Original Article

Association between Thyroid Function and Gall Stone Disease

Md. Nahid Reza[1], M Fardil Hossain Faisal[2], Tahmina Noor[3], Riaz Mahmud[4], Monsur Miah[5], Ibrahim Siddique[6], Md. Manir Hossain Khan[7].

Abstract

Background: *There was a long term perception that gall stone disease may have a hidden association to alteration of thyroid function.* ***Objective:*** *To find out the association between thyroid function status in gall stone disease.* ***Materials and Methods:*** *This case control study was conducted in department of Surgery, Bangabandhu Sheikh Mujib Medical University Hospital from July 2017 to June 2018. This study recruited 152 gall stone patients diagnosed with Ultrasonography (USG). The control group underwent USG to exclude any asymptomatic cholelithiasis. Fasting blood samples were taken from all participants for measurements of Fasting Blood Sugar (FBS), serum free thyroxine (FT4), serum thyroid stimulating hormone (TSH), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).* ***Results:*** *The mean serum TSH levels among cases (3.56±4.6) was higher than controls (2.46±1.68) ($p<0.05$). Subclinical hypothyroidism was noted in 11.8% of cases and all were found female and 3.8% of controls, whereas hypothyroidism was detected in 3 (3.8%) controls and 22 (14.5%) cases. The mean total cholesterol levels in cases was much higher than in controls, and was significant ($p<0.05$).* ***Conclusion:*** *Hypothyroidism has a significant role on development of gall stone disease with increasing age especially in female.*

Key words: *Gall stone, Thyroid function, Thyroid Stimulating Hormone (TSH).*

Date of received: *14.11.2020*

Date of acceptance: *25.02.2021*

KYAMC April.2021;12(1): 36-40.

DOI: https://doi.org/10.3329/kyamcj.v12i1.53366

Introduction

Gallstones, most common biliary pathology, can be divided into three main types: cholesterol, pigment (black, brown) or mixed stones. In the USA and Europe, 80% are cholesterol or mixed stones, whereas in Asia, 80% are pigment stones.[1] Cholesterol or mixed stones contain 51-99 % cholesterol plus admixture of calcium salts, bile acids, bile pigment and phospholipids.[2] Gallstones may be single or multiple, large or small those containing calcium salts are radio-opaque. Gallbladder stone prevalence varies among different parts of the world, about 10% in western countries and around 4% in India.[3] A cross-sectional, comparative, case control study was done in department of Endocrinology, King George Hospital, and Visakhapatnam during the period of February 2011 to February 2013 by Srinivas et al.[4] Study by Hossain et al., recruited 151 patients with preliminary diagnoses of common bile duct stone who underwent Endoscopic retrograde cholangiopancreatography (cases).[5] The control group comprised healthy people who met the study criteria in the same hospital. The control group underwent ultrasonography to exclude any asymptomatic bile duct lithiasis. They found that thyroid dysfunction is more common among patients with common bile duct (CBD) stones and it may be a risk factor for biliary stone formation. It was considered to be a disease of fat, forty, fertile, flatulent and female disease. Hypothyroid is also quite common in Indian population around 5-15%, and subclinical hypothyroidism around 8-12%.[6] The recent study; the prevalence of thyroid disorders among healthy subjects was 2.6%. There has been a discussion, whether thyroid disorders could cause gallstone disease or not.[7] The change of composition of bile is mainly responsible for gall stone formation. It is multifactorial.[2] Impaired liver cholesterol metabolism, diminished Bile secretion and reduced sphincter of

1. Resident Surgeon , Department of Surgery, Mugdha Medical College Hospital, Dhaka, Bangladesh.
2. Assistant Professor, Department of General Surgery, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh.
3. Assistant Registrar, Department of Obstetrics and Gynaecology, Bangladesh Medical College Hospital, Dhaka, Bangladesh.
4. Assistant Professor, Department of Surgery, Tairunnessa Memorial Medical College Hospital, Tongi, Gazipur, Bangladesh.
5. Assistant Surgeon, Officer on special duty, Directorate General of Health Services, Government of Bangladesh.
6. Professor, Department of Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
7. Associate Professor, Department of Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Correspondence: Correspondence: Dr. Md. Nahid Reza, Resident Surgeon, Department of Surgery, Mugdha Medical College Hospital, Dhaka, Bangladesh. Email: nrnahid10@gmail.com . Mobile No.:+8801716400383.

