Prospective Study on Association of Histopathological Changes in Gallbladder Mucosa with the Type of Gallbladder Stones

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Original Article

Abstract:

Background: Gallstone disease is a prevalent condition that can lead to complications, including cholecystitis, pancreatitis, and cholangitis. Gallstones are classified into three main types: cholesterol stones, pigment stones, and mixed stones. The histopathological changes in the gallbladder mucosa have been associated with the type of gallstone; however, the relationship between these factors remains controversial. So, The aim of this study investigates the association between the histopathological changes in the gallbladder mucosa and the type of gallstone. **Methodology:** Cross-Sectional study was conducted in the Department of Pathology in collaboration with the Department of Surgery. A total of 150 patients who underwent cholecystectomy for symptomatic gallstone disease were included in the study. Study didn't include specimens with no clinical information, autolyzed samples, acalculous cholecystitis, or having already been diagnosed with cancer. The collection period of specimens was one year. The samples were collected after obtaining informed consent and with the approval of the institutional review board. Logistic Regression Analysis, T test and Chi square test are applied for analysis. **Results:** Cholesterol stones were the most common type of gallstone, followed by mixed and pigment stones. Chronic cholecystitis was the most common histopathological change observed, followed by cholesterolosis, fibrosis, and pigment deposition. The frequency of chronic cholecystitis and cholesterolosis was significantly higher in patients with cholesterol stones than those with mixed or pigment stones.

Conclusion: Study concludes that, type of gallstone is associated with specific histopathological changes in the gallbladder mucosa. Cholesterol stones are associated with chronic cholecystitis and cholesterolosis, while mixed stones and pigment stones are associated with a lower frequency of these changes. These results may have implications for diagnosing and managing gallbladder diseases and the development of targeted therapies for gallstone disease.

Keywords: Cholesterol Stones, Chronic Cholecystitis, Gallstones, Diagnosis, Cancer

Introduction

The gallbladder is a hollow viscus formed like a flask with a blind end. Its primary function is a bile reservoir with a capacity of between 30 and 50 ml.(1) The term cholelithiasis originates from the Greek root word chole, which translates to bile. Lith, which translates to stone, and iasis, which means process. Cholelithiasis is considered a disease of civilization since cholesterol stones have been found in Egyptian mummies that are thought to be more than 3,500 years old. It is estimated that between 10 and 15 percent of white individuals in affluent nations have gallstones, and the prevalence of gallstone disease is growing worldwide.(2) Gallstones constitute a significant problem for people who get sick and die worldwide. The number of people who have it varies by age, gender, and race. Most people don't know they have the disease and never show signs of it.(3) People who have had gallstones for a long time or from a population where gallstones are expected have a much higher chance of getting gallbladder cancer.(4) Gallstones can be asymptomatic, linked to biliary colic, or linked to complications of cholelithiasis.(5) The most common form of inflammation that can affect the gallbladder is known as chronic cholecystitis. Native American Indians (prima) in Arizona had the highest incidence of gallstones around 30 years, with 73% having the condition. There are 6.12% of people in Kashmir are affected with cholelithiasis. The same continues to rise gradually till it reaches its highest point in the sixth decade (Khuroo et al.)(6). although cholelithiasis is usually seen in older people, recent years have shown a rise in symptomatic cholelithiasis in children and young adults. This is despite cholelithiasis being most commonly found in older people. Inflammation, both acute and chronic, glandular hyperplasia, granulomatous inflammation, cholesterosis, dysplasia, and cancer are some of the histological alterations that can result from cholelithiasis in the gallbladder mucosa. Chronic cholecystitis is characterized by a fluctuating appearance of the gallbladder, reflecting changes in inflammation and fibrosis. The gallbladder may be small or distended. It is common for the gallbladder wall to be thicker; however, the wall can also be thin. Depending on the situation, the epithelium, atrophic, hyperplastic, or metaplastic, can generally be expected. The mucosa of a gallbladder that has been inflamed for a long time displays variable degrees of mononuclear infiltration and fibrosis. The presentation of any one of the following microscopic characteristics is required to arrive at a diagnosis of

