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Hypothyroidism as a risk factor for choledocholithiasis: A case-control study in an Indian population

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Abstract
Hypothyroidism causes dyslipidemia and biliary stasis both of which predispose to the formation of CBD stones. If hypothyroidism is determined as an independent factor in the etiology of choledocholithiasis, it alters the preoperative diagnostic and therapeutic work up of patients with CBD stones. Early diagnosis and treatment of CBD stones can prevent complications of surgical jaundice, sepsis, cholangitis, liver abscess and dysfunction, biliary cirrhosis and pancreatitis. A case control study was done where 140 cases and 140 controls were sampled. A significant proportion of the cases were found to have hypothyroidism in comparison to controls with odds ratio of 12.21. Other variables included female sex, age greater than 60 years, non-vegetarian diet, increased LDL, VLDL and Triglyceride levels. This study proves that hypothyroidism is a significant independent risk factor for choledocholithiasis, and this can give validation to inculcate change in the approach and management of a case of choledocholithiasis.

Keywords: Hypothyroidism, choledocholithiasis, etiopathology, case-control study

Introduction
In the Indian population the prevalence of common bile duct (CBD) stones in patients with gallbladder stones varies from 8 to 16%. The prevalence of choledocholithiasis in the Western population is 2.25% [1] and are predominantly made of cholesterol stones. The Asian population differs in having a higher prevalence of pigmented and mixed stones due to higher incidence of infections and hemolytic anemia. In the course of clinical practice, it was observed that a number of patients with CBD stones had hypothyroidism in their medical history [2]. Previously the significance of hypothyroidism as a risk factor for cholelithiasis had been satisfactorily proven but because of the lack of previous studies on the etiology of choledocholithiasis, the possible relation between undiagnosed hypothyroidism and subclinical hypothyroidism and CBD stones was proposed for investigation in this study. Studies similar to the proposed research have been carried out in Western population and European population but the validity of findings in an Indian population has not been investigated.
The pathogenesis of gallstones is a complex process involving factors affecting bile content and bile flow. A crucial factor in the formation of bile duct stones is biliary stasis, which can be caused by sphincter of Oddi stenosis, sphincter of Oddi dyskinesia or bile duct strictures [3]. The effects of thyroid hormone on Sphincter of Oddi contractility have been studied been studied only in animal models and its significance in the human physiology has not been fully established [4]. In this study we have investigated the role of hypothyroidism as an etiological factor for development of choledocholithiasis. Other parameters that directly or indirectly affect formation of choledocholithiasis have also been recorded and analyzed.

Materials and Methods
A case-control study was done at JSS Hospital, Mysore. A total of 140 cases and 140 controls were recruited and analyzed.

Inclusion criteria
Cases
- Patients with CBD stones confirmed by USG/ ERCP/MRCP
- Clinically euthyroid/ undiagnosed hypothyroid
- Age > 18 years

Controls
- Patients confirmed not to have CBD/ Gall stones by USG
- Clinically euthyroid/ undiagnosed hypothyroid
- Age >18 years

Exclusion criteria
Cases
- Patients previously treated for hypothyroidism with oral Thyroxin
- Patients on Phenytoin/ Carbamazepine
- Pregnant women or on OCP
- Patients who have previously undergone cholecystectomy or thyroid surgery

Controls
- Patients previously treated for hypothyroidism with oral Thyroxin
- Patients on Phenytoin/ Carbamazepine
- Pregnant women or on OCP
- Patients who have previously undergone cholecystectomy or thyroid surgery
- Elevated liver enzymes
- Symptomatic of hepatic/ biliary disease

