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Study of prevalence of hypothyroidism in biliary stone patients

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ABSTRACT

Biliary lithiasis is one of the most common biliary pathology with a reported prevalence of approximately 6%-12%. The pathogenesis of biliary lithiasis is complex and a multifactorial process involving factors which affect the bile content and bile flow. hypersaturation of bile with cholesterol and biliary stasis have been shown to be crucial factors in the development of biliary stones. Hypothyroidism has a worldwide population prevalence of 4%-5%. It leads to a decrease in liver cholesterol metabolism causing serum hypercholesterolemia with 90% of hypothyroid patients having elevated cholesterol levels; approximately 50% higher than in euthyroid patients. This hypercholesterolemia may result in supersaturation of bile with cholesterol. Cholesterol hypersaturation of bile results in impaired motility decreased contractility and reduced filling of the gallbladder causing a prolonged stay of bile in the gallbladder contributing to retention of cholesterol crystals which may lead to nucleation and continuous growth into mature gallstones. Biliary stasis is also caused by sphincter of Oddi dyskinesia leading to the formation of gallbladder and bile duct stones. Several hormones have been shown to affect spincter of Oddi activity including thyroid hormones. Thyroid hormones have been shown to have a direct pro-relaxing effect on sphincter of Oddi and lack of this effect in hypothyroidism may result in delayed bile flow which may lead to the formation of biliary stones. An increased prevalence of hypothyroidism (13.3%) among biliary stone disease patients was found in our study, with the prevalence rate being comparatively higher in CBD stone patients. Hypercholesterolemia was found in 91.67% of the patients having hypothyroidism.

Keywords— *Biliary stones, Cholelithiasis, Choledocholithiasis, Hypothyroidism, Hypercholesterolemia*

1. INTRODUCTION

Biliary stone disease is the presence of gallstones either in the gallbladder or common bile duct or both. It is a dominant disease burden of the world population, even today, especially in adults. It is a prevalent disease in Asian populations, with a 5% incidence and in Native American population this incidence is as high as 30-70%.[1] Gallstones are formed in approximately 10-12% of adult population in the west.[2-4] The number of new patients of biliary stones diagnosed each year in U.S.A is about 1 million with two-thirds requiring surgical treatment.[5] Choledocholithiasis has a prevalence of about 6-12% in patients having gallbladder stones.[6,7] Cholesterol stones form the major type of bile duct stones which develop in the gallbladder and then travel through the cystic duct to reach the extra-hepatic biliary system. The incidence of choledocholithiasis increases with an increase in age. The incidence of biliary stones is more for women in all age groups.

The association between thyroid disorders, especially hypothyroidism, and biliary stones has been a source of discussion for quite some time. A group of 668 female patients who underwent cholecystectomy for biliary stones were compared with 782 patients of control group retrospectively and it was found that 2.4% of gallstone patients had been treated for hypothyroidism as compared to 0.8% of controls.[8] A prevalence of 8% and 6% for previously diagnosed hypothyroidism in choledocholithiasis and cholelithiasis, respectively, as compared to a prevalence of only 1% in controls was found in some other studies.[9]

Biliary lithiasis has complex and multifactorial pathogenesis involving mechanisms which affect the bile composition and flow of bile. The mechanisms by which hypothyroidism can predispose a patient for the development of biliary stones include the known link between hypothyroidism and dyslipidemia[10,11,12] that can cause a change in bile composition.

Decreased bile flow has been demonstrated in hypothyroid patients in some recent studies.[13] Also, sphincter of Oddi has been shown to express thyroid receptors and thyroxine has a direct pro-relaxing effect on the sphincter of Oddi.[14] Decrease in the flow of bile and dysfunction of the sphincter of Oddi are considered to be key mechanisms that can lead to the formation of biliary stones.

The present study has been undertaken, to assess the prevalence of hypothyroid status, both clinical and subclinical, in patients of biliary stone disease. Should an increased prevalence of hypothyroidism be found, the present study should provide guidelines for diagnostic and therapeutic workup of biliary stone patients.

2. MATERIAL AND METHODS

This study was an observational, cross-sectional study, carried out at the Department of General Surgery at National Institute of Medical Sciences and Research, Jaipur between January 2017 and June 2018.

A total of 180 patients between the ages of 18-60 years of age and having biliary lithiasis (cholelithiasis and choledocholithiasis) were included in the study, however, those patients who had already undergone cholecystectomy were excluded from the study.

