al.	2005	Survey-based observational study (USA)	22,579 (female); aged 50–79	Estrogen therapy and female gender were strong risk factors for GS	Monitor for symptoms of GD after use of oral contraceptives, multiparous and older age pregnancies
Moghaddam et al.	2013	Random trial (Iran)	380 (female) in their first trimester of pregnancy	Pregnancy parity after 35 years related to GS occurrence	Monitor for GD symptoms in postmenopausal women on estrogen hormone therapy
Murray et al.	1994	An observational follow-up study (UK)	46,000 (female)	Symptomatic GS associated with multiple pregnancies	
Racine et al.	2013	Survey-based observational study (France)	70,928 (female); 16 years of follow-up	Oral estrogen hormone therapy associated with risk of GD	

Note. GD = gallstone disease; GS = gallstones.

TABLE 2.

Factors Related to Serum Lipids and Cholelithiasis Risks

Reference	Year	Study Design	Sample Size	Results Related to the Risk of Cholelithiasis	Implications for Practice
Fu et al.	1997	A case control study (China)	66	Serum apo A [1], C [2], E, and high LDL level, no association with TC, TG, HDL	Recommend lowering of serum LDL, TG, and raising HDL through diet and medications
Han et al.	2000	A case control study (China)	631	TC, low LDL, apo B level	Recommended further studies to clarify the serum lipid level in relation to GD in different ethnicity
Tang et al.	1996	A case control study (China)	109	Apo A, B, serum insulin level, high HDL, lower LDL	
Thijs et al.	1990	A case control study (Netherlands)	776	Low HDL, high TG, but no association with TC	Monitor for elevated cholesterol, LDL, TG, and low HDL after symptoms of GD

Note. Apo = apolipoprotein; GD = gallstone disease; GS = gallstones; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

TABLE 3.

Factor Related to Body Weight (Obesity and Weight Loss) and Cholelithiasis Risks

Reference	Year	Study Design	Sample Size	Results Related to the Risk of Cholelithiasis	Implications for Practice
Chen et al.	2006	A random trial (Taiwan)	3,647 (male = 2,305; female = 1,343)	Aging, high BMI, DM, glucose intolerance	Monitor glucose levels when BMI levels are high in women over 40 years
Katsika et al.	2007	A retrospective data-based twin study (Sweden)	58,402	High BMI associated with symptomatic GD; high alcohol consumption inversely associated with GD; no association with tobacco consumption	Encourage weight loss and diets with a low glycemic index. Increase physical activity
Li et al.	2009	A retrospective data-based study (USA)	717	Aging, female gender, high BMI, DM, hyperlipidemia, weight loss > 25%	Encourage patients to quit smoking and to set healthy weight loss goals
Stampfer et al.	1992	An observational follow-up study based on survey (USA)	90,302 (female); 8 years of follow-up	Women with BMI > 45 have seven times the risk of GD. Female smokers also have greater risk of GD	Monitor for severe weight fluctuation (≥ 20 lb of weight loss or gain) after symptoms of GD
Stender et al.	2013	An observational follow-up study (Denmark)	77,679; up to 34 years of follow-up	High BMI associated with symptomatic GD in women	Encourage an active, healthy lifestyle
Syngal et al.	1999	An observational follow-up study based on survey (USA)	47,153 (female); 16 years of follow-up	High weight cycling (≥ 20 lb of weight loss or gain) associated with cholecystectomy	Educate patients to adopt healthy weight loss goals
Tsai et al.	2006a	An observational follow-up study based on survey (USA)	51,529; 10 years of follow-up	Larger weight fluctuation, high BMI in men	
Volzke et al.	2005	A data-based population study (Pomerania)	4,202	Aging, female gender, high BMI, low HDL	

Note. BMI = body mass index; DM = diabetes mellitus; GD = gallstone disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

TABLE 4.

Factors Related to Diet and Physical Activity and Cholelithiasis Risks

Reference	Year	Study Design	Sample Size	Results Related to the Risk of Cholelithiasis	Implications for Practice
Almario et al.	2001	A random trial (USA)	13 postmenopausal females	Walnuts beneficially alter lipid distribution	Recommend nut consumption as part of a prescribed cholesterol-lowing diet
Leitzmann et al.	1998	An observational follow-up study based on survey (USA)	45,813 (male); 8 years of follow-up	30-min × five times per week endurance training prevents GD	Educate patients 30-min daily exercise to decrease the risk of GD
Leitzmann et al.	1999	An observational follow-up study based on survey (USA)	60,290 (female)	Women sitting > 60 hrs per week higher chance for cholecystectomy	Recommend 2–3 hrs of recreational exercise per week to reduce the risk of GD
Misciagna et al.	1999	A random trial (Italy)	390	A sedentary lifestyle, diet rich in animal fat, refined sugar, poor in vegetable, fat, and fibers	Evaluate each patient's eating and activity pattern, and set for realistic goals for each individual
Moerman et al.	1994	An observational follow-up study (Netherlands)	860; 25 years of follow-up	Sugars (monosaccharaides and disaccharides), and calcium intake inversely associated	
Rajaram et al.	2001	A random trial (USA)	23 (male = 14; female = 9)	Pecans rich in monounsaturated fat diet improve lipid profile, decreased TC, LDL, and increase HDL	
Tsai et al.	2004b	An observational follow-up study based on survey (USA)	45,756 (male); 457,305 person-years	Men consuming five or more units of nuts (peanuts and other nuts) per week (frequent consumption) had a lower risk of GS	Further assessment and study on the preventive effects of nuts on GD is recommended
Tsai et al.	2005a and 2005b	An observational follow-up study based on survey (USA)	51,529 (male) 70,408 (female); up to 16 years of follow-up	High intake of carbohydrate, GL and GI associated with the risk of symptomatic GD in men and women	Recommend dietary management to balanced diet (a variety of foods including fruits and vegetable, healthy carbohydrates, proteins, and fats) calorie reduction, and low carbohydrate diet
Tsai et al.	2006b	An observational follow-up study based on survey (USA)	77,090 (female); up to 16 years of follow-up	Greater fruit and vegetable consumption against risk of cholecystectomy in women	
Tsai et al.	2008	An observational follow-up study based on survey (USA)	44,524 (male); up to 17 years of follow-up	High intake of long-chain saturated fats associated with GS and cholecystectomy	Encourage a diet low in animal fat, refined carbohydrates and of moderate caloric intake to decrease risks of GD
Tsunoda et al.	2004	A retrospective data-based study (Japan)	1,264 (male)	Per daily calorie intake	

Note. GD = gallstone disease; GI = glycemic index; GL = glycemic load; GS = gallstones; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol.