ORIGINAL ARTICLE

Comparative Study of Analysis of Macro/ Micronutrients (Cholesterol, Bilirubin, Urea, Creatinine, Uric Acid, Calcium, Phosphorus, Magnesium) in Bile and Serum in the Study of Gall Stone Diseases

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ABSTRACT

Introduction: Gallstone disease affects 15–20% of the global population and lead to complications like cholecystitis, cholangitis, and pancreatitis. This study aimed to analyze the concentrations of macro/micronutrients—cholesterol, bilirubin, urea, creatinine, uric acid, calcium, phosphorus, and magnesium—in bile and serum of individuals with gallstones. **Methods:** A cross-sectional study was conducted on 100 patients with cholelithiasis at Saveetha Medical College and Hospital. Blood and bile samples were analyzed using the VITROS 5600 dry-chemistry analyzer. Patients with renal disease, diabetes, endocrine disorders were excluded. Statistical analysis was performed using SPSS, with $p < 0.05$ considered significant. **Results:** Serum cholesterol (mean: 191.48 mg/dL) was significantly higher than bile (mean: 61.99 mg/dL; $p < 0.001$). Conversely, bile exhibited higher levels of bilirubin (45.951 mg/dL vs. 0.7210 mg/dL; $p < 0.001$), urea (26.02 mg/dL vs. 21.411 mg/dL; $p < 0.001$), creatinine (1.1425 mg/dL vs. 0.676 mg/dL; $p < 0.001$), calcium (11.577 mg/dL vs. 9.000 mg/dL; $p < 0.001$), phosphorus (8.306 mg/dL vs. 4.255 mg/dL; $p < 0.001$), and magnesium (6.865 mg/dL vs. 1.878 mg/dL; $p < 0.001$). Correlation analysis revealed significant relationships for urea ($r = 0.253$, $p = 0.011$) and creatinine ($r = 0.333$, $p = 0.001$). Females comprised 76% of the study, with males showing elevated serum bilirubin levels ($p = 0.04$). **Conclusion:** This study highlights distinct biochemical profiles of serum and bile, emphasizing the potential role of systemic factors like renal function in gallstone formation. Future research should explore these mechanisms in larger, diverse cohorts to improve diagnostic and therapeutic strategies.
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INTRODUCTION

Gallstone disease is a prevalent gastrointestinal disorder, that impacts around 15 – 20% of the global population. Gallstone formation is the defining feature of this condition[1]. While most individuals do not experience any symptoms and require no intervention, approximately 2% of those diagnosed may suffer from intense abdominal pain, nausea, and vomiting. If left untreated, this condition could lead to problems such as cholecystitis, cholangitis, and pancreatitis[2]. Addressing the biochemistry behind the production of Gallbladder stone (GBS) is essential for developing effective strategies for prevention and treatment.

This study aims to analyze the concentrations of macro and micronutrients of specific macro and micronutrients in the bile and serum of individuals diagnosed with gallstone disease. More specifically, this study focuses on analyzing the levels of cholesterol, bilirubin, urea, creatinine, uric acid, calcium, phosphorus, and magnesium.

GBS are primarily composed of cholesterol and bilirubin. Cholesterol stones are the most prevalent form, while pigment stones mostly constitute of bilirubin[3]. The precise involvement of macro nutrients, such as calcium, phosphorus, and magnesium, in the development of GBS is not well understood. While previous studies

have primarily focused on cholesterol and bilirubin in gallstone formation, the role of other macro and micronutrients such as creatinine, urea, and uric acid in the pathophysiology of gallstone disease remains poorly understood. This study provides a comprehensive analysis of these underexplored nutrients, adding critical insights into gallstone pathogenesis. This study aims to identify potential metabolic abnormalities related to the production of GBS, by comparing the concentrations of these nutrients in bile and serum. The objectives of the study includes, to determine the differences in nutrient levels, to assess the correlation between the serum and bile nutrient levels, to investigate potential biochemical markers, to examine its systemic influences and to contribute to the existing literature to tackle GBS.

