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Association of thyroid dysfunction in patients with biliary calculus: A study in tertiary care hospital

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Abstract
Background: For decades there has been discussion whether thyroid disorders could cause gall stone disease. There could be several explanations for possible relation between hypothyroidism and gall stone disease.
Objective: To know the association of thyroid functions tests in diagnosed cases of gall stone disease.
Setting: It is a prospective study. 200 patients with biliary calculi were included in the study.
Result: 143(71.5%) were females and 57(28.5%) were males with median age was 40 yrs. Thyroid disorder in form of hypothyroidism was found in 37(18.5%) patients (high TSH levels than normal value for their age), 28(19.6%) were females and 9(15.8%) males. Among 37 hypothyroidism cases 21(10.5%) are subclinical hypothyroidism and 16(8%) were clinical hypothyroidism. Clinically 37 out of 200 patients high level of TSH is statistically not significant (p= 0.849). However low levels of T3 levels associated with high TSH in clinical hypothyroidism is statistically significant (p=0.047).
Conclusion: It was concluded in our study there was high TSH levels in patients with biliary calculi but it's not statistically significant however low T3 with high TSH has statistically significant.

Keywords: Thyroid dysfunction, thyroid disorder, hypothyroidism, biliary calculi

Introduction

Introduction: In Indian population, 10 to 12% of adults develop gallstones. In patients with gallbladder stones the prevalence of common bile duct stones ranges from 8 to 15%. The gallstones formation is complex process which involves factors affecting bile content and bile flow. A crucial factor in the forming of bile duct stones is biliary stasis, which can be caused by sphincter of Oddi (SO) stenosis, SO dyskinesia or bile duct strictures. First demonstrated the hormonal action of cholecystokinin (CCK) on the SO is done by Sandblom in 1935, then several other hormones have been shown to affect SO activity. Among the steroid hormone family, it has been suggested that estrogen affects the motility of the SO in a prairie dog model. Still, effects on sphincter of oddi contractility of thyroid hormones (TH) and steroid hormones other than estrogen, have not been studied [1].

In clinical practice it was seen that a number of patients with CBD stones had hypothyroidism in their medical history. Because of the lack of previous studies on this particular topic, the possible relation between diagnosed hypothyroidism and gall stones was investigated in a study. A positive correlation was found which raised further questions as to the direct effect of thyroxine (T4) on the SO, and a series of studies was therefore undertaken to further investigate the possible reasons for this clinical association [2, 3].

A adult thyroid weighs 10 to 20 g in normal condition and it is a bi-lobed structure that lies next to the thyroid cartilage, anterior and lateral to the junction of the larynx and trachea. The thyroid gland encircles approximately 75% of the diameter of the junction of the larynx and upper part of the trachea [4].

T3 is significantly more potent than T4 in the periphery. T3 formation is more from most of the T4, which has a high affinity for the peripheral nuclear thyroid hormone receptor (TR) and this thyroid receptor is a member of the steroid hormone receptor family. That's the reason, the action of thyroid hormones in the periphery consists of the interaction of T3 with the nuclear TR, which then binds to regulatory regions in various gene-regulated processes.TR production and activity is regulated by two genes, the α and β forms, which are located on chromosomes 17 and 3.

The β form of TR is contained within the liver; the central nervous system contains predominantly a form of TR [4].
The gallbladder concentrates the solute components two- to tenfold by rapidly absorbs water and solutes from bile. The hepatic bile to gallbladder bile there is change in solute concentration. The gallbladder absorb water and solutes against significant concentration gradients. Water absorption causes transport of ions. Active and passive absorption are the two major mechanisms. The passive absorption causes sodium and chloride enter the gallbladder epithelial cells along the electrochemical gradients. The water flows into the cell along osmotic gradient. By active transport intracellular sodium is crossed across the basolateral membrane into the lateral intercellular spaces. The extrusion of sodium at the basolateral membrane may occur by electrogenic or nonelectrogenic mechanisms, or both. Water enters the lateral intercellular space through the tight junctions at the mucosal surface in response to the solute concentration. Flow through the tight junctions into the lateral spaces is a passive mechanism. The transport of chloride is linked with sodium transport, and, in experimental models, sodium absorption does not occur in the absence of chloride. This coupling between sodium and chloride probably occurs by an electrically neutral coupled mechanism and results in neutralization of any charge, preventing an electrochemical gradient [5]. Hence the present study is conducted to know the association of thyroid functions tests in diagnosed cases of gall stone disease.

