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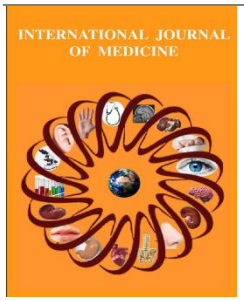

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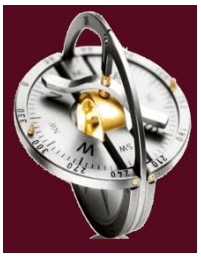

Review Article

Association Of Hypothyroidism in Gall Bladder Stone Disease -- An Observational Study.

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Abstract

Background: Cholelithiasis is one of the most common biliary disorders, characterized by the formation of gallstones composed of cholesterol, bile pigments, and calcium salts within the gallbladder. Thyroid disorders are also among the most prevalent endocrine diseases, and altered thyroid function—particularly reduced thyroid hormone levels—affects nearly all nucleated cells. The sphincter of Oddi possesses thyroid hormone receptors, and thyroxine exerts a relaxing effect on this sphincter. In hypothyroidism, decreased thyroid hormone levels impair gallbladder contractility and lipid metabolism, leading to biliary stasis and gallstone formation. ***Aims and Objectives***: To assess the possible correlation between hypothyroidism and cholelithiasis. Materials and ***Methods***: A single-centre observational study was conducted among 273 patients diagnosed with cholelithiasis and confirmed by ultrasonography. All participants underwent thyroid function tests, liver function tests, and fasting lipid profile assessment. Patients with a known history of hypothyroidism were excluded. ***Results***: Of the 273 patients, 59 (21.6%) had hypothyroidism and 74 (27.1%) had subclinical hypothyroidism. A total of 137 patients (50.2%) were overweight (BMI 25.0–29.9 kg/m²). Among the hypothyroid group, 36 (61.0%) exhibited hypertriglyceridemia and 22 (37.3%) had hypercholesterolemia. Elevated alkaline phosphatase (ALP) levels were observed in 51 (86.4%) of hypothyroid patients. ***Conclusions***: Decreased hepatic cholesterol metabolism, impaired bile emptying, and reduced relaxation of the sphincter of Oddi appear to contribute to gallstone formation in hypothyroid individuals. This study demonstrates a significant association between hypothyroidism and cholelithiasis, with affected patients commonly showing higher BMI and elevated cholesterol, triglyceride, and ALP levels.

Keywords: Gall stones,Thyroid Disorders, Hypothyroidism, Dyslipidemia, BMI.

Introduction:

The earliest known evidence of gallstones was found in the mummy of a priestess of Amen from Egypt's 21st Dynasty (1085–945 BC). Gallstones, or cholelithiasis, were first described by the Greek physician Alexander Trallianus in the 5th century. The first documented cholecystectomy was later performed by Carl Langenbuch in Berlin in 1882.[1]

The incidence of gallstones is notably higher in South-East Asian countries, where a strong association with gallbladder carcinoma has been observed. The development of gallstones is influenced by several factors, including bile supersaturation within the gallbladder, bile stasis resulting from sphincter of Oddi dysfunction, the presence of biliary sludge, and chemical imbalance among the components of bile. [2]

Thyroid disorders constitute a significant group of endocrine diseases with important implications for biliary physiology. In hypothyroidism, bile supersaturation may occur as a result of elevated serum cholesterol levels. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) regulate the activity of HMG-CoA reductase, a key enzyme in cholesterol metabolism. Consequently, reduced thyroid hormone levels lead to diminished cholesterol metabolism, resulting in hypercholesterolemia and dyslipidemia.[3]

Furthermore, hypothyroidism reduces relaxation of the sphincter of Oddi, leading to gallbladder hypomotility, decreased contractility, and diminished bile flow. This impaired biliary emptying results in prolonged bile retention, reduced flow capacity, and delayed clearance, thereby promoting bile nucleation and the subsequent formation of gallstones.[4,5]