This study is among the first to perform a comparative analysis of macro and micronutrient levels in serum and bile, providing potential biochemical markers for gallstone disease. The results of this study can improve our comprehension of the metabolic disruptions that cause the formation of GBS and aid in the creation of more specific diagnostic and treatment methods and would be crucial in order for researchers to develop successful methods for both early detection and treatment.

MATERIALS AND METHODS

This study is a cross-sectional observational research conducted on patients diagnosed with cholelithiasis in the General Surgery Department of Saveetha Medical College and Hospital. A total of 100 patients, irrespective of their gender, diagnosed with Cholelithiasis, after detailed history and physical examination were included in the study over a period of 1 year between June 2023 and June 2024. The required sample size was estimated using a power analysis based on an expected mean difference of 10 mg/dL in nutrient levels between bile and serum, with a standard deviation of 15 mg/dL. Using a two-tailed t-test with a significance level of 0.05 and a power of 80%, the minimum required sample size was calculated to be 36 participants per group. To enhance statistical robustness and for a more flourished data, a total of 100 participants were included in the study. The study protocol has received its approval from Saveetha Medical College and Hospital Institutional Ethics Committee (SMCH-IEC) on 20 June 2023 with reference number: 038/06/2023/IEC/SMCH. Patients who were willing to enrol in the study, between the ages of 20yrs to 65yrs of age diagnosed with GBS are encompassed within the scope of the research, while patients those who have Medical renal disease, Pregnant women, Diabetic or other endocrine related problems (thyroid/ parathyroid), Gout, GB malignancies, other malignancies, patients taking drugs for hypercholesterolemia, or regular micronutrient supplement intake are excluded from the study. USG abdomen/ MRCP was done for all selected patients, with which confirmation of the diagnosis is done.
Blood samples were collected on the day of surgery, by a trained phlebotomist drawing approximately 5-10 ml of venous blood from each participant using standard aseptic techniques. Blood samples were collected in red-top tubes and processedin VITROS- 5600 dry chemistry analyzer.

Bile was collected intra operatively [Fig 1], from patients undergoing cholecystectomy. After the GB was isolated during surgery, but before the specimen was removed, approximately 10 ml of bile will be aspirated directly from the GB using a sterile syringe.
Bile samples were collected in labelled sterile containers. Samples would be transferred right after the procedure to the department of biochemistry, for analysis, without storage delay.

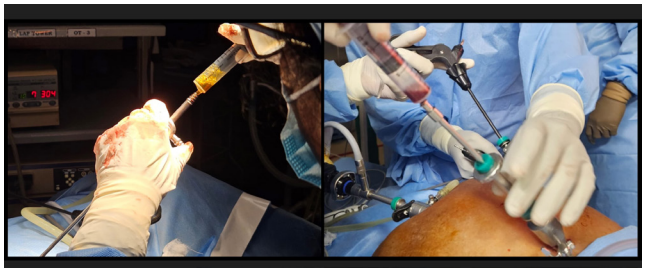

Fig 1: Intra operative aspiration of bile for analysis.

Serum levels of cholesterol, bilirubin, urea, creatinine, uric acid, calcium, magnesium, and phosphorus were estimated using the VITROS 5600 automated dry chemistry analyzer, employing various enzymatic and colorimetric methods, with no specific calibration. For bile samples, processing was done with a 1:10 dilution using deionized water before analysis.

Nutrient level of each patient was documented in a structured methodical format. The patient data has undergone anonymization in order to guarantee confidentiality. The access to those data will be held only authorized personnel only. Appropriate consent for the procedure and study would be obtained from the patient, in patient's native language in the presence of a witness prior to sample collection.

RESULTS

The data was gathered, categorized, and processed into MS Excel. All analyses were performed using SPSS version 26. Descriptive statistics for age, gender and procedure were mentioned in percentage frequency mean and standard deviation appropriately. Association of gender with bile and serum parameter as well as procedure with bile and serum parameters were analysed using independent T test. The association between serum and biliary parameters was assessed using the Pearson correlation test. P value of less than 0.05 was considered statistically significant. Appropriate Graph and tables were used when needed.