Oddi (SO) relaxation[8-10] may contribute to the formation and/or accumulation of CBD stones in hypothyroid patients. Hypothyroidism is a common secondary cause of hypercholesterolemia; patients with hypothyroidism have serum level of cholesterol approximately 50% higher than level in euthyroid and 90% of all hypothyroid patients have elevated cholesterol level.[10] Stone growth is dependent on cyclical changes in biliary substance, this may explain the permissive or causal role of endogenous hormones in gallstones formation, that mean gallstones disease has a multifactorial causations, including gall bladder infection, decreased gall bladder motility after surgery for obesity and/or weight loss, ileal disease or resection, hemolytic disease, familial hypercholestereamia and metabolic defect in hepatic bilirubin glucuronidation.[11] Recently, it has been proven that some thyroid receptors are expressed in sphincter of oddi. So, there is a pro-relaxing effect of serum total thyroxin (T4) on sphincter of Oddi.[10] Possibly, the lack of T4 may contribute to so contractility which in turn not only disturbs the normal bile flow but also prohibits the passage of stones formed in the gallbladder to the duodenum.Besides, in hypothyroid state low bile flow has also been evident.[10] Both low bile flow and sphincter of Oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation.[12]

Materials and Methods

This study was performed in department of Surgery, BSMMU, Dhaka, from July 2017 to June 2018 (one year).All patients admitted in department of Surgery, BSMMU with diagnosis of gall stone disease (case) and people served by the hospital both admitted and OPD (control) and directly interviewed each individual and a questionnaire that included demographic and anthropometric data, past and present medical histories, drug history, and hypothyroidism symptoms completed for each subject. Statistical analyses were done by SPSS version 23.0. Quantitative data were expressed as mean ± standard deviation (SD). P-values less than 0.05 were considered to be significant. We used the Mann-Whitney U, fisher's exact and unpaired t-tests for comparison between groups. For qualitative variables, cross-tables and the chi-square test were performed. The association between the presence of gallstones and risk factors was evaluated by bivariate correlation coefficient analysis. The significance level for bivariate analysis was 0.05. This study was approved by the Institutional Review Board of BSMMU, Dhaka.

Results

Patients' medical characteristics

A total of 152 patients with mean age of 43.75±13.74 years comprised the case (gall stone) group and 78 healthy individuals with a mean age of 39.17±10.49 years were in the control group. There were 80.9% females in the case group and 74.4% in the control group (Table I) Mean BMI of cases was 26.35±2.48 kg/m² and mean BMI for control subjects was 25.59±4.13 kg/m². Among the cases diabetic was 38.2% in study group and in controls 20.5% (p <0.05).

Table I: Distribution of the patients according to socio-demographic variables by groups

Socio-demographic variables	Groups		p value
	Case (n=152)	Control (n=78)	
Age (Years)			
15-25	17 (11.2)	10 (12.8)	
25-35	33 (21.7)	15 (19.2)	
35-45	34 (22.4)	34 (43.6)	
45-55	40 (26.3)	15 (19.2)	
55-65	19 (12.5)	4 (5.1)	
65-75	9 (5.9)	0 (0.0)	
Mean ± SD	43.75 ± 13.74	39.17 ± 10.49	0.010
Sex			
Male	29 (19.1)	20 (25.6)	0.250
Female	123 (80.9)	58 (74.4)	
BMI (kg/m^2)			
Under weight	0 (0.0)	2 (2.6)	
Normal	49 (32.2)	34 (43.6)	
Over weight	86 (56.6)	31 (39.7)	
Obese	17 (11.2)	11 (14.1)	
Mean ± SD	26.35 ± 2.84	25.59 ± 4.13	0.104
Fasting blood sugar			
Abnormal	58 (38.2)	16 (20.5)	0.007
Normal	94 (61.8)	62 (79.5)	

Biochemical parameters in groups:

The mean serum TSH levels among cases (3.56±4.6) was higher than controls (2.46±1.68; p=<0.05). Subclinical hypothyroidism was noted in 11.8% of cases and all were found female and 3.8% of controls, whereas hypothyroidism was detected in 3 (3.8%) controls and 22 (14.5%) cases. If those with serum TSH levels between 5.5 and 10.0 µIU/ml were considered at risk for subclinical hypothyroidism, then a difference between case and control groups (p<0.05) was observed. The mean serum T4 levels between the case (1.65 ± 3.23) and control (1.27± 0.24) groups was not statistically significant (p=0.507) (Table II and III)