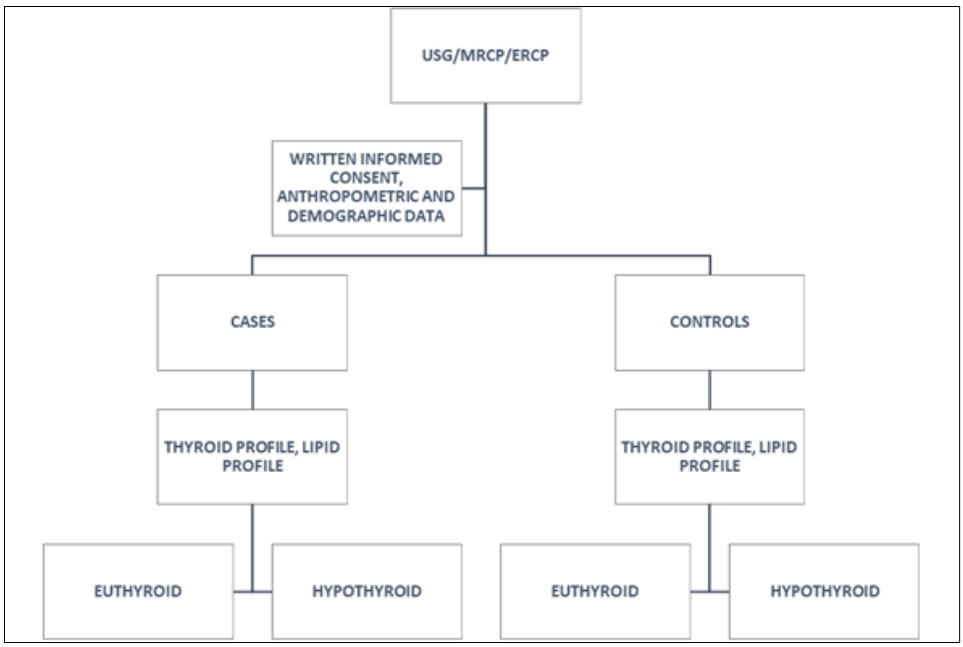

Fig 1: Flow-chart depicting the methodology of the study

Measurement of exposure: Hypothyroidism was defined as TSH >4.2mU/L, T3 < 0.8 or T4<5.13. Fasting Lipid profile and other anthropometric data was recorded and analyzed. Multiple regression analysis was done and statistics with p value of less than 0.05 was considered significant.

Results

Age distribution of the study

Mean age in the case group was 53 and the mean age in the control group was 52 with similar standard deviation of 17 and 18 respectively. They were matched adequately for age leading to less age bias. The maximum age distribution was found in the 60 to 70 age group for both case and control group. Further analysis shows that in the case group, hypothyroidism was most common bimodally in the 81 and above age group (83%) and in the 51-60 age group (41%). Age as a risk factor was not significant in case of control population.

Table 1: Descriptive statistics: age as a risk factor in the incidence of hypothyroidism

		Group							
		Case				Control			
		Hypothyroidism				Hypothyroidism			
		No		Yes		No		Yes	
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Age category	<30	8	57.1%	6	42.9%	21	100.0%	0	.0%
	31-40	26	89.7%	3	10.3%	18	90.0%	2	10.0%
	41-50	17	81.0%	4	19.0%	22	100.0%	0	.0%
	51-60	13	59.1%	9	40.9%	22	100.0%	0	.0%
	61-70	24	82.8%	5	17.2%	29	96.7%	1	3.3%
	71-80	14	73.7%	5	26.3%	20	95.2%	1	4.8%
	>81	1	16.7%	5	83.3%	4	100.0%	0	.0%
	p	0.003				0.43			

Study of sex distribution in the study

The total number of females in the case group was 76 (54%) and the males was 64 (46%).

The total number of females in the control group was 50 (36%) and males was 90 (64%). Males were statistically higher in the control group.

Study of BMI and waist circumference affecting CBD stone formation

The mean BMI in cases was 23 and in controls was 22.14 with a standard deviation of 3.9 for both categories. 22% of the cases were overweight and 13.6% of the controls were overweight with BMI > 25 kg/m2. Further analysis showed that 29% of the study that was in the over-weight age group with BMI of more than 25 were hypothyroid.

Mean waist circumference was 92 cm in cases and 85 cm in controls with standard deviation of 14.65 and 10.16 respectively. In the female population, in cases the mean was 91cm and in the control population mean was 83 cm which was statistically significant. Similarly, in the male population the controls had a mean circumference of 86 cm and cases had a mean of 93 cm which was also statistically significant.