The participants between the years 20 and 30 are 25% of this study population. While the age group between 31-40 has the maximum number participants in the study with about 30% followed by 19% in the category of 41-50 years of age. Above the age of 50, about 26 individuals were considered into research [Table I]. The minimum age of the participants in this study was 20 years and maximum age of the participant was 65 years with a standard deviation 11.815.

Table I: Age distribution of the participants in the study.

		Frequency(n)	Percent(%)
Age in years	20-30	25	25.0
	31-40	30	30.0
	41-50	19	19.0
	>50	26	26.0
	Mean		40.73
	Std. Deviation		11.815

The mean age of the participants was 40.73 years, with a standard deviation of 11.815 years, suggesting an increased prevalence towards middle-aged individuals. The age distribution indicates that GBS is more common among individuals in their 30s and 40s, which is consistent with previous epidemiological data showing greater rates of occurrence in middle-aged adults.

76% of the study population was female population. There was a no disparity in serum bilirubin levels between males and females, with males exhibiting elevated levels (p = 0.04) [Table II]. Otherwise, no other notable incongruity was seen in the serum and biliary parameters between males and females, suggesting that gender does not have a significant impact on the concentrations of the majority of macro and micronutrients in this investigation.

Table II: Association between gender and parameters

	GENDER	Mean	Std. Deviation	df	T value	P value
SERUM CHOLESTEROL	Male	191.04	41.704	98	0.071	0.9
	Female	191.61	30.617			
SERUM BILIRUBIN*	Male	.8704	.44093	98	2.138	0.04
	Female	.6764	.36321			
SERUM UREA	Male	24.509	10.6445	98	1.565	0.122
	Female	20.486	10.8684			
SERUM CREATININE	Male	.761	.2190	98	1.770	0.08
	Female	.651	.2732			
SERUM URIC ACID	Male	4.322	1.8594	98	0.404	0.68
	Female	4.186	1.2612			
SERUM CALCIUM	Male	8.935	.6169	98	0.548	0.5
	Female	9.019	.6598			
SERUM PHOSPHORUS	Male	4.322	.7373	98	0.424	0.5
	Female	4.235	.8926			
SERUM MAGNESIUM	Male	1.800	.3289	98	1..148	0.23
	Female	1.901	.3827			
BILE CHOLESTEROL	Male	62.87	25.284	98	.0.182	0.8
	Female	61.73	26.727			
BILE BILIRUBIN	Male	50.5870	26.47759	98	.833	0.4
	Female	44.5661	31.46884			
BILE UREA	Male	28.39	12.269	98	1.138	0,23
	Female	25.31	11.118			
BILE CREATININE	Male	1.2261	.52762	98	.884	0.38
	Female	1.1175	.51362			

CONTINUE

	GENDER	Mean	Std. Deviation	df	T value	P value
BILE URIC ACID	Male	4.5652	1.58361	98	.401	0.6
	Female	4.3647	2.23585			
BILE CALCIUM	Male	12.422	5.6512	98	.729	0.46
	Female	11.325	6.5215			
BILE PHOSPHORUS	Male	7.883	3.6376	98	.245	0.8
	Female	8.484	11.5705			
BILE MAGNESIUM	Male	7.235	3.2239	98	0.612	0.4
	Female	6.755	3.3261			

df- Degrees of Freedom; Test used was independent T-Test;

"*" represents P value <0.05- stastically significant

The study compared macro and micronutrient levels in serum and bile of patients with GBS. Significant differences were observed between the two fluids [Table III, IV]. Serum cholesterol levels (mean: 191.48 mg/dL) were significantly higher than bile cholesterol levels (mean: 61.99 mg/dl), reflecting cholesterol's systemic circulation versus its concentration in bile. Conversely, bile had significantly higher levels of bilirubin (mean: 45.951 mg/dl vs. 0.7210 mg/dl in serum), urea (mean: 26.02 mg/dl vs. 21.411 mg/dl in serum), creatinine (mean: 1.1425 mg/dl vs. 0.676 mg/dl in serum), calcium (mean: 11.577 mg/dl vs. 9.000 mg/dl in serum), phosphorus (mean: 8.306 mg/dl vs. 4.255 mg/dl in serum), and magnesium (mean: 6.865 mg/dl vs. 1.878 mg/dl in serum).

