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ASSOCIATION BETWEEN CHOLELITHIASIS AND THYROID PROFILE – A TERTIARY HOSPITAL CARE BASED STUDY

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ABSTRACT

Background: Biliary stones are hardened concretions that develop due to supersaturation of bile. The known risk factors for development of biliary stones include genetics, body weight, high fat diet, diabetes, women taking estrogen containing pills and decreased motility of gall bladder. Of late there has been discussion whether hypothyroidism could lead to formation of biliary stones. **Aims and Objectives:** The aim of this study was to find any association between cholelithiasis and thyroid profile in patients undergoing elective cholecystectomy for gall stone disease and to find the difference in the chemical composition of gallstones in these patients. **Material and methods:** This case control study was conducted in the Postgraduate Department of Surgery, Govt. Medical College Srinagar and associated SMHS hospital with a total of 300 patients recruited for this study, 150 patients each in case and control group over a period of two years. Cases were defined as patients diagnosed with gallstone diseases and undergoing cholecystectomies. The control group underwent ultrasonography to exclude any asymptomatic cholelithiasis. Fasting blood samples were taken from all participants for measurements of serum T3, T4, Free T4 and thyroid stimulating hormone (TSH). The gallstones received after cholecystectomy examined grossly and categorized according to their morphology and biochemical analysis. **Results:** In the cholelithiasis group a 4:1 Female to Male ratio was observed. There was a prevalence of 38.6% of hypothyroidism in cholelithiasis patients as compared to 22% in the control group. Subclinical hypothyroidism was seen in 30.0% in cases as compared to 17.3% in controls. Maximum number of cholelithiasis patients with hypothyroidism were females. Stone analysis among the hypothyroid and euthyroid patients showed 93.1% cholesterol stones in hypothyroid patients as compared to 69.6% cholesterol stones in euthyroid patients. **Conclusion:** Hypothyroidism was more common in the gallstone patients compared with controls. Prevalence of hypothyroidism in gallstone patients was more common in females compared to males.

KEYWORDS: Gall Stones, Hypothyroidism, TSH.

INTRODUCTION

Gallstone disease is one of the most prevalent gastrointestinal disease with a substantial burden to health care system. In the US 10% to 15% of the adult population, meaning 20 to 25 million Americans have (or will have) gall-stones.[1,2,3,4] Gallstones are mostly asymptomatic the majority will not develop symptoms: up to 80% will never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis.[5] Hence, most gallstones are clinically "silent" an incidental finding often uncovered during abdominal ultrasound being performed for another reason.[6]

In India the prevalence of gallstones has been reported as 2-29 % and seven times more common in north India.[7]

For decades, there has been a discussion, whether thyroid disorders could cause gallstone disease. Particularly, there are several explanations for a possible relation between hypothyroidism and gallstone disease, these explanations include the known link between thyroid failure and disturbances of lipid metabolism[8] that may consecutively lead to change of composition of the bile.

Recent studies also demonstrated low bile flow in hypothyroid subjects. Furthermore, the sphincter of Oddi expresses thyroid hormone receptors both TR β1 and β2 and thyroxine has a direct prorelaxing effect on the sphincter.[9,10] Both low bile flow and sphincter of Oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation.[11] The usage of thyroxine was even suspected to dissolve gallstones, however, a spontaneous passage of the stone to the duodenum could not be excluded in the case report.[12] In an animal model of rabbits in whom a fatty diet induced gallstone formation, administering thyroxine was associated with a low gallstone weight, but did not dissolve the gallstones.[13]
There is dysmotility of digestive tract in hypothyroidism and biliary secretion of cholesterol is reduced in hypothyroidism, bile may also become supersaturated with cholesterol causing sludge or gall stone disease.[14] In some studies, hypothyroidism has been associated with reduced bilirubin excretion due to decreased activity of UDP glucuronyl transferase.[15,16]

Ninety percent of hypothyroid patients have elevated cholesterol levels, triglyceride levels, or both.[17-21] Treatment of hypothyroid patients with concomitant hyperlipidemia will have beneficial effects on serum cholesterol levels.[20] In hypothyroidism, decreased LDL receptor activity leads to impaired removal of cholesterol from the serum[17,22,23] and reduced regulation of HMG-CoA reductase expression leads to decreased cholesterol synthesis.[24,25] Even though thyroid hormones reduce the synthesis of bile salts in human hepatocytes,[25] a decrease in biliary bile salt concentration in hypothyroidism has been reported.[26]

Serum hypercholesterolemia in hypothyroidism may cause bile to supersaturate in cholesterol. A direct consequence of cholesterol supersaturated bile is reduced motility,[27] Decreased Contractility,[28] and impaired filling of the gallbladder,[29] giving rise to prolonged residence 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.[30]

AIMS AND OBJECTIVES

The aim of this study was:

- To find any association between cholelithiasis and thyroid profile in patients undergoing elective cholecystectomy for gall stone disease.
- To find the difference in the chemical composition of gallstones in these patients.