Table 2: Influence of BMI on the incidence of hypothyroidism in cases and controls

		group							
		Case				Control			
		Hypothyroidism				Hypothyroidism			
		No		Yes		No		Yes	
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
BMI	<25 kg/m2	81	74.3%	28	25.7%	117	96.7%	4	3.3%
	>25 kg/m2	22	71.0%	9	29.0%	19	100.0%	0	.0%
	p	0.7				0.4			

Table 3: Study of waist circumference across male and female population

	Gender							
	Female				Male			
	group				group			
	Control		Case		Control		Case	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Waist circumference cm	83.22	9.10	91.02	15.11	85.90	10.67	92.83	14.13
p	0.001				0.001			

Study of comorbidities affecting the study

60% of the cases and 64% of the control group had no comorbidities 38 of the cases and 44 of the controls had HTN, DM or IHD.

Table 4: Study of various co morbidities in the case and control population

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Comorbidities	Aki	1	.7%	0	.0%
	CLD, PHTN	2	1.4%	0	.0%
	Corrosive esophageal injury.	1	.7%	0	.0%
	DM	14	10.0%	16	11.4%
	DM, HTN	8	5.7%	4	2.9%
	DM, IHD	0	.0%	1	.7%
	HAV positive (hepatitis A)	1	.7%	0	.0%
	Hepatitis b positive, dili.	1	.7%	0	.0%
	Hookworm infection	1	.7%	0	.0%
	HTN	16	11.4%	24	17.1%
	HTN, IHD	0	.0%	1	.7%
	HTN DM seizure disorder	3	2.1%	0	.0%
	HTN IHD	0	.0%	1	.7%
	HTN IHD DM	2	1.4%	1	.7%
	IHD	3	2.1%	1	.7%
	IHD HTN	1	.7%	1	.7%
	nil	84	60.0%	90	64.3%
	Parkinson's disease, IHD	1	.7%	0	.0%
	Portal vein thrombosis	1	.7%	0	.0%

Effect of diet, alcohol intake and smoking on CBD stone formation

People who consumed a non-vegetarian diet have a higher incidence of CBD stones (113/140) while in the control population, 84 out of 140 consumed non vegetarian food. This has a significant odds ratio of 3.

Table 5: Study of diet, alcohol, smoking among cases and control

		group					
		Case		Control			
		Count	%	Count	%		OR
DIET	non vegetarian	113	81.3%	84	59.6%	<0.001	3.0(1.7-5.2)
	vegetarian	26	18.7%	57	40.4%		
ALCOHOL	no	99	71.2%	99	70.2%	0.8	1(0.6-1.6)
	yes	40	28.8%	42	29.8%		
SMOKING	no	114	82.0%	107	75.9%	0.2	0.7(0.4-1.2)
	yes	25	18.0%	34	24.1%		

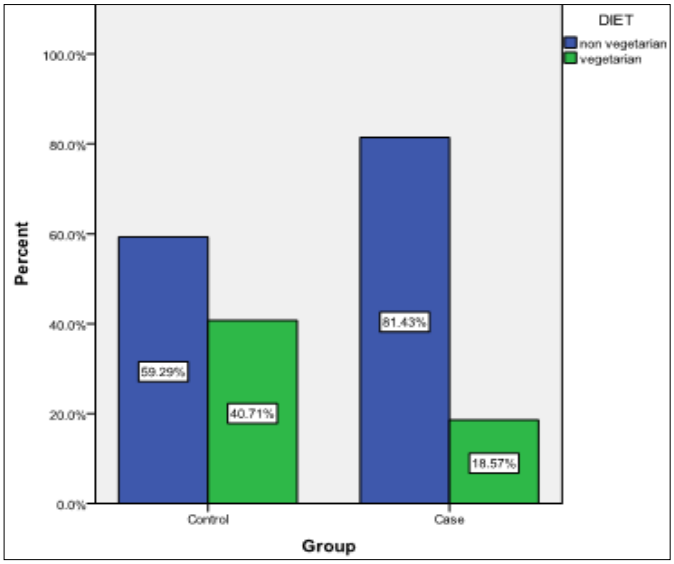

Fig 2: Effect of diet on the formation of choledocholithiasis

Primary objective: effect of TSH on formation of choledocholithiasis and effect of lipid profile on the formation of choledocholithiasis

The mean value of TSH in case group was 3.98 and in controls was 2.51 with a standard deviation of 6.6 and 1.26 respectively. This was statistically significant.

