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THE ASSOCIATION BETWEEN HYPERCHOLESTEROLEMIA AND GALLSTONE FORMATION: A PROSPECTIVE STUDY

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ABSTRACT

Background: Gallstone is the most common biliary problem. The main etiology for stone formation is the abnormal deposition of cholesterol in bile. The main component of bile is cholesterol, which is insoluble in water, which requires the presence of phospholipids and bile acid to assist its dissolution in water. The imbalance between these components leads to the formation of gallstones. Elevated levels of cholesterol have been associated with several gallbladder disorders such as cholesterolosis and gallstone formation. Furthermore, obesity is regarded as the major risk factor for cholesterol gallstone disease. **Aim of the study:** To assess the relationship between hypercholesterolemia and gallstone disease. **Patients & Methods:** A cross-sectional study was conducted at Al-Kindy Teaching Hospital-Department of Surgery, over a period extending from the 1st of December 2021 to the 1st of December 2022. The sample size would be all cases admitted to the above-mentioned hospital and the decision of elective cholecystectomy was made. Measurement of the lipid profile of all participants, with an estimation of the incidence of hyperlipidemia and its risk factors. **Results:** The study included 213 participants, and all of them were diagnosed with gallstones. Measurement of the lipid profile showed that the prevalence of hyperlipidemia in the studied sample was 25.8%. hyperlipidemia is commonly found in hypertensive patients, cholesterol gallstone was commonly found in hyperlipidemia cases, and single gallstones and yellow gallstones were commonly found in hyperlipidemia cases. Distribution of lipid profile according to the type of gallstone showed that cases of cholesterol gallstone associated with a high level of serum cholesterol, low-density lipoprotein, very low-density lipoprotein, and serum triglycerides, with a low level of high-density lipoprotein. **Conclusion:** Hyperlipidemia is associated with an increased rate of cholesterol gallstone. The incidence of hyperlipidemia in gallstone disease (who is a candidate for surgery) was found to be 25.8%.

KEYWORDS: Gallstone, cholecystectomy, hyperlipidemia, cholesterol.

INTRODUCTION

Gallstone disease is a common condition that affects millions of people worldwide, and is associated with a range of risk factors including obesity, female gender, age, and sedentary lifestyle. Hypercholesterolemia has also been identified as a significant risk factor for gallstone formation, with elevated levels of cholesterol in the blood leading to the secretion of excess cholesterol into the bile and the formation of gallstones.[1]

Gallstone disease is a common condition, with an estimated 10-15% of adults in Western countries affected.[2] The prevalence is higher in women than men, with women having a two- to three-fold increased risk of developing gallstones compared to men.[3] The incidence of gallstone disease also increases with age, with the highest rates observed in individuals over the age of 60.[4] Obesity is another important risk factor for gallstone disease, with obese individuals having a two- to three-fold increased risk compared to those with a healthy weight.[5] The prevalence of hypercholesterolemia is also high, with an estimated 95 million adults in the United States alone affected.[6] Given the association between hypercholesterolemia and

gallstone disease, it is likely that these two conditions frequently coexist.

Clinical implications

The association between hypercholesterolemia and gallstone formation has important clinical implications for the management and prevention of gallstone disease. Patients with hypercholesterolemia should be advised of their increased risk of developing gallstones, and measures should be taken to reduce this risk where possible. This may include lifestyle modifications such as weight loss and increased physical activity, as well as pharmacological interventions such as statins to lower cholesterol levels.[7]

The management of gallstone disease in patients with hypercholesterolemia may also differ from that in patients without this risk factor. For example, the use of ursodeoxycholic acid (UDCA) may be more effective in patients with hypercholesterolemia, as this drug has been shown to reduce the cholesterol saturation index of bile.[8] Similarly, the use of bile acid sequestrants such as cholestyramine may be effective in reducing the risk of gallstone formation in patients with hypercholesterolemia, as these drugs bind to bile acids and prevent their reabsorption, leading to an increased demand for cholesterol and reduced cholesterol secretion into the bile.[9]

