

Thyroid Profile And Biochemical Predictors In Biliary Tract Stones

M M Ahmad, H M Dar, H A Wani, S I Gul, I N Mir, W Hamza

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Abstract

Background :

The prevalence of hypothyroidism is increased in patients of choledocholithiasis . Sr.bilirubin, ALP, ALT, AST are biochemical predictors of CBD stones and can be used effectively to establish a definitive diagnosis.

Aims and Objectives :

To find the prevalence of hypothyroidism in patients of choledocholithiasis and to determine role of Sr.bilirubin, ALP, ALT, AST as biochemical predictors of choledocholithiasis.

Material and Methods :

This study was conducted in Post graduate dept.of surgery,SMHS over a period of 2 years on a total of 100 patients, 50 each in case and control group. A complete history, detailed clinical examination followed by evaluation as per protocol defined in proforma was done.

Results :

There was an increased prevalence of choledocholithiasis with increasing age (max. pts. in age group 51-60) with female predominance in patients diagnosed as choledocholithiasis,thereby implying increasing age and female gender as risk factors for choledocholithiasis. There was a prevalence of 16% of hypothyroidism in patients of choledocholithiasis in comparison to 8% in cholelithiasis group with subclinical hypothyroidism present in maximum no. of patients (75%). Further Sr.bilirubin, ALP, AST, ALT are significantly elevated in patients of choledocholithiasis in comparison to control group.

Conclusion:

Hypothyroidism is more common in the choledocholithiasis patients as compared to cholelithiasis group,with female predominance and with subclinical variant in maximum no. of patients which support the hypothesis that hypothyroidism might play a role in the formation of CBD stones. In addition,Sr.bilirubin, ALP,AST,ALT can be effectively used as predictors of choledocholithiasis.

INTRODUCTION

Choledocholithiasis have been noted in 6-12 % of patients with Cholelithiasis and may be small or large, single or multiple and this incidence increases with age to over 80% in those who are over 90 years old¹ . In relevance to fact that choledocholithiasis can be diagnosed in intraoperative setting or perioperative period² ,accurate preoperative diagnosis of choledocholithiasis is bound to reduce operative

risk and health care cost for want of further procedures. A beforehand diagnosis of choledocholithiasis can help treating team to formulate a plan for further management & treatment. It can help to decide about type of surgical exploration, particularly can define minimal access surgery candidates. The standard preoperative workup for predicting choledocholithiasis includes liver function tests (LFTs) and transabdominal ultrasonography (USG). Combining these

investigations with history and clinical examinations is a part of entire workup for most patients. With deviation in these tests, it may mark the presence of choledocholithiasis. Among the biochemical markers, that are quite useful for detection of CBD stones, Sr. Bilirubin 3,4, ALP 3,4, GGT 4 are nearly ideal predictors of CBD Stones and can effectively be used for screening purpose for selecting and performing advanced diagnostic tests when need is felt. In addition, the serum transaminases ALT, AST 5,6 levels can be elevated profoundly (upto 2000 IU/L), mimicking acute viral hepatitis. With biliary stones, however these levels tend to decline rapidly over several days rather than slowly over several weeks, as occurs in viral syndromes. In this clinical setting sequential follow-up of the pattern of LFT may be helpful diagnostically. However, it is difficult to fetch a diagnosis on clinical evaluation and biochemical tests only. Imaging tests, particularly ultrasonography is the most commonly used screening tool. Other imaging modalities include endo/lap ultrasound, CECT abdomen with focus on hepatobiliary system, MRCP, ERCP, intraoperative cholangiography (IOC) & at times PTC.

The pathogenesis of gall stones & common bile duct stones is a complex process involving multiple factors affecting cholesterol metabolism, bile contents & bile kinetics. Sandblom⁷ first demonstrated the hormonal action of CCK on the sphincter of oddi, since then it has been studied that many other hormones influence the SOD activity and biliary kinetics, prominent among which is estrogen and thyroid hormones.

Choledocholithiasis patients on medical evaluation have been found to have hypothyroidism. Hypothyroidism is a common endocrine disorder, the incidence being about 350/1000000 mostly in women⁸. The hypothyroidism can be either a subclinical variant or overt hypothyroidism. Subclinical hypothyroidism is diagnosed when T3, T4 hormones are within normal range but serum TSH levels are mildly elevated⁹. It is a common problem in the population with an estimated prevalence of 3%-8% in the population with no background of thyroid disorders.^{10,11}.

In clinical practice, it has been found on evaluation that there are several ways to explain a possible relation between hypothyroidism and cholelithiasis & choledocholithiasis, these explanations can be summed up as:

1. Known link between thyroid failure and disturbances of lipid metabolism that may consequently lead to a change of composition of bile^{12,13,14}.