Mean value of T3 was 1.18 in cases and 1.24 in controls. Mean value of T4 was 8.67 and 9.50 in controls.

The statistically significant components of lipid profile included HDL where cases had a lower mean value of 35.8 and controls had a mean value of 50. VLDL was also found to be of significance with mean value of 32.39 in cases and 19.63 in controls. Total cholesterol also came out to be significant with cases having a mean value of 177.3 and controls having a mean value of 201.9 In case group, out of 140, 37 patients (26.4%) were found to have hypothyroidism. In control group, 4 out of 140 was found to have hypothyroidism (2.9%). This was statistically significant with p value of less than 0.0001 and a significant ODDS ratio of 12.21.

Table 6: Study of Thyroid profile and Lipid profile across cases and controls

	group				
	Case		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	p
TSH	3.98	6.60	2.51	1.26	0.01
T3	1.18	1.16	1.24	.35	0.6
T4	8.67	2.87	9.50	8.27	0.3
LDL	108.47	60.95	118.26	34.59	0.1
HDL	35.81	10.06	50.04	9.02	<0.0001
VLDL	32.39	16.56	19.63	3.90	<0.0001
TG	165.11	89.62	164.50	33.25	0.9
TC_	177.31	72.73	201.90	34.62	<0.0001

Table 7: Study of incidence of hypothyroidism in cases and controls

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Hypothyroidism	No	103	73.6%	136	97.1%
	Yes	37	26.4%	4	2.9%

<0.0001OR- 12.21 (4.22-35.35)

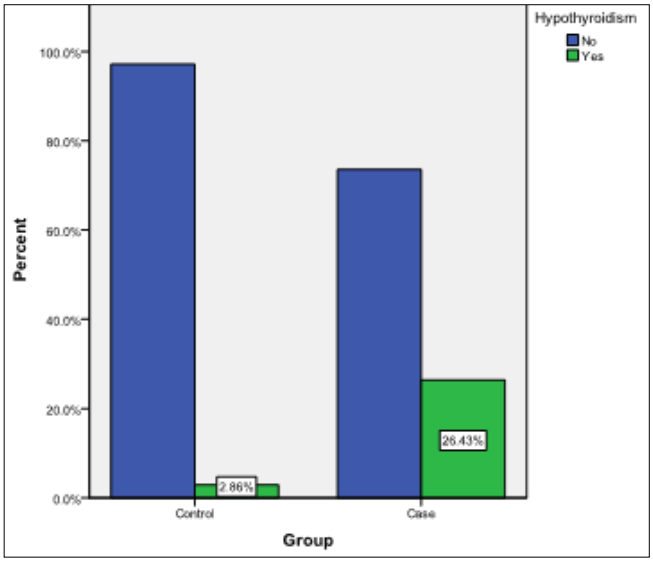

Fig 3: Hypothyroidism in cases and controls

Table 8: study of lipid profile in case and control group

		Group					
		Case		Control			
		n	%	n	%	p	
LDL	Normal	70	50.0%	43	30.7%	0.001	0.4(0.3-0.7)
	Increased	70	50.0%	97	69.3%		
HDL	Normal	47	33.6%	122	87.1%	<0.0001	13.41(7.3-.24.6)
	Decreased	93	66.4%	18	12.9%		
VLDL	Normal	120	85.7%	140	100.0%	<0.0001	NA
	Increased	20	14.3%	0	.0%		
TG	Normal	74	52.9%	52	37.1%		
	Increased	66	47.1%	88	62.9%	0.008	0.5(0.3-0.85)
Total Cholesterol mg/dl	Normal	110	78.6%	56	40.0%		0.2(0.1-0.3)
	Increased	30	21.4%	84	60.0%	<0.0001	

Discussion

Secondary choledocholithiasis which are predominantly cholesterol stones result from stones originating in the gallbladder and migrating through the cystic duct. Behavioral factors associated with cholesterol gallstones include nutrition, obesity, weight loss, and physical activity [5]. Biologic factors linked to gallstones include increasing age, female sex and parity, serum lipid levels, and the Native American, Chilean and Hispanic race [6]. Primary bile duct stones, on the other hand, form within the bile ducts and usually are of the brown pigment variety, tend to be lower in cholesterol content and higher in bilirubin content as compared with secondary stones [7, 8, 9].

