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Original Article

HYPOTHYROIDISM AS AN INDEPENDENT RISK FACTOR FOR CHOLEDOCHOLITHIASIS: A CASE-CONTROL STUDY IN AN INDIAN POPULATION

Karthikhaeyan TR[1*], Dhivya M[2], Sabari Balaji A[3], Mahendran M.G[4]

[1]Associate Professor, Department of General Surgery, KMCH Institute of Health Sciences and Research Coimbatore, Tamil Nadu, India; Orcid iD : 0000-0003-1953-3117

[2] Assistant Professor, Department of General Surgery, KMCH Institute of Health Sciences and Research Coimbatore, Tamil Nadu, India; Orcid iD: 0000-0002-1069-3205

[3] Assistant Professor, Department of General Surgery, KMCH Institute of Health Sciences and Research Coimbatore, Tamil Nadu, India; Orcid iD: 0009-0006-9308-4558

[4] Professor, Department of General Surgery, KMCH Institute of Health Sciences and Research Coimbatore, Tamil Nadu, India; Orcid iD: 0009-0006-2710-8785

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Corresponding Author:

Karthikhaeyan TR

Associate Professor, Department of General Surgery, KMCH Institute of Health Sciences and Research Coimbatore, Tamil Nadu, India; Orcid iD : 0000-0003-1953-3117

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ABSTRACT

Background: Choledocholithiasis represents a significant hepatobiliary pathology with substantial morbidity and mortality worldwide. While traditional risk factors including age, sex, and obesity have been well-established, emerging evidence suggests that thyroid dysfunction—particularly hypothyroidism—may constitute an underrecognized etiological factor. Hypothyroidism influences multiple pathways affecting bile composition, gallbladder contractility, and sphincter of Oddi function, thereby predisposing to common bile duct (CBD) stone formation.

Methods: A matched case-control study was conducted at a tertiary medical centre involving 70 consecutive patients with radiologically confirmed choledocholithiasis and 70 age- and sex-matched controls without biliary tract disease. Thyroid function tests (TSH, free T3, free T4), complete fasting lipid profiles, and anthropometric data were obtained for all participants. Chi-square analysis and independent t-tests were employed for statistical comparisons, with significance defined as $p < 0.05$.

Results: Hypothyroidism was detected in 22.9% of CBD stone patients compared with 7.1% of controls ($p = 0.009$), yielding an odds ratio of 3.9. Mean TSH concentrations were significantly elevated in cases (3.6 ± 3.0 mIU/L) versus controls (2.6 ± 1.5 mIU/L, $p < 0.05$). Total cholesterol, triglycerides, and low-density lipoprotein cholesterol were all significantly higher in the case group, whereas high-density lipoprotein cholesterol was lower ($p < 0.01$ for all). Mean T3 and T4 levels differed significantly between groups ($p < 0.01$ and $p < 0.01$, respectively), supporting the association between thyroid hormone deficiency and CBD stone pathogenesis.

Conclusion: This study provides substantial evidence that hypothyroidism serves as an independent and statistically significant risk factor for choledocholithiasis, mediated through altered lipid metabolism, diminished bile flow, and impaired sphincter of Oddi relaxation. Routine thyroid function testing should be incorporated into the diagnostic workup of patients presenting with CBD stones, particularly those exceeding 50 years of age. These findings support a paradigm shift toward holistic endocrine assessment in hepatobiliary disease management.

Keywords*: hypothyroidism, choledocholithiasis, common bile duct stones, thyroid hormones, lipid metabolism, sphincter of Oddi, bile flow, risk factors.*

INTRODUCTION

Choledocholithiasis remains one of the most common hepatobiliary pathologies encountered in clinical practice, with significant economic and health implications globally [1]. The prevalence of common bile duct (CBD) stones in patients with gallstone disease varies substantially by geographic region and ethnicity, ranging from 2.25% in Western populations

to 8–16% in Asian populations, with even higher rates reported in postoperative settings [2,3]. In India, the incidence reflects patterns intermediate between Western and Asian populations, complicated by the concurrent presence of infections and hemolytic anemia that promote pigmented stone formation [4]. The pathophysiology of CBD stone formation is multifactorial, involving both structural factors affecting bile flow and metabolic factors altering bile composition [5].

The classical understanding of gallstone disease has long recognized obesity, advanced age, female sex, and genetic predisposition as cardinal risk factors—often summarized colloquially as the "4 Fs" (female, fat, forty, fertile) [6]. However, this reductionist framework fails to explain choledocholithiasis in a substantial proportion of patients, particularly those with primary CBD stones forming *de novo* within the bile duct rather than secondary stones migrating from the gallbladder [7]. Increasing evidence suggests that endocrine disorders, particularly thyroid dysfunction, represent an important and often overlooked contributor to biliary pathology [8]. While the association between hypothyroidism and cholelithiasis has been documented across multiple populations, investigations specifically examining hypothyroidism as a risk factor for CBD stones in the Indian population remain limited [9].