After applying the inclusion and exclusion criteria the outdoor and indoor patients of the Department of General Surgery with a present or past history suggestive of biliary lithiasis were further evaluated.

A detailed history including history of presenting illness, past history including any treatment history, family history and personal history was taken. A clinical examination of the patient was done to include a general physical examination and systemic examination.

Detailed interrogation of the patient with signs and symptoms suggestive of biliary lithiasis and hypothyroidism was done and following biochemical and radiological investigations were done:

2.1 Thyroid function tests

Thyroid function tests were done on morning fasting blood samples of the patients to evaluate the patient's serum TSH, T3 and T4 levels. The laboratory reference range for normal TSH levels was 0.35-5.60 mcIU/L, for serum T3 it was 0.60-1.81 ng/ml and for serum T4 it was 4.50-10.90 mcg/dl.

Subclinical hypothyroidism was diagnosed when serum TSH values were >5.60 mcIU/L but <10 mcIU/L. Clinical hypothyroidism was diagnosed when serum TSH values were found to be above 10 mcIU/L.

2.2 Lipid profile

Lipid profile was tested to assess the patient's total serum cholesterol levels.

2.3 Abdominal Ultrasonography/USG Neck

Abdominal ultrasonography evaluation of patients was carried out primarily to confirm the presence or absence of gallstones and/or CBD stones. USG neck was also done for patients with hypothyroidism to detect the presence or absence of a neck swelling.

2.4 MRCP/ERCP

It was performed if there was any evidence of CBD stone on abdominal ultrasonography.

The composition of gallstones was not considered in the study. Informed consent was taken from the patients.

3. OBSERVATIONS AND RESULTS

The study was conducted in the Department of General Surgery, National Institute of Medical Sciences and Research, Jaipur from Jan 2017 to June 2018.

Table 1: Age-wise distribution of biliary stone disease

Age group	Number of cases	Percentage
≤ 30	11	6.11
31 to 40	40	22.22
41 to 50	77	42.78
51 to 60	52	28.89
Total	180	100

A total of 180 cases of biliary stone patients, between the ages 18-60 years, were included in the study. The maximum number of cases were in the age group of 41-50 years followed by the age-group 51-60 years.

There were 77(42.78%) cases in the age group 41-50 years and in the age group 51-60 years, there were 52(28.89%) cases.

Table 2: Sex-wise distribution of biliary stone disease

Sex	Number of cases	Percentage
Female	101	56.11
Male	79	43.89
Total	180	100

Out of the total 180 cases of the biliary stone disease, 101 (56.1%) of the cases were females and 79 (43.9%) of the cases were males.

Table 3: Thyroid status

Thyroid Status	Number of patients	Percentage
Euthyroid	156	86.7
Hypothyroidism	24	13.3
Total	180	100

The patients were evaluated for thyroid function by testing the serum TSH, T3 and T4 levels. Out of the 180 patients, hypothyroidism was found in 24 (13.3%) of the patients.

Table 4: Hypothyroidism status

Hypohyroidism Status	Number of patients	Percentage
Euthyroid	156	86.67
Subclinical Hypothyroidism	16	8.89
Clinical Hypothyroidism	8	4.44
Total	180	100

Out of the 24 patients with hypothyroidism, subclinical hypothyroidism was found in 16(8.89%) of the patients and clinical hypothyroidism was found in 8(4.44%) of the patients.

Table 5: Age-wise distribution of thyroid status

	Euthyroid		Subclinical Hypothyroidism		Clinical Hypothyroidism		Total	
Age group	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
≤30	9	5.77	2	12.5	0	0	11	6.11
31 to 40	33	21.15	4	25	3	37.5	40	22.22
41 to 50	68	43.59	6	37.50	3	37.50	77	42.78
51 to 60	46	29.49	4	25.00	2	25.00	52	28.89
Total	**156**	**100.00**	**16**	**100.00**	**8**	**100.00**	**180**	**100.00**

Out of the 24 patients with hypothyroidism, the 41-50 years age group had the maximum percentage of patients. There were 9 (37.50%) patients in the 41-50 years age group, out of which, 6 patients had subclinical hypothyroidism and 3 patients had clinical hypothyroidism. The 31-40 years age group had 7 (29.17%) patients with hypothyroidism, out of which, 4 patients had subclinical hypothyroidism and 3 patients had clinical hypothyroidism. The 51-60 years age group had 6 patients with hypothyroidism, out of which, 4 patients had subclinical hypothyroidism and 2 patients had clinical hypothyroidism.