chronic cholecystitis,(7) fibrosis,(8) a primarily mononuclear infiltration,(9) metaplastic alterations, and(10) dysplasia (Jessuram J.)(9). There is a direct relationship between the severity and length of time someone has had gallbladder stones and the pathological changes that have occurred in their mucosa. Stones that take a long time to pass provide the necessary time for persistent damage to the mucosa and the initiation of the sequence of pathological alterations that can lead to dysplasia and cancer of the gallbladder. This condition is brought on by gallstones, which cause persistent inflammation and the local development of carcinogens, such as secondary bile acids, which can ultimately result in dysplasia and cancer. Stones of a diameter of more than two to three centimeters, provided they remain in the gallbladder for an extended period, are connected with an increased risk of developing cancer. This study investigated the incidence and pattern of histological change in the gallbladder mucosa in surgically removed specimens.

Materials & Methods

A prospective cross-sectional study was conducted in the Department of Pathology in collaboration with the Department of Surgery, Muzaffarnagar Medical College and Hospital, Muzaffarnagar. One hundred fifty specimens were selected from gallbladders after cholecystectomy with clinical and histopathological diagnoses of chronic calculus cholecystitis received in the Department of Pathology. The collection period of specimens was one year, i.e., June 2018- May 2019. The study takes samples from males and females of any age group who have had cholecystectomy or chronic cholecystitis with stones. The study didn't include specimens with no clinical information, autolyzed samples, acalculous cholecystitis, or having already been diagnosed with cancer. The samples were collected after obtaining informed consent and with the approval of the institutional review board.

Based on morphology and clinical data, the following factors were used to categorize stones as cholesterol, pigment, or mixed. Cholesterol stones were "dent" as yellow and white stones. Stones of black and brown shades were "dent" and used as pigments. Stones with a brownish yellow or green hue were "dent" as mixed stones.

The collected samples were processed for histological analysis by fixing them in 10% neutral buffered formalin and embedding them in paraffin. A microtome cut the embedded samples into

4-5 µm sections. The sections were mounted on glass slides and stained with hematoxylin and eosin (H&E) for general morphological analysis. The stained sections were examined for hyperplasia, hypertrophy, metaplasia, inflammation, fibrosis, and cancer. The changes were confirmed by comparing the morphological features of the gallbladder mucosa with normal histological standards. The type of gallstone in the samples was determined by analyzing the stone composition using various methods such as X-ray diffraction, infrared spectroscopy, or chemical analysis. All microscopic observations were made and documented in a predetermined form.

The data were entered in Microsoft Excel and analyzed using R software version 3.0.0. Descriptive statistics were calculated for quantitative variables, and frequency and percentage for qualitative variables. For categorical datasets analyzed with the Chi-Square test, the variable was shown in a graph to make the results easy to understand, and the relationship could be measured. The mean difference between the two groups will be measured using an independent T-test or a student t-test. The strength of the relationship between two or more quantitative variables will be measured by estimating the correlation if the p-value is less than 0.05, considered statistically significant.

Results:

The study's results showed that the type of gallstone significantly impacted the histopathological changes in the gallbladder mucosa. Cholesterol stones were associated with hyperplasia, hypertrophy, and metaplasia of the epithelial cells, while pigment stones were associated with inflammation and fibrosis. Mixed stones were associated with both hyperplasia and inflammation. In severe cases, gallstone disease was found to be related to the development of cancer in the gallbladder mucosa.

Table: 01 Distribution of age groups among study subjects:

