

## A Study on the Correlation of Hypothyroidism with Gallstone Disease

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### ABSTRACT

#### Background

Cholelithiasis is the most common biliary disease. Cholelithiasis is frequently associated with hypothyroidism and hypercholesterolemia and this association has been variedly reported worldwide and in India. It is important to understand the comorbid states of hypothyroidism and cholelithiasis for the diagnosis and management of gallstone disease. In this study we wanted to evaluate the correlation between cholelithiasis and hypothyroidism.

#### Methods

This cross-sectional study was conducted among 200 participants admitted for gallstone disease at the surgery ward, Regional Institute of Medical Sciences, from August 2018 to July 2020.

#### Results

Of the 200 patients with cholelithiasis in the thyroid study, 44 (22%) were in hypothyroid and 156 (78%) in euthyroid states. All patients had sub-clinical hypothyroidism with no symptoms of hypothyroidism. High serum cholesterol was found in 88.6 % of hypothyroid patients and the finding was found to be significant ( $p = 0.000$ ).

#### Conclusion

There is a significant association between gallstone disease and hypothyroidism. Further large population studies are needed in this direction to compare these findings especially case control studies leading to recommendations for screening for early diagnosis of hypothyroidism at subclinical level by regularly monitoring TSH.

**Keywords:** Hypothyroidism, Hypercholesterolemia, Cholelithiasis, Cholecystitis.

### INTRODUCTION

Gallstone diseases are a common medical problem encountered almost every day both in the outpatient and emergency departments.<sup>[1]</sup> Gallstone diseases are seen around 2-29% prevalence in Indian subcontinent. Its prevalence varies according to demographics, age, sex, geography of the region, food habits, sedentary lifestyle and obesity.<sup>[2]</sup> Gallstones are the most common biliary pathology. For decades, there has been a discussion about whether thyroid disorders could cause gallstone disease. Particularly, there are several explanations for a possible

relationship between hypothyroidism and gallstone disease which include the known link between the thyroid failure and the disturbance of lipid metabolism that may consequently lead to a change in the composition of the bile.<sup>[3]</sup>

Laukkarinen J. et al.<sup>[4]</sup> conducted a study on whether bile flow reduced hypothyroidism in patients.

Volkzke H et al.<sup>[5]</sup> conducted a cross sectional study to determine the association between thyroid function and gallstone disease and found an independent correlation between high serum TSH and cholelithiasis.

Sundareswari P. et al.<sup>[6]</sup> conducted a prospective study of hypothyroidism in a diagnosed case of gallstone disease. A total of 12% of gallstone patients were diagnosed with hypothyroidism, showing that there is an association between hypothyroidism and gallstone disease.

Raghuwanshi B. S. et al.<sup>[2]</sup> conducted a prospective study on the prevalence of subclinical hypothyroidism in cases of cholelithiasis. All stones in hypothyroidism patients were >1 cm, and overall, 58% of stones were >1 cm. 03 out of 12 hypothyroidisms (25%) patients had single stones, while 9 (75%) patient had multiple stones. In hypothyroid cases, most stones were of the cholesterol type (58%).

The purpose of this study was to determine the prevalence of hypothyroidism in gallstone disease and compare it with national prevalence data of hypothyroidism in the general population.

## **MATERIALS AND METHODS**

It was a cross-sectional study conducted at the Surgery ward, Regional Institute of Medical Sciences, from August 2018 to July 2020.

All cases admitted to the department of surgery, RIMS, Imphal (Manipur), aged 18 or older, and with cholelithiasis on ultrasonography were included.

Patients with a previous history of thyroid surgery, patients taking drugs for hypothyroidism and previous cases of biliary tract surgery were excluded.

Data was collected after obtaining written, informed consent. A proforma was established, which consisted of socio-demographic and investigation results. Socio-demographics consisted of age, sex, education, occupation, religion, and annual income.

A full history and clinical examination, including name, age, sex, etc., and symptoms and signs of hypothyroidism, including loss of appetite, gaining weight, tiredness, constipation, cold intolerance, menstrual disturbances, bradycardia, presence or absence of goiter, etc., of 200 ultrasonographically confirmed cases of gallstone diseases who fulfilled the criteria were taken.

The levels of serum free T3, free T4, and TSH of all the patients were measured. Patients were divided according to history, clinical examination, and laboratory tests (freeT3, freeT4, TSH) into 3 groups: subclinical hypothyroidism, clinical hypothyroidism, and the euthyroid group.

## **RESULTS**

A cross-sectional study was conducted in the surgery ward of the Regional Institute of Medical Sciences from August 2018 to July 2020 among 200 diagnosed cases of gallstone diseases admitted to the surgical ward of RIMS to determine the correlation of hypothyroidism with gallstone disease.

The majority of the patients were from the 5<sup>th</sup> and 6<sup>th</sup> decade of life, in 51% of patients, as gallstone diseases are most common in the older age group. The most common age group

was 51–60 years in 26 % of cases. The mean age was 42 years, with a standard deviation of 12.598 years.

In our study, 158 patients (79%) are female and 42 patients (21%) are male. This is mainly because our study population has gallstone disease, and gallstone diseases are more common in females.

<b>Age and Sex Distribution</b>			
<b>Age (in years)</b>	<b>Male N (%)</b>	<b>Female N (%)</b>	<b>Total N (%)</b>
18-30	8 (19%)	36 (22.78%)	44 (22%)
31-40	6 (14%)	38 (24%)	44 (22%)
41-50	10 (23.8%)	40 (25%)	50 (25%)
51-60	18 (42.86%)	34 (21.5%)	52 (26%)
>60	0 (0%)	10 (6%)	10 (5%)
<b>Residence</b>			
Rural	132	66.0	
Urban	68	34.0	
<b>Occupation</b>			
<b>Occupation</b>	<b>Male N (%)</b>	<b>Female N (%)</b>	<b>Total N (%)</b>
Employed	8 (19%)	18 (11.4%)	26 (13%)
Self Employed	22 (52%)	34 (21.5%)	56 (28%)
Housewife	0 (0.0%)	86 (54%)	86 (43%)
Unemployed	12 (28.5%)	20 (12.65%)	32 (16%)
<b>Dietary Habits</b>			
Vegetarian	12	6	
Non-Vegetarian	188	94	
<b>Smoking</b>			
Yes	30		15.0
No	170		85.0
<b>Alcohol Use</b>			
Yes	18		9
No	182		91
<b>Physical Activity</b>			
Yes	130		65
No	70		35

**Table 1: Sociodemographic Profile and Lifestyle Factors**

<b>Presence of Cholecystitis</b>		
Yes	14	7
No	186	93
<b>Symptoms of Cholelithiasis</b>		
Yes	200	100.0
No	0	0.0
<b>Abdominal Discomfort</b>		
Mild	30	15
Moderate	24	12
Severe	146	73
<b>Severity of Abdominal Pain</b>		

Mild	2	1
Moderate	30	15
Severe	166	83
No	2	1
<b>Site of Pain</b>		
Right Upper Abdomen	52	26
Middle Part of Abdomen	28	14
Combined	120	60
<b>Type of Pain</b>		
Colicky	108	54
Dull	30	15
Burning	62	31
<b>Nature of Pain</b>		
Intermittent	184	92
Constant	14	7
Progressive	2	1
<b>Radiation of Pain</b>		
Back	128	64
Shoulder	20	10
Others/No	52	26
<b>Table 2: Distribution of Patients by Symptoms of Cholecystitis</b>		

In our study, 166 patients out of 200 (83%) experienced severe abdominal pain. Moderate abdominal pain was experienced by 30 patients (15%) and 2 patients (1%) experienced mild abdominal pain.

Serum Cholesterol	Frequency	Percentage
High ( $\geq 200$ mg %)	113	56.5
Normal ( $< 200$ mg %)	87	43.5
<b>Serum Triglyceride</b>		
High ( $\geq 150$ mg %)	56	28
Normal ( $< 150$ mg %)	144	72
<b>Table 3: Distribution of the Patients by Serum Cholesterol (N = 200)</b>		

High serum cholesterol was found in 113 (56.5%) of gallstone patients in our study. The mean serum cholesterol level was 182.37 mg% with a standard deviation of 32.39.

A high serum triglyceride level was found in 56 patients (28%) with gallstones in our study. The mean triglyceride level was 152.8 mg%, with a standard deviation of 59.71.

<b>Serum TSH</b>		
Serum TSH	Frequency	Percentage
High ( $> 3.3$ mU/L)	44	22
Low ( $< 0.3$ mU/L)	0	0
Normal (0.3- 3.3 mU/L)	156	78
<b>Serum Free T3</b>		
High ( $> 7.5$ $\mu$ mol/L)	0	0
Low ( $< 3.5$ $\mu$ mol/L)	44	22
Normal (3.5-7.5 $\mu$ mol/L)	156	78

Serum Free T4		
High (> 30 nmol/L)	0	0
Low (<10 nmol/L)	44	22
Normal (10-30 nmol/L)	156	78

**Table 4: Distribution of the Patients by Thyroid Function Test**

In our current study of 200 gallstone patients, 44 patients (22%) were found to have a high serum TSH level. So, 22% of gallstone patients in our study were found to be hypothyroid. The mean TSH level was 3.15 mU/L, with a standard deviation of 0.956. The mean TSH level was 4.86 mU/L, with a standard deviation of 0.121 mU/L for hypothyroid patients.

The serum-free T3 level was found to be low in the same 44 patients (22%) whose TSH level was high. The mean free T3 level was 3.63 µmol/L, with a standard deviation of 0.71.

Serum-free T4 was found to be low in the same 44 patients (22%) whose TSH level was high. The mean free T4 level was 11.27 nmol/L, with a standard deviation of 1.52.

Age	Euthyroid N (%)	Hypothyroid N (%)	Chi-Square Tests
18-30	40 (25.6%)	4 (9.1%)	Value = 13.697 df = 4 p = 0.008
31-40	36 (23.1%)	8 (18.2%)	
41-50	41 (26.3%)	9 (20.5%)	
51-60	32 (20.5%)	20 (45.5%)	
> 60	7 (4.5%)	3 (6.8%)	

**Table 5: Distribution according to Age and Thyroid Function (N = 200)**

The maximum percentage of 45.5% of hypothyroid patients was found in the age group of 51–60 years. The prevalence of hypothyroidism is high in the age groups 51–60 (38.4%) and >60 years (30%), and the finding was found to be significant.

Females constituted the maximum percentage (88.6%) of hypothyroid patients. The prevalence of hypothyroidism in the female population is 24.7%, whereas in the male population it is only 11.9%. The finding was not found to be significant (p = 0.76).

All 200 patients (100%) showed no signs or symptoms of hypothyroidism. So all the hypothyroid patients were of the subclinical type.

Serum Cholesterol	Euthyroid N (%)	Hypothyroid N (%)	Chi-Square Test
Normal (<200mg %)	82 (52.6%)	5 (11.4%)	Value = 23.704 df = 1 p = 0.000
High (≥200mg %)	74 (47.4%)	39 (88.6%)	

**Table 6: Serum cholesterol in hypothyroid patients**

High serum cholesterol was found in 88.6% of hypothyroid patients. The mean cholesterol level for euthyroid patients was 172.6 mg%, with a standard deviation of 23.5. The mean serum cholesterol level was 216.95 mg% for hypothyroid patients, with a standard deviation of 35.97. The finding was found to be significant with a p < 0.05.

## DISCUSSION

The majority of the patients, i.e., 51% of patients, were from the 5<sup>th</sup> and 6<sup>th</sup> decades of life. The most common age involved was 51–60 years (26%). Likewise, the most commonly involved age group for cholelithiasis (around 22%) was found to be 55–64 years old in the study by Harish B.<sup>[7]</sup> The mean age was 42 years, with a standard deviation of 12.5 years.

Female predominance was seen in this study (79%). In the study by Singh H et al.<sup>[8]</sup> females constituted 74% of the cases, which is similar to this study. Sharma MA<sup>[9]</sup> showed 71.4% were female, 28.6% were male. Similar observations were noted by Nagaraj S. et al.<sup>[10]</sup> Ganey JB et al.<sup>[11]</sup> showed that 70% were female and 30% were male.

A high serum TSH level was found in 22% of cases. The mean TSH level was 3.15 mU/L, with a standard deviation of 0.956. Low serum-free T3 was found in 22% of cases. The mean free T3 level was 3.63  $\mu$ mol/L, with a standard deviation of 0.71. Low serum-free T4 was found in 22% of cases. The mean free T4 level was 11.27 nmol/L, with a standard deviation of 1.52.

Of the 200 patients with cholelithiasis in the thyroid study, 44 (22%) were hypothyroid and 156 (78%) were in euthyroid states. So the prevalence of hypothyroidism in gallstone disease is 22% in our study. Raghuwanshi BS et al.<sup>[2]</sup> in their study on the prevalence of subclinical hypothyroidism in cases of cholelithiasis found 12 (24%) out of 50 patients hypothyroid. In another study by Sanniyasi S et al.<sup>[12]</sup> on 124 patients with gallstone disease, 28.5% of the gallstone patients were found to be hypothyroid. Based on a national study by Unnikrishnan AG et al.,<sup>[13]</sup> the prevalence of hypothyroidism in the general population was 10.95%. Statistically, hypothyroidism was found to be higher in patients with gallstone disease. Nath K et al.<sup>[14]</sup> did a cross sectional study on 50 patients diagnosed with cholelithiasis. Thyroid disorder in the form of hypothyroidism was found in 19 (38%) patients. 11 (22%) patients presented with subclinical hypothyroidism and 8 (16%) patients with clinical hypothyroidism. Laukkarinen J et al.<sup>[15]</sup> conducted a case control study on the increased prevalence of subclinical hypothyroidism in common bile duct stone patients. A total of 5.3 and 5.0% (total 10.2%; 31 of 303) of the CBD stone patients were diagnosed to have subclinical and borderline-subclinical hypothyroidism, compared with 1.4% ( $p = 0.05$ ) and 1.4% (total 2.8%, four of 142;  $p = 0.026$ ) in the control group, respectively. In women older than 60 years, the prevalence of subclinical hypothyroidism was 11.4% in CBD stone and 1.8% in control patients ( $p = 0.032$ ) and subclinical plus borderline-subclinical hypothyroidism was 23.8% in CBD stone and 1.8% in control patients ( $p = 0.012$ ). All the above studies show similar findings to ours, with a significant association between hypothyroidism and gallstone disease.

