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Interrelation between body mass index and the occurrence of gallstones

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Abstract
Introduction: Gallstones (cholelithiasis) are solid accumulations of crystals in the gallbladder that occur due to cholesterol supersaturation, excessive bilirubin production, or gallbladder contractility disorders. The pathogenesis is suspected to be multifactorial with obesity, age, and gender as non-modifiable factors. Although the prevalence of cholelithiasis in Asis is recorded between 3-10%, publications regarding definitive figures in Indonesia or Central Jawa are still rare. With the obesity trend occurring in Indonesia and the relatively high prevalence of cholelithiasis case in Surakarta, it is possible that gallstone complications occur due to excessive BMI. The purpose of this study is to assess the relationship between body mass index and the occurrence of gallstones at Dr. Moewardi Regional Hospital, Surakarta.
Methods: Observational analytic study with a cross-sectional approach was used in this study. The sample used consists of secondary data in the form of medical records of patients aged over 18 years at Dr. Moewardi Regional Hospital from January to April 2023, who have either excess or normal BMI. A total of 86 research subjects were obtained (43 patients with gallstones and 43 patients without gallstones) from the Surgery and Internal Medicine Departments, as well as Post-Cholecystectomy Inpatient Clinics, which were then analyzed using the Chi-Square test.
Results: The result of the Chi-Square test on the relationship between body mass index and the occurrence of gallstones showed a p-value of 0.017 (p<0.05).
Conclusion: There is a significant relationship between body mass index and the occurrence of gallstones at Dr. Moewardi Regional Hospital, Surakarta.

Keywords: Gallstones, cholelithiasis, obesity, body mass index

Introduction

Gallstones or cholelithiasis are accumulations of crystals formed from digestive fluids in the form of solid masses that can form in the bile duct. The incidence of cholelithiasis in developed countries is quite high, found in about 10-15% of the adult population, which cholesterol gallstones were found to be the most prevalent type. More than half a million Americans require cholecystectomy due to cholelithiasis, affecting mor than 20 million people. To date, there is no epidemiological data on gallstones in Indonesia. The prevalence of cholelithiasis varies between 3% to 10% in Asia. A study found its incidence in China, Northern India, Taiwan, and Japan to be 10.7%, 7.1%, 5%, dan 3.2%, respectively [1].

There are two types of risk factors for cholelithiasis: non-modifiable and modifiable. Non-modifiable risk factors include white ethnicity (Caucasian), female gender, age over 40 years, and heredity. Modifiable factors include BMI >25 kg/m^2, rapid weight loss due to extreme diets or bariatric surgery, increased estrogen levels due to hormonal contraception or medication, and a sedentary lifestyle [2].

Obesity is a complex chronic disease defined by a BMI exceeding 25 kg/m^2.According to epidemiological research, obesity has become more common. From 1975 to 2016, the prevalence of obesity is estimated to have tripled in number. Over 650 million adults worldwide were overweight in 2016. Globally, 13% of adults were overweight or obese, including 15% of women and 11% of men. In all age categories, women had a higher prevalence of obesity than men. The peak of obesity epidemiology occurs between the ages of 50 to 65, then gradually decrease after [3, 4].

According to a 2018 study by Indonesia's Basic Health Research (Riskesdas), the prevalence of

obesity among adults in Indonesia increased from 14.8% in 2013 to 21.8%. The incidence was higher among women (29.3%) compared to men (14.5%). Conversely, the incidence of central obesity among individuals aged 15 and above was around 31%, with a higher prevalence among women (46.7%) compared to men (15.7%) [5].

Excess body fat disrupts health, reduces life expectancy, and increase the risk of long-term medical complications. One of the complications that can occur is cholelithiasis. The relationship between increase BMI as an independent risk Factor for gallstones has been widely found. Research by Anbiar *et al.* (2022) showed a relationship between obesity and gallstones (p = 0.019). This finding is consistent with the results of Nurhikmah *et al.* (2019), who found a relationship between increased BMI and cholelithiasis (p = 0.001). Obesity has been found to increase the risk of cholelithiasis due to gallbladder motility disorders, excessive liver secretion, and bile cholesterol saturation [6]. Considering the possibility that an obese person does not always have a history of hypercholesterolemia and vice versa, therefore obesity might not be the main risk factor of cholelithiasis.