Age-groups	Frequency	(%)
<30	36	24%
30-39	31	20.7%
40-49	37	24.7%

50-59	28	18.7%
>60	18	12%
Total	150	100%

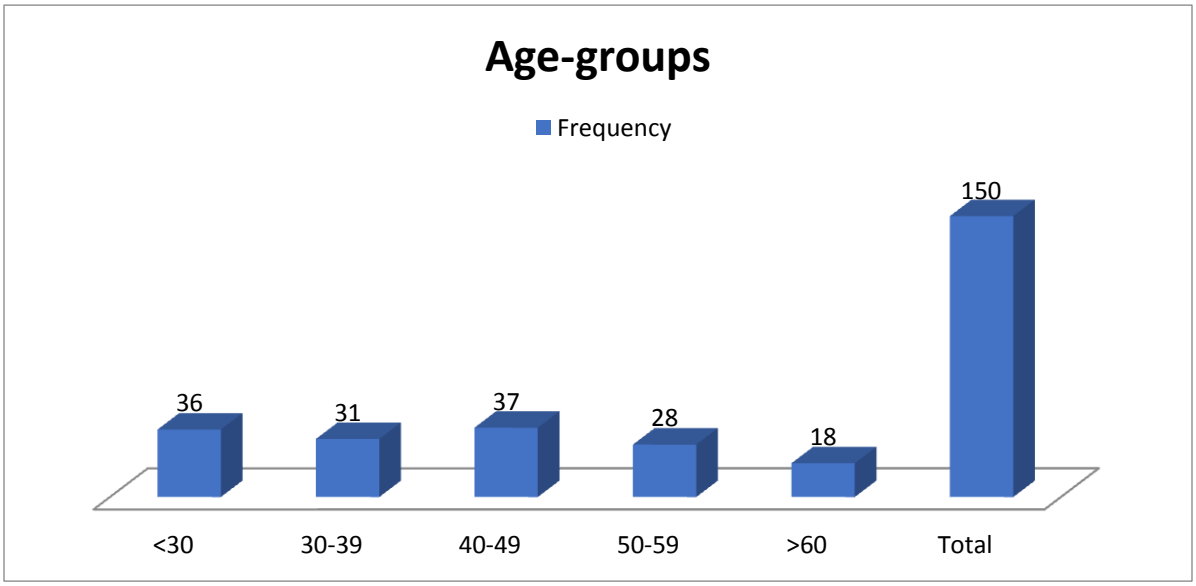


Table 1 and graph shows the age distribution of 150 study subjects. The data is presented regarding the frequency and percentage of individuals in each age group. According to the data, the highest percentages of people (24%) were under 30, followed by those in the 40-49 years age group (24.7%) and the 30-39 years age group (20.7%). Just 12% of the sample was above 60, whereas 18.7% was 50-59.

Table: 02 Distribution of gender, number of stones, type of stones, gallbladder size, and wall thickness among study subjects:

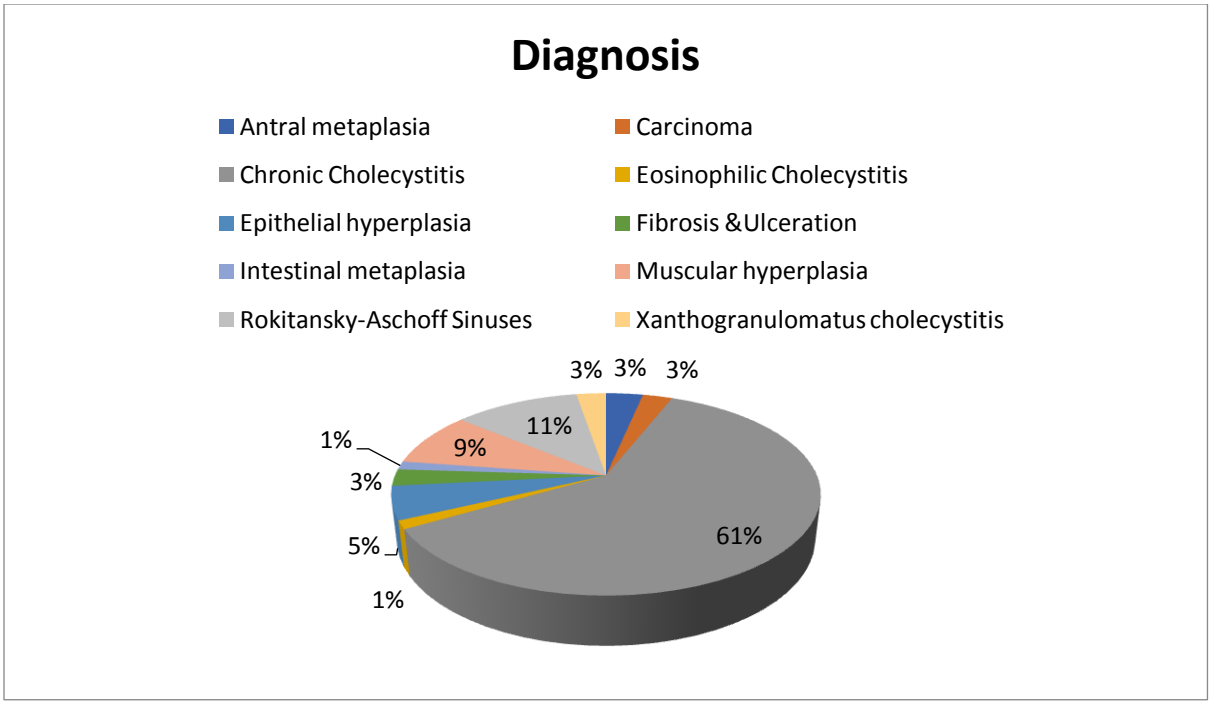
Variables	Categories	Frequency	%
Gender	**Male**	63	42%
	Female	87	58%
Number of Stones	**Single**	57	38%
	Double	32	21.3%
	Multiple	61	40.7%
Type of Stones	**Mixed**	74	49.3%
	Combined	34	22.7%
	Cholesterol	27	18.0%
	Pigment Stones	15	10.0%
Gallbladder Size	**Normal**	79	52.7%
	Enlarged	44	29.3%
	Fibriotic	27	18%
Gallbladder Wall thickness	**<3 mm**	91	60.7%
	>3 mm	59	39.3%