Hypothyroidism may present as either overt or subclinical disease. Overt hypothyroidism is characterized by a reduction in serum thyroxine (T4) concentrations below the normal reference range,[6] while subclinical hypothyroidism (mild thyroid failure) is defined by normal serum thyroid hormone levels accompanied by mildly elevated serum thyroid-stimulating hormone (TSH) levels.[7]

This study was undertaken to evaluate the potential correlation between hypothyroidism and cholelithiasis. Given that thyroid hormones influence lipid metabolism, gallbladder motility, and sphincter of Oddi function, alterations in thyroid function may contribute to gallstone formation. By assessing thyroid profiles, lipid parameters, and gallbladder characteristics in patients with cholelithiasis, this study aims to determine the prevalence of overt and subclinical hypothyroidism in this population and to explore the possible mechanistic link between thyroid dysfunction and gallstone disease. Understanding this relationship could provide insight into risk stratification and management strategies for patients with gallstones.

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Material and Methods:

Type of Study: Single-centre, observational study.

Study Setting: Tertiary care hospital – KPC Medical College & Hospital, West Bengal.

Study Duration: January 2024 – January 2025.

Study Population: 273 patients diagnosed with gallstones out of 712 screened cases.

Data Collection:

Thyroid function tests (TSH, T3, T4)
Liver function tests (including ALP)
Fasting lipid profile
Radiological investigations to confirm gallstones
Patient Management: Managed according to standard clinical protocols following diagnosis.
Inclusion Criteria
Patients of both sexes, aged 18 to 80 years.
All patients admitted with diagnosed gallbladder stones.
Exclusion Criteria
Patients younger than 18 years or older than 80 years.
Pregnant women.
Patients with a history of thyroid cancer.
Patients on antiepileptic drugs.
Patients with septicemia.
History of hemolytic disorders.
History of hypersplenism.
Patients with diagnosed choledocholithiasis.

All patients underwent routine laboratory investigations, including liver function tests (serum bilirubin, AST/SGOT, ALT/SGPT, Gamma-GlutamylTransferase, and Alkaline Phosphatase), thyroid function tests (TSH, total T4, and total T3), and lipid profile (total cholesterol, triglycerides, and LDL). Additionally, patients' weight (kg) and height (m) were recorded to calculate Body Mass Index (BMI).
Statistical Analysis:
Data were entered into Excel and subsequently analyzed using SPSS and GraphPad Prism. Continuous variables were summarized as means with standard deviations, while categorical variables were presented as counts and percentages. Comparisons between independent groups were performed using two-sample t-tests, and paired t-tests were applied for correlated (paired) data. Categorical data were compared using chi-square tests, with Fisher's exact test applied when expected cell counts were small. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Table: 1.AgeDistributionamongStudyPopulation

Age	Frequency	Percentage
18-30 years	23	8.40%
31-50 years	159	58.30%
51-80 years	91	33.30%
Total	273	100%

Table: 2. Gender Distribution among Study Population

Gender	Frequency	Percentage
Men	102	37.40%
Women	171	62.60%
Total	273	100%

Table: 3. Thyroid profile and liver function test

Variables		Clinical Hypothyroidism	Subclinical Hypothyroidism	Hyperthyroidism	Euthyroid
Albu min	Low	15 (5.5%)	7 (2.6%)	0 (0%)	6 (2.2%)
	Normal	44 (16.1%)	67 (24.5%)	37 (13.6%)	97 (35.6%)
Direct Biliru bin	Normal	59 (21.6%)	70 (25.6%)	37 (13.6%)	101 (37.0%)
	High	0 (0%)	4 (1.5%)	0 (0%)	2 (0.7%)
ALP	Normal	8 (2.9%)	18 (6.6%)	37 (13.6%)	103 (37.7%)
	High	51 (18.7%)	56 (20.5%)	0 (0%)	0 (0%)