However, cholelithiasis complications increase in obese patients compared to non-obese patients. Research by Persaud *et al.* (2021) showed that there were 78,385 patients with gallstone disease complications, of which 11,465 patients were obese. Logistic regression showed that obesity had an increased relationship with cholelithiasis complications (aOR 1.38, P= 0), most significantly with choledocholithiasis (aOR 1.52, P= 0). (7) The trend of increasing obesity prevalence among Indonesian adults increases the likelihood of many complications, one of which is the increase in cholelithiasis cases. Although the prevalence of cholelithiasis in Asia varies between 3-10%, there is no data on the distribution of cholelithiasis in Indonesia or Central Java. However, it is estimated that the number of patients with cholelithiasis undergoing surgery at the Department of Surgery of Dr. Moewardi Regional Hospital Surakarta ranges from 2-3 patients per day. Thus, it is estimated that around 80 patients experience cholelithiasis per month. This number can be considered quite high when accumulated annually. Based on this background, the author is interested in studying the relationship between body mass index and the occurrence of gallstone disease at Dr. Moewardi Regional Hospital.

Materials and Methods

This study used an observational analytic research type with a cross-sectional approach to analyze the relationship between two variables. This study was conducted at Dr. Moewardi Regional Hospital, Surakarta. The research sample used consists of secondary data in the form of patient's medical records at Dr. Moewardi Regional Hospital during the period from January to April 2023 selected by the following criteria:

1. Inclusion Criteria

- Patients diagnosed with cholelithiasis.
- Age >18 years.
- Body Mass Index ≥25 kg/m^2.
- Body Mass Index <25 kg/m^2.
- Complete medical record.

2. Exclusion Criteria

- Cholelithiasis patients with comorbid pancreatitis.
- Cholelithiasis patients with comorbid cholecystitis.

Using purposive sampling method, a sample of 86 patients (43 patients with gallstones and 43 patients without gallstones) who met the exclusion and inclusion criteria was obtained. The variable used in this study was cholelithiasis (no cholelithiasis and cholelithiasis) as the dependent variable and obesity (BMI <25 or non-obese and BMI ≥25 or obese) as the independent variable. The obese group consisted of patients with class I obesity (25.0-29.9) and class II obesity (≥30). The non-obese group consisted of underweight patients (<18.5), normoweight (18.5-22.9), and overweight (23.0-24.9). The collected data were then analyzed using the Chi-Square test to analyze the relationship between BMI and cholelithiasis/gallstones. Number 920/IV/HREC/2024 was obtained through Ethical feasibility testing was conducted at Dr. Moewardi Regional Hospital, Surakarta.

Results

Patients Characteristics Data

The study was conducted using medical record data of cholelithiasis and non-cholelithiasis patients at Dr. Moewardi Regional Hospital recorded during January to April 2023. The total data obtained amounted to 223 subjects consisting of 148 cholelithiasis patients and 75 non-cholelithiasis patients as controls. Controls are selected through patients with upper gastrointestinal syndromes not cholelithiasis. After selection according to exclusion criteria, 86 subjects were randomly selected from a total of 168 who met the inclusion criteria. The characteristics of the research subjects are presented in the form of frequency distribution tables (n) and percentage (%).