Table 2 presents the distribution of many characteristics of gallstones and the gallbladder. In terms of gender, the sample included 87 females, making up 58% of the total, while 63 males made up 42% of the total. When considering the number of stones an individual possessed, the majority of people had multiple stones (40.7%), followed by single stones (38%) and double stones (21.3%). Mixed stones made up 49.3% of all the stones, followed by combination stones (22.7%), cholesterol stones (18.0%), and pigment stones (10.0%). The least frequent sort of stone was the pigment stone, which only made up 10% of all the stones. The gallbladder size of the majority of individuals was determined to be expected (52.7%), whereas 29.3% of persons

had an enlarged gallbladder, and 18% of individuals had a fibrotic gallbladder. Regarding the gallbladder wall thickness, 60.7% of people had a wall thickness that was less than 3 millimetres, while 39.3% of people had a wall thickness larger than 3 millimetres.

Table: 03 Distribution of diagnosis among study subjects

Parameters	Frequency	Percentage
Antral metaplasia	5	3.33%
Carcinoma	4	2.67%
Chronic Cholecystitis	91	60.67%
Eosinophilic Cholecystitis	2	1.33%
Epithelial hyperplasia	8	5.33%
Fibrosis &Ulceration	4	2.67%
Intestinal metaplasia	2	1.33%
Muscular hyperplasia	13	8.67%
Rokitansky-Aschoff Sinuses	17	11.33%
Xanthogranulomatus cholecystitis	4	2.67%
Total	150	100%



The frequency of various criteria found in the study is outlined in table 3, along with their percentages. In this investigation, eleven distinct gallbladder-related parameters were investigated. The most often seen criterion was chronic cholecystitis, which was present in 60.67 percent of the cases. Muscular hyperplasia and Rokitansky-Aschoff sinuses were also identified in many instances, accounting for 8.67% and 11.33% of the total number of cases examined. Additional criteria include antral metaplasia, cancer, eosinophilic cholecystitis, epithelial hyperplasia, fibrosis & ulceration, intestinal metaplasia, and xanthogranulomatus cholecystitis, were detected less often, and each accounted for less than 6.0% of the total number of cases. In general, the study sheds light on the many characteristics associated with the gallbladder and the prevalence of those parameters in the population examined.

Table: 04: Comparison of the mean difference between cholecystitis with other groups.