Table II: Distribution of the patients according to thyroid profile by groups

Thyroid profile	Groups		p value
	Case (n=152)	Control (n=78)	
TSH			
Normal serum TSH	130 (85.5)	75 (96.2)	0.014
High serum TSH	22 (14.5)	3 (3.8)	
Mean ± SD	3.56± 4.60	2.64 ± 1.68	
Mean Rank	117.45	111.69	0.534
FT4			
Low FT4	7 (4.6)	3 (3.8)	0.999
Normal FT4	145 (95.4)	75 (96.2)	
Mean ± SD	1.65 ± 3.23	1.27 ± 0.24	
Mean Rank	117.59	111.44	0.507

Table III: Distribution of the patients according to subclinical hypothyroidism

Sub clinical hypothyroidism	Groups		p value
	Case (n=152)	Control (n=78)	
Yes	18 (11.8)	3 (3.8)	0.046
No	134 (88.2)	75 (96.2)	

Table IV: Distribution of the patients according to lipid profile by groups

Lipid profile	Groups		p value
	Case (n=152)	Control (n=78)	
Total Cholesterol			
Abnormal (>200)	78 (51.3)	14 (17.9)	<0.001
Normal (<200)	74 (48.7)	64 (82.1)	
Mean ± SD	211.80 ± 36.70	193.77 ± 19.56	<0.001
LDL			
Abnormal (>130)	65 (42.8)	22 (28.2)	0.031
Normal (<130)	87 (57.2)	56 (71.8)	
Mean ± SD	128.89 ± 12.49	124.26 ± 19.12	0.028
HDL			
Abnormal (<40)	98 (64.5)	38 (48.7)	0.017
Normal (>40)	54 (35.5)	40 (51.3)	
Mean ± SD	37.12 ± 5.85	41.40 ± 6.19	<0.05

Table V: Mean ± SD of quantitative variables by groups

Variables	Groups		p value
	Case (n=152)	Control (n=78)	
TSH	3.56± 4.60	2.64 ± 1.68	
Mean Rank	117.45	111.69	0.534
FT4	1.65 ± 3.23	1.27 ± 0.24	
Mean Rank	117.59	111.44	0.507
TC	211.80 ± 36.70	193.77 ±19.56	<0.05
LDL	128.89 ± 12.49	124.26 ± 19.12	0.028
HDL	37.12 ± 5.85	41.40 ± 6.19	<0.05
Fasting blood sugar	7.12 ± 2.97	6.69 ± 2.95	0.302

There are significant differrance in total cholesterol,HDL and LDL levels between two groups (Table IV and Table V).

Thyroid function pattern in case group:

The three groups were compared with respect to sex and serum FT4 with low, normal and high serum TSH. There were 4 persons (2.6%) with low, 126 persons (82.9%) with normal and 22 persons (14.5%) with high serum TSH levels. All low serum TSH level cases were found in female and in cases of high serum TSH 4 were male (18.2%) and 18 were female (81.8%). Total 18 cases (11.8%) were found subclinically hypothyroid and all were found female, 4 cases (2.6%) were clinically hypothyroid and 119 cases (78.2%) with gall stone patients were euthyroid (Table VI).

Table VI: Distribution of the patients according to gender by serum TSH level incases (n= 152)

	TSH			p value
	Low serum TSH	Normal serum TSH	High serum TSH	
Sex				
Male	0 (0.0)	25 (19.8)	4 (18.2)	0.606
Female	4 (100.0)	101 (80.2)	18 (81.8)	
Total	**4 (100.0)**	**126 (100.0)**	**22 (100.0)**	
FT4				
Low FT4	0 (0.0)	3 (2.4)	4 (18.2)	
Normal FT4	2 (50.0)	119 (94.4)	18 (81.8)	
High FT4	2 (50.0)	4 (3.2)	0 (0.0)	
Total	**4 (100.0)**	**126 (100.0)**	**22 (100.0)**	<0.05

Table VII shows that the bivariate correlation of each other. All parameters of lipid profile were significant with each other and fasting blood sugar was significant with total cholesterol and LDL.