Table: 4. Thyroid Profile and Lipid Profile Test

	Variables	Hypothyroidism	Subclinical Hypothyroidism	Hyperthyroid	Euthyroid
Total Cholesterol	Normal	37 (13.6%)	32 (11.7%)	10 (3.7%)	88 (32.2%)
	High	22 (8.1%)	42 (15.4%)	27 (9.9%)	15 (5.5%)
Triglyce rides	Normal	23 (8.4%)	21 (7.7%)	28 (10.3%)	82 (30.0%)
	High	36 (13.2%)	53 (19.4%)	9 (3.3%)	21 (7.7%)
LDL	Normal	44 (16.1%)	49 (18.0%)	27 (9.9%)	64 (23.4%)
	High	15 (5.5%)	25 (9.2%)	10 (3.7%)	39 14.3%)

Figure: 1. Distribution of Patients According to Body Mass Index (BMI)

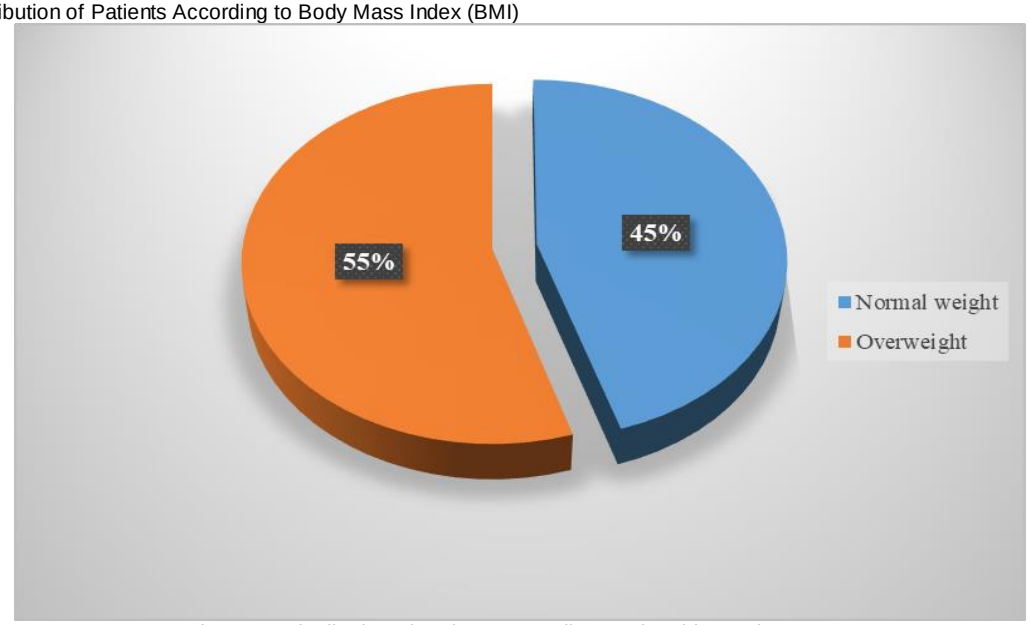
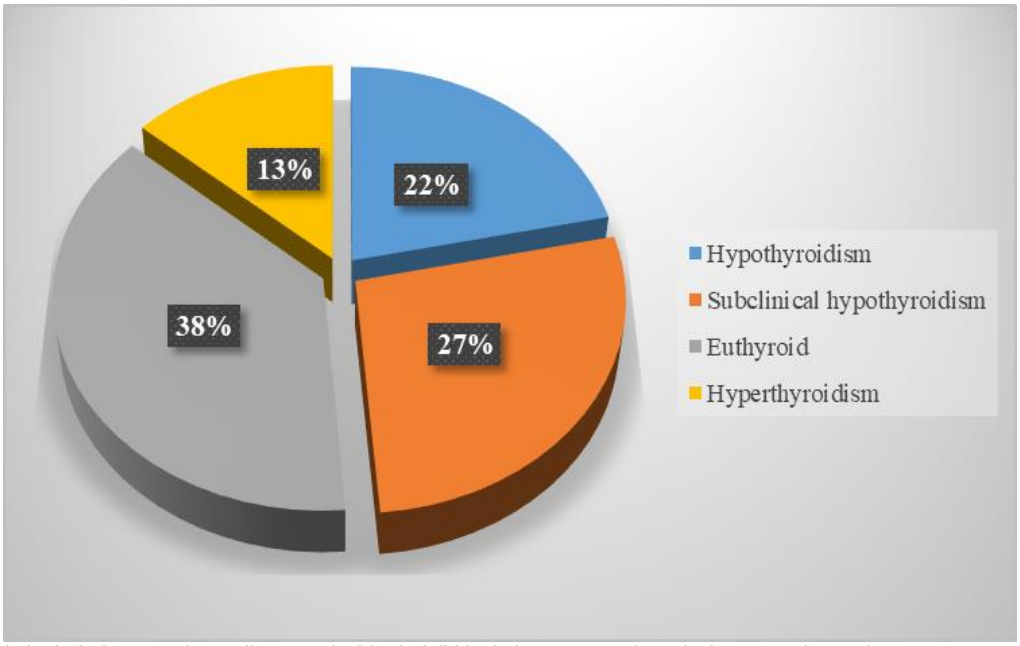


