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A STUDY ON BIOCHEMICAL VARIANTS OF GALL STONE IN CORRELATION WITH CLINICAL AND SERUM PARAMETERS

1. DR. BISWAJITA RAUTARAY, JUNIOR RESIDENT. DEPARTMENT OF GENERAL SURGERY. MKCG MCH, BERHAMPUR
2. DR. RAMANI RANJAN MUND, ASSOCIATE PROFESSOR, DEPARTMENT OF GENERAL SURGERY, MKCG MCH, BERHAMPUR
3. DR. UTSAV KUMAR SENAPATI, SENIOR RESIDENT, DEPARTMENT OF GASTROENTEROLOGY. APOLLO HOSPITAL. BBSR
4. DR. RAJANIKANT DAS. JUNIOR RESIDENT. DEPARTMENT OF GENERAL SURGERY. MKCG MCH, BERHAMPUR

CORRESPONDING AUTHOR: DR. BISWAJITA RAUTARAY

EMAIL ID – RAUTARAYBISWAJITA@GMAIL.COM

ABSTRACT

Gallstone disease (GSD is one of the most common causes among patients presenting to emergency rooms with abdominal discomfort. It accounts for significant burden for health-care systems worldwide and This study Is aimed to evaluate the incidence of the types of Extra hepatic biliary calculi in southern Odisha and to know the association of biochemical parameters with clinical parameters in development of GSD.

This is an Observational study done with 230 patients attending outpatient department, Emergency as well as In-patients of general surgery, MKCG MCH. BERHAMPUR from April 2022 to December 2023. Data collection was done on a self-designed pretested interview schedule and all the patients were investigated for relevant biochemical parameters. Data collected was analysed using SPSS 29 for comparison and conclusive study.

In southern part of Odisha, mixed type (59.6%) of gall stone is found to be maximum in incidence followed by pigment (22.6%) and cholesterol stone (17.8%). A significant correlation was found between incidence of cholesterol stone with dyslipidaemias, obesity, diabetes and hypertension.

Key words: Gall stone disease, biliary calculi, biochemical parameters, dyslipidaemias, diabetes, obesity

INTRODUCTION

Gallstone disease (GSD is one of the most common causes among patients presenting to emergency rooms with abdominal discomfort. It accounts for significant burden for health-care systems worldwide with prevalence of 11 to 36%. Extra hepatic biliary calculi includes both gallbladder as well as Common bile duct (CBD) stones. Gallstone diseases affect nearly 20% of the population in Western countries[1,2,3]. The prevalence of gallstones increases with age, and reaches as high as 57% in women at the age of seventies[4]. Many recent studies have shown that gallstone disease is related to age, sex, and metabolic disorders, such as obesity, dyslipidaemias (hypertriglyceridemia), and type 2 diabetes[5,6,7]. The pathogenesis of gallstone disease is

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

suggested to be multifactorial and probably develops from complex interactions between many genetic and environmental factors[8,9]

The gallstones are solid crystalline precipitates in the biliary tract usually formed in the gallbladder. Cholesterol and calcium bilirubinate are the two main substances involved in gallstone formation. Gallstones derived from bile consist of mixture of cholesterol, bilirubin with, or without calcium. Based on their chemical composition, gallstones found in the gallbladder are classified as cholesterol, pigmented, or mixed stones. Gallstones can be mostly white, yellow, brown, black, and green coloured. In Asian population approximately 80% of the gallstones are Mixed gallstones, which chiefly consist of cholesterol plus bile salts. Cholesterol stones are usually yellow but are sometimes white in color. These are divided into two subtypes as pure (90-100% cholesterol) or mixed (50-90% cholesterol). Cholesterol gallstones develop when bile contains too much cholesterol or not enough bile salts. Pure stones often are solitary, whitish, and larger than 2.5 cm in diameter.

Mixed stones usually are smaller, multiple in number, and occur in various shapes and colors. The remaining 20% are usually referred to as pigment gallstone, which mainly consists of bilirubin (the pigment) and calcium salts such as calcium carbonate. These occur in two subtypes brown and black. Brownstones are usually made up of calcium bilirubinate. Black stones typically form in the gallbladder

result when excess bilirubin enters the bile and polymerizes into calcium bilirubinate. Bilirubin stones are formed from cholesterol and bilirubin, which are mainly seen in people who have hereditary blood disorders such as thalassemia, sickle cell anemia, biliary tract infections, and cirrhosis. Composite (mixed) stones also occur in the gallbladder, i.e., those consisting of a mixture of cholesterol, bilirubin, and calcium. Diets high in cholesterol and fat, increase the chance of developing stones. Gallstones have a high prevalence among elderly adults.