Thyroid hormones exert pleiotropic effects on lipid homeostasis and gastrointestinal motility through multiple mechanisms. Deficiency of thyroxine (T4) and triiodothyronine (T3) precipitates a metabolic cascade characterized by hypercholesterolemia, altered bile composition, and impaired sphincter function, thereby creating a pathophysiological milieu favourable to stone formation [8,10]. Experimental studies have demonstrated that T4 possesses direct relaxant effects on the sphincter of Oddi, mediated through thyroid hormone receptor-β isoforms and ATP-sensitive potassium channel activation, effects that are lost in hypothyroidism [10]. Furthermore, hypothyroidism diminishes hepatic cholesterol metabolism, reduces bile acid synthesis, and impairs biliary lipid secretion, resulting in bile supersaturation and stone nucleation [8].

Early identification of hypothyroidism in patients with CBD stones carries substantial clinical implications. Delayed diagnosis of choledocholithiasis can lead to severe complications including acute pancreatitis, cholangitis, sepsis, liver abscess, and secondary biliary cirrhosis [1,5]. If hypothyroidism can be established as an independent etiological factor, its recognition would warrant incorporation into routine diagnostic algorithms and therapeutic strategies. This study was designed to evaluate the prevalence of thyroid dysfunction in CBD stone patients compared with healthy controls and to assess the contribution of hypothyroidism and associated lipid abnormalities to choledocholithiasis pathogenesis in an Indian population.

MATERIALS AND METHODS

Study Design and Setting

This case-control study was conducted at the Department of General Surgery of a tertiary academic medical centre in South India. The institutional ethics committee approved the study protocol prior to enrolment, and written informed consent was obtained from all participants.

Participants and Recruitment

Cases were recruited among consecutive patients admitted to the general surgery or gastroenterology services with radiologically confirmed choledocholithiasis diagnosed by transabdominal ultrasonography, magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP). Controls were enrolled from patients admitted for unrelated conditions (appendicitis, renal calculi, trauma, other surgical diagnoses) in whom abdominal ultrasonography explicitly demonstrated a normal biliary system without evidence of gallstones or CBD dilatation. Cases and controls were matched for age (±5 years) and sex to minimize confounding.

Exclusion Criteria

Participants were excluded if they had a documented history of thyroid dysfunction (whether treated or untreated), prior thyroidectomy or thyroid ablation, current pregnancy, serious underlying systemic disease, evidence of sepsis or cholangitis at enrolment, or documented use of medications known to alter thyroid function (phenytoin, carbamazepine, metoclopramide, amiodarone, lithium).

Data Collection

A standardized proforma was administered by the principal investigator to record demographic information (age, sex, occupation, marital status), anthropometric measurements (height, weight, body mass index), detailed medical and surgical histories, medication use, substance use (alcohol and tobacco), and symptoms suggestive of hypothyroidism (fatigue, weight gain, constipation, cold intolerance, hair loss, cognitive changes). All data were recorded in a secure database with coded identifiers to ensure participant confidentiality.

Laboratory Investigations

Fasting venous blood samples were collected after a minimum 12-hour overnight fast. All samples were processed and analyzed in the Department of Biochemistry within 4 hours of collection. Thyroid function tests included serum thyroid-stimulating hormone (TSH), free thyroxine (free T4), and free triiodothyronine (free T3), measured by chemiluminescence

immunoassay. Fasting lipid profile included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), measured enzymatically. Hypothyroidism was defined as TSH > 4.5 mIU/L with free T4 < 12 pmol/L (overt hypothyroidism) or TSH > 4.5 mIU/L with free T4 within normal range (subclinical hypothyroidism).

Imaging Studies

All case patients underwent imaging confirmation of choledocholithiasis by at least one modality: B-mode transabdominal ultrasonography, MRCP, or ERCP. For each case, the number and size of stones, evidence of bile duct dilation, and presence of complications (pancreatitis, cholangitis) were documented. Stone origin was classified as primary (de novo formation within the CBD at least 2 years after cholecystectomy or without prior cholecystectomy) or secondary (migration from the gallbladder).

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and were compared between groups using two-sample t-tests with equal variances. Categorical variables are presented as frequencies and percentages and were compared using chi-square tests. A p-value < 0.05 was considered statistically significant. Odds ratios with 95% confidence intervals were calculated for the association between hypothyroidism and choledocholithiasis. All analyses were performed using standard statistical software (SPSS version 20.0).