Materials & Methods

A cross sectional study was done in MS RAMAIAH hospital, Bangalore between in which 200 patients with gallstones were taken, 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 goitre)
Investigations were included, neck ultrasound and level of serumT3, T4, and TSH and ECG changes.
Patients were divided according to history, clinical examination, ultrasound of the neck and laboratory test (T3, T4, TSH) into 3 groups:

1. Subclinical hypothyroidism includes the symptom free patients with TSH concentrations above the upper limit of normal range and T4 and / or T3 decrease below normal limit. (According to our laboratory readings)
2. Clinical hypothyroidism in which there are symptoms of hypothyroidism with TSH level above the upper limit and T4 and / or T3 decrease below the normal limit.
3. Euthyroid group where clinical and laboratory tests were normal.

All these groups may present with or without goiter.

Inclusion criteria

Patients with cholelithiasis and choledocholithiasis

Exclusion criteria

- Patients with previous history of hypothyroidism on treatment.

Sample size estimation

Based on previous study conducted it was found that % of subclinical hypothyroidism was 30.6% among cases of choledocholithiasis and 10% in cholelithiasis, in present study sample size is calculated. Expecting similar proportion considering the absolute precision of 7% and desired confidence level of 95% which was calculated to be 166.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation. Independent t test or was used as test of significance to identify the mean difference between two quantitative variables.

Result

In this cross-sectional study a 200 patients with gallstones were randomly selected. 143(71.5%) were females and 57(28.5%) were males with median age was 40 yrs (range 24-65) yrs and 37yrs (30-43) yrs respectively.
Most of the patients with biliary calculi presented with pain abdomen (95.5%) as symptom and others were dyspepsia (50%) and jaundice and fever.
Symptoms of hypothyroidism like increase in weight in spite of loss of appetite (commonly seen symptom in our study), cold intolerance and dysmenorrhea/amenorrhea were seen with 14% of females and 5% of males but symptoms of hyperthyroidism like palpitation and loss of weight seen in only 1 patient. But obvious goitre is seen in only 2 patient with hypothyroidism in our study. But none of the patients had pressure symptoms due to goitre. Signs of hypothyroidism seen in only 5% of female patients. (Table 6) and none has signs of hyperthyroidism.
Thyroid disorder in form of hypothyroidism was found in 37(18.5%) patients, 28(19.6%) were females and 9(15.8%) males. In our study among 37 hypothyroidism cases 21(10.5%) are subclinical hypothyroidism and 16(8%) were clinical hypothyroidism. According to sex differentiation, among the 28 females with hypothyroidism, 19(13.28%) diagnosed as subclinical hypothyroidism and 9 (6.3%) as clinical hypothyroidism while in males 2 (3.5%) were subclinical hypothyroidism and 8 (14%) were clinical hypothyroidism.
Clinically 37 out of 200 patients had high TSH levels than normal value for their age, but high level of TSH is statistically not significant (p= 0.849). However low levels of T3 levels associated with high TSH in clinical hypothyroidism is statistically significant (p=0.047). 8 patients had low T4with high TSH levels but it's not statistically significant. Table 1

Table 1: Thyroid functions and correlations.

Variables	Gender		Total (n=200)	P value
	Female (n=143)	Male (n=57)		
TSH (microIU/L)				0.849
<0.5	5(3.5%)	2(3.5%)	7(3.5%)	
0.5-4.3	110(76.9%)	46(80.7%)	156(78.0%)	0.849
>4.3	28(19.6%)	9(15.8%)	37(18.5%)	
T3 (nmol/L)				0.047
<1.08	13(9.1%)	8(14%)	21(10.5%)	
1.08-4.14	127(88.8%)	44(77.2%)	171(85.5%)	0.047*
>4.14	3(2.1%)	5(8.8%)	8(4%)	
T4 (pmol/L)				0.175
<59	9(6.3%)	8(14%)	17(8.5%)	
59-135	124(86.7%)	44(77.2%)	168(84%)	0.175
>135	10(7%)	5(8.8%)	15(7.5%)	

