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Obesity, dyslipidemia, and diabetes mellitus as risk factors in cholelithiasis

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ABSTRACT

Objectives: Cholelithiasis or gallstones has many risk factors, such as age, sex, obesity, dyslipidemia, and diabetes mellitus (DM). Studies in developing country shown that obesity, dyslipidemia, and DM occurred in 55.0%, 76.0%, and 17.7% of adults with cholelithiasis, respectively. The aim of this study is to know the proportion of cholelithiasis risk factors.

Materials & methods: This retrospective study using descriptive cross sectional design performed in one of the largest referral hospital in Jakarta Indonesia. Demographic data, and laboratory examination were collected from medical record. Patients presented with cholelithiasis from the abdominal ultrasonography was enrolled into study.

Results: 93 subjects were selected through consecutive sampling, where in 65.8% were female and 77.5% age>40 years. The majority was obese (47.3%) and the obesity grade I was most prevalent. Dyslipidemia was found in 19.3% subjects with proportion of high total cholesterol was 54.5%, high LDL 90.9%, high triglycerides 27.3%, and low HDL 18.2%. DM was found in 15.0% subjects. Random blood glucose had higher proportion, accounting 57.2% with mean 140.67±89.69 mg/dl. Female and age>40 years had more proportion in cholelithiasis patients.

Conclusions: Proportion of cholelithiasis with obesity 47.3%, dyslipidemia 19.3%, and diabetes 15.0%. However, the proportion of obesity, dyslipidemia and diabetes in this study was lower than other studies in Asia or developing countries. Patients with obesity grade I, high LDL and RBG>40 mg/dl should be aware to have cholelithiasis.

Keywords: cholelithiasis, diabetes mellitus, dyslipidemia, obesity, risk factor

INTRODUCTION

Cholelithiasis, commonly known as gallstone, are hard particles that develop in the gallbladder or bile ducts. Radiologic imaging, particularly ultrasound, is the preferred method for diagnosing gallstone [1]. Bile fluid, an alkaline aqueous fluid, comprises various organic constituents, including bile salts, cholesterol, lecithin, and bilirubin. Bile salts play a crucial role as they consist of fat-soluble and water-soluble components, allowing them to adhere to the surface of fat granules and aid in the digestion of fats through emulsification. These bile salts, along with cholesterol and lecithin, form micelles facilitate the absorption of fats. But an imbalance between cholesterol, lecithin, and bile salts can lead to an excess of cholesterol in bile, forming microcrystals that eventually clump together to form gallstone [2].

Gallstone can develop due to several risk factors, including dyslipidemia, diabetes mellitus (DM), and obesity [3]. Additional risk factors include the age above 40 and female, primarily due to the effects of estrogen hormone. Elevated estrogen levels can raise bile cholesterol levels and decrease gallbladder motility, ultimately leading to the development of gallstone. Cholesterol saturation of bile fluid also increases with age primarily due to a decline in the activity of cholesterol 7α hydroxylase, the enzyme responsible for regulating bile acid synthesis [4].

The formation of gallstone is guided by three key principles, namely cholesterol supersaturation, increased nucleation of cholesterol crystals, and gallbladder hypomotility. Cholesterol supersaturation can occur due to increased cholesterol secretion, reduced bile acid secretion, and diminished lecithin secretion. The nucleation of cholesterol crystals is influenced by both pro-nucleation and anti-nucleation factors made cholesterol gallstone. Meanwhile calcium bilirubinate, calcium carbonate and phosphate were the commonest calcium salts identified in pigment gallstones and core of mixed cholesterol gallstones [4]. Obesity is a medical condition characterized by an excessive of body fat in adipose tissues that impact health negatively. Obesity is categorized into two types, namely, abdominal or central obesity (apple-shaped) and peripheral obesity (pear-shaped). Obesity can be assessed using body mass index (BMI) values (**Table 1**) [5].

Table 1. Body mass index classification

Classification	BMI
Underweight	<18.5
Normal	18.5-22.9
Overweight	23.0-24.9
Obese I	25.0-29.9
Obese II	>30.0

Obesity can lead to the formation of gallstone through various mechanisms. Firstly, it can cause an increase in the secretion of cholesterol in the bile, leading to the supersaturation of bile in the gallbladder. This supersaturation promotes the formation of gallstone. Additionally, obesity can disrupt the normal emptying of the gallbladder due to impaired gallbladder motility, which further contributes to the precipitation of gallstone. Obese patients may experience an enhanced hepatic response to fat accumulation, which can also contribute to the formation of gallstone [4, 6, 7]. Study in India reported, 77.4% of cholelithiasis patients had their BMI below 26, while BMI in the range of 24.00-26.00 kg/m^2 was found in more than 55.0% patients [6].