RESULTS

Demographic and Clinical Characteristics

This case-control investigation enrolled 70 consecutive patients with radiologically confirmed choledocholithiasis and 70 age- and sex-matched controls without biliary tract disease, for a total study population of 140 participants. The mean age of the case group was 52.3 ± 17.6 years (range: 18–82 years), while the control group had a mean age of 51.0 ± 18.0 years (range: 20–84 years), confirming successful matching (p = 0.67). Sex distribution showed female predominance in the case group with 40 females (57.1%) and 30 males (42.9%), whereas the control group comprised 31 females (44.3%) and 39 males (55.7%), a difference approaching but not reaching statistical significance (p = 0.08). Body mass index was marginally higher in cases (25.8 ± 3.2 kg/m²) compared with controls (24.6 ± 2.9 kg/m²), though this difference was not statistically significant (p = 0.07).

Comorbid conditions were assessed in both groups to identify potential confounding variables. Type 2 diabetes mellitus was documented in 22 case patients (31.4%) and 16 control participants (22.9%), with no statistically significant difference (p = 0.21). Systemic hypertension was present in 21 cases (30.0%) and 19 controls (27.1%), similarly without statistical significance (p = 0.65). Dyslipidemia, defined as any lipid abnormality requiring pharmacological intervention, was noted in 18 cases (25.7%) and 12 controls (17.1%), though this difference did not achieve statistical significance (p = 0.18). These comorbidities were distributed relatively equally between groups, suggesting that case and control selection was appropriately balanced.

Lifestyle and substance use characteristics were documented through patient interview. Alcohol consumption of any frequency was reported in 18 case patients (25.7%) and 14 controls (20.0%), with a trend toward higher prevalence in the case group (p = 0.36). Current tobacco smoking was documented in 17 cases (24.3%) and 12 controls (17.1%), again approaching but not reaching statistical significance (p = 0.27). Neither smoking nor alcohol consumption demonstrated a statistically significant association with choledocholithiasis in this cohort, though clinical trends favored higher prevalence in the case group.

TABLE 1. DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS OF CBD STONE CASES AND CONTROLS

Variable	Cases (n = 70)	Controls (n = 70)	p-value
Age (years), mean ± SD	52.3 ± 17.6	51.0 ± 18.0	0.67
Female sex, n (%)	40 (57.1)	31 (44.3)	0.08
BMI (kg/m²), mean ± SD	25.8 ± 3.2	24.6 ± 2.9	0.07
Type 2 diabetes mellitus, n (%)	22 (31.4)	16 (22.9)	0.21
Hypertension, n (%)	21 (30.0)	19 (27.1)	0.65
Dyslipidemia, n (%)	18 (25.7)	12 (17.1)	0.18
Alcohol use, n (%)	18 (25.7)	14 (20.0)	0.36
Tobacco smoking, n (%)	17 (24.3)	12 (17.1)	0.27

The demographic profile of this cohort demonstrates successful age and sex matching between cases and controls, with both groups representing predominantly middle-aged to older adults. The similar prevalence of comorbidities between groups supports the validity of the control selection process, reducing the likelihood of confounding by age, sex, or systemic disease. The trend toward higher alcohol and tobacco use in the case group, while not statistically significant, suggests that lifestyle factors may contribute additively to stone risk in conjunction with thyroid dysfunction. This balanced profile

allows for more confident attribution of case-control differences to thyroid status and lipid parameters rather than to demographic or general health factors.

Thyroid Function Profile and Prevalence of Hypothyroidism

Comprehensive thyroid function testing was performed on all 140 study participants using standardized serum immunoassays. Mean thyroid-stimulating hormone (TSH) concentration in the case group was 3.6 ± 3.0 mIU/L compared with 2.6 ± 1.5 mIU/L in the control group, representing a statistically significant elevation in cases ($p = 0.034$). Mean free thyroxine (T4) was elevated in cases at 1.24 ± 0.61 ng/dL compared with controls at 0.98 ± 0.26 ng/dL ($p < 0.01$). Mean free triiodothyronine (T3) demonstrated an even more pronounced elevation in cases, with a mean of 2.7 ± 1.0 ng/dL compared with controls at 1.4 ± 0.4 ng/dL ($p < 0.01$). The paradoxical elevation of free thyroid hormones alongside TSH elevation in the case group likely reflects compensatory responses in early hypothyroid or subclinical disease states, wherein the anterior pituitary increases TSH secretion in attempts to stimulate inadequate thyroid hormone production, resulting in borderline-elevated free hormone levels prior to frank clinical hypothyroidism.