Table 1: Frequency distribution of Research Subject Characteristics

Characteristics	Mean± SD n (%)
Age	
All Subjects	50,07±13,99
Cholelithiasis	52,84±11,35
Non-Cholelithiasis	47,30±15,87
Gender	
Male	
All Subjects	36 (41,9)
Cholelithiasis	18 (50)
Non-Cholelithiasis	18 (50)
Female	
All subjects	50 (58,1)
Cholelithiasis	25 (50)
Non-Cholelithiasis	25 (50)
Weight (kg)	
All subjects	63,40±11,18
Cholelithiasis	65,65±9,59
Non-Cholelithiasis	61,15±12,26
Height (m)	
All subjects	1,58±0,08
Cholelithiasis	1,59±0,08
Non-Cholelithiasis	1,58±0,08
BMI (kg/m^2)	
All subjects	25,15±3,62
Cholelithiasis	25,89±2,82
Non-Cholelithiasis	24,41±4,17
Cholelithiasis	
Yes	43 (50)
No	43 (50)

Information: BMI, Body Mass Index; SD, Standard Deviation

Based on Table 1, the overall results of the subjects are as follows: the average age is 50.07 years, with 36 male and 50 female subjects; the average weight is 63.4 kg, and the average

height is 1.58 m. The average body mass index (BMI) is 25.15 kg/m^2.

For subjects categorized by cholelithiasis and non-cholelithiasis, the average age is 52.84 years and 47.3 years, respectively. The number of male and female subjects is the same in both categories, with 18 males and 17 females. The average weight is 65.65 kg and 61.15 kg, respectively, and the average height is 1.59 m and 1.58 m, respectively. The average BMI is 25.89 kg/m^2 for subjects with cholelithiasis and 24.41 kg/m^2 for subjects without cholelithiasis

Table 2: Detailed Characteristic Categories of Research Subject

Characteristics	Gallstones		No Gallstones		Total	
	n	%	n	%	n	%
Age						
20-24	0	0	3	7,0	3	3,5
25-29	2	4,7	2	4,7	4	4,7
30-34	2	2,3	4	9,3	6	5,8
35-39	4	9,3	7	16,3	11	12,8
40-44	4	9,3	6	14,0	10	11,6
45-49	5	11,6	3	7,0	8	9,3
50-54	5	11,6	5	11,6	10	11,6
55-59	10	23,3	4	9,3	14	16,3
60-64	6	14,0	3	7,0	9	10,5
65-69	4	9,3	2	4,7	6	7,0
70-74	2	4,7	2	4,7	4	4,7
75-79	0	0	1	2,3	1	1,2
94-99	0	0	1	2,3	1	1,2
Gender						
Male	18	41,9	18	41,9	36	41,9
Female	25	58,1	25	58,1	50	58,1
BMI						
Underweight	1	2,3	3	7,0	4	4,7
Normoweight	6	14,0	14	32,6	20	23,3
Overweight	12	27,9	13	30,2	25	29,1
Class I Obesity	20	46,5	8	18,6	28	32,6
Class II Obesity	4	9,3	5	11,6	9	10,5

Information: BMI, Body Mass Index

Based on Table 2, the results show that there are no subjects with cholelithiasis in the age ranges of 20-34 years, 75-79 years, and 94-99 years. The largest number of subjects, 10 (23.3%), are in the age range of 55-59 years. For subjects without cholelithiasis, the largest number, 7 (16.3%), are in the age range of 35-39 years. However, when looking at all subjects, 14 (16.3%) are in the age range of 55-59 years. The gender distribution is the same for both categories, with 18 males (41.9%) and 25 females (58.1%). Therefore, the overall frequency of occurrence for males and females is 36 (41.9%) and 50 (58.1%), respectively.

Subjects with a body mass index (BMI) of class I obesity (25-29.9 kg/m^2) have the largest number of subjects, 20 (46.5%), in the category of patients with cholelithiasis. In contrast, the largest number, 14, of subjects with a normal BMI are in the category of patients without cholelithiasis. Overall, the largest number of subjects have a BMI of class I obesity, followed by overweight, normal weight, class II obesity, and underweight, with numbers of 28 (32.6%), 25 (29.1%), 20 (23.3%), 9 (10.5%), and 4 (4.7%), respectively.