Chemical analysis of all gallstones is essential to determine etiopathogenesis of gall stone disease. This study aims to evaluate the incidence of the various types of extra hepatic biliary calculi in southern parts of Odisha and correlation with biochemical and clinical parameters so as to minimize morbidity and mortality improving patient outcomes.

AIMS AND OBJECTIVE

This study aims to establish the clinical correlation between chemical constituents of gallstone and serum biochemical parameters.

PRIMARY OBJECTIVE

1. To analyse all the stones removed after surgery to determine their biochemical variety.

SECONDARY OBJECTIVES

2. To establish the correlation between biochemical type of gallstone with clinical parameters (age, sex, built, diet, lifestyle and comorbidities)
3. Attempt to establish a correlation with gallstones and decrease serum iron levels and increased serum bilirubin.
4. To evaluate the antecedent risk factors in causation of gallstone disease amenable to primary prevention.
5. To find the prevalence of gallstone disease in southern Odisha.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

MATERIALS AND METHOD

This observational study was conducted on 230 patients attending outpatient or emergency department and admitted to inpatient department of general Surgery, MKCG MCH, Berhampur and underwent cholecystectomy (lap and open) from the period of March 2022 to December 2023.

Inclusion criteria:

- All patients diagnosed with cholelithiasis or choledocholithiasis or both in imaging studies.

Exclusion criteria:

- Patients with acalculous cholecystitis
- Patients that denied admission or surgery.

The patients admitted to In-patient wards were subjected to preformed questionnaire and clinical examination.

As per their lifestyle and physical activity, patients were categorised into

- Sedentary (desk job, No exercise): engineers, teachers, doctors, corporate employees etc.
- Moderate activity (moderate exercise 3-5 days per week): servants, carpenters, electricians etc.
- Heavy activity (heavy exercise, everyday): farmer, daily wage labourers, stone cutter, sportsmen etc.

The weight (in kg) and height (in meter) were recorded and BMI was calculated so as to categorize the patients as per their body built.

BMI = weight (in kg) / height (in meters)^2 (As per WHO guidelines for Asian population, 2022)

- Underweight < 18.5
- Normal 18.5 – 22.99
- Overweight 23 – 27.4
- Obese > 27.4

DIAGNOSTIC CRITERIA:

- Gallstone disease was defined as the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadowing) during abdominal ultrasonography.
- Obesity was defined as a body mass index (BMI) ≥ 23 kg/m^2 in both men and women according to the redefined World Health Organization criteria for the Asia Pacific Region.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

- High blood pressure was defined as a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg or a history of hypertension.
- Subjects with an FPG ≥ 126 mg/dL and/or a history of diabetes were considered to have diabetes mellitus (DM).
- Hypertriglyceridemia was defined as a triglyceride concentration ≥ 150 mg/dL. Low HDL-C was defined as an HDL-C level < 35 mg/dL in men or < 39 mg/dL in women. Hypercholesterolemia was defined as a total cholesterol level ≥ 220 mg/dL. High LDL-C was defined as an LDL-C level ≥ 155mg/dL.

After pre-operative evaluations and blood parameters, patients were subjected to elective cholecystectomy (laparoscopic or open) with or without ERCP/ CBD exploration. Stones obtained following surgery were subjected to physical and biochemical analysis.

- Stage of Extraction: the stone were powdered in a Pestel and mortar and dissolved in different solvents. To determine the total cholesterol and total bilirubin, 30 mg of powdered stone was dissolved in 3ml chloroform in a test tube. The tube was kept in boiling water bath or 2 minutes. The stone thus obtained was used or determination of total cholesterol and total bilirubin. To determine calcium 30 mg stone powder was dissolved in 3ml HCl in graduated 10ml tube and its final volume made up to 10 ml with distilled water. The tube was kept in boiling water bath or 1hr.
- Chemical analysis – colorimetry
  Bilirubin – Erba LIQUIXX BILIRUBIN (BIT &BID)
  Diazo Method, End point.
  Cholesterol- Erba- CHLOSTEROL DES KIT
  Dynamic extended stability
  CHOD-PAP METHOD (with LCF), END POINT
  Calcium- SIMENS- AUTOPAK CALKIT
  Cresolphalein complexone method

Quantitative analysis of metabolites and cation and anions in different types of biliary calculi expressed as mg per gm dry stone powder.