Table III: Mean and standard deviation of micronutrients level of study population in Serum and Bile

	Micronutrients	Minimum	Maximum	Mean	Std. Deviation
SERUM	*CHOLESTEROL	112	275	191.48	33.259
	*BILIRUBIN	.10	1.86	.7210	.38887
	*UREA	4.0	68.0	21.411	10.8974
	*CREATININE	.4	2.5	.676	.2648
	*URIC ACID	1.0	8.0	4.217	1.4116
	*CALCIUM	7.6	10.9	9.000	.6481
	*PHOSPHORUS	2.5	5.6	4.255	.8566
	*MAGNESIUM	1.2	3.6	1.878	.3719
BILE	CHOLESTEROL	50	188	61.99	26.280
	BILIRUBIN	.41	99.30	45.951	30.373
	UREA	4	49	26.02	11.404
	CREATININE	.20	3.00	1.1425	.51622
	URIC ACID	.50	11.00	4.4108	2.09813
	CALCIUM	1.0	23.5	11.577	6.3215
	PHOSPHORUS	.382	104.	8.306	10.308
	MAGNESIUM	.7	14.5	6.865	3.2930

Table IV: Correlation between Variables

	Correlation coefficient (r)	P value
SERUM CHOLESTEROL & BILE CHOLESTEROL	-.151	.135
SERUM BILIRUBIN & BILE BILIRUBIN	.027	.790
SERUM UREA & BILE UREA*	.253	.011
SERUM CREATININE & BILE CREATININE*	.333	.001
SERUM URIC ACID & BILE URIC ACID	.068	.499
SERUM CALCIUM & BILE CALCIUM	-.184	.067
SERUM PHOSPHORUS & BILE PHOSPHORUS	.018	.859
SERUM MAGNESIUM & BILE MAGNESIUM	.005	.961

"*" represents P value <0.05- stastically significant

Correlation analysis identified significant relationships for urea and creatinine between serum and bile (r = 0.253, p = 0.011) and creatinine (r = 0.333, p = 0.001) between serum and bile, indicating some systemic influence on these metabolites. However, other nutrients showed no significant correlations, suggesting independent regulation in serum and bile. These findings highlight the distinct metabolic environments of serum and bile, with implications for understanding gallstone pathogenesis and potential biomarkers for diagnosis and treatment.

The scatter plots [Fig 2] depict the relationship between serum cholesterol and bile cholesterol and serum bilirubin and bile bilirubin shows a wide dispersion of data points without any discernible association pattern. The correlation coefficient is -0.151, with a p-value of 0.135 for serum and bile cholesterol, suggesting that there is no statistically significant link. Similarly, the correlation coefficient for serum and biliary bilirubin is r = 0.027, with a p-value of 0.790. This suggests that there is no substantial correlation between the two variables. These findings suggest that the levels of cholesterol and bilirubin in the blood do not accurately reflect their levels in bile. This emphasizes that the regulation of these nutrients in serum and bile is independent of each other.

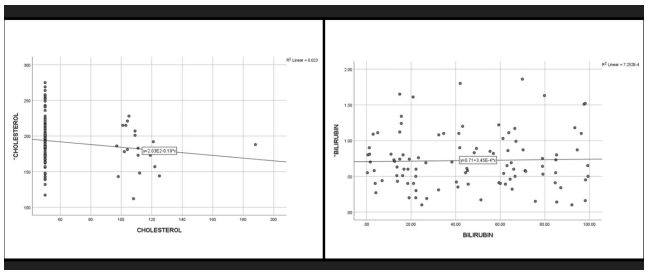

Fig 2: SCATTER PLOT between Serum & Bile Cholesterol and Serum & Bile Bilirubin.

