Gallstone and Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus (DM) is a metabolic disease which has high prevalence among the population. The prevalence is increasing in accordance to life style changes in the society. Gallstone is frequently found in diabetic patients especially in women with type 2 DM. Nevertheless, studies on the prevalence of gallstone among diabetic patients population have shown inconsistent/contradictive results.

Insulin resistance which is frequently found in type 2 DM patients is the underlying factor that correlates obesity, central adiposity, and low physical activity with gallstone disease. Two important physiological reasons in diabetic patients that may increase the risk of gallstone formation are: (1) Increased total cholesterol synthesis that causes bile becomes more easily transformed into cholesterol stone (lithogenic); (2) Diabetic patients have larger size and probably reduced motility of the gallbladder that cause increased formation of cholesterol crystals. However, recent study demonstrated that DM that merely exists without any contribution of other factors is not significant to increase the risk of gallstone formation.

The gallstone management in diabetic patients is the same as the management in non-diabetic patients. Elective surgery with laparoscopic cholecystectomy is the treatment of choice for symptomatic cases. Drug treatment is indicated for patients with cholesterol stone, small stone (diameter <5 mm), and well-functioned cystic duct.

Keywords: *diabetes mellitus, gallstone, insulin resistance, cholesterol synthesis, motility, laparoscopic cholecystectomy*

INTRODUCTION

Alexander Tralles (525-605) from Byzantine Empire is the first doctor who reported the existence of gallstone disease. Gallstone disease can affect people of all social class, race, either young or old, women or men, regardless of their health status. However, the prevalence is increasing with age and three times more common in women than in men. [1] In the western world, gallstone is one of the most frequent digestive problems that cause hospital admission. In the US among the adult population, 10-15% (more than 20,000,000) people suffer from gallstone; there are more than one million new patients annually, and more than 600,000 patients undergo cholecystectomy each year. [1]

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With the changing life style that adopt western culture, increasing prevalence of obesity, diabetes, sedentary life style, excessive fat consumption in developing countries including in Indonesia will also induce the increasing prevalence of gallstone in our country. There has been no study yet in the national scale about the prevalence of gallstone disease in Indonesia. The risk factor of gallstone formation including obesity, estrogen, ethnic/race, gender, age, cholesterol lowering drugs, diabetic drugs, rapid weight loss, and prolonged fasting.[2]

Diabetes Mellitus (DM) is a metabolic disease with high prevalence among the population. The prevalence of this disease is increasing in accordance to life style changes in the society. Gallstone is frequently found in diabetic patients especially in women with type 2 DM.[3,4] Nevertheless, studies on the prevalence of gallstone among diabetic patients population have shown inconsistent/contradictive result.[5] This article will review the correlation between DM and its effect on gallstone, particularly in the aspect of pathogenesis and

the treatment. With better understanding on the risk factors, especially diabetes, hopefully we will also be able to prevent and provide better treatment for the patient.

EPIDEMIOLOGY

Reports of two studies: the autopsy and epidemiologic study show conflicting result. Large scale case control study in Canada did not reveal the correlation between cholesterol cholelithiasis and DM.[5,6] Several supporting studies include the cohort study conducted by Pangliarulo et al. The study showed that the prevalence of gallstone formation is significantly higher in the DM population compared to general population (24.8% versus 13.8%).[5] The prevalence of gallstone formation is two to three times higher in diabetic patients compared to non-diabetic patients.[7]

Furthermore hyperinsulinemia, insulin resistance, beta cell dysfunction, are also associated with the risk factor of gallstone formation in women with type 2 DM.[3]

Epidemiologic study in Italy showed that there were multiple risk factors (e.g. hyperinsulinemia, age, obesity, type 2 DM) associated with the formation of gallstone.[8] Recent study shows that diabetes is associated with gallstone formation in univariate analysis but not in multivariate analysis.[9] On the other hand, age and obesity, that are frequently found in type 2 DM patients, are strong risk factors for the development of gallstone.[3,9,10,11] Study conducted by Alokaba, et al. in Nigeria reported that increased age is a risk factor for gallstone formation in diabetic patients. Hyperlipidemia, overweight, female gender, duration of DM disease were also associated with such risk factor.[12,13]