Type of calculi	Total cholesterol	Total bilirubin	Calcium
Cholesterol stone	594.98 ±33.22	2.10±0.32	10.66±1.85
Mixed stone	594.78±24.91	1.72±0.19	26.52±2.39
Pigment stone	489.85±28.68	4.87±0.49	27.60±3.13

At the end a correlation was looked for between the type of calculi and physical and serum biochemical parameters. The data collected was tabulated and analysed using SPSS 29.0

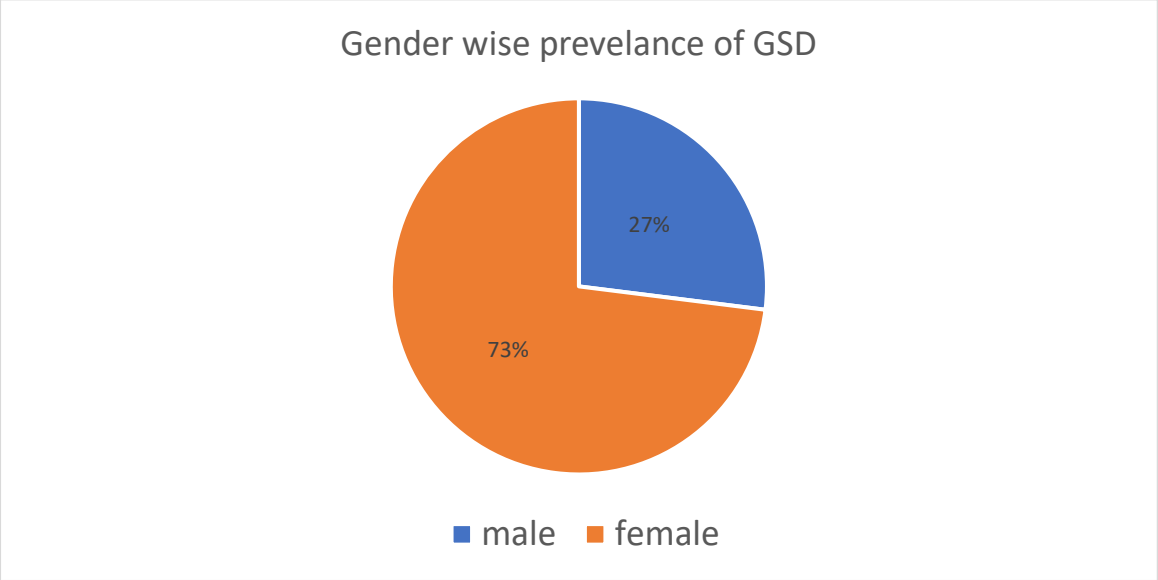
RESULTS

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

- Out of 230 patients, 145 were female and 85 were male. The age group ranged from 19 to 78 years. Maximum prevalance was noted in the age group of 41 to 50 years.

AGE GROUP	MALE (n = 85)		FEMALE (n = 145)		TOTAL (N= 230)	
19-30	09	10.58%	13	8.96%	22	9.56%
31-40	19	22.35%	36	24.82%	55	23.9%
41-50	**21**	**24.7%**	**53**	**36.55%**	**74**	**32.17%**
51-60	17	20%	21	14.48%	38	16.52%
61-70	11	12.9%	13	8.96%	24	10.43%
71-80	8	9.4%	9	6.2%	17	7.39%

Table 1. demographic distribution of gall stone disease.



Graph 1. Gender distribution of Gall stone disease.

- In this study, out of 230 patients, 118 (51.3%) were found to be sedentary workers, 61 (26.6%) moderate and 51 (22.1%) heavy workers. Out of 230 cases, 169 (73.6%) consumed mixed non-vegetarian diet.
- 8 (3.5%) were found to be under weight, 73 (31.7%) normal, 98 (42.6%) over weight and 51 (22.1%) were obese.
- 37.3% had diabetes mellitus, 48.9% had hypertension and 35.7% were having dyslipidaemias.