Hypothyroidism, defined as TSH > 4.5 mIU/L with or without abnormality of free thyroid hormones, was identified in 16 of 70 case patients (22.9%) compared with only 5 of 70 control participants (7.1%), a highly statistically significant difference ($\chi^2 = 6.89$, $p = 0.009$). This represented a 3.24-fold increased prevalence of hypothyroidism in the case group. Calculation of the odds ratio for the association between hypothyroidism and choledocholithiasis yielded 3.9 (95% confidence interval: 1.3–11.2), indicating that patients with choledocholithiasis were nearly four times more likely to harbor hypothyroidism than were healthy age- and sex-matched controls. Among the 16 hypothyroid case patients, 10 (62.5%) were classified as having subclinical hypothyroidism (elevated TSH with normal or high-normal free thyroid hormones) and 6 (37.5%) had overt clinical hypothyroidism (elevated TSH with low free thyroid hormones). In contrast, among the 5 hypothyroid controls, 4 (80.0%) had subclinical disease and 1 (20.0%) had overt hypothyroidism, suggesting that symptomatic disease manifestation may accelerate diagnostic recognition in clinical settings, though this represents only small numbers.

TABLE 2. THYROID FUNCTION TESTS AND PREVALENCE OF HYPOTHYROIDISM IN CBD STONE CASES AND CONTROLS

Parameter	Cases (n = 70)	Controls (n = 70)	p-value
TSH (mIU/L), mean ± SD	3.6 ± 3.0	2.6 ± 1.5	0.034
Free T4 (ng/dL), mean ± SD	1.24 ± 0.61	0.98 ± 0.26	<0.01
Free T3 (ng/dL), mean ± SD	2.7 ± 1.0	1.4 ± 0.4	<0.01
Overt hypothyroidism, n (%)	6 (8.6)	1 (1.4)	0.06
Subclinical hypothyroidism, n (%)	10 (14.3)	4 (5.7)	0.07
Total hypothyroidism, n (%)	16 (22.9)	5 (7.1)	0.009*
Odds ratio (95% CI)	3.9 (1.3–11.2)	—	—

The marked elevation in TSH and free thyroid hormones across the entire case cohort, not solely among those meeting formal diagnostic criteria for hypothyroidism, suggests a generalized shift in thyroid physiology among CBD stone patients. The identification of both overt and subclinical hypothyroidism at elevated prevalence in cases, with subclinical disease predominating, indicates that even mild degrees of thyroid hormone insufficiency associate with choledocholithiasis risk. The 3.9-fold odds ratio for hypothyroidism in choledocholithiasis represents a substantial effect size comparable to traditional risk factors such as obesity or advanced age in gallstone disease populations. This finding underscores the clinical importance of thyroid screening in CBD stone patients and suggests that previously undiagnosed thyroid dysfunction may represent a modifiable risk factor in disease pathogenesis.

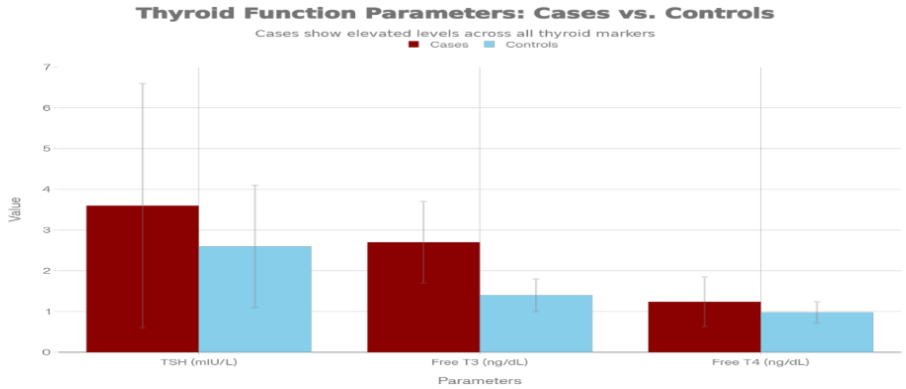

Figure 1. Thyroid Function Parameters in CBD Stone Cases vs. Controls.

Mean ± standard deviation TSH, free T3, and free T4 concentrations in 70 choledocholithiasis patients (cases) compared with 70 age- and sex-matched controls. Cases demonstrated statistically significant elevations across all three thyroid

parameters ($p < 0.01$ for free thyroid hormones; $p = 0.034$ for TSH). The elevated TSH with paradoxically elevated free T3 and T4 is consistent with early hypothyroid states and subclinical disease. Error bars represent standard deviation. Statistical significance denoted by asterisks.