PATHOGENESIS AND THE EFFECT OF DIABETES MELLITUS ON GALLSTONE

There are two types of gallstone, i.e. cholesterol stone and pigment stone. Cholesterol stone is usually in yellow-greenish color and mostly derived from hardened cholesterol. Eighty percent of gallstone is cholesterol stone. Some of the gallstone is pigment stone, dark colored and made from bilirubin.[14]

Figure 1. Two types of gallstone; white (cholesterol stone), brown/black (pigment stone).[2]

Genetic Factors and Environment

In western countries, more than 75% of gallstones are cholesterol type. There are different prevalences of gallstone according to ethnic group in a country, this condition indicates the evidence that genetic factor affects the incidence of gallstone formation. In America, the highest prevalence is found in Pima Indian North America, Chilean, and Caucasians. In Asian population, the prevalence is low; but there is medium prevalence in European countries. The role of genetic factor in gallstone formation has been proven through animal experimental study.[14]

The influence of environmental factor is very supportive in the progressive increase of gallstone prevalence. Recent studies have demonstrated significant evidences that lifestyle and behavior factor including central obesity, low physical activity, diet, and drugs are predisposing factors for symptomatic/asymptomatic gallstone. Insulin resistance that is frequently found in type 2 DM patients is the underlying mechanism associating/correlating obesity, central adiposity, and low physical activity with gallstone disease.[14]

Studies conducted by Misciagna et al, Pagliarulo et al, Chi Ming Liu et al, and Constance et al have demonstrated evidence that hyperinsulinemia, insulin resistance, beta cell dysfunction, obesity, family history of gallstone were associated with risk factors of gallstone formation in women with type 2 DM.[3,7,15,16]

Table 1. Differences on pathogenesis and clinical correlation between cholesterol stone and pigment stone[14]

Characteristics	Cholesterol stone	Black pigmented stone	Brown pigmented stone
Anatomic location	Gallbladder	Gallbladder	Bile duct and gallbladder
Geographic and clinical association	Western countries overweight/obesity, diabetes, pregnancy, sedentary life style	Western and Asian countries, chronic hemolysis, cirrhosis, healthy person	Mostly in Asia, biliary infection
Bile culture	Usually sterile	Usually sterile	Infected (enteric and anaerobic organism)
Major component	Cholesterol, calcium bilirubinate/carbonate	Pigment polymer, calcium phosphate/carbonate	Calcium bilirubinate, calcium, fatty acid, cholesterol
Etiology	Cholesterol, hypersecretion, gallbladder stasis, pro nuclease factors in bile	Increased excretion and hydrolysis of conjugated bilirubin	Bacterial hydrolysis, bile stasis

Synthesis and Metabolism of Biliary Fat

Bile is fluid substance containing lipid, protein, and electrolyte. There are three kinds of major biliary lipid/fat, i.e: cholesterol, bile acid, and phospholipids (mainly phosphatidylcholine). In addition, protein derives from serum, which is synthesized by the liver, bile duct and gallbladder epithelium. Gallstone formation is determined by chemical and physical interaction between various biliary lipid and biliary protein as follows.:[14,17]

(1) Cholesterol solubilization: Biliary secretion is the main pathway of cholesterol elimination. Cholesterol is not water soluble in nature and it may easily become water-soluble with the addition of bile. Within the bile, cholesterol is dissolved with biliary lipid, bile salt, and phospholipids. Maximal cholesterol solubility to be eliminated from the body is defined by cholesterol saturation index (CSI). *In vitro,* CSI can be calculated by the ratio of the amount of cholesterol and bile to reach the maximum capacity of cholesterol transport. Supersaturation is defined if CSI >1;[14,17] (2) Cholesterol supersaturation; Cholesterol secreted by the liver sometimes exceeds the transport capacity of biliary lipid that makes the bile becomes supersaturated and easily get precipitated. The failure in maintaining the homeostasis of biliary secretion results in biliary cholesterol hypersecretion or relative hyposecretion of bile acid. Clinical condition associated with biliary cholesterol hypersecretion including obesity, rapid weight loss, increasing age, effect of drug treatment (e.g. clofibrate, estrogen, and progesterone). Clinical condition associated with relative hyposecretion of the bile acid e.g. chronic cholestatic disease; ileal disease;[14,17] (3) Cholesterol crystal nucleation; The early stage of gallstone formation is the formation of stone nucleus and precipitation of solid cholesterol crystal in saturated bile (nucleation). Several studies found that there are factors that may increase the nucleation (pronucleation) or inhibit the nucleation (anti-nucleation) in animal study *in vitro*. Pro-nucleation factors e.g. mucin of the gallbladder, alpha-1 glycoproteinic acid, aminopeptidase N, immunoglobulin M and G, haptoglobin, fibronectin and alpha-1 antichemotrypsin. Moreover, anti-nucleation factors include biliary protein, immunoglobulin A and apolipoprotein AI and AII. If this early stage (nucleation) continues, it will increase precipitated and hardened cholesterol crystal leading to the gallstone formation.[14]