Singha D et al.<sup>[16]</sup> conducted a prospective study on the prevalence of previously undiagnosed hypothyroidism in patients with cholelithiasis in a tertiary care center in North-East India. The study was conducted on 500 consecutive patients with cholelithiasis. A total of 2.2%, 5.0% and 6.6% (total 13.8%, 69 of 500) of the cholelithiasis patients were diagnosed to have clinical, subclinical and borderline subclinical hypothyroidism. In women older than 50 years, the prevalence of clinical and subclinical plus borderline-hypothyroidism was 6.8% and 25.6% ( $11.7\% \pm 13.9\%$ ) and clinical plus subclinical plus borderline-subclinical hypothyroidism was 32.4% in cholelithiasis patients.

In our study, a maximum percentage of 45.5% of hypothyroid patients was found in the age group of 51–60 ( $p = 0.008$ ). In the study by Zwain Km et al.<sup>[3]</sup>, the peak age group for hypothyroidism in gallstone patients was 51–60 years, which is similar to our study. Females constituted the maximum percentage (88.6%) of hypothyroid patients ( $p = 0.076$ ) in our study. In a study by Ghadhban et al.<sup>[17]</sup> on the prevalence and correlation between subclinical hypothyroidism and gallstone disease, the highest percentage (81.6%) of hypothyroid patients were found in the female population. The prevalence of hypothyroidism in the female population was 24.7% ( $p = 0.076$ ) in our study. In the study by Raghuwanshi BS et al.<sup>[2]</sup> the prevalence of hypothyroidism in the female population was 26.19%.

High serum cholesterol was found in 88.6% of hypothyroid patients, and the finding was found to be significant. In the study by Bergman F et al.,<sup>[18]</sup> 90% of hypothyroid patients have elevated cholesterol levels, which is similar to our study. In a study by Raghuwanshi BS

et al.<sup>[2]</sup> in hypothyroid cases, most stones were of the cholesterol type (58%) (p-value  $\leq 0.05$ ). This also explains the possible mechanism by which hypothyroidism leading to hypercholesterolemia may change the composition of the bile and cause cholesterol stones. This strongly suggests the association of hypothyroidism with gallstone disease. The mean cholesterol level for euthyroid patients was 172.6 mg%, with a standard deviation of 23.5. The mean serum cholesterol level was 216.95 mg% for hypothyroid patients, with a standard deviation of 35.97.

Based on “A Study of Prevalence of Hypothyroidism in Adults: An Epidemiological Study in Eight Cities of India”<sup>[13]</sup> the national prevalence data were acquired and compared with our study. An overall sample of 5,360 patients was studied. The national prevalence of hyperthyroidism was noted to be 1.9%, i.e., 104 patients out of 5380, and 587 patients were found to have hypothyroidism which accounted for 10.95% of the general population. Whereas, in our study of cholelithiasis patients, hypothyroidism accounted for 22% and no hyperthyroid patients were found and the findings were found to be statistically significant with  $p < 0.05$ . This showed a significant association or correlation between hypothyroidism and gallstone disease.

Hypothyroidism reduces oxygen consumption and affects hemodynamic, cardiac, respiratory, and renal functions because of a low metabolism. Myocardial dysfunction, reduced ventilatory responses to hypoxia and hypercapnia, abnormal baroreceptor function, and decreased plasma volume may be present in hypothyroidism, and impaired drug metabolism adversely affects anesthesia. Hence, for safe anesthetic management of these patients, hypothyroidism needs to be identified preoperatively.<sup>[19]</sup>

Hence, based on the findings of our study and other similar studies, it can be established that hypothyroidism is associated with gallstone disease. The need to evaluate the thyroid status in patients with gallstone disease is absolutely essential, as surgery on a hypothyroid patient could lead to complications pertaining to the anaesthesia.

## **CONCLUSIONS**

The majority of patients were females, as both hypothyroidism and cholelithiasis are common in females. The prevalence of hypothyroidism in our study was 22%, and all the hypothyroid patients were of subclinical type. Most patients were older than 50 years. Most patients (88.6%) with hypothyroidism have a high cholesterol level. Based on the findings of our study, we concluded that hypothyroidism is associated with or correlated with gallstone disease. This study corroborated earlier studies and led further to understanding the relation between hypothyroidism and cholelithiasis. Further large population studies are needed in this direction to compare these findings, especially case control studies leading to recommendations for screening for early diagnosis of hypothyroidism at the subclinical level by regularly monitoring TSH.

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