83% of patients were having multiple gallbladder calculi and and 21% were having solitary gall bladder calculi and 11.2%

patients has cholelithiasis with choledocholithiasis (11.4% of females and 3.5% of males). Patients with choledocholithiasis (11.2%) abnormal LFT was seen in 8.5% of patients. Table 2

Table 2: Correlation of clinical variables in relation to incidence of Thyroid dysfunction of patients studied

Variables	Thyroid Dysfunction			Total (n=200)	P value
	Euthyroid (n=156)	Hypothyroidism (n=37)	Hyperthyroidism (n=7)		
Age in years					0.321
21-30	20(12.8%)	0(0%)	1(14.3%)	21(10.5%)	0.321
31-40	56(35.9%)	12(32.4%)	2(28.6%)	70(35%)	
41-50	34(21.8%)	10(27%)	3(42.9%)	47(23.5%)	
51-60	27(17.3%)	9(24.3%)	1(14.3%)	37(18.5%)	
61-70	16(10.3%)	5(13.5%)	0(0%)	21(10.5%)	
71-80	3(1.9%)	1(2.7%)	0(0%)	4(2%)	
Gender					0.822
Female	110(70.5%)	28(75.7%)	5(71.4%)	143(71.5%)	0.822
Male	46(29.5%)	9(24.3%)	2(28.6%)	57(28.5%)	

89.5% of patients underwent laparoscopic cholecystectomy. 5% of patients underwent ERCP + laparoscopic cholecystectomy and 0.7% of patients with ERCP+ open cholecystectomy. Failed ERCP with open cholecystectomy and CBD exploration done in 2 patients. Table 3

Table 8: Correlation of clinical variables in relation to incidence of Thyroid dysfunction of patients studied

variables	Thyroid Dysfunction			Total (n=200)	P value
	Euthyroid (n=156)	Hypothyroidism (n=37)	Hyperthyroidism (n=7)		
Diagnosis					
Cholelithiasis	143(91.7%)	32(86.5%)	6(85.7%)	181(90.5%)	0.293
Choledocholithiasis	13(8.3%)	4(10.8%)	1(14.3%)	18(9%)	
Cholelithiasis with goitre	0(0%)	1(2.7%)	0(0%)	1(0.5%)	
Treatment					
Laparoscopic cholecystectomy	140(89.7%)	33(89.2%)	6(85.7%)	179(89.5%)	0.039*
ERCP+ laparoscopic cholecystectomy	9(5.8%)	1(2.7%)	0(0%)	10(5%)	
ERCP+ open cholecystectomy	1(0.6%)	0(0%)	0(0%)	1(0.5%)	
Failed ERCP with open cholecystectomy +/-CBD exploration	1(0.6%)	0(0%)	1(14.3%)	2(1%)	
Laparoscopy converted open cholecystectomy	5(3.2%)	3(8.1%)	0(0%)	8(4%)	
Intra op findings					
Multiple gb calculi with normal CBD	1(0.6%)	0(0%)	0(0%)	1(0.5%)	0.836
Distended gb with omental adhesions	119(76.3%)	29(78.4%)	5(71.4%)	153(76.5%)	
Partially distended gb with ommental adhesion	30(19.2%)	5(13.5%)	2(28.6%)	37(18.5%)	
Distended/partially distended gb with omental and colonic adsions/difficult calots triangle leading to open cholecystectomy	6(3.8%)	3(8.1%)	0 (0%)	9(4.5%)	
HPE					
Acute calculous cholecystitis	19(12.2%)	6(16.2%)	2(28.6%)	27(13.5%)	0.401
Chronic calculous cholecystitis	137(87.8%)	31(83.8%)	5(71.4%)	173(86.5%)	
HPE suggestive of malignancy	0(0%)	0(0%)	0(0%)	0(0%)	

Chi-Square/Fisher Exact Test

In laboratory investigation we found that 16 cases recorded with high TSH and low T3, T4, 8 cases with high TSH and low T4 and 13 case with high TSH and low T3. Table 4

