

Risk Factors of Cholelithiasis: A Literature Review

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Abstract

Cholelithiasis is one of the major health problems around the world. The prevalence of cholelithiasis varies by country. The ethnicity of the people and the geographical location of a country has a huge role in the prevalence of gallstone disease. The etiology of gallstones is not well understood. The most important predisposition factor of gallstone formation is the supersaturation of cholesterol, hypomotility of the gallbladder, and excess bilirubin. Gallstones risk factors are multifactorial. Age, ethnicity, female gender, disease history, and family history are all known to play a role in the development of gallstones. Gallstones have also been linked to smoking, alcohol consumption, body mass index, and cholesterol levels. Sudden weight loss, contraception, and pregnancy in woman also shown to associate with cholelithiasis.

Keywords : Cholelithiasis, Gallstones, Risk Factors

1 Cholelithiasis

a. Definition

Cholelithiasis or gallstones are deposits of hardened bile fluids that form inside the gallbladder [1]. Cholelithiasis is a stone formed in the gallbladder consisting of cholesterol, bilirubin, and bile [2]. Gallstones are deposits of hardened bile fluid and can form inside the bile ducts. Rock sizes vary from as small as a grain of sand to the size of a golf ball [3]. Gallstones are formed from a combination of several elements that form inside the gallbladder. Gallstones are classified according to their chemical composition as cholesterol stones (>75%), pigment stones, and mixed stones [4].

b. Pathogenesis

The pathogenesis of gallstones is thought to be multifactorial and may develop from complex interactions between many genetic and environmental factors. Cholesterol hypersecretion and gallbladder

hypomotility affect the formation of cholesterol stones and the deposition of pigment stones influenced by calcium hydrogen bilirubin. Pigment supersaturation and deposition of inorganic salts, phosphates, and calcium bicarbonate affect the acceleration of stones deposition [5].

The etiology of gallstones is not fully known. The most important predisposition factors of gallstone formation are the supersaturation of cholesterol, hypomotility of the gallbladder, and excess bilirubin. Cholesterol supersaturation arises due to increased cholesterol levels produced by the liver and cannot be dissolved by bile. Hypomotility of the gallbladder causes a decrease in the emptying of the gallbladder so that stones are formed. Excess bilirubin can be caused by a hematological condition that causes the liver to produce too much bilirubin through the hemolysis process so that the bilirubin will settle in the gallbladder [1].

c. Epidemiology

Cases of cholelithiasis are pretty common in developed countries, about 10-15% of the adult population. Cholelithiasis was found in 6% of men and 9% of women. Cholesterol gallstones are the most common type found, namely 90-95%. Increased gallstones case can be seen in a high-risk group called "4 Fs": forty (over 40 years of age are more at risk), female (women are more at risk), fertile (parity), fatty (obesity) [6].

The highest prevalence of gallstone disease was reported in 64.1% of women and 29.5% of North American Indians. Native Indian Mapuche of Chile, 49.4% female and 12.6% male have gallstones. White Americans have an overall prevalence of 16.6% in women and 8.6% in men. Asians and black Americans have a moderate prevalence rate (13.9% of women and 5.3% of men). The lowest frequency occurs in sub-Saharan black Africa (<5%).

2 Cholelithiasis Risk Factors

a. Age

The frequency of gallstones increases with age, increasing sharply after the age of 40 to 4 to 10 times more likely in older people. The type of stone also changes with age. At first, it primarily consists of cholesterol but in old age tends to be black pigment stones [7]. One of the mechanisms known to affect the incidence of gallstones is the activity of cholesterol 7 α -hydroxylase, a rate-limiting enzyme for the synthesis of bile acids that decrease with age.

Reduced activity of cholesterol 7 α -hydroxylase causes the concentration of biliary cholesterol saturation so that the synthesis of bile acids becomes increased [3].

A southeastern Iranian study showed a higher prevalence of gallstone disease in populations 45 and older than people aged 30-44. These results align with most previous studies from other parts of the world, including Western countries and other parts of Asia [8]. Research in Ghana also found that the prevalence of gallstones was significantly higher among patients 40 years of age or older than patients under 40 years of age [9].

b. Gender

The female sex has the strongest association with gallstone disease, especially during the fertile period. Women are almost twice as likely to form stones than men. Female sexual hormones were found to influence the formation of gallstones. Parity, contraceptive use, and estrogen hormone replacement therapy are the underlying risk factors for gallstone formation [7].