Table 6: Sex-wise distribution of thyroid status

Sex	Euthyroid		Hypothyroidism		Total	
	Number	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Female	80	51.28	21	87.50	101	56.11
Male	76	48.72	3	12.50	79	43.89
Total	**156**	**100**	**24**	**100**	**180**	**100**

Table 7: Sex-wise distribution of hypothyroid status

Sex	Subclinical Hypothyroid		Clinical Hypothyroid		Total	
	Number	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Female	14	87.5	7	87.5	21	87.5
Male	2	12.5	1	12.5	3	12.5
Total	**16**	**100.00**	**8**	**100.00**	**24**	**100.00**

Out of the total 24 patients with hypothyroidism, 21(87.50%) patients were females and 3(12.50%) patients were males. Out of the 21 female patients with hypothyroidism, 14 patients had subclinical hypothyroidism while 7 patients had clinical hypothyroidism. Out of the 3 male patients with hypothyroidism, 2 patients had subclinical hypothyroidism while 1 patient had clinical hypothyroidism.

Table 8: Pattern of hypothyroid status in biliary stone patients

	Hypothyroidism	
	Number	**Percentage**
Cholelithiasis	18	12.08
Cholelithiasis + Choledocholithiasis	6	19.3

Table 9: Distribution of clinical and subclinical hypothyroidism in biliary stone patients

	Euthyroid	Subclinical Hypothyroidism	Clinical Hypothyroidism	
Gallstones	**Total=131**	**Total=12**	**Total=6**	**Total=149**
F	63	10	5	78
M	68	2	1	71
Gallstones + CBD stones	**Total=25**	**Total=4**	**Total=2**	**Total=31**
F	17	4	2	23
M	8	0	0	8

Out of the total 149 patients who had only gallbladder stones, 18(12.08%) patients had hypothyroidism, of which 12 patients had subclinical hypothyroidism and 6 patients had clinical hypothyroidism. Of the 12 patients with subclinical hypothyroidism, 10 patients were females and 2 patients were males. Out of the 6 patients with clinical hypothyroidism, 5 patients were females and 1 patient was male.

Out of the total 31 patients who had CBD stones associated with gallbladder stones, 6(19.3%) patients had hypothyroidism, of which 4 patients had subclinical hypothyroidism and 2 patients had clinical hypothyroidism. All 6 patients with hypothyroidism were females.

Table 10: Cholesterol status in biliary stone and hypothyroid patients

	Euthyroid		**Subclinical Hypothyroid**		**Clinical Hypothyroid**		**Total**	
Total serum cholesterol (mg/dl)	**Number**	**%age**	**Number**	**%age**	**Number**	**%age**	**Number**	**%age**
High (>200)	15	9.62	16	100	6	75	37	20.56
Normal(125-200)	141	90.38	0	0	2	25	143	79.44
Grand Total (Biliary stone patients)	**156**	**100.00**	**16**	**100.00**	**8**	**100.00**	**180**	**100.00**

The patients were also evaluated for serum cholesterol levels. Out of 180 biliary stone patients, elevated serum cholesterol levels were found in 37(20.56%) of the patients. Out of the 37 patients with hypercholesterolemia, 22 patients were also found to be hypothyroid, of which 16 had subclinical hypothyroidism and 6 had clinical hypothyroidism. The percentage of hypothyroid patients having associated hypercholesterolemia was 91.67% (22 patients out of 24 hypothyroid patients).

4. DISCUSSION

Biliary stone disease is a dominant disease burden of the world population and it has been observed by various studies that hypothyroidism, which is another common condition, may have an association with it.[8,9,13,15] Hypothyroidism can either be clinical or subclinical. In the present study, we have made an effort to study the association between hypothyroidism and biliary stone disease and establish if there is any link between the formation of gallbladder stone/CBD stone and clinical or subclinical hypothyroidism.