Table 8: The levels of T3, T4 and TSH of 24 hypothyroid patients with gallstone

	No. of Patients	High TSH	Low T3	Low T4	Low T3 & T4
Gallstones with low T3&T4	16	16	0	0	16
Gallstones with low T4	8	8	0	8	0
Gallstones with low T3	13	13	13	0	0
Total	37	37	13	8	20

Discussion

Earlier, an association between gallstone and diagnosed hypothyroidism and delayed emptying of the biliary tract in experimental and clinical hypothyroidism have been shown explained at least partly by the lack of prorelaxing effect of T4 on the sphincter of oddi contractility.

In our study most common age group is in the range of 31 to 40 years and most commonly biliary calculi are seen in females tan males. In this study the majority of patients age was between (31- 40) years, while in study done by Johanna L, Gediminas K (2007) [6] it was in women older than 60 years while in other study by Honore LH [7], and Inkinen [8] were conducted of a high gallstones prevalence in women were > 65 years old, this probably contributed to the sex hormonal imbalance at this age.

83% of patients were having multiple gallbladder calculi and and 21% were having solitary gall bladder calculi and 11.2% patients has cholelithiasis with choledocholithiasis (11.4% of females and 3.5% of males). Patients with choledocholithiasis (11.2%) abnormal LFT was seen in 8.5% of patients.

Thyroid disorder in form of hypothyroidism was found in 37(18.5%) patients, 28(19.6%) were females and 9(15.8%) males. In our study among 37 hypothyroidism cases 21(10.5%) are subclinical hypothyroidism and 16(8%) were clinical

hypothyroidism. According to sex differentiation, among the 28 females with hypothyroidism, 19(13.28%) diagnosed as subclinical hypothyroidism and 9 (6.3%) as clinical hypothyroidism while in males 2 (3.5%) were subclinical hypothyroidism and 8 (14%) were clinical hypothyroidism.

In study done by Johanna L, Gediminas K (2007) [6], the prevalence of subclinical hypothyroidism was 11.4% in gallstones and none of the patients was clinically hypothyroidism, [9] but in this study the prevalence of thyroid disorder in form of hypothyroidism was found in (10.6%), subclinical hypothyroidism was (8.0%) and (1.7%) was clinical in female and (0.9%) was subclinical hypothyroidism in males with no clinically significant association between hypothyroidism and gallstones (P=0.12 N.S).

Patients having choledcholithiasis underwent ERCP and CBD stenting and it was failed in 2 patients. And those 2 patients underwent open cholecystectomy and CBD exploration.

89.5% of patients underwent laparoscopic cholecystectomy. 5% of patients underwent ERCP + laparoscopic cholecystectomy and 0.7% of patients with ERCP+ open cholecystectomy. Failed ERCP with open cholecystectomy and CBD exploration done in 2 patients.

In this study, the higher proportion of hypothyroidism in women with cholelithiasis compared to men was mainly due the earlier symptomatology of gallstone disease in women as well as the higher incidence of thyroid disease in women in general. This leads to an earlier detection and treatment of hypothyroidism in women.

Clinically 37 out of 200 patients had high TSH levels than normal value for their age, but high level of TSH is statistically not significant (p= 0.849). However low levels of T3 levels associated with high TSH in clinical hypothyroidism is statistically significant (p=0.047). Our study conducted in south part of the India is suggestive of many patients (18.5%) of patients has high TSH levels than the normal levels however it is not statistically significant. We need further studies to confirm the relationship between alteration in thyroid function test and biliary calculi.

In a study done by Henry Volzke in 2005 [10] there were (10.3%) with low TSH which is the same as in this study (10.6%) and (88.6%) with normal TSH which is approximately the same as this study (89.7%). In this study, among males there was an independent relation between high serum TSH and cholelithiasis and there was a tendency towards an elevated risk of cholelithiasis in persons with low serum T3 and T4.

Conclusion

Some studies done in western countries were suggestive of statistically significant correlation between cholelithiasis and subclinical hypothyroidism. In our study there is high TSH levels in patients with biliary calculi but it's not statistically significant however low T3 with high TSH has statistically significant.

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