The scatter plots [Fig 3] depicting the relationship between serum urea and bile urea and serum creatinine and bile creatinine demonstrate patterns that suggest a link between these nutrients in both serum and bile. The scatter plot of serum urea and biliary urea displays a more clustered distribution, indicating a moderate positive connection. This is substantiated by the correlation coefficient (r = 0.253, p = 0.011), which suggests that there is a moderate association between urea levels in blood and urea levels in bile. This indicates a systemic relationship that is likely impacted by renal function. Similarly, the scatter plot depicting the relationship between serum creatinine and biliary creatinine reveals a distinct positive trend, suggesting a link between the two variables. The visual trend is supported by the strong correlation coefficient (r = 0.333, p = 0.001), indicating a connection amongst serum creatinine levels and bile. This correlation demonstrates the collective impact of both renal and hepatic processes on the metabolism of creatinine. Unlike prior studies that predominantly focused on cholesterol as the main contributor to gallstone formation, our findings underscore the potential involvement of urea and creatinine, thereby broadening the scope of GBS pathogenesis.

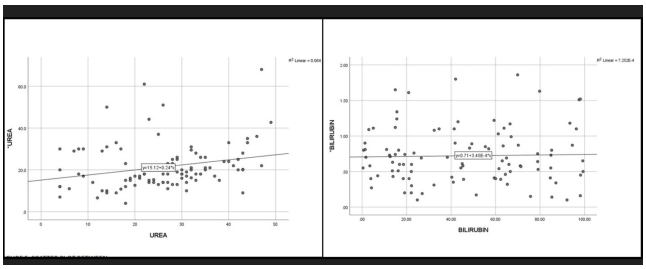

Fig 3: SCATTER PLOT between Serum & Bile Urea and Serum & Bile Creatinine.

DISCUSSION

The age distribution of patients in this study reveals that GBS primarily impacts individuals in the middle-aged and elderly population. To be more precise, 25% of the patients fall within the age bracket of 20-30 years, 30% were in the age range of 31-40 years, 19% were aged 41-50 years, and 26% were above the age of 50 years. The mean age of the participants was 40.73 years, with a standard deviation of 11.815 years.

This age distribution is consistent with the previous literature that emphasizes the higher occurrence of GBS in middle-aged and elderly people [4]. For example, a study conducted by Stinton and Shaffer (2012) observed that the occurrence of GBS becomes more common as individuals become older, especially beyond the age of 40[1]. This finding aligns with our own study, where we found that a majority of the individuals with cholelithiasis were in the middle-aged population, approximately 40 years old. And more than 50% of our study population is over the age of 40.

However, as stated in the Global Epidemiology of GBS in the 21st Century, the occurrence of GBS significantly rises with advancing age. The consistent trend discovered in many research studies and geographic regions indicates that the process of ageing has a significant influence in elevating the likelihood of getting GBS [5] Whereas in our study, 26% were older than 50years of age. One potential reason may be the study's limitations in excluding patients with related difficulties. As individuals age, the likelihood of developing linked illnesses also increases. Another factor could be the patients' loss of awareness beyond a certain age and their lack of knowledge with additional illnesses [6].

This study found a significant gender disparity in the prevalence of GBS, with females accounting for 76.0% of the study group and males representing 24.0% of the research sample. The gender pattern of GBS in the study aligns with the established higher prevalence of GBS in females [2, 5]. Various causes contribute to this discrepancy, with hormonal impacts, namely estrogen, playing a significant role. Estrogen enhances the level of cholesterol saturation in bile and decreases the movement of the GB, which in turn promotes the development of GBS [7].

The study demonstrates that gender has a substantial impact on serum bilirubin levels, with males displaying elevated amounts. This discovery is consistent with the function of bilirubin in the development of pigment stones and suggests that there may be a gender-specific mechanism involved in the development of GBS, which was not established in other noticeable studies and novel to our research. Another contributing factor may be the higher levels of alcohol intake among males compared to females [8], which could have had a substantial effect on the patient's liver and bilirubin levels. Nevertheless, the majority of other nutrient levels in blood and bile do not exhibit noteworthy disparities based on gender, indicating comparable regulatory mechanisms for these factors across both genders. These observations enhance our comprehension of the biochemical elements linked to GBS and reinforce the significance of taking gender into account when devising strategies for its management and prevention. It is encouraged to conduct further research using larger sample sizes and diverse populations, including individuals from other ethnic groups and regions of the world, in order to validate and build upon these findings.