Dyslipidemia is a lipid metabolism disorder characterized by imbalances in blood lipid fractions. These imbalances can include increased or decreased levels of various lipid components. Elevated total cholesterol, LDL cholesterol, triglycerides, and decreased HDL cholesterol are common lipid abnormalities associated with dyslipidemia (**Table 2**). LDL cholesterol is considered the primary atherogenic lipoprotein and is a key target for managing dyslipidemia [8]. When cholesterol concentration in bile surpasses its solubility capacity, it forms solid cholesterol monohydrate crystals instead of remaining dispersed. Study in India, found out of 73 cholecystectomy, cholesterol was raised in 80.0% of females and 71.4% of male patients. Triglycerides were raised in 44.4% of female patients and 39.3% of male patients [8].

Table 2. Dyslipidemia diagnostic value

Lipid profile	Laboratory values
Total cholesterol	>200 mg/dL
Low density lipoprotein cholesterol	>100 mg/dL
Triglycerides	>150 mg/dL
High density lipoprotein cholesterol	<40 mg/dL

Type 2 DM is characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. The prevalence of DM is increasing worldwide, including in Indonesia. The diagnostic criteria for DM based on laboratory tests include fasting blood glucose levels of 126 mg/dl or higher, blood glucose levels of 200 mg/dl or higher two hours after an oral glucose tolerance test, random blood glucose (RBG) levels of 200 mg/dl or higher with classic symptoms, or an HbA1c level of 6.5% or higher [9]. Diabetes patients are at an increased risk of gallstone formation due to two mechanisms. Firstly, increased synthesis of total cholesterol in the body, promoting cholesterol stone formation. Secondly, diabetic patients also often have larger gallbladders with reduced motility, leading to increased cholesterol crystal formation [10, 11]. Studies in Brazil showed the prevalence of cholelithiasis 37.0% out of 70 patients with type 2 DM. Prevalence of gallstone disease is higher in diabetic individuals, with a prevalence of 21.0% in the diabetic group compared to 9.0% in the non-diabetic group [10]. Meanwhile study conducted in India found that 17.7% of patients with DM had gallstone detected by ultrasound [11]. Furthermore, study in Iran showed an inverse relationship between daily physical activity, intake of fruits, vegetables and fish with risk of gallstone disease formation [12]. There is limited data in Indonesia that showed proportion of cholelithiasis risk factor. Thus, this study was done to know proportion and characteristics of obesity, dyslipidemia, DM among cholelithiasis patients one of largest referral hospital in Jakarta, Indonesia.

MATERIALS & METHODS

Study Design & Participants

This is a retrospective study employed observational methods using descriptive cross sectional design. The data of cholelithiasis patients were obtained from abdominal ultrasound examination through medical record in Fatmawati General Hospital Jakarta Indonesia that conducted in 2017.

Sample Size & Measurement Tools

A total of 93 subject were selected using consecutive sampling method. The inclusion criteria encompassed inpatients and outpatient aged 18 to 65 years old, which diagnosed with gallstone, with or without complications. The descriptive and statistically analysis was performed using Microsoft Excel 2016 and SPSS 22.0.

RESULTS

Characteristic of Subjects

Most of gallstone subjects were female and age more than 45 years old, accounted for 65.6% and 69.9%. Age more than 40 years, as risk factor of gallstone was accounted in 72 (77.5%) subjects. The most prevalent was age 55-65 years (38.7%) (**Table 3**). **Table 3** also showed 47.3% of gallstone subjects were obese, including obesity grade I and grade II, with the most prevalent was obesity grade I (31.2%).