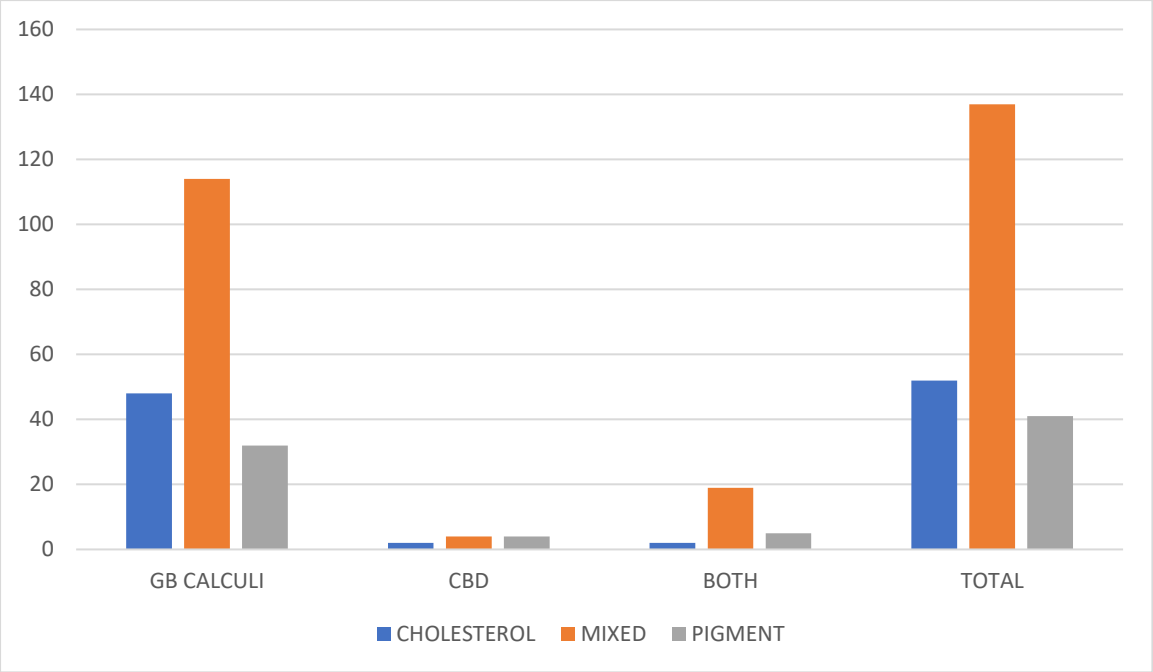
Biochemical type	GB calculi	CBD calculi	Both (CBD + GB calculi)	Total	Percentage

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Cholesterol	48	2	2	52	22.6%
Mixed	**114**	**4**	**19**	**137**	**59.6%**
Pigment	32	4	5	41	17.8%

Table 2. biochemical type of stone

In southern Odisha, mixed calculi were maximum (59.6%) followed by cholesterol and pigment stone.



Graph 2. biochemical type of stone

	Cholesterol	mixed	Pigment
Age (mean)	49.3±13.9	46.7±12.34	38.24±7.86

Table 3. correlation of age and biochemical variety of calculus (p = 0.008)

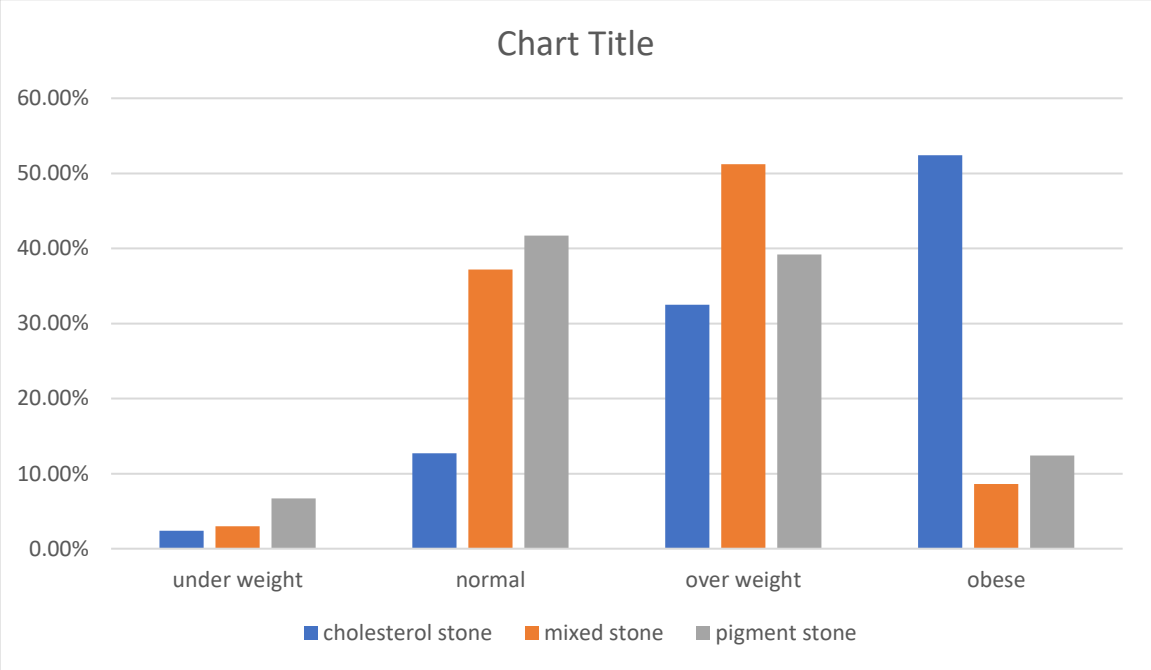
In this study, Pigment stones were more in younger age group as compared to other variants.