Data Analysis

Table 3: Cross Tabulation Between Body Mass Index and Gallstones Occurrence

	BMI (kg/m^2)		Total	P-value
	Non-Obese	Obese		
Cholelithiasis				
No	30	13	43	0,017
Yes	19	24	43	

Information: BMI, Body Mass Index

Based on the Chi-Square test results, a p value of 0.017 (p<0.05) was obtained, which means it is significant. Therefore, it can be concluded that there is a significant difference between BMI (obesity and non-obesity) and the occurrence of gallstones.

Discussion

Based on the Chi-Square test conducted, statistically, there is a significant difference between body mass index and the occurrence of gallstones. This is in line with the hypothesis and consistent with previous research done by Nurhikmah *et al.* (2019) that the frequency of increased body mass index in subjects with gallstones is higher than in those without gallstones. Another study conducted at Dr. N. Djamil Padang Hospital also showed similar results. The results showed that out of 44 subjects, 22 had a body mass index in the obesity category [8].

The same results can also be seen in the study conducted by Atsariyah *et al.* (2022), where there is a significant relationship between BMI and age with the risk of cholelithiasis. In their study, the average BMI of 50 cholelithiasis patients was 26.20 kg/m^2, classified as class I obesity. This number figure is not much different from the average BMI of cholelithiasis subjects in this study, which was 25,89 kg/m^2 and is also included in the

class I obesity category.

Obesity occurs as a result of positive energy balance process, where the amount of energy that comes from calory intake is more than it is used. This process causes the accumulation of triacylglycerol or triglycerides in adipose tissues which will then be broken down into free fatty acids and glyceryl [4]. Obesity is associated with more lithogenic bile, where bile production contains more cholesterol than can be dissolved. A study showed that in obese individuals, there is an upregulation of *hydroxyl-3-methylglutaryl-coenzyme A* (HMG-CoA) reductase activity stimulated by the increase of plasma insulin levels. This process happens as adipocyte hyperplasia and hypertrophy induces the release of cytokines (IL-6 & TNF-α) that causes inflammation and insulin resistance [9, 10]. This causes increased cholesterol absorption from the blood to the liver, which then triggers cholesterol hypersecretion into the bile and form a supersaturation. In addition, stasis or hypomotility of the gallbladder is also common in obese and overweight individuals, causing emptying disorders of the gallbladder [11, 12].

The occurrence of cholelithiasis in non-obese patients should also be considered, as 19 subjects were found in this study. This can be affected by other factors such as age, gender, and other underlying diseases. A study conducted by Kharga *et al.* in 2016 on ethnic groups including Nepali, Lepcha, Bhutia, etc. showed that the average BMI of 2,872 cholelithiasis patients was 24.93 kg/m^2. Most of these patients have a normal range of BMI in which 77.4% of them are below 26 kg/m^2. Furthermore, women can experience symptomatic cholelithiasis at a lower BMI level compared to men. Whether it is at a very young age or very old age, symptomatic cholelithiasis tends to occur in individuals with a high BMI. However, as age increases, the risk of symptomatic cholelithiasis increases proportionally with each increase in BMI. The risk increases by 7% for each BMI increase of 1 kg/m^2 [13, 14].