In addition to management strategies, the association between hypercholesterolemia and gallstone formation may also have implications for the diagnosis and screening of gallstone disease. Elevated levels of total cholesterol and low-density lipoprotein (LDL) cholesterol have been associated with an increased risk of gallstone disease, and measurement of these parameters may be useful in identifying individuals at risk.[10] Furthermore, the use of ultrasound to detect gallstones may also provide an opportunity to screen for hypercholesterolemia, as the presence of gallstones may be a marker of underlying metabolic abnormalities such as hypercholesterolemia.[11]

Hypercholesterolemia is associated with various health problems, but its relationship with gallstone formation is unclear. Gallstones are a common medical condition that can lead to complications, so understanding their risk factors is crucial. Previous studies have reported inconsistent results, and a prospective study is needed to clarify the association and adjust for potential confounding factors. Confirming an association could help identify individuals at high risk of gallstone formation, and the study could provide new insights into the pathogenesis and potential preventive and therapeutic strategies.

This study aims to assess the relationship between hypercholesterolemia and gallstone disease.

PATIENTS AND METHOD

A cross-sectional study conducted at Al-Kindy Teaching Hospital-Department of Surgery, over period extended from 1st of December 2021 till 1st of December 2022.

Sample size would be all cases admitted to the above-mentioned Hospital and decision of elective cholecystectomy was made.

Inclusion criteria

- Patients with gallstone disease admitted for elective cholecystectomy.

Exclusion criteria

- Chronic drug users (lithogenic drugs such as Progesterone, thiazide diuretics).
- Patients on lipid lowering agents.
- Patients refused to participate.

Data collection

All participants were interviewed with a checklist that included the demographic data, (age, gender, and body mass index). Clinical characteristics of gallstone disease include the presentation, duration of symptoms, previous hospital admission, ultrasound features of gallstone, including number of stones and size of the stone, gallbladder wall thickness. Basic blood investigations such as complete blood count, liver function test.

All cases would be investigated for the presence of hyperlipidemia by measuring serum level of lipid profile after 8 hours of fasting.

All cases underwent laparoscopic cholecystectomy and description of the stones were recorded (color, size, and number of the stones). Stones were sent for biochemical analysis to estimate the type of stone.

Laboratory analysis

Ten milliliters of venous blood were withdrawn from all participants, undergo analysis of AST and ALT, complete blood count and assessment of lipid profile.

Lipid profile measurement by collecting 5 ml of blood in red top test tube for 45 minutes allowing blood to clot and the clot retract. Centrifugation 1500 RPM for 30 minutes, sample preserved in -20°C till time of measurement. Thawing of samples then adding reagent, and measurement of using (Optima Sp-300 321513 spectrophotometer, Japan). Reference values provided by manufacturer as follow:

- Total serum Cholesterol (TC) <200 mg/dl.
- Serum Triglyceride (TG)<150 mg/dl.
- Serum high density lipoprotein (HDL) >60 mg/dl.
- Serum low density lipoprotein (LDL) <130 mg/dl.
- Serum very low-density lipoprotein (VLDL) <30 mg/dl.

Ethical consideration

Formal consent was obtained from each patient prior to collecting data, and information was anonymous. Names were removed and replaced by identification codes. All information is kept confidential in a password secured laptop and data used exclusively for research purposes.

Approval of the Council of Iraqi Board of Medical Specialization and the scientific committee of Al-Kindy Teaching hospital were obtained before starting the study.

Statistical analysis

All data were introduced into Microsoft Excel 16 and statistical analysis were conducted using IBM-SPSS (USA Chicago). and data were presented in the form of counts, percentage, mean, standard deviation (SD), minimum (Min) and maximum (Max) and presented in the form of tables, charts or graphs.