	CHOLESTEROL STONE (n=52)		MIXED STONE (n= 137)		PIGMENT STONE (n=41)	
<18.5 UNDER WEIGHT	1	2.4%	4	3%	3	6.7%
18.5 – 22.99 Normal weight	7	12.7%	51	37.2%	17	41.7%

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

23-27.4 Over weight	17	32.5%	70	51.2%	16	39.2%
>27.4 Obese	27	52.4%	12	8.6%	5	12.4%

Table 4.. correlation between BMI and type of calculus (p = <0.01)



Graph 3. correlation between BMI and type of calculus.

Out of all the types, cholesterol stone is more common in obese individuals where as pigment stones were more common in people with normal weight.

DIET	CHOLESTEROL (n =52)	MIXED (n=137)	PIGMENT (n=41)
Non vegetarian (N=169)	90.4%	58.7%	95.8%
Vegetarian (N=61)	9.6%	41.3%	4.2%

Table 5. correlation between diet and type of calculus. (p = <0.01)

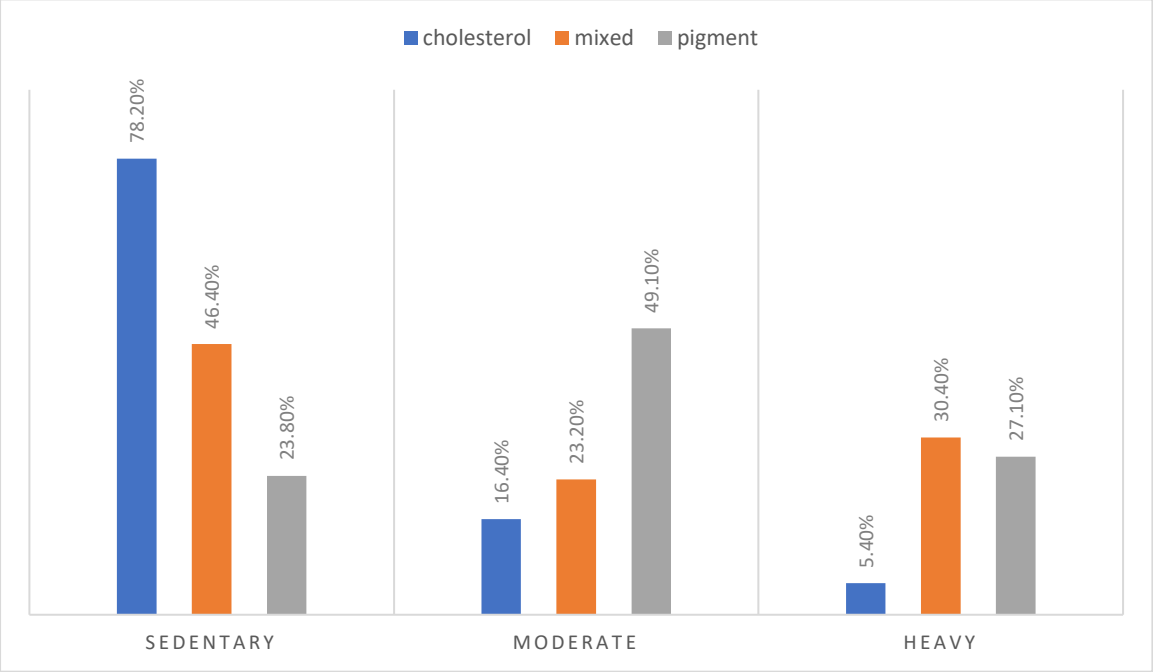
Biliary calculi were more common in people with non-vegetarian diet as compared to those on vegetarian diet.

PHYSICAL ACTIVITY	CHOLESTEROL (n=52)	MIXED (n=137)	PIGMENT (n=41)

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Sedentary	41	78.2%	63	46.4%	10	23.8%
Moderate	8	16.4%	32	23.2%	20	49.1%
Heavy	3	5.4%	42	30.4%	11	27.1%

Table 6. correlation between level of physical activity and type of calculus. (p = <0.01)



Graph 4.. correlation between level of physical activity and type of calculus

Cholesterol and mixed calculi were more common in people with sedentary life style. The incidence of biliary calculi was relatively less in people with heavy physical activity.