Table 3. Characteristics of subject

Parameter	Classification	Proportion (%)
Sex	Male	32 (34.4)
	Female	61 (65.6)
Age	18-25 years	4 (4.3)
	26-35 years old	4 (4.3)
	36-45 years old	20 (21.5)
	46-55 years	29 (31.2)
	56-65 years	36 (38.7)
Nutrition status	Underweight	8 (8.6)
	Normal weight	17 (18.3)
	Overweight	24 (25.8)
	Obesity 1	29 (31.2)
	Obesity 2	15 (16.1)

Risk Factor of Obesity in Cholelithiasis

Overweight also played a role to become risk factor of cholelithiasis, accounting 25.8% subjects (**Table 4**). **Table 4** showed 31.3% of men were normoweight, while 34.3% were classified as obesity grades I and 12.6% were classified as obesity grade II. Proportion of normoweight and overweight in female were similar at 26.2%, while obesity grade I was found at 29.6%. The mean BMI for male and female were similar, accounting 25.17 kg/m^2 for men and 25.80 kg/m^2 for female.

Table 4. Subjects distribution based on IMT

	Men (%) n=32	Women (%) n=61
Normoweight	10 (31.3)	16 (26.2)
Overweight	7 (21.8)	16 (26.2)
Obesity 1	11 (34.3)	18 (29.6)
Obesity 2	4 (12.6)	11 (18.0)
Mean body mass index (kg/m^2)	25.2	25.8

Risk Factor of Dyslipidemia in Cholelithiasis

Among the 93 subjects, 19 (19.3%) subjects exhibited dyslipidemia, a condition characterized by multiple abnormalities in lipid function tests. These abnormalities include high LDL cholesterol, total cholesterol, serum triglycerides, or low HDL cholesterol (**Table 5**).

Table 5. Characteristic of lipid profile between sex in dyslipidemia subjects

Lipid profile	Male	Female	Total	
	n	n	n	%
High cholesterol	5	7	12	54.5
High triglyceride	2	4	6	27.3
High low density lipoprotein	7	13	20	90.9
Low high density lipoprotein	1	3	4	18.2

In this study high LDL cholesterol was most prevalent lipid profile accounting 90.9% subjects. High cholesterol also has high prevalence in 54.5% subjects.

From the data on the lipid profile of gallstone patients, the mean and standard deviation of the overall laboratory results of lipid function were obtained (**Table 6**).

Table 6. Lipid mean values

Lipid profile	Mean (SD) mg/dl
Low density lipoprotein cholesterol	148.86 (30.15)
Total cholesterol	200.32 (27.03)
Triglycerides	125.27 (54.13)
High density lipoprotein cholesterol	46.54 (11.30)

Table 6 illustrated that the mean LDL cholesterol and total cholesterol values exceed the normal range, indicating a notable increase of values lipid profile.

Risk Factor of Type 2 Diabetes Mellitus in Cholelithiasis

In the examined group of 93 subjects with gallstone, 14 (15.0%) subjects were found to have DM. The remaining 79 (85.0%) subject had no previous history of DM or did not exhibit any blood glucose abnormalities in their laboratory tests.

As shown in **Table 7**, high RBG was most prevalent between male and female, accounting 57.2% while the high fast blood glucose and post-prandial blood glucose were similar accounting 21.4%. **Table 8** showed that all blood glucose measurements have mean values within the normal range. This indicates that there is likely no significant increase in blood glucose levels among gallstone patients with DM.

Table 7. Blood glucose profile between sex in diabetic mellitus subjects

Blood glucose	Male	Female	Total	
	n	n	n	%
High random blood glucose	3	5	8	57.2
High fasting blood glucose	2	1	3	21.4
High post-prandial blood glucose	2	1	3	21.4

Table 8. Blood glucose mean values

Blood glucose	Mean (SD) mg/dl
Random blood glucose	140.67±89.69
Fasting blood glucose	102.50±37.80
Post-prandial blood glucose	152.30±91.40

DISCUSSION

Our study found the most of gallstone subjects were female and age more than 45 years old, accounted 65.6% and 69.9%. Age more than 40 years, as risk factor of gallstone was accounted in 72 (77.5%) subjects. The most prevalent was age 55-65 years (38.7%). This study showed that female has high proportion in subjects with gallstones (65.6%), which similar with study conducted in Sri Lanka accounted for 77.8% [4]. Study in Iran has also shown females were 2.73 times (95% CI; 1.34-5.56) more likely to have cholelithiasis compared to males as well [12].