Testing of the level of significance of the categorical data was conducted using Chi square or Fisher exact test while continuous variables were tested using student t test or Mann Whitney u test when appropriate.

P value less than 0.05 considered statistically significant.

RESULTS

The study included 213 participants, all of them were diagnosed with gallstone. The mean age of the participants was 53.11 ±7.36 years with a range of (23-65) years. The male gender represents 14.1% of presented cases, as shown in

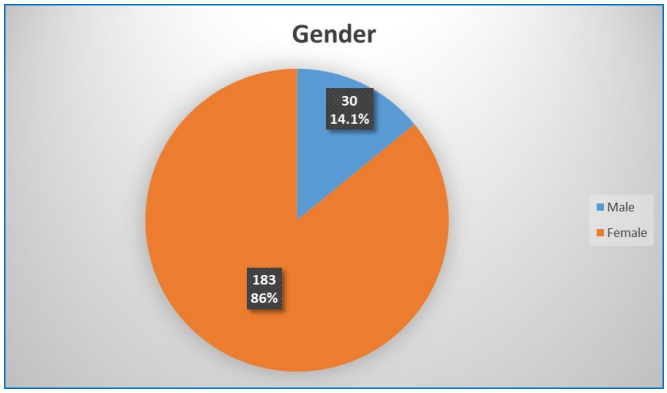

Figure 1: Distribution of the cases according to gender.

The majority of the cases (186 cases 87.3%) presented with multiple gallstones, the color of gallstone was mainly brown color (in 183 cases 85.9%) and only 14.1% of the cases (30 cases) had yellow gallstones. Wall thickness was increased in only 13 cases (6.1%).

The history of previous attack of biliary colic was reported in 89 cases (41.8%). The mean size of the stone reported by ultrasound (for the largest stone in cases of multiple stone) was 18.03±7.32 millimeter,

Table 1 showed the characteristics of gallstones in the studied sample.

Table 1: Characteristics of the stones.

Variables		No.	%
Number of stones	**Single**	27	12.7
	Multiple	186	87.3
Color	**Yellow**	30	14.1
	Brown	183	85.9
Type	**Cholesterol**	33	15.5
	Mixed	177	83.1
	Pigmented	3	1.4
Wall thickness	**Increased**	13	6.1
	Normal	200	93.9
Previous biliary colic	**Yes**	89	41.8
	No	124	58.2
		Mean	**Range**
Size of the stone (in mm)		18.03±7.32	7-30

Measurement of lipid profile showed that the prevalence of hyperlipidemia in the studied sample was 25.8%, as shown in Figure 2.

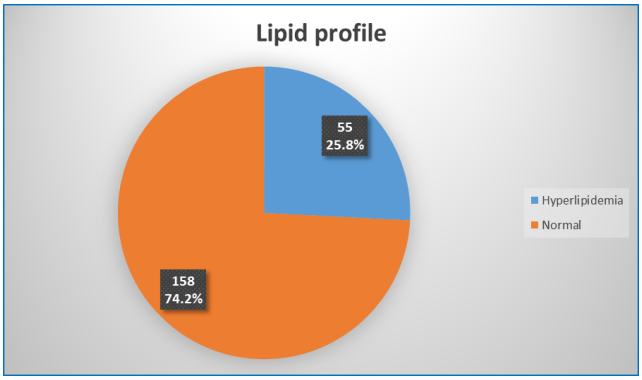

Figure 2: Lipid profile of 213 participants.

Comparison between cases of gallstone according to presence of hyperlipidemia showed that hyperlipidemia commonly found in hypertensive patients, cholesterol gallstone was commonly found in hyperlipidemia cases, single gallstone and yellow gallstones were commonly found in hyperlipidemia cases. Cases of hyperlipidemia had higher rate of previous attaches of biliary colic, as shown in Table **2**.

Table 2: Distribution of cases according to hyperlipidemia.