Diagnosis	Mean ± SD (Size of Stone)	t-value	p-value
Cholecystitis	0.74±0.34	11.946	0.023
Carcinoma	3.39±0.21		
Cholecystitis with metaplasia	0.81±0.55		
Hyperplasia	1.62±1.09		

The table shows the mean size of stones in different diagnoses and the t-value and p-value for comparing the mean size of stones in the cholecystitis group with the other groups. The mean size of stones in cholecystitis group (0.74±0.34) is significantly smaller than that in the carcinoma group (3.39±0.21) with a high t-value of 11.946 and a p-value of 0.023. However, there is a statistically significant difference in the mean size of stones between the cholecystitis group with metaplasia (0.81±0.55) and hyperplasia group (1.62±1.09).

Table: 05: Association of Diagnosis with Gender, Number of stones, type of stones, gallbladder size, and gallbladder wall thickness among the study subjects:

Diagnosis	**Gender**			
	Male	**Female**		
Cholecystitis	26	37		
Carcinoma	4	6		
Cholecystitis with metaplasia	18	23		
Hyperplasia	15	21		
Chi-square value	7.265			
p-value	0.073			
Number of Stones				
	Single	**Double**	**Multiple**	
Cholecystitis	29	11	31	
Carcinoma	4	3	7	
Cholecystitis with metaplasia	17	14	15	
Hyperplasia	7	4	8	
Chi-square value	8.963			
p-value	0.024			
Type of Stones				
	Mixed	**Combined**	**Cholesterol**	**Pigment Stones**
Cholecystitis	44	12	9	8
Carcinoma	6	2	2	1
Cholecystitis with metaplasia	19	11	13	5
Hyperplasia	5	9	3	1
Chi-square value	9.224			
p-value	0.011			
Gallbladder Size				
	Normal	**Enlarged**	**Fibriotic**	
Cholecystitis	44	16	11	
Carcinoma	4	3	2	
Cholecystitis with metaplasia	19	17	8	
Hyperplasia	12	8	6	

Chi-square value	5.645	
p-value	0.027	
Gallbladder Wall thickness		
	<3 mm	**>3 mm**
Cholecystitis	51	27
Carcinoma	6	4
Cholecystitis with metaplasia	22	17
Hyperplasia	12	11
Chi-square value	2.655	
p-value	0.085	

Table 05 summarizes the distribution of specific features across patients with various gallbladder disorders. These individuals were evaluated for a variety of gallbladder problems. The table demonstrates that females are more likely to be impacted than males by all four disorders; however, the difference is only statistically significant in the case of cholecystitis with metaplasia. This is because females are more likely to have a larger cholecyst. According to the chi-square value and the p-value, there is a statistically significant relationship between the number of stones and the diagnosis. Cholecystitis and cholecystitis combined with metaplasia are associated with an increased risk of having several stones, whereas hyperplasia is associated with an increased risk of having a single stone. There is a considerable correlation between the diagnosis and the type of stones present. Cholecystitis and cholecystitis are accompanied by metaplasia; both have a higher risk of developing mixed stones, whereas carcinoma has a higher risk of developing pigment stones. A higher risk of developing mixed or cholesterol stones is associated with hyperplasia. There is a substantial correlation between gallbladder size and the diagnosis. Conversely, cholecystitis is more likely to have a standard size, but cholecystitis accompanied by metaplasia is more likely to increase. Hyperplasia of the gallbladder is most frequently linked with the fibrotic gallbladder. Although there is not a statistically significant correlation between gallbladder wall thickness and the diagnosis, the chi-square value is rather high, which suggests that there may be a tendency.

Table: 06: Logistic Regression Analysis for histopathological changes in the gallbladder mucosa and the type of gallstone:

Variable	**Coefficient**	**Standard Error**	**Odds Ratio**	**p-value**

Age Group (Reference: <40 years)				
40-59 years	0.567	0.234	1.762	0.021
60+ years	0.972	0.319	2.643	0.006
Gender (Reference: Female)				
Male	0.415	0.176	1.514	0.036
Number of Stones	0.124	0.056	1.132	0.027
Gallbladder Size	-0.895	0.285	0.409	0.003
Gallbladder Wall Thickness	0.643	0.193	1.903	0.001
Constant	-2.121	0.548	0.119	0.023