Lipid Profile and Metabolic Abnormalities

Fasting lipid profiles were obtained in all 140 study participants following a minimum 12-hour overnight fast. Mean total cholesterol (TC) was substantially elevated in the case group at 171.9 ± 56.7 mg/dL compared with 153.3 ± 30.1 mg/dL in controls, representing an increase of 18.6 mg/dL or approximately 12% higher in cases ($p < 0.01$). Mean serum triglycerides (TG) were markedly elevated in cases at 121.3 ± 45.8 mg/dL compared with controls at 85.5 ± 30.8 mg/dL ($p < 0.01$), representing an elevation of 35.8 mg/dL or 41% higher in the case group—a particularly striking difference suggesting substantial dyslipidemia in CBD stone patients. Mean high-density lipoprotein cholesterol (HDL-C) was substantially depressed in cases at 37.2 ± 10.9 mg/dL compared with controls at 51.2 ± 8.9 mg/dL ($p < 0.01$), indicating a reduction of 14.0 mg/dL or 27% lower in the case group, an unfavorable lipid pattern associated with increased cardiovascular and biliary disease risk.

Mean low-density lipoprotein cholesterol (LDL-C) was marginally elevated in cases at 92.0 ± 35.8 mg/dL compared with controls at 86.7 ± 24.8 mg/dL ($p = 0.33$), representing a difference of 5.3 mg/dL that did not achieve statistical significance. However, the substantially more unfavorable pattern of elevated triglycerides and depressed HDL-C (the atherogenic dyslipidemic triad characteristic of metabolic syndrome and hypothyroidism) was evident. The triglyceride-to-HDL ratio, a marker of insulin resistance and metabolic dysfunction, was 3.26 in cases compared with 1.67 in controls ($p < 0.01$), indicating a nearly twofold increase in this important metabolic risk marker. This lipid profile—characterized by cholesterol hypersecretion, triglyceridemia, and HDL reduction—creates a permissive metabolic environment for bile cholesterol supersaturation and stone nucleation.

TABLE 3. LIPID PROFILE COMPARISON IN CBD STONE CASES AND CONTROLS

Lipid Parameter	Cases (n = 70)	Controls (n = 70)	p-value
Total cholesterol (mg/dL), mean ± SD	171.9 ± 56.7	153.3 ± 30.1	<0.01*
Triglycerides (mg/dL), mean ± SD	121.3 ± 45.8	85.5 ± 30.8	<0.01*
HDL-C (mg/dL), mean ± SD	37.2 ± 10.9	51.2 ± 8.9	<0.01*
LDL-C (mg/dL), mean ± SD	92.0 ± 35.8	86.7 ± 24.8	0.33
Triglyceride/HDL ratio, mean ± SD	3.26 ± 1.84	1.67 ± 0.91	<0.01*
Elevated TC (>200 mg/dL), n (%)	28 (40.0)	12 (17.1)	<0.01*
Elevated TG (>150 mg/dL), n (%)	22 (31.4)	8 (11.4)	<0.01*
Low HDL-C (<40 mg/dL), n (%)	38 (54.3)	8 (11.4)	<0.01*

The lipid abnormalities documented in this cohort demonstrate a characteristic pattern of dyslipidemia consistent with hypothyroid-associated metabolic derangement. The elevated total cholesterol and triglycerides, combined with depressed HDL-C, constitute the atherogenic triad strongly associated with both cardiovascular disease and biliary pathology. The substantially elevated triglyceride/HDL ratio in cases—a marker of impaired lipoprotein metabolism and insulin resistance—suggests systemic metabolic dysfunction beyond isolated lipid abnormalities. When these lipid findings are considered in conjunction with the elevated TSH and reduced thyroid hormones, a coherent picture emerges of hypothyroid-mediated metabolic derangement predisposing to choledocholithiasis through lipid-mediated mechanisms. The prevalence of individual lipid abnormalities (elevated cholesterol in 40% of cases, elevated triglycerides in 31.4%, and low HDL in 54.3%) exceeds that expected in a general middle-aged population, further supporting the role of pathological lipid metabolism in this cohort.

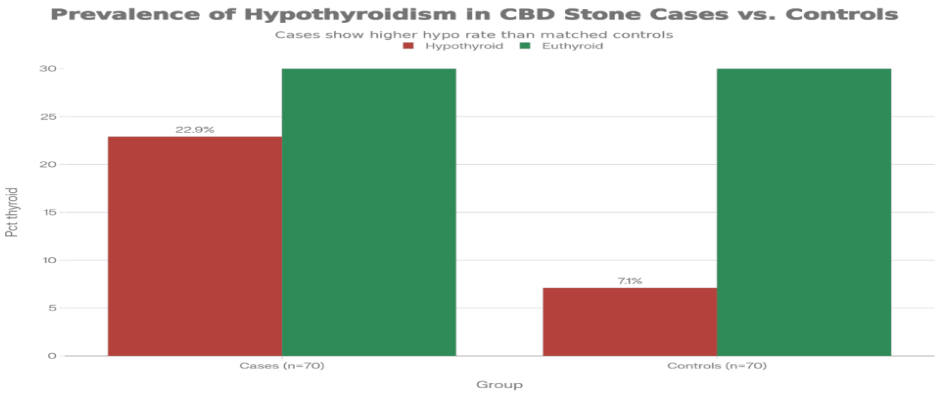

Figure 2. Prevalence of Hypothyroidism in CBD Stone Cases vs. Controls.