Variables		Hyperlipidemia N=55 No. (%)	Normal lipid profile N=158 No. (%)	Total N=213 No. (%)	P value
Age	**Mean ±SD**	53.56 ±7.08	52.95 ±7.47	53.11 ±7.36	0.586
Gender	**Male**	11 (20)	19 (12)	30 (14.1)	0.143
	Female	44 (80)	139 (88)	183 (85.9)	
BMI Group	**<18.5**	0 (0)	1 (0.6)	1 (0.5)	0.051
	18.5-24.9	8 (14.5)	46 (29.1)	54 (25.4)	
	25-29.9	26 (47.3)	76 (48.1)	102 (47.9)	
	≥30	21 (38.2)	35 (22.2)	56 (26.3)	
DM	**Yes**	6 (10.9)	8 (5.1)	14 (6.6)	0.132
	No	49 (89.1)	150 (94.9)	199 (93.4)	
HT	**Yes**	12 (21.8)	15 (9.5)	27 (12.7)	**0.018**
	No	43 (78.2)	143 (90.5)	186 (87.3)	
Smoking	**Yes**	8 (14.5)	11 (7)	19 (8.9)	0.089
	No	47 (85.5)	147 (93)	194 (91.1)	
alcohol	**Yes**	3 (5.5)	4 (2.5)	7 (3.3)	0.295
	No	52 (94.5)	154 (97.5)	206 (96.7)	
Type	**Cholesterol**	27 (49.1)	6 (3.8)	33 (15.5)	**<0.0001**
	Mixed	27 (49.1)	150 (94.9)	180 (84.5)	
	Pigmented	1 (1.8)	2 (1.3)	3 (1.4)	
Number of stones	**Single**	26 (47.3)	1 (0.6)	27 (12.7)	**<0.0001**
	Multiple	29 (52.7)	157 (99.4)	186 (87.3)	
Color	**Yellow**	15 (27.3)	15 (9.5)	30 (14.1)	**0.001**
	Brown	40 (72.7)	143 (90.5)	183 (85.9)	
Size	**Mean ±SD**	18.55 ±7.27	17.85 ±7.36	18.03 ±7.32	0.546
Previous attack	**Yes**	30 (54.5)	59 (37.3)	89 (41.8)	**0.026**
	No	25 (45.5)	99 (62.7)	124 (58.2)	

Distribution of lipid profile according to the type of gallstone showed that cases of cholesterol gallstone associated with elevated level of TC, LDL, VLDL, and TG, with low level of HDL as shown in Table 3.

Table 3: Distribution of lipid profile according to type of stone.

Variables	Type of stone		P value
	Cholesterol	Mixed and pigmented	
	Mean ±SD	Mean ±SD	

TC (mg/dl)	304.55 ±81.4	183.5 ±14.68	**<0.0001**
LDL (mg/dl)	220.27 ±84.78	89.3 ±17.8	**<0.0001**
VLDL (mg/dl)	42.45 ±7.4	35.3 ±3.96	**<0.0001**
HDL (mg/dl)	41.82 ±12.69	58.9 ±9.51	**<0.0001**
TG (mg/dl)	212.27 ±37	176.51 ±19.8	**<0.0001**

Cases of cholesterol gallstone were associated with older age when compared with other types of gallstones. There is no significant association between gender and the type of gallstone. cases of cholesterol stone had significantly higher BMI in comparison to other types of gallstones.

Diabetes was more common in cases of cholesterol gallstone than other types of stone. Hypertension was not associated with this type of stone. Smoking associated were more common in cholesterol gallstone, yellow stones were commonly found to be cholesterol stone. The size of the largest stone, gallbladder wall thickness, and previous attack of biliary colic were not associated with the type of gallstone, further details described in Table **4**.

Table 4: Patient characteristics according to the type of gallstone.