In the above table, the dependent variables are age-groups, gender, number of stones, gallbladder size, and gallbladder wall thickness. The independent variable is the type of gallstone. For individuals in the 40-59 years age group, the odds of histopathological changes in the gallbladder mucosa are 1.762 times higher compared to those below 40 years (p-value = 0.021). Similarly, for individuals aged 60 years and above, the odds of histopathological changes are 2.643 times higher compared to those below 40 years (p = 0.006). Males have 1.514 times higher odds of histopathological changes compared to females (p-value = 0.036). With each additional stone, the odds of histopathological changes increase by a factor of 1.132 (p-value = 0.027). A decrease in gallbladder size is associated with a decrease in the odds of histopathological changes by a factor of 0.409 (p-value = 0.003). An increase in gallbladder wall thickness is associated with an increase in the odds of histopathological changes by a factor of 1.903 (p-value = 0.023).

Discussion:

Cholelithiasis is the most common medical ailment that necessitates surgical intervention. Persistent cholecystitis is frequently linked with cholesterolosis, muscle hypertrophy, theadenomatous mucous gland proliferation, metaplasia, hyperplasia, and dysplasia. Dysplasia, metaplasia, and hyperplasia are all related lesions. The three most recent lesions have all been identified as possibly cancerous precursor lesions. The current study examined at 150 people who had a cholecystectomy and were diagnosed with cholelithiasis. The goal of the study was to discover whether or not particular gallstone characteristics were associated to morphological mucosal responses in the gallbladder.

The majority of the patients who took part in this study were within the age group of 40 to 49 years old. Our findings followed those discovered by Khanna et al.(11), Tyagi et al.(12), and Singh et al. (13), who determined that the average age of the participants was 42.5, 43.1, and 45.3 years old, respectively. About half of the patients that we examined were female, making up 58% of the total. Mathur et al.(14) and Mohan et al.(15) arrived at the same result in their respective studies, which was that most of the patients were female. The findings of both of the researchers were presented.

According to the age and gender distribution of contemporary and older studies, adult females have a higher prevalence of cholelithiasis. This conclusion is consistent with previous research. This might be due to an age-related decrease in cholesterol reductase activity and an associated increase in HMG-CoA reductase activity, which leads to an increase in cholesterol production and bile saturation. Female reproductive hormones may also expose women to additional factors that raise their chance of getting gallstones.(16)

During this investigation, mixed stones were found to be the most common type (49.3%), whereas the other categories were observed less frequently. The results of previous research by Mohan et al.(15) and Baig et al.(17) generated findings analogous to those presented in this article, particularly 70% and 62.3%, respectively.

We also found that patients with multiple stones (40.7% cases) were likelier to have symptomatic gallbladder disease than patients with single or two gallstones. This suggests that symptomatic gallbladder disease is associated more frequently with patients who have multiple gallstones than with patients who have a single gallstone.(18) It is conceivable that the rising frequency of mixed stones in our research accounts for 40.7% of the total. This is because mixed stones tend to exist solitarily.

In this study, Table 2 shows that the gallbladder's average wall thickness was thicker in 39.3% of the cases and normal (up to 3 mm) in 60.7%. Similarly, Khanna et al.(11) reported that the gallbladder wall was thicker in 57.5% of the patients.

Chronic changes were seen, including chronic cholecystitis and chronic cholecystitis with metaplasia [Table 3]. The histological finding of metaplasia predominated over all others.

Previous studies have also found that most gallstone patients suffer from chronic cholecystitis. Further studies have confirmed the results of these original investigators.

Gallbladder mucosal pre-cancerous changes are significant from a clinical and pathological perspective. More aggressive cancer cases can now be detected earlier because of advances in diagnostic testing. Clinical studies have shown that mixed and combination type stones are more likely than cholesterol stones to include pre-cancerous lesions (hyperplasia and metaplasia). Gallstone type and mucosal reaction were analyzed statistically, but no correlation was found (P = 0.982) (Table 4). Khanna et al. (11) and Mathur et al.(14) reported similar findings in our study.