The Role of Gallbladder

Gallbladder itself has an important role in the formation of cholesterol stone especially its mucosal layer and its motility. Gallbladder does not only serve as a storage organ; moreover, it absorps water, secretes hydrogen ion, concentrates and acidifies the bile. Principally, gallbladder modifies the solubility of cholesterol, calcium, and bilirubin. Thus, gallbladder concentrates and promotes the nucleation process. Gallbladder also produces mucin as an important pronucleus factor.[14,17]

Altered lipid metabolism in the mucosal layer of the gallbladder also contributes to gallstone formation. In physiologic condition, gallbladder absorps phospholipid and cholesterol from the bile, decreasing the bile hardening. In contrast, gallbladder in patients with cholesterol stone absorps less phospholipid and cholesterol.[14,17]

The gallbladder motility is one of the key factors. Gallbladder dysmotility and stasis are other risk factors for the formation of cholesterol stone. In human, prolonged parenteral nutrition may induce stasis and dysmotility of the gallbladder that promote the formation of the bile sludge. Pregnancy, oral contraceptive, obesity, diabetes mellitus, and ocreotide treatment are also associated with the weakness of gallbladder emptying and promote the gallstone formation. Gallbladder stasis makes the bile more concentrated and enhances the gallstone formation (lithogenic), as well as facilitates cholesterol crystal precipitation. In contrast, adequate gallbladder motility will remove cholesterol crystal quickly from the gallbladder and prevent the formation of gallstone.[14]

Diabetic patients are at increased risk of gallstone formation for two important physiologic reasons, i.e.:[5] (1) Increased total cholesterol synthesis in the body that promote easier cholesterol stone formation from the bile (lithogenic); (2) Diabetic patients have larger gallbladder with probably reduced motility that increase the formation of cholesterol crystal.[5,18,19] However, recent study suggests that diabetes mellitus alone without any contribution from other factors is not significant in increasing the risk for gallstone formation.[5]

Haber and Heaton examined lipid composition of the bile in diabetic patients and in control group. There were no significant difference in biliary cholesterol saturation in type 1 or type 2 DM patients compared to the control group. Type 1 DM patients have unsaturated bile to the cholesterol; while type 2 DM patients with higher body mass index (BMI) have more saturated bile compared to type 1 DM patients. Therefore, the risk of lithogenic stone was greater for type 2 DM patients than in type 1 DM patients and it has more correlation to the obesity than the diabetes. Similar fact has also been demonstrated by other studies, i.e. diabetes alone did not predispose abnormal secretion of the bile. There were no significant correlation between diabetes and the type of gallstone e.g. pigment stone or cholesterol stone, if other variables had been corrected such as the presence of cirrhosis, pigment, and cholesterol.[20]

In physiologic condition, the liver secretes

unsaturated bile. The presence of cholesterol, bile salt, and lecithin in the bile preserve the cholesterol in stable solubility.[21] Pathologic conditions that cause reduced bile salt secretion or increased cholesterol secretion will produce supersaturated bile formation with cholesterol, which result in more lithogenic bile and may develop into the formation of cholesterol crystal or even gallstone. Several risk factors that underlies lithogenic bile secretion are: the increased age, obesity, hypertriglyceridemia, and reduced bile salt depo.[22]

Cholecystographic study showed slower/reduced gallbladder emptying in diabetic patients.[23] Similar studies using ultrasonography and scintigraphy for analyzing gallbladder emptying showed contradictive/ inconsistent result. Most of reduced/weak gallbladder emptying in diabetic patients are associated with the presence of autonomic neuropathic complication. However, it was still difficult to determine the difference of motoric function/dysfunction of the gallbladder from such studies.[5]