Variables		Type of stone			
		Cholesterol N=33 No. (%)	Mixed and pigmented N=180 No. (%)	Total N=213 No. (%)	P value
Age	**Mean ±SD**	55.82 ±7.44	52.61 ±7.25	53.11 ±7.36	**0.027**
Gender	**Male**	4 (12.1)	26 (14.4)	30 (14.1)	0.724
	Female	29 (87.9)	154 (85.6)	183 (85.9)	
BMI Group	**<18.5**	0 (0)	1 (0.6)	1 (0.5)	**0.021**
	18.5-24.9	3 (9.1)	51 (28.3)	54 (25.4)	
	25-29.9	15 (45.5)	87 (48.3)	102 (47.9)	
	≥30	15 (45.5)	41 (22.8)	56 (26.3)	
DM	**Yes**	7 (21.2)	7 (3.9)	14 (6.6)	**<0.0001**
	No	26 (78.8)	173 (96.1)	199 (93.4)	
HT	**Yes**	7 (21.2)	20 (11.1)	27 (12.7)	0.109
	No	26 (78.8)	160 (88.9)	186 (87.3)	
Smoking	**Yes**	8 (24.2)	11 (6.1)	19 (8.9)	**0.001**
	No	25 (75.8)	169 (93.9)	194 (91.1)	
Alcohol	**Yes**	1 (3)	6 (3.3)	7 (3.3)	0.928
	No	32 (97)	174 (96.7)	206 (96.7)	
Number of stones	**Single**	27 (81.8)	0 (0)	27 (12.7)	N/A
	Multiple	6 (18.2)	180 (100)	186 (87.3)	
Color	**Yellow**	12 (36.4)	18 (10)	30 (14.1)	**<0.0001**
	Brown	21 (63.6)	162 (90)	183 (85.9)	
Size of the stone	**Mean ±SD**	18 ±7.87	18.04 ±7.24	18.03 ±7.32	0.979
Wall thickness	**Increased**	2 (6.1)	11 (6.1)	13 (6.1)	0.991
	Normal thickness	31 (93.9)	169 (93.9)	200 (93.9)	
Previous attack	**Yes**	18 (54.5)	71 (39.4)	89 (41.8)	0.106
	No	15 (45.5)	109 (60.6)	124 8.2)	

DISCUSSION

Cholelithiasis and hyperlipidemia are both common disorders with a tangled pathophysiology that had the cholesterol as a common link. The increased dietary intake of fat had increased the risk of both disorders.[12] In the current study we are investigating the relation between hyperlipidemia and gallstone.

The mean age of participants was 53.11 ±7.36 years, this age is the commonest age of presentation as stated by previous study, this finding consist with study of Shahzad et al[13] whom found that gallstone presentation commonly happened after 40 years.

The female gender was the commonest gender enrolled in the study, due to the fact gallstone disease is more common in females, as stated by Song et al[14] and Kelly et al[15] in Schwartz's surgical textbook.

The solitary gallstone in the current study found in only 12.7%, which represent mainly cholesterol stones as it is likely to be single stone as found by Raj et al.[16] Also,

the yellow color of stone associated with cholesterol stone was found in 15.5% of the cases. The exact incidence of cholesterol gallstone in previous studies was non-constant as it depends on ethnicity, diet factors, and body habits as stated by Di Ciaula.[17] The cholesterol stone tends to be a single stone due to the process of nidus formation with superimposition of cholesterol over it.

Previous attacks of biliary colic present in 41.8% as it is the commonest presentation. Previous studies found that cases of asymptomatic gallstone tend to have increasing risk of developing of symptoms with time (symptoms developed at approximately 2% per year as stated by Morris-Stiff et al.[18]

The incidence of hyperlipidemia in the studied sample was 25.8%. The age was not different regarding presence of hyperlipidemia (as majority of enrolled cases were older than 50 years). The incidence of hyperlipidemia tend to increase with age as stated by Karr et al.[19] The gender was insignificant difference in regard to presence of hyperlipidemia, but previous studies found that male gender is a risk factor for hyper lipidemia as stated by Shepard et al,[20] this difference may be explained by small sample of male gender enrolled in the current study.