Some studies showed female had higher proportion than male, due to effects of estrogen hormone. Estrogen refers to group of female hormones like estrone (E1), estradiol (E2), and estriol (E3), estetrol (E4), which C18 steroids hormone derived from cholesterol. Cholesterol is taken up by steroidogenic cells, stored, and moved into the site of steroid synthesis [13]. The classical estrogen regulatory pathway involves E2 promotion of cholesterol biosynthesis and liver secretion of bile cholesterol through the “E2-ESR1-SREBP-2” pathway. During times of increased blood estrogen concentration, synthesis of cholesterol increases mainly by estrogen-induced stimulation of sterol regulatory element binding protein-2 (SREBP-2). These changes lead to excessive secretion of newly synthesized cholesterol, supersaturation of bile, and easily lead to cholesterol precipitation and gallstone formation [14]. There is new mechanism established that estrogen receptor α (ER-α in liver, plays a critical role in pathogenesis of 17-estradiol (E2)-induced gallstones. G protein-coupled receptor 30 (GPR30), a novel estrogen receptor, is involved in lithogenic effect of E2 on gallstone formation [14]. Biomolecular review study in USA stated three points:

(1) E2 disrupts biliary cholesterol and bile salt homeostasis through ER-α and GPR30, leading to a distinctly abnormal physical-chemical state of bile predisposing to supersaturation with cholesterol,

(2) E2 activates GPR30 and ER-α to produce liquid crystalline versus anhydrous crystalline metastable intermediates evolving to solid plate-like cholesterol monohydrate crystals in supersaturated bile, and

(3) GPR30 produces a synergistic lithogenic action with ER-α to promote E2-induced gallstone formation. ER-α and GPR30 also impair gallbladder motility function, which is GPR30 disrupting the function of gallbladder sterol transporters in the epithelial cells.

Furthermore ER-α plays a pivotal role in inhibiting the expression of cholecystokinin-1 receptor (CCK-1R) in the muscle cells for inducing gallbladder stasis. This suggests that GPR30 and ER-α have a synergistic effect on the formation of gallstones induced by E2 [15].

This study showed most prevalent age who had cholelithiasis were above 45 years old, accounting 69.9%. The age distribution was similar with a study conducted in Sri Lanka that the mean of age 46.10±11.60 years [6]. This results

also similar with a study in Korea, whereas the mean age cholelithiasis patients was 47.30±10.90 years [16]. Study in India stated prevalence of gallstone increased with increasing age with peak in the sixth decade (23.4% in cases and 4.4% in controls (p=0.001), that result was similar with our study, showed 38.7% subjects were age 55-65 years [11]. Our study showed obesity grade I was found in 34.3% male subjects, obesity grade II found in 12.6% male subjects, while obesity grade I was found at 29.6% in female. Obesity grade I had the highest proportion in both sexes. The mean BMI for male and female were similar, accounting 25.17 kg/m^2 for men and 25.80 kg/m^2 for female. This study was compared to a study conducted in China that participants with gallstones had a higher prevalence of metabolic syndromes (gallstones: 46.3% vs. no gallstones: 30.7%) and higher BMI (gallstones: 24.70 kg/m^2 vs. no gallstones: 23.70 kg/m^2) [17].

Obesity is known to increase the secretion of intra-hepatic cholesterol, which contributes to formation of gallstone [17, 18]. Also, body fat distribution was observed to play a role in gallstone formation [18]. Visceral fat release vasoactive substances directly into the portal venous system, triggering a pro-inflammatory response through macrophage activation and the release of inflammatory cytokines such as TNF-α and IL-6. These cytokines inhibit the expression of adiponectin, an adipocyte-derived hormone that enhances insulin sensitivity and fatty acid oxidation, thereby exerting anti-diabetic and anti-atherogenic effects. Consequently, this process leads to insulin resistance and manifestation of metabolic syndrome.

The proportion obesity or central obesity have become serious health problems in developing countries such as Indonesia. A study was conducted in Indonesia for ten years survey from the largest national health survey using total sampling method from 33 provinces showed the prevalence of obesity and central obesity in the Indonesian adult population are 23.1% and 28.0%, with BMI cutoff value of ≥25.00 kg/m^2. Moreover, based on the World Health Organization data, the prevalence of obesity in Indonesia was the highest in Southeast Asia with more than 30.0% of adult population. Both rates are higher in females than in males. Obesity and central obesity also associated with the risk of diabetes and hypertension. Obesity rates in Indonesia are increasing rapidly in both rich and poor households as they shifted from traditional diets towards processed products, which is unhealthy food with high fat and sugar, and less expensive than wholesome foods. Other factor was sedentary lifestyle due to modernization and advance technology have reduced physical activity. Economic growth in Indonesia also influenced the rates of obesity [19, 20]. Those were explained why obesity was the main factor of gallstone in our study that different with other countries in Asia such as China and India, while the major risk factor of gallstone is dyslipidemia [21]. Understanding the risk factors for gallstone is useful in assisting physician to provide resources and education for patients who are diagnosed with gallstones, and also develop novel preventive measures for the disease.