MATERIAL AND METHODS

The present study entitled "Association Between Cholelithiasis and Thyroid Profile – A Tertiary Care Hospital Based Study" was conducted in the Postgraduate Department of General Surgery Government Medical College, Srinagar in cases undergoing elective cholecystectomies for gall stone disease for a period of 2 years.

All the patients were worked up & assessed according to the following protocol.

1) Detailed history
2) Complete clinical examination
3) Complete blood count, KFT, Na^+/K^+, Blood sugars, LFT
4) Chest radiograph, ECG
5) Trans abdominal USG
6) Thyroid profile (T3,T4,FT4,TSH)
7) Stone analysis.

This study was a hospital based case control study where two groups were formed, patients diagnosed as gall stone disease and subjected to elective cholecystectomies (cases) and patients admitted for other diseases (control). Subsequent evaluation was done with emphasis on thyroid profile and lipid profile.

Inclusion Criteria

Cases

Patients diagnosed with gall stone disease (cholelithiasis) were included and were subjected to elective cholecystectomy in the Department of General Surgery, at SMHS Hospital, Srinagar.

Control

The control group was matched for age and sex and consisted of

- Patients with no history of cholelithiasis, liver diseases such as elevation of serum bilirubin or liver enzymes and admitted for diseases other than those affected by thyroid dysfunction.
- In order to ensure that the control group did not have any asymptomatic gall stones all patients in this group were subjected to abdominal ultrasonography.

Exclusion Criteria

Excluded were patients with a history of

- Previous cholecystectomy
- Thyroidectomy
- Pregnancy
- Oral contraceptives
- PCOD
- Acute cholecystitis
- Liver or renal failure
- Cholangitis
- Sepsis or serious underlying diseases
- Those prescribed medications known to affect the thyroid function test such as phenytoin, carbamazepine, metoclopramide, amiodarone and lithium.

RESULTS

Age Distribution

Majority of the cases were in the 41-50 year age group (28.7%) whereas controls were in the 31-40 year age group (27.3%).

The mean age was 42.75 in cases and 44.97 in controls. P value = 0.398 (Insignificant) mean age was 42.75 in cases and 44.97 in controls.

Age Group	Cases	Controls
<20	5 (3.3%)	1 (0.7%)
21-30	29 (19.3%)	26 (17.3%)
31-40	38 (25.3%)	41 (27.3%)
41-50	43 (28.7%)	39 (26.0%)
51-60	19 (12.7)	16 (10.7%)
61-70	15 (10%)	25 (16.7%)
71-80	1 (0.7%)	2 (1.3%)

P value = 0.398 (Insignificant).

Sex Distribution

Females predominated in the cases group and there was female predominance in the control group also.

Sex	Cases	Controls
Males	30 (20%)	38 (25.3%)
Females	120 (80%)	112(74.7%)

P value = 0.270 (Insignificant).

Region Distribution

Majority of the patients were from rural areas in both cases and controls which might reflect the regional distribution of the population on the whole.

Region	Cases	Controls	Total
Rural	94 (62.7%)	111 (74.0%)	205 (68.3%)
Urban	56 (37.3%)	39 (26.0%)	95 (31.7%)

P value = 0.035 (Significant)

Thyroid Status

A significant number of patients in the cases group (38.7%) were hypothyroid compared to the control group (22%) and the difference was statistically significant. None among our subjects was hyperthyroid.

Thyroid Status	Cases (n=150)	Control (n=150)
Hypothyroid (TSH↑)	58 (38.7%)	33 (22%)
Euthyroid (TSH=Normal)	92 (61.3%)	117 (78%)
Hyperthyroid (TSH↓)	0 (0%)	0(0%)

P value= <0.001 (significant)

Subclinical Hypothyroidism

The total prevalence of subclinical hypothyroidism in our study was observed as 30.0% in cases as compared to 17.3% in controls showing a significant increased prevalence in the cholelithiasis (cases) group.

TFT	Cases	Control
Subclinical Hypothyroidism ↑TSH+Normal FT4	45 (30.0%)	27 (17.3%)
Overt Hypothyroidism	13 (8.6%)	6 (4.7%)
↑TSH+FT4↓		

Age Wise Distribution of Hypothyroidism

The majority of the hypothyroid patients in the cases group (cholelithiasis) were between 41 to 50 years.