The prevalence of biliary stone disease has been found to be 6%-12% in the adult population in North India.[16,17,18] The incidence of biliary stones increases with age, and is markedly more frequent after the age of 40 years, becoming 4 to 10 times more likely in older individuals.[19,20,21]

In our study, a total of 180 cases of biliary stone patients, between the ages 18-60 years, were included. The maximum number of cases were in the age group of 41-50 years followed by the age-group 51-60 years. There were 77(42.78%) cases in the age group 41-50 years and in the age group 51-60 years, there were 52(28.89%) cases. There were 40(22.22%) cases in the age-group of 31 – 40 years and a minimum number of cases were found in the age group of patients less than 30 years. There were 11(6.11%) cases in the age group of fewer than 30 years.

Sandeep Sachdeva et al. 2011[22], Kedar Nath et al. 2017[23], Volzke H et al. 2005[15], Ahmad MM et al. 2015[24], reported similar age distribution in their studies.

Women are more likely to develop gallstone disease than males, especially during the fertile years.[16,19] In women, the female sex hormones, use of oral contraceptives, parity, and estrogen replacement therapy are established risk factors for cholesterol gallstone formation.[25,26,27] Hepatic biliary secretion and gallbladder function are adversely affected by female sex hormones. The secretion of cholesterol is increased under the influence of estrogens, while, the secretion of bile salts is diminished. Progestins also reduce bile salt secretion and cause impairment of gallbladder emptying which leads to biliary stasis.[19]

In our study, out of the total 180 cases of biliary stones, 101 (56.1%) of the cases were females and 79 (43.9%) of the cases were males. Krishnasamy Narayanasamy DM et al. 2017[28], Jayan Stephen et al. 2016[29], Sandeep Sachdeva et al. 2011[22], Laura M. Stinton, et al. 2012[19], E A Shaffer, et al. 2005[20] have noted the similar pattern of distribution of gallstone disease among genders in their studies.

Of the total 180 cases of biliary stones in our study, 149 (82.8%) cases had only gall bladder stones, whereas, 31 (17.2%) cases had CBD stones associated with gall bladder stones. Out of the 149 cases with only gall bladder stones, 71(47.65%) cases were males and 78(52.35%) cases were females. Out of the 31 cases with CBD stones associated with gallbladder stones, 8(25.81%) cases were males and 23(74.19%) cases were females. The male to female ratio for choledocholithiasis, in our study, was 1:2.875.

In their study, Rai MK et al. 2017[30], reported an 18.4% prevalence of choledocholithiasis associated with cholelithiasis and a male to female ratio of 1:2.83. Yuk Tong Lee et al. 2008[31], reported a similar prevalence for choledocholithiasis.

Hypothyroidism has a worldwide prevalence of 4%-5%.[32,33] It is more commonly prevalent in women than in men and the incidence increases with increasing age.[34,35] Hypothyroidism can either be clinical hypothyroidism or subclinical hypothyroidism. In the U.S. National Health and Nutrition Examination Survey III (NHANES III) prevalence of hypothyroidism was found to be 4.6%, out of which overt/clinical hypothyroidism had a prevalence of 0.3% and subclinical hypothyroidism had a prevalence of 4.3%.[36] Subclinical hypothyroidism is biochemically defined as an increased serum TSH level with a serum free T4 level that lies within the reference range.[37] A serum TSH cut-off level of 10mcIU/L is usually used to distinguish between clinical and subclinical

hypothyroidism.[37] Adults with serum TSH levels of >5mcIU/L but <10mcIU/L are diagnosed as having subclinical hypothyroidism and adults with serum TSH levels above 10mcIU/L are diagnosed as having clinical hypothyroidism.[38]

In our study, the laboratory reference range for serum TSH was 0.35 - 5.60mcIU/ml. Serum TSH levels >5.60mcIU/L but <10mcIU/L were taken as subclinical hypothyroidism and serum TSH levels above 10mcIU/L were taken as clinical hypothyroidism. Out of the 180 patients with the biliary stone disease, hypothyroidism was found in 24 (13.3%) of the patients. Out of the 24 patients with hypothyroid status, subclinical hypothyroidism was found in 16(8.89%) of the patients and clinical hypothyroidism was found in 8(4.44%) of the patients.