A study in Korea showed that prevalence of asymptomatic cholelithiasis is higher in women less than 40 years old. It is most likely related to the effects of estrogen or pregnancy. On the other hand, the prevalence of asymptomatic cholelithiasis is higher in men than women over the age of 50 years. This change in prevalence is thought to occur due to a decrease in the effects of estrogen or pregnancy, thus reducing the formation of cholelithiasis in women. The increased prevalence in such males is due to an increase in other lithogenic factors [10]. Research in Ghana also found that the prevalence of gallstones was higher in women in all age groups except for patients under the age of 20 [9].

c. Ethnic Group

According to the *Kamus Besar Bahasa Indonesia*, ethnicity is a social group in the social or cultural system that has a specific meaning or position because of its descendants, tradition, religion, language, etc. Ethnicity is the main risk factor determining the type of stone to be formed, its location, and why it can develop [11]. In developed countries, the majority of people experience cholesterol stones (>85%), and the rest is black pigment stone (calcium bilirubin). A multi-ethnic cohort study involving African-American, Japanese, Native Hawaiian, and Latino and white populations showed results of 35.2% Latino, 23.3% Japanese, 19.4% white, 18.4% African-American, and 3.8% Native Hawaiian. Research in North India gave the result of

gallstone prevalence of 6.20%. Gallstones are more common with symptoms (7.12%) compared to asymptomatic (2.99%) [12].

d. Body Mass Index

People with a high Body Mass Index (BMI) have a higher risk of occurring cholelithiasis. High BMI affects the increase in cholesterol levels in the gallbladder. Obesity increases the risk of cholesterol gallstones by increasing the activity of reductase 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA Reductase), resulting in increased secretion of biliary cholesterol that causes the formation of gallstones [3]. Increased biliary cholesterol accompanied by a decrease in bile salts in bile fluids can increase the formation of gallstones [13].

A study in China showed that increased BMI is an independent risk factor for gallstone disease [14]. Research conducted by Su et al. (2019) showed an increased association of gallstones in younger people with metabolic syndrome and obesity [15]. Other studies have also shown that food and BMI factors are strongly associated with gallstone disease, along with positive family history and menopause [16].

e. Family History

Various studies have shown that family and genetic histories have a significant role in gallstones. The underlying mechanism for the familial tendency to gallstone disease is not well understood. It may be due to genetic susceptibility or shared lifestyle, or metabolic factors. The Cholesterol 7 α -hydroxylase gene is one of several genes that is suspected to be the underlying mechanism for the familial tendency to gallstone disease. People with a family history of gallstones have a five times greater risk factor than people without a family history of gallstones. Research on twin couples from the Swedish Twin Registry shows genetic factors constitute a 25% risk factor for gallstones [17]. A study in Shanghai also found that subjects with a family history of gallstones had a 21-fold risk of gallbladder cancer. In contrast, subjects with a history of gallstones and positive family history of gallstones increased to 57 times the formation of gallbladder cancer. Significant factors were seen for all first-rate relatives, including parents, siblings, and offspring, but not in couples [18].

f. Smoking

A meta-analysis study confirmed the presence of a 19% increased relative risk among smokers with a dose-response relationship with an increase in the number of cigarettes smoked per day. Meanwhile, former smokers and someone who has been smoking have a relative increased risk of 10 and 15% [19]. In contrast, a study conducted by Kono et al. (2002) did not provide evidence that smoking increases the risk of gallstones [20]. Biological mechanisms are still unclear, even if smoking can increase the predisposition of the occurrence of gallstones. Low HDL plasma concentrations associated with smoking may positively link smoking and gallstone disease [21].

A rational explanation of these contradictory findings may lie in the effects of the nicotine dose consumed. An experimental study in mice showed an increase in bile acid secretion in the low-dose nicotine-fed group of mice rather than the high-dose nicotine-fed and control group [22].

g. Alcohol Consumption

A meta-analysis study showed that alcohol consumption was associated with a significantly reduced risk of gallstone disease [23]. The basic mechanism of the relationship between alcohol consumption and gallstone disease is still not fully understood. Some studies have found mechanisms that explain the influence of alcohol consumption on the formation of gallstones. Alcohol can stimulate the emptying of the gallbladder and result in the protection of gallstone formation [24]. Other studies suggest alcohol can affect bile lithogenicity through increased serum concentrations of HDL and thus reduce the risk of gallstone disease [25].

On the other hand, excessive alcohol consumption can increase the risk of liver damage. Fatty liver and hepatic cirrhosis have been shown to be involved in the development of gallstones [26]. Reduce concentrations of apolipoprotein A1 and A11 is known to be a related mechanism in the cause of liver damage as a result of excessive alcohol consumption [27].

h. Diabetes Mellitus

A meta-analysis study showed that diabetic patients had a 56% increased relative risk of developing gallbladder disease [19]. The basic mechanism of association between diabetes mellitus and gallstones is multifactorial. Changes in glucose metabolism in people with type 2 diabetes mellitus may increase the risk of gallstone formation. Hyperglycemia inhibits the

secretion of bile fluid from the liver and can cause contraction of the bile ducts as well as the effect on gallbladder motility. Gallstone patients have higher concentrations of fasting insulin than those without gallstones [28].