Figure: 2. Distribution of Patients According to Thyroid Function Status



The present study included 273 patients diagnosed with cholelithiasis by sonography, of whom 171 (62.6%) were women and 102 (37.4%) were men. The majority of patients were aged between 31 and 50 years (58.3%), while 23 patients (8.4%) were below 30 years of age. Regarding body mass index (BMI), 137 patients (50.2%) were classified as overweight (BMI 25.0–29.9 kg/m²), and 113 patients (41.4%) had a normal BMI (18.5–24.9 kg/m²).

Thyroid function analysis revealed that 59 patients (21.6%) exhibited elevated TSH and decreased T4 levels, consistent with clinical hypothyroidism, while 74 patients (27.1%) demonstrated elevated TSH with normal T4, indicative of subclinical hypothyroidism. Euthyroid status was observed in 103 patients (37.7%), and hyperthyroidism was present in 37 patients (13.6%).

Liver function tests and lipid profiles were also assessed. Hypoalbuminemia was noted in 15 patients (5.5%) with clinical hypothyroidism and in 7 patients (2.6%) with subclinical hypothyroidism, whereas no cases were observed in hyperthyroid patients and only 6 euthyroid patients (2.2%). Elevated alkaline phosphatase levels were detected in 51 patients (18.7%) with clinical hypothyroidism and 56 patients (20.5%) with subclinical hypothyroidism, while none of the euthyroid or hyperthyroid patients showed increased levels.

Dyslipidemia was common among the study population. High total cholesterol was observed in 22 patients (8.1%) with clinical hypothyroidism, and elevated triglycerides were noted in 36 patients (13.1%) with subclinical hypothyroidism. In comparison, 10 hyperthyroid patients (3.7%) had high cholesterol, and 88 euthyroid patients (32.2%) exhibited elevated triglycerides. Additionally, increased LDL levels were present in 15 patients (5.5%) with clinical hypothyroidism and 25 patients (9.2%) with subclinical hypothyroidism.

DISCUSSION

Our study was conducted among 273 patients with radiological evidence of cholelithiasis, with a predominance of women (62.6%) compared to men. This female preponderance is consistent with multiple previous studies, which have reported a higher prevalence of gallstones in women [8–11]. Ghadhban et al. observed an even higher incidence (81.6%) among females [12]. Similarly, studies by Sarda et al., Rajan et al., and Sachdeva et al. demonstrated comparable results, highlighting the role of sex hormones and pregnancy in increasing gallstone risk [8–10]. Estrogen is known to promote a hypercholesterolemic and lithogenic state by increasing biliary cholesterol secretion [10].