Diabetic	CHOLESTEROL	MIXED	PIGMENT
Yes	83.2%	17.6%	3.5%
No	16.8%	82.4%	96.5%

Table 7. correlation between blood glucose level (DM) and type of calculus. (p = <0.01)

HYPERTENSIVE	CHOLESTEROL	MIXED	PIGMENT
Yes	92.7%	27.3%	3.6%
No	7.3%	72.7%	96.4%

Table 8. correlation between Hypertension and type of calculus. (p = <0.01)

DYSLIPIDEMIA	CHOLESTEROL	MIXED	PIGMENT

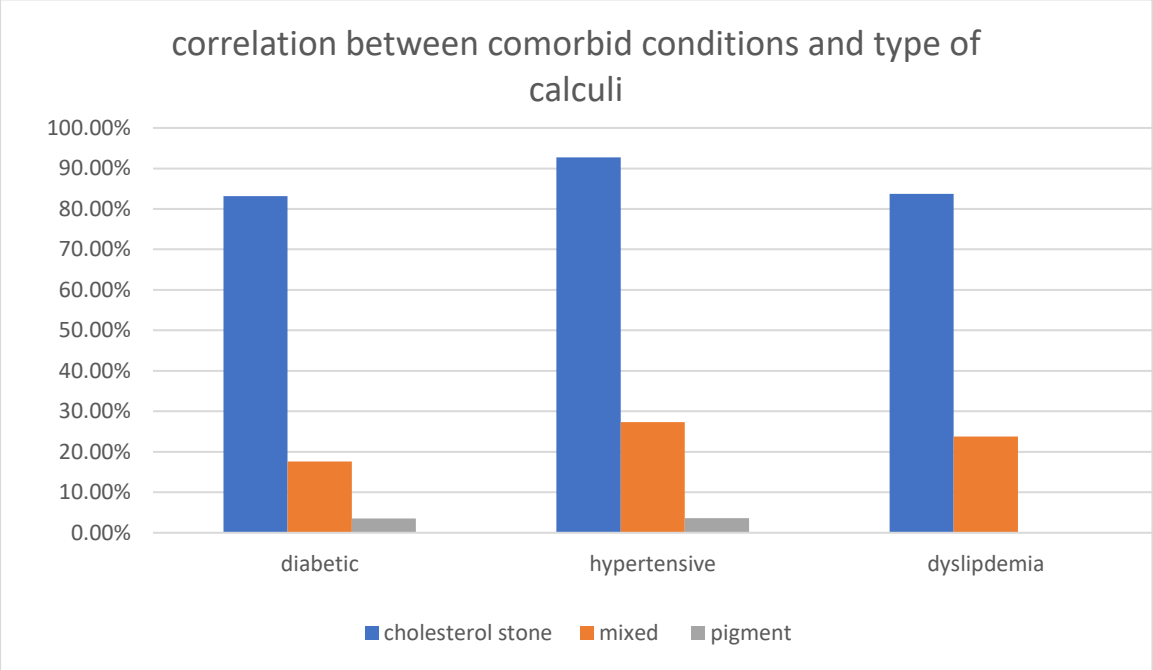
ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Yes	83.7%	23.8%	0
No	16.3%	76.2%	100

Table 9. correlation between Dyslipidaemia and type of calculus. (p = <0.01)

LIPID PARAMETERS	CHOLESTEROL STONE mean (SD)	MIXED STONE Mean (SD)	PIGMENT STONE Mean (SD)
CHOLESTEROL	288	158	124
TRIGLYCERIDE	194	156	110
LDL	155	116	82
HDL	46	56	58

Table 10. correlation between lipid parameters and type of calculus. (p = 0.06)



Graph 5. correlation between comorbidities and type of calculus.

Cholesterol stone were the commonest (83.2%) variety seen in diabetics followed by mixed and pigment calculi. 92.7% patients with cholesterol stone were hypertensive. Cholesterol calculi were more common (83.7%) in patients with dyslipidaemias followed by mixed calculi.

LIVER FUNCTION TEST	Mean

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Sr.Bilirubin	1.32±0.65
SGOT	38±12.8
SGPT	65±18.2
ALP	320±22.4

Table 11. liver function test

Sr. IRON	NO. OF PATIENTS
Increased	2%
Decreased	91%
Normal	7%

TYPE OF CALCULUS	SR. IRON (MEAN ±SD)
Cholesterol	54.63±12.87
Mixed	55.24±16.21
Pigment	52.86±14.34

Table 12(a), 12(b). correlation between sr. iron and type of calculus. (p = 0.08)

In this study 91% cases had decreased serum iron values and only 7% had normal sr. iron values. Mean serum iron was found to be highest in mixed followed by cholesterol followed by pigment calculi. How ever these results were not statistically significant.

TYPE OF CALCULUS	SR. BILIRUBIN (mean± SD)
Cholesterol	0.81±0.16
Mixed	1.34±0.78
Pigment	1.72±0.66

Table 13. correlation between sr. bilirubin and type of calculus. (p = 0.02)

In the present study mean sr. bilirubin was highest in pigment calculi followed by those with mixed calculi.