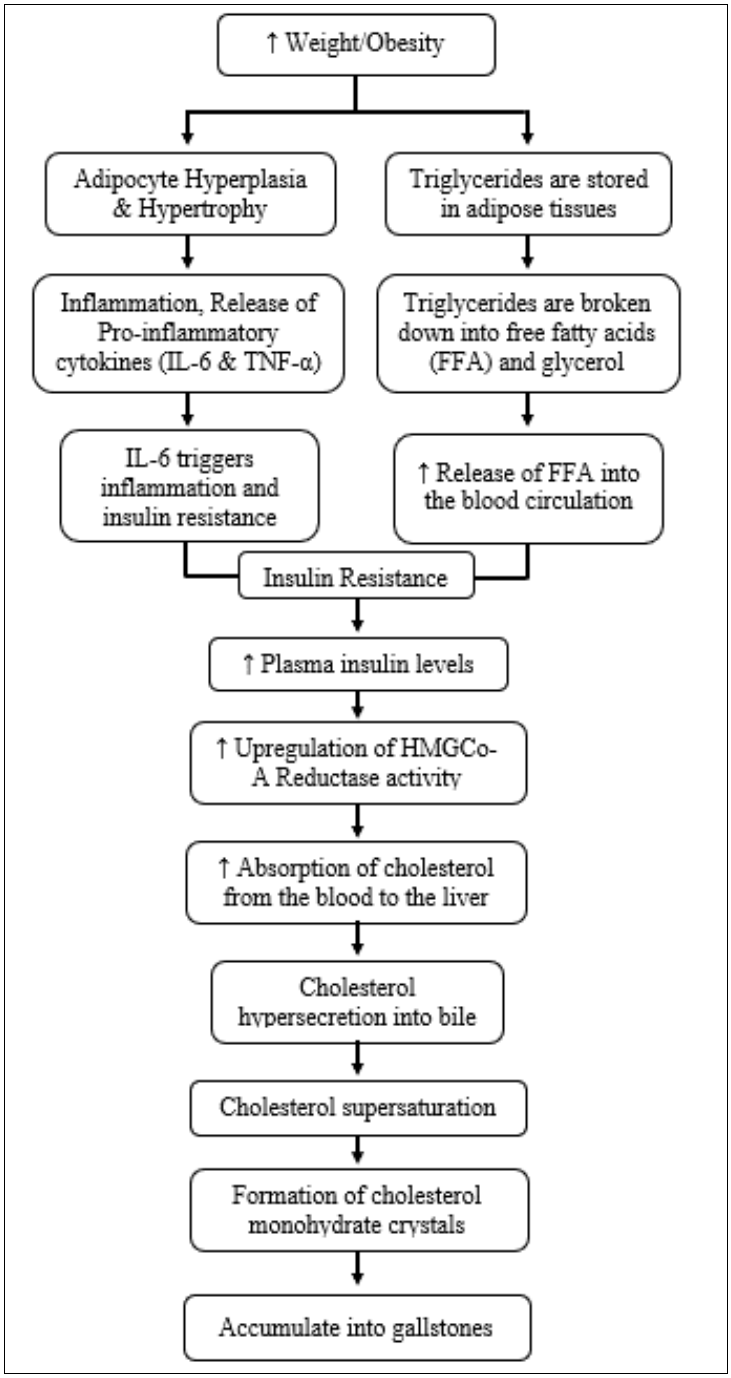

Fig 1: Obesity's role in the formation of gallstones

Out of the 43 study subjects with cholelithiasis, the average age of the subject is 52.84 years with female gender as a majority (25 subjects). This data is alike with the study conducted by Atsariyah *et al.* in 2022 which found a significant relationship between age and cholelithiasis, where the average age of patients was 51.05 years (pre-elder). Changes in the amount of cholesterol secretion in the bile and a decrease of bile acid due to the lowering of cholesterol 7α-hydroxylase enzyme (CYP7A1) activity are related to age because of the dyslipoproteinemia process. In addition, women are more prone to gallstones due to the presence of estrogen.

Between the age group of 55-59 years, women in Indonesia often already had their menopause. When menopause occur, estrogen level in women will experience a decrease in number which would cause a series of disturbing syndromes. These syndromes could be avoided using hormone therapy in which could cause the increase of estrogen levels. Increase of estrogen levels will then stimulate the synthesis and secretion of cholesterol through its binding with estrogen receptors in the liver. Estrogen suppresses HMGCo-A reductase activity and increases ATP-Binding Cassette (ABC) transporters activity, including ABCG5 and ABCG8 that have a role in controlling cholesterol efflux from hepatocytes to the bile [15, 16]. Estrogen also increases bile cholesterol saturation and decreases the amount of acid bile secretion as well as gallbladder's contractility when combined with progesterone hormone therapy [17-19].