MANAGEMENT/TREATMENT

Two-third of gallstone patients is asymptomatic and the annual risk for biliary colic is about 1-4%. Preventive cholecystectomy is not recommended since asymptomatic patients rarely develop serious complication.[1,2] Patients with symptomatic gallstone will develop complication for about 1-2% each year and 50% of them will have reccurent episode of biliary colic. Therefore, definitive therapy (surgery) is recommended for symptomatic patients.[1,2]

Cholecystectomy

The role of surgery in diabetic patients with asymptomatic gallstone is still controversial. In the past, it was believed that DM patients with asymptomatic cholelithiasis should better have surgery to prevent further increased mortality and morbidity. This aggressive therapy was proposed by Rabinowitch in 1932. He stated that DM patients with cholecystitis will have worse complication than non-diabetic patients.[5] In 1961, Turrill et al, reported that the mortality rate after gallstone surgery was increased to five-fold in diabetic patients.[5]

Other authors also stated similar facts; i.e. there is increased mortality and morbidity in patients who have undergone emergency cholecystectomy. Limited analysis in diabetic patients in the 5^{th}-6^{th} decades of age that have undergone cholecystectomy showed 20-fold increased mortality compared to non-diabetic patients. Another author suggested elective surgery for diabetic patients. The rate of mortality and morbidity in diabetic patients underwent elective surgery was similar to non-diabetic patients. Both Turril et al and Mundth recommend all diabetic patients to undergo screening and oral cholecystography and when there is gallstone, elective surgery will be conducted.[5] Ileus gallstone is one of the rare complication of post-cholecystectomy cholelithiasis that may lead to serious and fatal condition. It is reported to increase the mortality rates by 7.5-15%, which is usually associated with elderly women, diabetes mellitus, and cardiorespiratory impairment.[24,25]

In the later study, diabetic patients showed lower morbidity and mortality than the previous reports. These are first due to advanced development of medical treatment and surgery, particularly in the era of antibiotic nowadays. Second, previous studies did not report the influence of comorbidity in diabetic patients (e.g. atherosclerosis) that probably may contribute to the increased post-operative mortality. Finally, previous studies did not use either appropriate control group or similar period of observation, which none of final data suggests elective cholecystectomy for asymptomatic gallstone patients. However, since emergency cholecystectomy in patients with acute cholecystitis is associated with the increased morbidity and mortality, we should consider elective cholecystectomy in diabetic patients with biliary symptoms especially when there are no serious comorbidity existed. Laparoscopic cholecystectomy is recommended and is probably safer than abdominal cholecystectomy.[5]

Non-surgical Treatment (Medical Dissolution)

This method is suitable for patient who is unable to undergo definitive treatment by laparoscopic or open cholecystectomy. Two bile acid, i.e. cenodioxycholic acid (3 alpha, 7 alpha-Dihydroxycholanoic acid (CDCA) and 7 beta epimer (3 alpha, 7 beta dihydroxycholanoic acid, ursodioxycholic acid) had been widely used for gallstone dissolution. These two bile acids induce the secretion of less/un-saturated hepatic bile, and do not increase the absolute amount of bile acid secretion. Biological effect of CDCA and UDCA treatment include suppression of hepatic cholesterol synthesis by inhibiting hydroxymethyl glutaryl Co-A reductase, increasing the activity of 7 alpha hydroxylase, and reducing cholesterol absorption in the intestine.

The recommended dosage is 8–12 mg/kg body weight/day. Preparation of patient selection is the most important factor for success of such treatment. It is indicated for cholesterol stone (radiolucent stone), small stone (diameter < 5 mm), and well-functioned cystic duct.[15]

CONCLUSION

Diabetes mellitus is a risk factor that should be concerned in gallstone formation. Insulin resistance, hyperinsulinemia, increased cholesterol synthesis, impairments of gallbladder motility or gallbladders

emptying due to autonomic neuropathy are factors associated with increased incidence of gallstone formation in diabetic patients. However, diabetes mellitus do not contribute significantly to the gallstone formation without the presence of the other risk factors. Elective surgery with laparoscopic cholecystectomy is the treatment of choice and it is only indicated for symptomatic patients.

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