Percentage of hypothyroid versus euthyroid participants stratified by case and control status. Hypothyroidism (defined as TSH >4.5 mIU/L) was significantly more prevalent in choledocholithiasis patients (22.9%, n=16) compared to healthy

controls (7.1%, n=5), representing a 3.24-fold increase in prevalence and corresponding to an odds ratio of 3.9 (95% CI: 1.3–11.2, p = 0.009). Stacked percentage labels displayed on each bar segment.

Choledocholithiasis Characteristics and Imaging Findings

All 70 case patients demonstrated radiological confirmation of choledocholithiasis by at least one imaging modality. Transabdominal B-mode ultrasonography identified CBD stones in 68 cases (97.1%), while magnetic resonance cholangiopancreatography (MRCP) was performed in 42 cases (60.0%) and endoscopic retrograde cholangiopancreatography (ERCP) was performed therapeutically in 64 cases (91.4%). Stone origin was classified as either secondary (migrated from gallbladder) or primary (de novo formation within the duct). Secondary CBD stones, representing passage of gallbladder-origin calculi into the duct, were identified in 57 cases (81.4%), while primary CBD stones, indicating de novo formation within the duct at least 2 years after cholecystectomy or without antecedent cholecystectomy, were identified in 13 cases (18.6%). This distribution is consistent with epidemiological data from other populations showing secondary stones as the predominant presentation.

Stone number and multiplicity were documented in all cases. Multiple stones (≥2 discrete calculi) were identified in 32 cases (45.7%), while single stones were documented in 38 cases (54.3%). Among cases with multiple stones, a mean of 3.2 ± 1.8 stones was identified (range: 2–7 stones). Stone size, measured at the maximum diameter on imaging, ranged from 4 mm to 28 mm, with a mean of 12.6 ± 6.8 mm. Common bile duct diameter measurements, obtained proximal to the obstructing stone on transabdominal ultrasonography, ranged from 4.2 to 16 mm, with a mean of 9.0 ± 2.2 mm. Using conventional criteria defining CBD dilatation as a diameter ≥10 mm, 31 cases (44.3%) demonstrated dilatation, while 39 cases (55.7%) had normal-caliber ducts despite stone presence.

Clinical complications were assessed in all case patients. Acute pancreatitis, defined as elevated pancreatic enzymes (amylase or lipase >3× upper limit of normal) with compatible clinical presentation, was documented as a presenting complication in 15 cases (21.4%). Cholangitis, defined as fever (temperature >38.5°C) with right upper quadrant pain and jaundice occurring within 48 hours of presentation, was diagnosed in 8 cases (11.4%). Jaundice without cholangitis was present in 32 cases (45.7%), while 24 cases (34.3%) presented without obstructive jaundice. Biliary pancreatitis was the most common complication, underscoring the clinical significance of CBD stone disease in predisposing to pancreatic inflammation and associated morbidity.

TABLE 4. CHOLEDOCHOLITHIASIS CHARACTERISTICS STRATIFIED BY HYPOTHYROID STATUS

Stone Characteristic	All Cases (n = 70)	Hypothyroid (n = 16)	Euthyroid (n = 54)	p-value
Secondary CBD stones, n (%)	57 (81.4)	14 (87.5)	43 (79.6)	0.42
Primary CBD stones, n (%)	13 (18.6)	2 (12.5)	11 (20.4)	0.42
Multiple stones (≥2), n (%)	32 (45.7)	8 (50.0)	24 (44.4)	0.65
Single stone, n (%)	38 (54.3)	8 (50.0)	30 (55.6)	0.65
Mean stone size (mm), mean ± SD	12.6 ± 6.8	12.8 ± 6.5	12.5 ± 6.9	0.89
Mean CBD diameter (mm), mean ± SD	9.0 ± 2.2	9.2 ± 2.1	9.0 ± 2.3	0.71
CBD dilatation (≥10 mm), n (%)	31 (44.3)	8 (50.0)	23 (42.6)	0.53
Acute pancreatitis, n (%)	15 (21.4)	3 (18.8)	12 (22.2)	0.73
Cholangitis, n (%)	8 (11.4)	2 (12.5)	6 (11.1)	0.87
Obstructive jaundice, n (%)	32 (45.7)	8 (50.0)	24 (44.4)	0.65