Age	Hypothyroid patients
<= 20	0
21 - 30	8
31 - 40	14
41 - 50	18
51 - 60	8
61 - 70	9
71 - 80	1

Age wise distribution of hypothyroidism in controls

The controls showed a bimodal distribution of hypothyroid patients.

Age	Hypothyroid
<= 20	0
21 - 30	7
31 - 40	8
41 - 50	5
51 - 60	5
61 - 70	8
71 - 80	0

Sex distribution of hypothyroidism in cholelithiasis

Sex	Hypothyroid	Euthyroid
Males	12 (20.7%)	18 (19.6%)
Females	46 (79.3%)	74 (80.4%)

The males affected with hypothyroidism was (20.7%) as compared to females (79.3%) which shows higher prevalence among females in our population.

Stone Analysis

Among the cholelithiasis group majority number of patients had cholesterol stones 91.3% and 8.7% of patients had mixed stones.

Type of Stones	Number of cases (N=150)
Cholesterol	118 (78.7%)
Mixed	27 (18.0%)
Pigment	5 (3.3%)

Stone analysis between hypothyroid and euthyroid patients

The percentage of formation of cholesterol stones was higher in the hypothyroid patients (93.1%) as compared to euthyroid patients (69.6%) with a significant result.

Type of stone	Hypothyroid	Euthyroid
Cholesterol	54 (93.1%)	64 (69.6%)
Mixed	4 (6.9%)	23 (25.0%)
Pigment	0 (0%)	5 (5.4%)

P value<0.005(significant).

DISCUSSION

Gallstones are one of the commonest surgical problems encountered with an incidence ranging from 5-30%. The incidence increases with age and in female gender the predisposition to gallstone formation is more with increasing age, parity, dyslipidemia and hypothyroidism etc.

The possible relation between cholelithiasis and hypothyroidism has been an area of interest for researchers all over the world and it needs further research to draw any conclusion and to establish facts.

Age distribution of the patients

In our study the age group of patients in both the study and the control group was 11-90 yrs with majority of patients in both groups 41-50 yrs. The mean age was 42.75 in cases and 44.97 in controls. The age group was similarly distributed in both groups. There was no statistical difference in age group between two groups. **Nakeeb et al**[31] in their study found that the subjects with a history of symptomatic gallstones were significantly older than those subjects with no history of gallstones (58.2±10.1 vs. 50.9±14.0 years, $P<.001$) whereas in our study the average age group was younger. Our finding is consistent with the study of **Evehart et al**[32] who had similar results and has reported that the female to male ratio of gallstone and gallbladder disease approaches 4:1 in younger subjects (<40 years of age). The female to male ratio decreases to 2:1 in older age groups. Both the prevalence and incidence of gallstone diseases increases with age.

Sex Distribution

In our study there was a female predominance with a total of 232 (77.33%) females and 68 (22.67%) males. In the cases there was a distribution of 80% females and 20% males in the cholelithiasis group showing a 4:1 Female to Male ratio. **Schirmer et al**[2] also had similar results in the gender pattern among cholelithiasis patients and has reported that cholelithiasis is more common in females then males, with female to male ratio about 4:1, while the incidence becomes equal in both gender in older age. This may be because of the basic hormonal differences between males and females, together with the differences that might exist due to co-expression of sex hormone receptors in the gallbladder of both sexes.

Regional Distribution

Maximum number of patients who became a part of this study were from rural areas, thus reflecting the pattern of patients attending our hospital. The number of patients from rural areas were 205 (68.3%) and those from urban areas were 95 (31.7%). The reason of this rural urban gap can be attributed to the fact that our hospital is one of the oldest and largest hospital of Jammu & Kashmir state and caters to almost all the referrals from peripheral health service institutions and hospitals and majority of the population living in rural areas.

Thyroid Status

In our study there was a prevalence of 38.7% of hypothyroidism in cases as compared to 22% in the controls, showing an increased prevalence in the cases as compared to the control group. This difference was statistically significant. None of our subjects were hyperthyroid. In our study among the cholelithiasis patients (cases) the prevalence of subclinical hypothyroidism was 30% and that of overt hypothyroidism was 8.6% respectively whereas in controls the prevalence of subclinical hypothyroidism was 17.3% and overt hypothyroidism was 4.7%. **Bashir H et al**[33] in their study found a prevalence of subclinical hypothyroidism as 21.3% and overt hypothyroidism 9.0% with a total percentage of hypothyroid patients 30.6% in Kashmir. The results from our study are almost similar to this study but show an increased prevalence among the cholelithiasis group as compared to controls. **Ajdarkosh et al**[34] had similar results in his study of thyroid status among choledocholithiasis. Subclinical hypothyroidism was noted in 30.6% of cases and 22.5% of controls. Overt hypothyroidism was observed as 11.3% in cases and 10.8% in controls. **Laukkarinen J et al**[35] in their study found a prevalence of hypothyroidism in 10.2% in choledocholithiasis group as compared to 2.8% in the control group and in the same study found a prevalence of 23% subclinical hypothyroidism in females more than 60 years of age. These results were almost similar to our study. **Laukkarinen J et al**[36] in another study concluded that hypothyroidism is common in bile duct stones, thus supporting our findings with cholelithiasis.