The body mass index, diabetes were not different in regard to the presence of hyperlipidemia, Charlton et al[21] found that hyperlipidemia, diabetes, and obesity were had the same etiological factors and all are parts of metabolic syndrome, the result found by the current study could be attributed to the sample size collected that could raise the chances of type II statistical error.

The rate of hypertension was significantly higher in cases of hyperlipidemia, this attributed to atherosclerosis that accompany hyperlipidemia as found by Hu et al.[22]

Smoking and alcohol consumption was not different in the rate of hyperlipidemia cases in the current study, on the contrary Lin et al[23] and Ramírez et al.[24] who found that smoking and alcohol consumption were associated with increased risk of hyperlipidemia, the difference from the current study due to small sample size of hyperlipidemia cases (55 cases) which increase the chance of type II error.

Regarding the stone's characteristics we found that, cholesterol stone were more common in hyperlipidemia cases, similarly found by Saldanha et al.[25]

The size of the stone was not different regarding hyperlipidemia status.

The cases of hyperlipidemia were more likely to have previous attacks of biliary colic, this happened due to cholesterol type of gallstone that more likely to be symptomatic as stated by Sheng et al.[1]

The distribution of the parameters of lipid profile showed that cases of cholesterol gallstone were more likely to have high TC, LDL, VLDL, and TG with low HDL. As cholesterol is the major component of gallstone, its increased concentration lead to supersaturated bile with cholesterol leading to the formation of gallstone as stated by Sun et al.[26]

The relation that link gallstone disease with hyperlipidemia may be explained by the ability of high serum triglyceride to attenuate gallbladder responsiveness to cholecystokinin (as stated by Jonkers et al.[27]) this further aggravated by increased biliary cholesterol saturation with increased bile viscosity by increasing production of mucin as stated by Banim et al.[28] This pathological process further aggravated by the fact that hyperlipidemia associated with increased hepatic insulin resistance (as part of metabolic syndrome) which further increase cholesterol secretion and reduces bile acid synthesis, leading to bile crystallization and stone formation. Hepatic insulin resistance has been identified as a key determinant of cholesterol gallstones formation by itself, as stated by Nakeeb et al.[29] and Tran et al.[30]

The cholesterol stone in this study were associated with increased patient age, this probably due to decreased ability of liver to detoxify cholesterol as stated by Mc Auley et al.[31]

The gender were not different in regard to the type of gallstone, similarly found by Chaudhary et al.[32]

The obesity and diabetes were found to be higher in cases of cholesterol gallstone than other types of stone, similar result found by Chaudhary et al.,[32] Raj et al.,[16] and Nair et al.[33]

Hypertension was not different in regard to the type of the stone. Similar result found by Chaudhary et al.[32]

Smoking was found to be associated with increased rate of cholesterol gallstone. Gao et al.[34] found in animal experiment that nicotine hand anti-lithogenic effect (i.e., preventive of gallstone formation), while epidemiological studies showed that this effect could be limited to low BMI participants, on the other had Yuan et al.[2] found that smoking increase the rate of cholesterol gallstone. These conflicting results need to be investigated further.

Only seven participants drinks alcohol, no statistical difference was found, Yuan et al.[2] found significant association between alcohol consumption and cholesterol gallstone formation.

All solitary stones found in the study were cholesterol gallstone. regarding the color of the stones, not all cholesterol stones were yellow in color, there is

significant proportion were brown in color, Peter et al.[35] found that pure cholesterol stone is rare and its color is pale white in color, while yellow to brown stones were known as composite cholesterol stone rather than mixed or pigmented stone (this depends on the concentration of cholesterol in comparison to bile acid content of the stone).

CONCLUSION

Hyperlipidemia is associated with increased rate of cholesterol gallstone. The incidence of hyperlipidemia in gallstone disease (who is candidate for surgery) was found to be 25.8%

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