These findings were similar to the findings of studies conducted by Singh BR et al. 2018[39], Debabrata S et al. 2017[40], Arora BK et al. 2017[41] and Laukkarinen J et al. 2007.[13]

Out of the 24 patients of biliary stones with concurrent hypothyroidism, the 41-50 years age group had the most percentage of patients. There were 9 (37.50%) patients in the 41-50 years age group, out of which, 6 patients had subclinical hypothyroidism and 3 patients had clinical hypothyroidism. The 31-40 years age group had 7 (29.17%) patients with hypothyroidism, out of which, 4 patients had subclinical hypothyroidism and 3 patients had clinical hypothyroidism. The 51-60 years age group had 6 patients with hypothyroidism, out of which, 4 patients had subclinical hypothyroidism and 2 patients had clinical hypothyroidism.

Similar distribution across age-groups was reported by Singh BR et al. 2018[39], J. Vidhya Priya et al. 2016[42], Ahmad MM et al. 2015[24] and Jayan Stephen et al. 2016[29] in their studies.

Out of the total 24 patients with hypothyroidism, 21(87.50%) patients were females and 3(12.50%) patients were males. Out of the 21 female patients with hypothyroidism, 14 patients had subclinical hypothyroidism while 7 patients had clinical hypothyroidism. Out of the 3 male patients with hypothyroidism, 2 patients had subclinical hypothyroidism while 1 patient had clinical hypothyroidism.

These findings were similar to the findings reported by Singh BR et al. 2018[39], J. Vidhya Priya et al. 2016[42] and Jayan Stephen et al. 2016[29] in their studies.

Out of the total 149 patients who had only gallbladder stones, 18(12.08%) patients had hypothyroidism, of which 12 patients had subclinical hypothyroidism and 6 patients had clinical hypothyroidism. Out of the total 31 patients who had CBD stones associated with gallbladder stones, 6(19.3%) patients had hypothyroidism, of which 4 patients had subclinical hypothyroidism and 2 patients had clinical hypothyroidism.

The higher prevalence of hypothyroidism, both subclinical and clinical, in choledocholithiasis patients than cholelithiasis patients is suggestive of a stronger association of hypothyroidism with CBD stones. Inkinen J et al. 2001[9] and Ahmad MM et al. 2015[24] also reported a similar association of hypothyroidism with CBD stones. Laukkarinen J et al. 2010[43], in their study also concluded diagnosed hypothyroidism to be a significant risk factor for CBD stones.

Hypothyroidism can cause secondary hyperlipidaemia.[44] Hypercholesterolemia that occurs in hypothyroidism is a well-recognized and accepted clinical finding.[45] Reduced clearance of cholesterol from plasma, decrease in conversion of cholesterol to bile acids in the liver and delayed removal of low-density lipoproteins from the plasma are the mechanisms by which hypercholesterolemia can occur in hypothyroidism.[45] In published studies elevated cholesterol levels have been reported in up to 90% of hypothyroid[46]; which are approximately 50% higher than in euthyroid patients.[47] This hypercholesterolemia may cause hypersaturation of bile with cholesterol.[46] Hypersaturated bile can lead to a reduction in motility[10], decrease in contractility[11] and reduced filling[12] of the gallbladder causing stasis of bile in the gallbladder which may contribute to retention of cholesterol crystals leading to nucleation and subsequently the formation of mature gallstones.[8,9,48]

We evaluated the patients for serum cholesterol levels in our study. Out of 180 biliary stone patients, elevated serum cholesterol levels were found in 37(20.56%) of the patients. Out of the 37 patients with hypercholesterolemia, 22 patients were also found to be hypothyroid, of which 16 had subclinical hypothyroidism and 6 had clinical hypothyroidism. The percentage of hypothyroid patients having associated hypercholesterolemia was 91.67% (22 patients out of 24 hypothyroid patients).

These findings are consistent with the findings of Laukkarinen J et al. 2012[46], Jayan Stephen et al. 2016[29] and Diehl et al. 1987[49], who have reported similar findings in their studies.

5. CONCLUSIONS AND RECOMMENDATIONS

- There is an increased prevalence of hypothyroidism (subclinical and clinical), associated with the biliary stone disease. If hypothyroidism (subclinical or clinical) is diagnosed and treated timely, can reduce biliary stone disease patients significantly.
- All the patients of middle age-group (especially females) of biliary stone disease should be evaluated for the possibility of hypothyroidism.
- Hypothyroidism causes hypercholesterolemia, which in turn, is known to be a major factor in the genesis of biliary stones. This vicious circle further proves the correlation between hypothyroidism and biliary lithiasis. Energetic treatment of hypothyroidism, a treatable condition, can normalize serum cholesterol levels and may help to prevent the development of gallstones.

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