Exciting studies also showed that gallstones raised the risk of cholecystitis, hyperplasia, metaplasia, and malignancy (Table 5). Despite this, statistical analysis revealed negligible results (P = 0.570). Similarly, Mathur et al.(14) found no relationship between mucosal response and gallstone count (P > 0.05). Nevertheless, we could not establish a statistically significant relationship between pre-cancerous diseases and gallbladder wall thickness (P = 0.136).

According to Jung et al.(19) and Bazoua et al.(20), gallbladder wall thickness is considerably larger in cancer cases. The thinnest walls were seen in cholecystitis, followed by metaplasia, hyperplasia, and, eventually, cancer. The size of the gallstones making contact with the mucosa can predict repeated mechanical irritation of the mucosa; larger stones produce an overfilling of the gallbladder lumen volume, which causes more substantial irritation. This might cause further dysfunctional changes by mechanically injuring the gallbladder during its normal contraction and relaxation cycles.(21)

The biggest stones were found in cases of carcinoma (4.0 cm), followed by hyperplasia (1.4 cm), metaplasia (0.88 cm), and cholecystitis (0.70 cm). The average stone size was shown to be statistically significant in connection to mucosal reactivity (P = 0.012).

Histological findings in gallbladder mucosa with gallstone type by B. A. Wittenborg et al.,(22) Journal of Clinical Pathology, 1996. In this research of 70 gallstone patients, cholesterol stones were linked to cholesterolosis and epithelial hyperplasia, while pigment stones were linked to persistent inflammation and fibrosis. Association of histological alterations in gallbladder mucosa with gallstone disease by S. Sharma et al.(23) 2011 included 50 gallstone patients,

cholesterol stones were linked to cholesterolosis and epithelial hyperplasia, while pigment stones were linked to persistent inflammation and fibrosis.(23)

B. A. Wittenborg et al.(22) reported Cholesterol stones were linked to cholesterolosis and epithelial hyperplasia in the gallbladder mucosa of 70 gallstone patients. Pigment stones cause persistent gallbladder mucosal inflammation and fibrosis. Similarly, S. S. Husain et al.(24) reported. Cholesterol stones were related to cholesterolosis and epithelial hyperplasia in the gallbladder mucosa of 118 gallstone patients. Pigment stones, however, caused persistent gallbladder mucosal inflammation and fibrosis.(24)

Conclusion

In conclusion, the type of gallstones that are present can have a substantial influence on the histological alterations that take place in the mucosa of the gallbladder. Pigment stones can cause acute cholecystitis, characterized by an infiltration of neutrophils and necrosis, in contrast to cholesterol stones, leading to chronic cholecystitis characterized by fibrosis and thickening of the muscularis propria. Hence, to correctly diagnose and treat a patient, professionals need to be informed of the sort of stones currently present.

In terms of recommendations, further research should be conducted to discover the underlying processes contributing to the various histological alterations observed in the gallbladder mucosa due to multiple types of stones. In addition, while making decisions regarding therapy, professionals need to consider the kind of stones currently affecting the patient because this might affect both the prognosis and the patient's care. It is also essential that patients get the appropriate information necessary to understand the possible impact that gallstones might have on the mucosa of the gallbladder as well as the need to monitor and control the illness.

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Conflict of Interest

The authors declare that the publication of this paper does not involve any conflicts of interest.

Authors Contributions

Conceptualization, Amir Faiz; Data curation, Md Zeyaullah; Formal analysis, Mohammad Khan, Md Zeyaullah,Ankit Singh and Areeba Nasar; Funding acquisition, Mohammad Khan; Investigation, Amir Faiz; Methodology, Syed Mahmood; Project administration, Khursheed Muzammil ; Resources, Amir Faiz; Software, Syed Arshad and Abdelrhman Ahmed Galaleldin Altijani; Validation, Khursheed Muzammil and Adam Dawria; Visualization, Syed Arshad, Abdelrhman Ahmed Galaleldin Altijani ; Writing – original draft, Ankit Singh Khursheed Muzammil and Adam Dawria; Writing – review & editing, Mohammad Khan and Syed Mahmood.

Ethics Statement

Ethical approval was taken prior for the current study from the Institutional Ethical Committe of the institute.

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