DISCUSSION

This study included a total of 230 patients all of which underwent cholecystectomy (laparoscopic or open). The gallstones thus obtained were subjected to chemical analysis and were classified into 3 categories, namely, cholesterol stones, mixed stones, and pigment stones. **It was found out that of the 230 patients studied, 137 (59.6%) had mixed stones, 52 (22.6%) had cholesterol stones, and 41 (17.8%) had pigment stones, which suggests majority of our patients had mixed stones** *(table 2, graph 2)* which is in contrast to the studies carried out by Taher[10] (cholesterol stones 49%, mixed stones 25%, and pigment stones 18%), Tassaduqe *et al.*[11] and Shareef *et al.* [12] (cholesterol stones 54%, mixed stones 40%, and pigment stones 6%), Jarrar and Al Rowaili.[13] (cholesterol stones 54%, mixed stones 43%, and pigment stones 3%), and Channa *et al*.[14] (cholesterol stones 68%).

In this study, 145 of the 230 (63%) patients were female. *(table1, graph 1).* which might be because estrogen increases biliary cholesterol secretion causing cholesterol supersaturation of

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

bile, rendering it lithogenic. These findings are in accordance with Studies done by Weerakoon HT et al.[15], Gul H et al.[16] and Halgaonkar P et al.[17]also showed that the majority of the patients belonged to the female gender suggesting hormonal role in pathogenesis of gallstones.

The prevalence of gallstones, regardless of the anatomical locations, significantly increased with the age till 50 years (P<0.001), especially for the GB stones whose prevalence increased from 9.56% (age <30) to 32.17% (age 40-50) (Table1). Although the prevalence of GB stones increased with a higher BMI, fasting glucose level or total triglyceride level it was maximum with the cholesterol type of calculi. Personal risk factors such as sedentary lifestyle, overweight or obesity, and high W/H ratio were significantly associated with the development of GSD, reason for such finding may be because obesity increases cholesterol synthesis, biliary cholesterol secretion, and cholesterol supersaturation.

In the study, the mean age of the patients was 43.90 ± 12.5 years. Similar results were also seen in the studies conducted by Gul H et al. [16] and Weerakoon HT et al.[15] with the mean ages of 43.18 ± 13.970 years and 44.6 ± 10.4 years respectively. However, in the study performed by Öner C et al.[18] illustrated that mean age of the patients was 52.6 ± 13.07 years. Pigment stones were more in younger age group as compared to other variants.

With respect to dietary preference of patients, majority of patients in the present study preferred a non-vegetarian diet (73.6%) *(Table 5)*. Studies to find out association between dietary habits and prevalence of Gall Stone disease has shown a higher risk of occurrence in non-vegetarians as compared to vegetarians. The reason for such finding may be because in Indian population, preparation of nonvegetarian diet generally involves lots of fat as compared to nonvegetarian preparation in other parts of world. *Pixley and Mann et al*.[19] showed frequency of GS to be more than twice in non-vegetarians (24.6%) as compared to vegetarians (11.5%). In a previous study too, Pixley et al. found the prevalence of Gall stone disease to be 25% in non-vegetarians and 12% in vegetarians[20]. In present study ratio of non-vegetarians to vegetarians was 3.14:1. However, a much higher ratio of non-vegetarians to vegetarians (1:9) was reported in a study from Nepal by Pradhan et al. in 2009.[21] The dietary habits in different ethnicities might be different. Thus, the findings suggest that association between dietary preference and prevalence and Gall stone disease need a review. Daily intake of high calories and high fats Favors the formation of gallstones, and high protein diet shows protective effect against gallstone formation. Reason for such finding may be because high energy intake leads to obesity and high fat intake leads to loss of bile acids in faeces and decreased bile acid pool, promoting supersaturation of bile and rendering it more lithogenic. Proteins exerted an inhibitory effect on biliary cholesterol crystallization, which is the determinant step in gallstone genesis.

In the present study, majority of the patients fall in the overweight and obese (64.78%) category with only 73 (31.7%) in normal BMI category *(Graph 3, table 4)*. Elevated BMI has been proven to be a causal risk factor for symptomatic Gall Stone disease. Obesity measures such as increased BMI and waist-hip ratio have also been shown to be associated positively with prevalence of Gall stone disease. Main risk factor for GS disease in cases with known heredity of GS disease was found to be BMI. A high prevalence of patients with elevated BMI as observed in present study endorses these findings (Tîrziu et al. 2008)[22].