Cases and controls were analyzed, and they were adequately matched for age. The male population of the control group was more than the cases since gall stone disease is more common in females. Subclinical or undiagnosed hypothyroidism was most common in the older age group of more than 51 due to attributing the symptoms to other factors and neglect of health in the older age group. BMI analysis in cases and in controls was not found to statistically affect CBD stone formation. However central obesity seemed to play a larger role in affecting the formation of CBD calculi. Diet analysis showed that People who consumed a non-vegetarian diet have a higher incidence of CBD stones. Non vegetarian food consumption leads to higher levels of cholesterol in the blood and early onset of fatty liver. This can alter bile composition and lead to formation of GB sludge and subsequently cholelithiasis. Alcohol consumption and smoking did not seem to have any direct effect on the formation of choledocholithiasis.

The mean value of TSH in case group was 3.98 and in controls was 2.51. In case group, out of 140, 37 patients (26.4%) were found to have hypothyroidism. In control group, 4 out of 140 was found to have hypothyroidism (2.9%). This was statistically significant with ODDS ratio of 12.21. In conclusion, patients with hypothyroidism are 12 times more likely to develop choledocholithiasis in comparison with euthyroid population.

In a similar study done in Finland [10, 11, 12], there was no difference in the median values of TSH and S-FT4 between the groups. 10.2% had subclinical or borderline subclinical hypothyroidism, compared with 2.8%, in the control group. Our study has significantly higher prevalence of subclinical hypothyroidism that is 26.4 % which can be explained by the fact that the cut off taken for the Finnish study was 5 in comparison to our cut off of 4.2. Also in developing countries like India, patients with symptoms of hypothyroidism tend to neglect and delay diagnosis and medical care for the same leading to a larger number of undiagnosed hypothyroid cases [13].

An Iranian study done by Hossein Ajdarkosh *et al* [14] was a case control study similar to our study with 151 cases and control. The mean TSH in patients (2.59) was higher than the control (2.53), similar to our study where the mean value of TSH in case group was 3.98 and in controls was 2.51. Serum TSH levels higher than 5 MU/L were found in 30.6% of cases compared with 22.5% of controls (Odds ratio of 1.53). In our study, in the case group, 26.4% and in control group 2.9% were found to be hypothyroid (Odds ratio of 12.21). They also concluded that the HDL and LDL levels were significant. Reviewing literature of similar studies done across the world, a cross sectional study

done in Bhadgad [15] in 2015 examined 103 cases of cholelithiasis. The results showed 8 out of 103 that is 7.8% had subclinical hypothyroidism. Our study examines only choledocholithiasis in contrast and has a higher incidence rate of 26.4%.

Conclusion

The purpose of the study was to establish a relationship between hypothyroidism prevailing as a significant factor in the formation of choledocholithiasis. The results and analysis reveal that, patients who had subclinical or undiagnosed hypothyroidism were 12 times more likely to have choledocholithiasis compared to the normal population. In comparison to previous studies done on the impact of hypothyroidism on the formation of only cholelithiasis, this seems to have a higher impact that is hypothyroidism affects the incidence of choledocholithiasis more significantly. Also the value of TSH had more impact in comparison to the T4, and T3 values. Other factors that were studied came to the conclusion that the at risk population also included people who were above the age group of 51, with central obesity affecting both male and female population equally. People who consumed non vegetarian diet and with high HDL, VLDL and total cholesterol values were more likely to have choledocholithiasis. There are a few recommendations from this study that will help modify and give a more wholistic approach to the treatment of a patient with gall stone disease. These include routine screening of patients admitted with gall stone disease for subclinical hypothyroidism where a minimal investigation of TSH will help identify those patients that require further management. Thyroid hormone supplementation at low doses is recommended to those patients who have subclinical hypothyroidism with a lower cut off value of TSH to initiate treatment. Patients in the age group of more than 51 who are newly diagnosed as hypothyroid should get a routine ultrasound scan done to detect gall stones before they become symptomatic. Further scope of study includes a prospective study where subclinical hypothyroid patients can be treated with thyroxine supplementation and followed up long term to check for the formation of gall stones [16].

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