In terms of age distribution, the most affected group in our study was 31–50 years (58.3%). Herman et al. documented a comparable frequency, while Shaffer et al., in a global survey, reported that the risk of gallstone formation increases with age [13–14]. Aging is associated with decreased bile acid production, increased cholesterol secretion in bile, and reduced activity of cholesterol 7α-hydroxylase (CYP7A1), a rate-limiting enzyme in bile acid synthesis [15–16]. Additionally, the accumulation of various risk factors over time may further predispose individuals to lithogenesis [17].

Our study also observed that the majority of patients (137; 50.2%) had a BMI of 25.0–29.9 kg/m² (overweight), while 16 patients (5.8%) had a BMI >30 kg/m² and were classified as obese. Previous studies by Sarhan et al. and Sodhi et al. have suggested that high BMI is a significant contributor to gallstone formation [18–19]. Alexander et al. and Hayat et al. further reported that elevated blood cholesterol and increased BMI are key risk factors for gallstones [20–21].

Thyroid function analysis revealed that 103 patients (37.7%) were euthyroid, 59 (21.6%) had clinical hypothyroidism, and 74 (27.1%) had subclinical hypothyroidism. Völzke et al. demonstrated a correlation between elevated TSH levels and sonographically detectable gallstones [22]. Kotwal et al. and Rinchen et al. reported that 14.4% of hypothyroid patients in Sikkim, India, also had cholelithiasis [23], while studies by Yousif et al., Ibrahim et al., and Abdulbary et al. reported similar findings [24–25]. Arbab et al. noted that 16 of 193 patients (8.16%) undergoing cholecystectomy for cholelithiasis were diagnosed with hypothyroidism [26].

Regarding lipid metabolism, our study found that dyslipidemia was more pronounced in hypothyroid patients compared to euthyroid individuals. Marwaha et al. reported significant increases in serum total cholesterol and LDL levels in adults with hypothyroidism [27], while Hussain et al. observed elevated cholesterol, triglycerides, and LDL in subclinical hypothyroid patients [28]. Pedrelli et al. also noted higher total cholesterol and LDL in hypothyroid subjects [29]. These alterations are attributed to the effect of thyroid hormones on HMG-CoA reductase activity and thyroxine-mediated regulation of hepatic lipid metabolism [30]. However, Ahmmed Hassan Issa et al., in a study of 232 patients with dyslipidemia, found that only 25 patients were hypothyroid, suggesting variability in this association [31].

Alkaline phosphatase (ALP), an enzyme produced by the biliary epithelium, was elevated in 56 hypothyroid patients but remained normal in euthyroid and hyperthyroid individuals. This may be due to impaired thyroid hormone-mediated biliary motility, leading to bile stasis and sphincter of Oddi dysfunction, which in turn increases biliary pressure and ALP levels [32]. This finding is clinically significant, as such patients may be at increased risk for choledocholithiasis. Previous studies by Steenbergen et al. and Inkinen et al. have also reported that the higher incidence of biliary stones in hypothyroidism is related to hypercholesterolemia, gallbladder hypotonia, and reduced bilirubin excretion [33–34].

LIMITATIONS

This study is limited by its small sample size, single-center design, and the exclusion of patients with choledocholithiasis. To strengthen the evidence and improve generalizability, we propose conducting a multi-center, large population-based study in the future.

Conclusion

Our study demonstrates a significant correlation between cholelithiasis and hypothyroidism, with a higher prevalence observed among females. Most affected patients were over 31 years of age, and the incidence of both cholelithiasis and hypothyroidism was greater in overweight individuals (BMI >25 kg/m²). Based on these findings, we recommend that patients with cholelithiasis and dyslipidemia undergo evaluation of thyroid function. Additionally, assessment of alkaline phosphatase (ALP)

levels is advised, as hypothyroid patients may have an increased risk of primary biliary stones due to biliary dysmotility and impaired relaxation of the sphincter of Oddi.

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