Table VII: Correlation matrices of the patients according to thyroid profile, lipid profile and fasting blood sugar of cases (n= 152)

Variables	TSH	FT4	Total cholesterol	LDL	HDL	Fasting blood sugar
TSH	-					
FT4	-0.108	-				
Total cholesterol	0.152	-0.031	-			
LDL	0.026	-0.044	0.565**	-		
HDL	-0.011	-0.007	-0.292**	-0.258**	-	
Fasting blood sugar	-0.046	-0.056	0.185*	0.217**	-0.105	-

Discussion

This single centered observational study was conducted to evaluate the association between the thyroid function status and gall stone formation. During last two decades the etiologies of cholelithiasis have been evaluated more seriously. In addition to classic predisposing factors such as age, gender, obesity and genetics, the associations between gall stones and delayed emptying of the biliary tract due to hypothyroidism have been demonstrated.[10] An association between CBD stones and delayed emptying of the biliary tract in experimental and clinical hypothyroidism had been shown earlier Hossein et al. explained at least partly by the lack of the pro-relaxing effect of T4 on the sphincter of Oddi contractility.[5]

In this study, we investigated the prevalence of previously undiagnosed thyroid function abnormalities in gall stone patients in our population and found a significant number of patients had thyroid dysfunction. The two study groups were comparable for age, BMI, and gender distribution and diabetes. The gall stone patients were diagnosed to have gall stones at USG. Because there was no suspicion of gall stones in the control patients, no imaging techniques except for USG were used to confirm the absence of gall stones. The most sensitive test for detecting early thyroid failure is an increased serum TSH concentration. In the subclinicalform, an increased serum TSH level is accompanied by a normal serum T4 level, and the patient is asymptomatic. In the present study, none of the patients were clinically hypothyroid but biochemically 4 patients in case group.

It was found that in the gall stone patients, SCH was significantly more common compared with the non-gallstone controls (11.8% vs. 3.8%; $P < 0.05$).These findings were similar to that shown by Laukkarinen et al and Hossein et al.[5, 13]

In the study by Laukkarinen et al.[13] 303 patients with CBD stones were compared with 142 healthy controls of similar age and BMI. They had observed Sub Clinical Hypothyroidism (SCH) is more common in the CBD stone patients, compared with non Sub Clinical Hypothyroidism (SCH), (10.2% vs. 2.8%: P =0.026) supporting the hypothesis that hypothyroidism might play a role in the forming of gall stones. Hossein et al. compared 151 CBD stone patients with controls and showed a prevalence of 30.3% in cases compared to 22.5% in the control group. In our study and the study by Hossein et al. revealed more number of patients with SCH even in the control group. This indicates probably there is increased prevalence of SCH in general population. The prevalence of thyroid dysfunction was more frequent in females than males (11.8% vs. 2.6). In the study by Laukkarinen et al.[13] the prevalence of SCH in women with CBD stone patients older than 60 year was 11.4% compared with 1.8% in the controls (P = 0.032). They also suggested that at least this subgroup of patients might need to be screened for current thyroid dysfunction. But in our present study none of the female patients older than 60 years were found to have thyroid dysfunction. This might be due to small sample size and less number of females compared to males in our study. A study of Hossein et al.[5] found that the mean TSH in patients (2.59 ± 4.86mg/dl) was higher than the control group (2.53± 4.13 9mg/dl). In subclinical hypothyroidism, serum TSH levels higher than 5 MU/L were found in 30.6% of cases compared with 22.5% of controls. Hypothyroidism was detected in 10.8% of the control group and in 11.3% of cases. This study is expected that increasing age increases subjects' exposure to risk factors of gall stones or hypothyroidism. In case group, 22 patients out of 152 showed hypothyroidisms characterized by increased serum TSH from normal value in their thyroid profile, with prevalence rate of 14.5%. Total 18 cases (11.8%) were found subclinical hypothyroidism and all were found female (p = <0.001), 4 cases (2.6%) were clinically hypothyroid and 119 cases (78.2%) with gall stone patients were euthyroid. So in the present study, there were more females with subclinical hypothyroidism with gall stone disease which is clinically significant and is almost similar to the study result of Kedar et al.[3]