A study found a higher prevalence of type 2 diabetes mellitus (36.3%) in gallstone patients and a link between type 2 diabetes mellitus and gallstones [29]. A cohort study also showed the same result that the cumulative incidence of surgery for symptomatic gallstones in the diabetic group was 13.06 cases per 1000 people per year [14].

i. Hypertension

The relationship between gallstones and cardiovascular disease can occur due to the same pathophysiology of cholesterol metabolic pathways. Hypertension is one of the cardiovascular diseases that can cause cholesterol build up in blood vessels. Cholesterol accumulation is a crucial feature of atherosclerosis and gallstones. The formation of atherosclerosis in blood vessels can increase blood pressure which also leads to an increased risk of cardiovascular disease and indirectly also increases the risk of gallstone disease. A meta-analysis study showed a substantially increased risk of cardiovascular disease among patients with a medical history of gallstone disease [30]. Other studies have also confirmed gallstone disease is linked to the development of peripheral, coronary, and cerebrovascular artery disease [31].

j. History of Liver Disease

Non-Alcoholic Fatty Liver Disease (NAFLD) covers a broad spectrum of liver conditions ranging from pure fatty liver to Non-Alcoholic Steatohepatitis (NASH), which can eventually develop into cirrhosis, portal hypertension, and hepatocellular carcinoma. Liver insulin resistance, associated with obesity, type 2 diabetes mellitus, and dyslipidemia, is a metabolic condition that supports the occurrence of NAFLD [32]. The very high prevalence of gallstone and NAFLD makes it highly likely to occur simultaneously in a large number of cases, but NAFLD and gallstone also share the same risk factors. An experimental study reported that insulin resistance in the liver might be associated with biliary cholesterol secretion, thus encouraging the formation of cholesterol gallstones [33]. High insulin levels can increase liver cholesterol secretion, biliary cholesterol supersaturation, and gallbladder dysmotility, while insulin resistance has been linked to metabolic syndrome and susceptibility to gallstone formation.

k. Serum Cholesterol

A study by Atamanalp et al. (2013) showed that high cholesterol serum levels and high LDL serum could lead to the formation of cholesterol gallstones by increasing cholesterol excretion with bile fluids [34]. In contrast, high HDL serum was found not to contribute to the formation of gallstones. Another study conducted by Serin et al. (2017) showed that low HDL levels are known to play a role in the formation of gallstones [35]. Studies in China have also shown that TC, TG, and LDL levels are risk factors for gallstones, while HDL is a protective factor [36]. Similar results were also shown by a comparative analytical study, in which it was found that high TG serums and low HDL serums were positively correlated to several studies. However, no significant LDL relationship was found with the formation of gallstones [37].

l. Sudden Weight Loss

Sudden weight loss is one of the predisposing factors for the formation of gallstones. During weight loss, there is an increase in cholesterol saturation that may occur due to the mobilization of cholesterol from adipose tissue. In addition, impaired gallbladder contractions and decreased nucleation time during these phases tend to increase the risk of gallstone formation [38]. A study showed that the prevalence of gallstone formation at 16 weeks of sudden weight loss was 10.9% [39]. Factors that affect the formation of gallstones during sudden weight loss include initial BMI and the amount of BMI lost. On the other hand, a study did not show any link between weight loss and gallstone formation. However, there was a change in gallbladder motility in patients who experienced weight loss >10% [40].

m. Contraception

Contraception is defined as the prevention of intentional conception through the use of various devices, sexual practices, chemicals, drugs, or surgical procedures [41]. A case-control study by Scragg et al. (1984) showed that age variations with concentrations of sex hormones in women, such as oral contraceptive use and pregnancy, were associated with a risk of gallstone formation, especially in young women who were metabolically susceptible to it [28]. In postmenopausal women, the risk factors for gallstone formation are influenced by an endogenous factor, such as increased concentrations of the estrogen hormone. A cohort study by Etminan et al. (2011) showed a statistically significant slight increase in the risk of gallstone disease associated with the use of oral contraceptive drugs [42]. In contrast, a meta-analysis study by

Wang et al. (2017) showed that oral contraceptives had no significant association with cholelithiasis, while hormone replacement therapy was positively associated with the risk of cholelithiasis [43].

n. Pregnancy History

Pregnancy may increase the risk of gallbladder stone formation. In pregnancy, most often, cholesterol stones arise. Changes in the hepatobiliary function that occur during pregnancy cause the gallbladder to become stasis, increase the amount of cholesterol, and decrease the amount of chenodeoxycholic acid [44]. Women who have a history of gallstones before pregnancy may present symptoms such as pain to acute cholecystitis. Physiological changes in postpartum women can also cause changes in the composition of bile and can accommodate the regression of stones or bile fluids. In postpartum women, after gallbladder motility returns to normal, stones and bile fluids can come out on their own and can cause biliary colic as well as other complications. Several have shown that there is an increase in the incidence of gallstones in women during pregnancy. On the other hand, Walcher et al. (2005) research shows that pregnancy and the number of pregnancies are not risk factors for gallstones [45].

3 Conclusion

This paper concludes that cholelithiasis may arise due to various risk factors. However, the etiology of cholelithiasis are still well not understood. Preventive steps must be taken for people with risk factors mentioned to prevent and reduce the occurrence of gallstones.

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