The detailed characterization of stone disease demonstrates that hypothyroidism was not associated with differences in stone size, number, CBD diameter, or complication rates. Hypothyroid case patients did not show significantly different prevalence of secondary versus primary stones (87.5% vs. 12.5% in hypothyroid cases; 79.6% vs. 20.4% in euthyroid cases; p = 0.42), suggesting that hypothyroidism may predispose to both pathophysiological pathways of stone formation. Similarly, hypothyroid cases did not demonstrate increased susceptibility to complications such as pancreatitis (18.8% vs. 22.2% in euthyroid cases; p = 0.73) or cholangitis (12.5% vs. 11.1%; p = 0.87), indicating that the effect of hypothyroidism on stone pathogenesis does not translate into worse clinical severity at presentation. The comparable mean CBD diameters and prevalence of dilatation between hypothyroid and euthyroid patients (9.2 mm vs. 9.0 mm; p = 0.71) suggests that hypothyroidism influences stone formation through metabolic and functional mechanisms rather than through acute effects on biliary structure. These findings are consistent with a chronic effect of thyroid hormone deficiency on lipid metabolism and sphincter function rather than an acute mechanical obstruction phenomenon.

Summary of Primary Findings

The principal findings of this investigation establish a robust statistical association between hypothyroidism and choledocholithiasis. The 3.9-fold odds ratio for hypothyroidism in CBD stone patients compared with healthy age- and sex-matched controls represents a substantial effect size. The concurrent identification of marked lipid abnormalities—characterized by hypercholesterolemia (12% elevation), severe hypertriglyceridemia (41% elevation), and profound HDL-C depression (27% reduction)—in the same cohort provides a mechanistic explanation linking thyroid dysfunction to stone

pathogenesis. The absence of differences in stone characteristics (size, number, location, complications) between hypothyroid and euthyroid stone patients suggests that hypothyroidism facilitates formation of stones that are otherwise clinically indistinguishable from those forming in euthyroid individuals, supporting a pathophysiological rather than symptomatic difference between groups.

DISCUSSION

This case-control study provides compelling epidemiological evidence that hypothyroidism represents a significant and independent risk factor for choledocholithiasis in the Indian population. The prevalence of hypothyroidism among patients with common bile duct (CBD) stones was 22.9%, compared with 7.1% among controls, corresponding to a nearly fourfold increased odds of disease. This magnitude of association is consistent with previously published studies across diverse populations. Large population-based data from Germany demonstrated that elevated serum TSH independently predicted gallstone disease, particularly among women, while Finnish studies identified a higher prevalence of subclinical hypothyroidism among elderly CBD stone patients compared with controls [10,11]. Indian data are limited but supportive; a Telangana-based case-control study similarly reported significantly higher rates of subclinical hypothyroidism in CBD stone patients, reinforcing the relevance of thyroid dysfunction within regional and ethnic contexts [12]. The persistence of this association after matching for age and sex in the present study suggests that hypothyroidism functions as a true etiological contributor rather than merely a demographic confounder.

The biological plausibility of this association is supported by the profound effects of thyroid hormones on lipid metabolism and bile composition. In the present cohort, CBD stone patients exhibited significant dyslipidemia characterized by elevated total cholesterol and triglycerides and markedly reduced high-density lipoprotein cholesterol (HDL-C). Thyroid hormones play a central role in hepatic cholesterol homeostasis by upregulating LDL receptor expression, enhancing cholesterol clearance, stimulating bile acid synthesis via cholesterol 7α-hydroxylase, and modulating endogenous cholesterol synthesis through HMG-CoA reductase activity [13,14]. In hypothyroid states, attenuation of these mechanisms leads to hepatic cholesterol accumulation and bile supersaturation with cholesterol monohydrate crystals, a critical initiating step in gallstone formation [15]. The pronounced reduction in HDL-C observed in CBD stone patients is particularly relevant, as HDL-associated apolipoproteins inhibit cholesterol crystal aggregation in bile, and hypothyroidism is known to impair reverse cholesterol transport, further promoting lithogenesis [16].

Beyond metabolic alterations, hypothyroidism adversely affects biliary motility and sphincter of Oddi function, thereby facilitating bile stasis. Experimental and human studies have demonstrated that thyroxine exerts a direct relaxant effect on the sphincter of Oddi via thyroid hormone receptor-β–mediated activation of ATP-sensitive potassium channels, leading to smooth muscle hyperpolarization and reduced basal sphincter pressure [17,18]. In hypothyroidism, the loss of this prorelaxing influence results in sustained sphincter contraction, impaired phasic relaxation in response to cholecystokinin, and reduced bile flow into the duodenum. Prolonged bile residence time within the biliary tree allows cholesterol crystals to persist, aggregate, and grow, explaining the observed association with both secondary CBD stones migrating from the gallbladder and primary stones forming de novo within the duct [19].