Hypothyroidism is consistently associated with elevations of total cholesterol, LDL, as well as elevated concentrations of serumtriglycerides and C-reactive protein that improves with T4 treatment. A direct consequence of cholesterol supersaturated bile is reduced motility, depressed contractility, and impaired filling of the gallbladder, giving rise to prolonged stay of bile in the gallbladder. This may contribute to the retention of cholesterol crystals, thereby allowing sufficient time for nucleation and continuous growth into mature gallstones. Most studies have shown that serum HDL levels are not influenced by thyroid status. In our present study, we compared the lipid profile between cases and controls This study evaluated a number of metabolic factors that included HDL, LDL and total cholesterol. The mean total cholesterol levels in cases was much higher than in controls, and was significant (p<0.05). There was a statistically significant difference in total cholesterol, HDL and LDL levels between the two groups (p <0.05). These results were similar to those of Hossein et al.[5] in which the mean cholesterol levels in cases were higher than the control group (p<0.05). Serum hypercholesterolemia in hypothyroidism results in supersaturated bile with cholesterol.

Conclusion

There was an increase in prevalence of hypothyroidism in cholelithiasis in this study. Subclinical hypothyroidism was more common and had a higher prevalence in females than males. Patients more than 40 years of age with cholelithiasis were more likely to have hypothyroidism. TSH should be measured as most are subclinically hypothyroid with special consideration to patients of more than 40 years of age.

Acknowledgement

We are grateful to Professor Dr. Towhidul Alam, Chairman, Department of Surgery, Bangabandhu Sheikh Mujib Medical University, for continues support during this study.

References

1. Farzaneh SA, Zavvareh HT, Gharadaghi J, Sheikhvatan M. Prevalence and characteristics of GB stone disease in an Iranian population: a study on cadavers. Hepatobiliary Pancreat Dis Int. 2007; 6:509-512.

2. Laukkarinen J, Sand J, Autio V, Nordback I. Bile duct stone procedures are more frequent in patients with hypothyroidism large, registry-based, cohort study in Finland. Scand J Gastroenterol. 2010; 45:70-74.

3. Kedar N, Ashok K, Jitendra A. Prevalence of Hypothyroidism in Cholelithiasis Patients in Bikaner, Rajasthan India. Ijmrp. 2017; 65-69.

4. Srinivas S, Babulreddy H, Vivekanand B, Mythili A, Subramanyam V. Prevalence of hypothyroidism in common bile duct stone patients. Thyroid Research and Practice. 2018; 123(108):246.206.

5. Hossein A, Mohammad R K, M Reza S, Golam R H, Najmeh Shamspour, Nafiseh Abdolahi, et al.Thyroid Dysfunction and Choleduocholithiasis. Middle East Journal of Digestive Diseases. 2013; 5(3).

6. Brijendra SR, Sandeep J, Mahendra D, Naveen KP.Prevalence of subclinical hypothyroidism in cases of cholelithiasis. International Surgery Journal Singh BR et al. Int Surg J. 2018; 5(1):34-38.

7. Inkinen J, Sand J, Nordback I. Association between common bile duct stones and treated hypothyroidism. Hepatogastroenterology. 2001; 47:919-921.

8. Andreini JP, Prigge WF, Ma C, Gebhard RL. Vesicles and mixed micelles in hypothyroid rat bile before and after thyroid hormone treatment: evidence for a vesicle transport system for biliary cholesterol secretion. Journal of Lipid Researc. 1994; 35(8):1405-1412.

9. Field FJ, Albright E, Mathur SN. Effect of dietary cholesterol on biliary cholesterol content and bile flow in the hypothyroid rat. Gastroenterology. 1986; 91(2):297-304.

10. Laukkarinen J, Sand J, Saaristo R, Salmi J, Turjanmaa V, Vehkalahti P, et al. Is bile flow reduced in patients with hypothyroidism. 2003; 133:288-293.

11. Kleinero, Rsmesh J , Huleihel M , Cohen Z , Mordechai S . A comartive study of gallstone from children and adult using FTIR spectroscopy and flurorescence microscopy. BMC Gastroenteology. 2002; 2:3-15.

12. Cicala M, Habib FI, Fiocca F, Pallotta N, Corazziari E. Increased sphincter of Oddi basal pressure in patients affected by gall stone disease: a role for biliary stasis and colicky pain. Gut. 2001; 48:414-417.

13. Laukkarinen J, G. Kiudelis, M. Lempinen et al. Increased prevalence of subclinical hypothyroidism in common bile duct stone patients. Journal of Clinical Endocrinology and Metabolism. 2007; 92:(11):4260-4264.