Being a hospital based study, the positive cases are expected more, but it gives an idea about the high incidence rates in the society as well. However, for getting a clear picture, an extensive epidemiological study is required. The people, living in goiter endemic zone like Kashmir surrounded by mountains and hills where soil is deficient in iodine mineral, are dependent upon external sources like iodized salts and diet rich in iodine. This is attributed to the fact that food grown in iodine deficient regions can never provide enough iodine to the population.

However the increased prevalence of hypothyroidism (both subclinical and clinical hypothyroidism) in cases as compared to controls clearly demonstrate that hypothyroidism plays a role in gallstone formation.

Gender and age wise distribution of hypothyroidism

In this study, the higher proportion of hypothyroidism in women with cholelithiasis compared to men was mainly due to the earlier symptomatology of gallstone disease in women as well as the higher incidence of thyroid disease in women in general. The majority of the patients having hypothyroidism were in the age group 41-50 years, 79.3% females and 20.7% males. **Laukkarinen J et al**[35] in their study found similar results and concluded that with increasing age there was increased prevalence

of hypothyroidism with maximum number of patients in the age group of around 60 years predominantly females. The findings are consistent with our study. **Bashir H et al**[33] had similar results in their study and observed prevalence of hypothyroidism more in females 81.8% as compared to males 18.2%.

Gall Stone Analysis

Majority of the patients had cholesterol stones 78.7% with prevalence of mixed stones as 18.0% and pigment stones 3.3% respectively. Stone analysis varies in different studies all over the world depending upon dietary pattern, ethnicity, and regional variation. **June S et al**[7] in a study observed the pattern of type of gall stone distribution in USA was 88% cholesterol stones whereas **Whiting J et al**[38] observed a prevalence of 91% cholesterol stones in Australia. Study conducted by **Sarin et al,**[39] **RK Tandon et al**[40] concluded that around eighty percent of gallstones in northern India are cholesterol stones, similar study done in Kashmir by **Hussain A et al**[41] also had results that were similar to our study and showed maximum percentage of cholesterol gall stones in this region.

Stone analysis in hypothyroid patients

In our study among the hypothyroid patients the prevalence of cholesterol stones was 93.1% as compared to 69.6% in euthyroid patients. Thus, showing a positive association between hypothyroidism and cholesterol stones was observed in our study. Similar results were observed by **Hassan H et al**[42] in their study where they observed cholesterol stones more prevalent in high TSH group as compared to mixed and pigment stones, also the serum cholesterol levels were higher in cholesterol type gallstone. However it further needs an elaborate and a larger epidemiological study and research to find out the prevalent gallstone type in hypothyroid patients.

CONCLUSION

A prevalence of 38.6% of hypothyroidism in the cholelithiasis patients with female predominance was observed in our study, thereby indicating that patients diagnosed as cholelithiasis should be screened for concomitant thyroid disorder and it should be a part of their baseline investigation during workup. The thyroid profile should become an indicator of possible gallstone disease and vice versa patients with gallstone disease should be screened for a possible deranged thyroid profile. Stone analysis among the hypothyroid and euthyroid patients showed 93.1% cholesterol stones in hypothyroid patients as compared to 69.6% cholesterol stones in euthyroid patients, thus indicating that cholesterol stone formation is more likely in hypothyroid patients than euthyroid patients due to multiple factors that needs further research and an elaborate study. Stone analysis among the hypothyroid and euthyroid patients showed 93.1% cholesterol stones in hypothyroid patients as compared to 69.6% cholesterol stones in euthyroid patients, thus indicating that cholesterol stone formation is more likely in hypothyroid patients than euthyroid patients due to multiple factors that needs further research and an elaborate study.

The trend of mixed and pigment stones is also being overtaken by cholesterol stones thus showing possible relation to dietary habits sedentary lifestyle, ethnicity and thyroid disorders in this mountainous and northernmost state of India.

Patients of renal stones are most often evaluated for any underlying metabolic disorder but the same is not an established practice in gall stone patients. Thus, our study has laid emphasis on routine checkup of underlying hypothyroidism in patients of gallstones and it should form a part of baseline investigation during the workup of patients with gallstones. As it was a hospital-based study, further epidemiological, diet, environment and socio-economic development related studies are required for better comprehension of the hypothesis.

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