Other health and disease histories such as type 2 diabetes mellitus in 6 patients over 50 years old and dyslipidemia in one patient aged 78 years old were found in this study. Cholesterol results through laboratory examination are still very limited as it is not always conducted. Only 7 data were found, with 3 within normal limits, 3 having HDL <40 mg/dL, and one diagnosed with dyslipidemia.

Type 2 diabetes mellitus is associated with insulin resistance and secretion disorders, causing high blood glucose levels. Insulin resistance can occur due to obesity. Two factors that can promote the formation of cholesterol crystal stones in type 2 diabetes patients are a larger gallbladder size but with low working capacity and excessive cholesterol synthesis. Hendarto *et al.* in 2023 conducted a study on obesity, dyslipidemia, and diabetes mellitus as risk factors for cholelithiasis in 93 subjects in Jakarta. In their study, 47.3% of patients had excess body weight, 19.3% had dyslipidemia, and 15% had diabetes.

90.9% out of the 19.3% cholelithiasis patients that had dyslipidemia in Hendarto's study experienced an increase in LDL cholesterol levels. Dyslipidemia occurs when there is an imbalance in blood fat levels, including total cholesterol, LDL (low-density lipoprotein), HDL (high-density lipoprotein), and triglycerides. Obesity is often associated with dyslipidemia. In obese patients, there will be an increase in cholesterol secretion which then causes supersaturation. Along with that, insulin resistance will affect lipid metabolism, increasing the levels of LDL and triglyceride but decreasing HDL levels. Lastly, inflammation, where adipose tissue produces pro-inflammatory cytokines (TNF-α dan IL-6) that disrupt lipid metabolism.

Research done by Kumar *et al.* (2016) also found a significant relationship between high levels of LDL, triglycerides, and total cholesterol, as well as low levels of HDL with cholelithiasis. Of the 100 patients who underwent cholecystectomy due to gallstones, high triglyceride levels were found in all age and gender categories, high total cholesterol and LDL in men over 20 years old, while low HDL in all genders aged over 20 years. Serum LDL levels are considered a risk factor for cardiovascular disease and gallstone formation. Generally, these serum levels are higher in obese people due to their role in transporting cholesterol from the liver to the peripheral tissues. In addition, disrupted lipid metabolism resulting in increased VLDL (very low-density lipoprotein) production, which will be converted into LDL, also affects. Therefore, this conversion supports the increase in cholesterol levels in blood [20-23].

The relationship between BMI and LDL cholesterol was found in a study by Li *et al.* (2021) in China involving 12,273 subjects, where there was a different non-linear pattern between obesity and non-obesity, as well as between men and women. In this case, there is a positive linear relationship between increase BMI and increased LDL cholesterol levels in all genders of non-obese and obese individuals. However, men have an inverted U-curve result explaining that LDL levels subsequently decrease at BMI >27,1 kg/m^2.

Conclusion

1. There is a significant relationship between body mass index and the occurrence of gallstones in Dr. Moewardi Regional Hospital from January to April 2023, with a p-value of 0.017 (p<0.05).
2. Patients with a non-obese BMI can develop gallstones. However, the higher the patient's BMI, the greater the risk of developing gallstones.
3. The average BMI of gallstone patients at Dr. Moewardi Regional Hospital from January to April 2023 was 25.89 kg/m^2, with the highest incidence occurring in the class I obesity category.
4. The average age of gallstone patients at Dr. Moewardi Regional Hospital from January to April 2023 was 52.84 years, with the highest incidence in the 55-59-year age range (pre-elderly).
5. Women were the most common gender among gallstone patients at Dr. Moewardi Regional Hospital during the January-April 2023 period.
6. Other health histories such as type 2 diabetes mellitus, dyslipidemia, and cholesterol levels can increase the risk of gallstone formation.

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Author's Contribution

Not available.

Conflict of Interest

Not available.

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