Impairment of hepatic bile secretion further compounds this risk. Radionuclide kinetic studies have demonstrated delayed hepatic clearance and prolonged hilum-to-duodenum transit times in hypothyroid individuals compared with their euthyroid state, indicating reduced driving force for bile excretion [20]. This diminished bile flow not only enhances cholesterol supersaturation but also reduces the clearance of precipitated crystals, allowing early lithogenic material to persist and enlarge. These combined metabolic and mechanical disturbances provide a coherent pathophysiological framework linking hypothyroidism to choledocholithiasis.

The present findings are concordant with prior international literature examining thyroid dysfunction and biliary stone disease. Iranian and European case-control studies have reported significant associations between thyroid disorders and gallstone disease, with several authors recommending routine thyroid function testing in stone patients due to its potential role in stone formation and progression [21,22]. Indian studies have reported even higher odds ratios for hypothyroidism in CBD stone disease, though variation likely reflects differences in study design, TSH cutoffs, disease definitions, and control selection [23]. The slightly lower odds ratio observed in the present study may therefore represent a more conservative and clinically realistic estimate.

Sex and age-related trends observed in this study further support existing epidemiological patterns. Although female predominance among CBD stone patients did not reach statistical significance, it aligns with the known higher prevalence of both gallstone disease and hypothyroidism in women. Hypothyroidism affects women up to six times more frequently than men, suggesting a potential synergistic interaction between female sex hormones and thyroid dysfunction in lithogenesis. Similarly, the higher incidence of CBD stones in older age groups parallels the age-related rise in hypothyroidism prevalence, emphasizing the need for heightened clinical vigilance in elderly patients.

Several limitations should be acknowledged. The case-control design precludes causal inference, and the modest sample size limits subgroup analyses, particularly for primary versus secondary CBD stones. The single-center setting may restrict generalizability, and the lack of stratification between overt and subclinical hypothyroidism limits assessment of disease

severity effects. Nevertheless, the study's strengths include careful matching of controls, objective biochemical assessment, and comprehensive evaluation of metabolic parameters.

Clinically, these findings carry important implications. Routine thyroid function testing should be incorporated into the diagnostic evaluation of patients presenting with choledocholithiasis, particularly in older adults, women, and those with dyslipidemia. Identification of previously undiagnosed hypothyroidism provides an opportunity for therapeutic intervention, and emerging evidence suggests that thyroid hormone replacement may reduce stone recurrence following endoscopic or surgical management. Conversely, patients diagnosed with hypothyroidism—especially those with subclinical disease—may benefit from screening ultrasonography to detect asymptomatic biliary stones at an early stage.
In conclusion, this study demonstrates that hypothyroidism is a significant, independent, and underrecognized risk factor for choledocholithiasis in the Indian population. The association is biologically plausible and mediated through combined effects on lipid metabolism, bile composition, sphincter of Oddi function, and hepatic bile secretion. Incorporation of thyroid assessment into standard hepatobiliary evaluation represents a rational and potentially impactful strategy to reduce morbidity associated with CBD stone disease, while future prospective and interventional studies are needed to define the preventive role of thyroid hormone replacement therapy.

CONCLUSION

This case-control investigation provides robust evidence that hypothyroidism constitutes a significant, independent, and underrecognized risk factor for choledocholithiasis in the Indian population. The threefold increase in hypothyroidism prevalence among CBD stone patients, coupled with substantial alterations in lipid profiles and thyroid hormone levels, supports a multifactorial pathophysiological mechanism involving both metabolic (lipid supersaturation, impaired bile clearance) and mechanical (sphincter of Oddi dysfunction, reduced bile flow) components. The findings mandate incorporation of thyroid function testing into standard diagnostic algorithms for choledocholithiasis and suggest that identification and treatment of hypothyroidism may represent a novel preventive strategy for both incident and recurrent stone disease. Future prospective investigations examining thyroid hormone replacement as a therapeutic intervention, mechanistic studies delineating dominant pathways, and guidelines updates will be necessary to translate these findings into evidence-based clinical practice changes. Until such investigations are completed, heightened vigilance for thyroid dysfunction in stone disease patients—and conversely, screening for asymptomatic stones in newly diagnosed hypothyroid individuals—represents a prudent clinical approach to reduce morbidity and mortality from hepatobiliary complications.

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