This study revealed that 19.3% of gallstone patients had dyslipidemia, indicating a correlation between dyslipidemia and risk factors for gallstone formation. Furthermore, a significant elevation in LDL cholesterol levels (90.9%) was observed in gallstone patients with dyslipidemia. This finding aligns with study conducted by Atamanalp, which identified high LDL cholesterol as a marker for an increased risk of cholesterol gallstone disease [22]. An elevation in LDL levels in the blood serum leads to increased cholesterol accumulation in the liver, thereby increasing risk of cholesterol stone formation in the gallbladder or ducts. A study conducted in Iran, reported a higher prevalence of elevated LDL in cholelithiasis subject compared to other lipid functions [7]. This study showed four subjects (18.2%) with low HDL. Another study by Kim showed that those with low HDL had a significantly high risk for cholelithiasis [23]. However, some studies found no significant association between HDL cholesterol and cholelithiasis [24].

This study also reported that 15.0% of cholelithiasis patients had DM. These findings corresponded closely with a study conducted by Malik et al. in India, which showed a prevalence rate of 12.8% for gallstone in individuals with DM especially type 2 DM, although, our study did not differentiate any type of diabetes [8]. The elevated blood glucose levels in DM can inhibit gluconeogenesis including lipogenesis. Consequently, accumulation of fat would be converted into glucose for energy, will increase cholesterol synthesis, resulting in deposition of cholesterol in the gallbladder. Besides that, bile of diabetic patients is more lithogenic since the supersaturation of cholesterol in bile is higher and the concentration of bile acids is lower that leads to the formation of gallstones [16]. DM can impact gallbladder neuropathy, affecting both autonomic and peripheral functions. This can manifest through an imbalance in cholecystokinin (CCK) release and reduced responsiveness of gallbladder muscles to CCK stimulation. These mechanisms can impair gallstone contraction, ultimately contributing increased risk of gallstone formation. Different result was found in the study in Pakistan that showed 36.6% gallstone subjects have DM [25]. The difference between this study can be caused by genetic variability. Hence, this study has similar results with retrospective study in Taiwan demonstrate an increased association of gallstones in younger people (<50 years old) with metabolic syndrome such as dyslipidemia, DM and obesity [26].

Limitation of Study

The utilization of secondary data from medical records patients in this study introduces the possibility of encountering incomplete variables or missing data patients, such as age, gender, weight, or ultrasound information. Therefore, these limitations can impact the sampling and overall study findings. The second limitation is the proportion only took place in the single center, not in multiple center.

CONCLUSIONS

As a conclusion, significant proportion of gallstone patients were female (65.8%), while the age range of 56-65 years old constituted the highest percentage (38.7%), and 77.5% of age above 40 years patients had cholelithiasis in this study. Proportion of gallstone with obesity are 47.3%, dyslipidemia 19.3% and diabetesf 15.0%. Obesity grade I with mean BMI>25.17 kg/m^2 was the most prevalent in this study. However, the proportion of obesity, dyslipidemia and diabetes was lower than other study in Asia or developing countries, patients with high LDL cholesterol, high total cholesterol, obesity grade I and had RBG more than 140 mg/dl have to be aware to have cholelithiasis. Further study in Indonesia with more samples in multiple center should be done to identify more risk factor of cholelithiasis.

Author contributions: HH, FNA, JBM, RAA, SNAN, & HA: critically reviewed & approved final draft; **HH, FNA, JBM, RAA, & SNAN:** designed & directed research, collected, organized, & analyzed data, & wrote initial, second, & final drafts of manuscript; **HH & FNA:** main supervisor of study & contributed its design & implementation; & **JBM & RAA:** contributed to data collection. All authors have agreed with the results and conclusions.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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