There is an inverse correlation between cholesterol and calcium based on the data. As serum levels of cholesterol and calcium decline, their corresponding levels in bile increase. In contrast, other micronutrients show a positive correlation between their levels in the bloodstream and in bile. Correlation analysis between micronutrients in serum and bile reveals that most nutrients do not exhibit a significant relationship between their serum and bile levels, except for urea and creatinine, with P-values of 0.011 and 0.001, respectively. This further suggests that the metabolic processes and regulatory mechanisms for these nutrients in bile are largely independent of their concentrations in serum. Understanding these associations is crucial for managing patients with GBS and undergoing cholecystectomy. Monitoring the levels of serum creatinine and urea can offer valuable information about the concentration of bile, which is crucial for the diagnosis and management of biliary disorders.

Our research aligns with the existing literature that examines the relationship between creatinine and urea. There is an unambiguous link between gallstone illnesses and chronic kidney problems [9]. Moreover, as chronic kidney disease (CKD) advances, the frequency and prevalence of GBS also increases. The prevalence of GBS among patients with chronic kidney disease (CKD) before starting dialysis was greater than that in the whole population. The possible cause of this occurrence could be related to metabolic changes, including abnormalities in lipid metabolism and increased cholesterol saturation in bile. Individuals with chronic kidney disease (CKD) often follow low-protein diets, which have been associated with an increased susceptibility to GBS due to changes in the composition of bile [10].

In addition, CKD may influence GB motility, resulting in bile stagnation and the formation of GBS [10]. Also both the illness share common predisposing factors such as obesity, metabolic syndrome, diabetes mellitus, and dyslipidemia. There is also a bidirectional relationship between the GBS and CKD, especially in patients with high risk [9]. However, the relationship between Urea and Creatinine, which enter the GB through passive diffusion, and their potential involvement in

the development of GB sludge and stones, remains unexplored.

LIMITATIONS

The possible limitations of the study include the restricted number of patients undergoing surgery who consented to participate. Variations due to dietary intake such as food with high cholesterol content, and environmental factors could influence results. Potential laboratory errors during sample handling or data entry could not be entirely ruled out. Also, the study is a single centered study which compromises the population diversity and regional variations.

RECOMMENDATIONS

Multi centric, large scale studies can be put forward, across various strata of people from different region and dietary practices with a diverse population can be considered to provide a more comprehensive understanding of the biochemical parameters in gallstone disease. Age specific studies can also be put forth so that, more structured understanding about the macro/micro nutrients in various age groups can be studied. Bile composition analysis can be incorporated in regular surgical practice to expand our knowledge about nutrients in bile. These findings challenge the predominant focus on cholesterol and bilirubin in gallstone research, suggesting that systemic factors like renal metabolism may play a larger role than previously recognized.

CONCLUSION

This study demonstrates that GBS mostly impacts individuals in the middle-aged and elderly population, with a notable prevalence in individuals aged over 40 years, in line with previous research. An evident gender imbalance was noted, with females (76%) experiencing a higher degree of impact compared to males (24%), possibly attributed to hormonal factors such as the influence of estrogen on cholesterol saturation and GB motility. Elevated serum bilirubin levels in males may suggest a gender-specific mechanism in gallstone formation, potentially linked to higher alcohol consumption, which is a potential area that are yet to be explored.

The majority of nutrient levels did not exhibit any notable gender disparities, with the exception of urea and creatinine, suggesting autonomous regulating mechanisms in bile. The study also emphasizes a reciprocal relationship between GBS and chronic kidney disease (CKD) which is correlation with the existing literature, underscoring the necessity for additional investigation into the processes that connect these illnesses.

Future research should build upon these findings by exploring the mechanistic roles of these nutrients in larger, more diverse cohorts to enhance our understanding of gallstone disease and its systemic implications.

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INSTITUTIONAL ETHICS COMMITTEE NUMBER:
038/06/2023/IEC/SMCH

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