Majority of the patients (51.3 %) with gall bladder stones were having a sedentary lifestyle with mild daily physical activity, 26.6 % patients were involved in moderate daily activity and 22.1% were involved with severe/heavy physical activity work. In all categories of physical activity, cholesterol stones were prominent. *(table 6, Graph 4)*. The finding of this study shows

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

a negative relation between physical activity and occurrence of gall stones, thus supports the findings of previous studies by Singh A et al.[23]

This study shows high fasting blood sugar level is significantly associated with the development of Gall stone disease *(Table 7, Graph 5)*; it might be because people with diabetes have hypotonic gallbladder and the bile of patients with diabetes mellitus is supersaturated with cholesterol; this is corroborated with the findings of De Santis *et al*.[24] This study also suggests positive correlation between hypertension and risk o gall stone disease. *(Table 8, graph 5).*

In the present study we found that high level of plasma triglycerides, total cholesterol, and LDL cholesterol were significantly associated with the development of Gall stone disease where as low level of plasma HDL cholesterol was found to be a risk factor for the same. Similar findings were seen in previous studies by Channa NA et al,[25] Gomati A et al[26] and Tîrziu S[27]; whereas some showed that hyperlipidaemia, plasma HDL cholesterol, and plasma triglycerides were not significantly associated with GSD[28,29.] **The mean serum cholesterol levels were high in the patients with cholesterol calculi (83.7%) (P < 0.01)**. Although the saturation of bile with cholesterol has definite role in pathogenesis of gallstones but association of gallstones and high level of serum cholesterol levels in patients is controversial in literature and can be explained by multiple factors like genetics, geographical, social and dietary habits in pathogenesis of different type of gallstones. The main source of biliary cholesterol is HDL cholesterol but studies have shown that low HDL cholesterol has positive correlation with gallstones. In this study, mean serum LDL level in the patients was high in patients with cholesterol calculi. Study carried out by Al-Saadi N et al.[30] showed that LDL concentration had no significant difference compared to the control. These results were in contrary with the other studies by Batajoo H et al[31] and Gul H et al [16] demonstrated positive correlation between serum LDL levels and gallstones patients.
In this study 91% cases had decreased serum iron values and only 7% had normal sr. iron values. Mean serum iron was found to be highest in mixed followed by cholesterol followed by pigment calculi. How ever these results were not statistically significant. *(table 12a, 12b)*

This study also shows derangement of liver functions in some of patients *(table 11).* **In the present study mean sr. bilirubin was highest in pigment calculi followed by those with mixed calculi.** *(table 13).* Serum bilirubin and serum alkaline phosphatase (SALP) levels were also seen to be above normal range in 9.8% and 8.6% patients. Gall Stone disease often restrict the communication of biliary fluid owing to constriction of common bile duct. Bateson et al[32]., reported that in patients with bile stone, liver function tests typically include raised glutamyl transferase and alkaline phosphatase activities, but the alanine aminotransferase activity may also be affected, and the bilirubin concentration may rise in patients with acute gallbladder symptoms but no obvious bile duct problems (Bateson et al[32]. 1999). These findings may reflect the passage of a stone through the bile duct with transient "hold up" at the lower end. In their Studies, Sun *et al*[2] reported Liver enzymes (AST and ALT) and total bilirubin were not significantly associated with gallstone formation.

CONCLUSION

In this study the most common type of extra hepatic biliary calculi in southern Odisha was found to be Mixed calculi (59.6%) followed by cholesterol calculi (22.6%). Females were at a higher risk as compared to males. Demographic, dietary and anthropometric parameters like age, gender, diet and BMI did show a significant association with Gall stone disease. The

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

findings of present study showed that cholesterol is the most common component in Gall Stone disease and amount of cholesterol was associated with dyslipidaemias. Gallstones were more common in patients having mixed diet as compared to strict vegetarians which might be correlated to increased cholesterol content of the food. In this study we also found that serum iron was found to be low in majority of the patients indicating iron deficiency might be a cause of gallstone formation. A significant correlation was found to be between serum bilirubin levels and gallstones formation indicating that increased bilirubin may predispose to gallstone formation. This study also suggests increased risk of gall stone disease mainly cholesterol and mixed calculi in individuals with diabetes and hypertension. Thus, Maintenance of controlled plasma levels of total cholesterol, triglycerides, and LDL cholesterol and blood sugar might help in the prevention of GSD.

Sedentary life style, Obesity, non-vegetarian diet and increased levels were possible etiological risk factors warranting lifestyle and dietary modification as a possible preventive measure. As total cholesterol, triglycerides, and LDL cholesterol level were independently associated with the development of GSD, individuals those have raised levels of these biochemical parameters with or without dietary or lifestyle risk factors should be screened for these biochemical parameters. Furthermore, routine screening of these biochemical parameters in adult patients presenting to hospitals with different diseases might help in the early diagnosis of gallstone disease. Individuals with raised levels of total cholesterol, triglycerides, and LDL cholesterol should be screened regularly for the early diagnosis as well as prevention of complications because of the sudden onset of severe gallstone disease.

CONFLICTING INTERESTS

The authors declare that they have no conflicting interest.

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