2. Low bile flow to duodenum in the hypothyroid state¹⁵.
3. Sphincter of oddi express thyroid hormone receptors and thyroxine has a direct pro-relaxing effect on the sphincter of oddi¹⁶.
4. Thyroxine usage in certain cases has been suspected to dissolve Gall stones & CBD stones¹⁷.
5. There is dysmotility of digestive tract in hypothyroidism¹⁸.
6. Bile becomes supersaturated in hypothyroid state secondary to decreased biliary secretion of cholesterol leading to sludge balls and gallstones.
7. In some studies, hypothyroidism has been associated with reduced bilirubin excretion due to decreased activity of UDP glucuronyl transferase^{19,20}.

MATERIALS AND METHODS

The Present study was conducted in the Department of Surgery at SMHS Hospital over a period of 2 years.. This study was performed on 50 documented cases of choledocholithiasis and 50 documented cases of cholelithiasis attending the outpatient department as well as the emergency department of surgery, SMHS hospital, Srinagar.

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

1. Detailed history.
2. Complete clinical examination.
3. Complete Blood Count
4. KFT
5. LFT
6. Hepatitis Serology
7. TFT
8. Sr. Amylase
9. Coagulation profile
10. Routine Urine Examination.
11. Chest Radiograph.
12. ECG
13. Transabdominal USG
14. MRCP
15. ERCP – If needed

The patients were grouped into two groups, patients diagnosed as choledocholithiasis (cases) and patients diagnosed as cholelithiasis (controls). Subsequent evaluation of patients was done with emphasis on thyroid profile and LFT.

Patients suspected of having choledocholithiasis by dilated CBD and elevated biochemical markers (Sr. bilirubin, Sr. ALP, Sr. ALT, Sr. AST), were subjected to further imaging by MRCP and managed by ERCP/ Surgery as indicated.

Patients with a serum level TSH of 0.5 - 4.7 m IU/L was considered as normal. Serum level TSH of 4.7 - 10 m IU/L

with normal T3, T4 level is considered as subclinical hypothyroidism. Levels of TSH > 10 m IU/L is considered as clinical hypothyroidism

RESULTS

Majority of the cases and controls were in the 51-60 year age group. The mean age of cases was 57.89 in cases and 52.64 in controls. Females predominated in the Gallstone group and there were equal number of males and females in the Choledocholithiasis group.

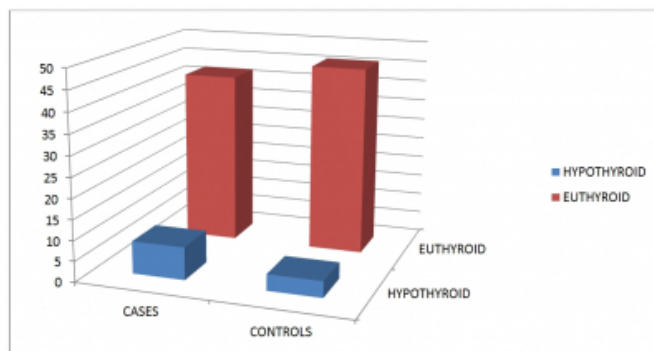
A significant number of patients in the choledocholithiasis group compared to the gallstone group were hypothyroid and the difference was statistically significant.

Table 1

THYROID STATUS	CASES	CONTROLS
HYPOTHYROID	8 (16%)	4 (8%)
EUTHYROID	42 (84%)	46 (92%)

P value = <0.001(significant)

Graph 1



Majority of the patients in the hypothyroid group were having subclinical hypothyroidism with females predominating.

Table 2

SEX	SUBCLINICAL	CLINICAL
MALE	1	0
FEMALE	5	2
TOTAL	6	2

Hypothyroid patients were in the age group of 41 to 70 years with majority being in the age group of 51 to 60 years.

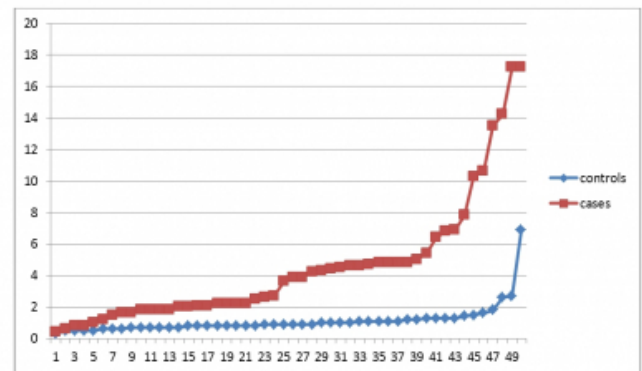
Majority of cases had hyperbilirubinemia with a mean bilirubin of 4.49, compared to control group which had a mean bilirubin of 0.97.

Table 3

SERUM BILIRUBIN	CASES	CONTROLS
< =1.5	7 (14%)	46 (92%)
>1.5	43 (86%)	4 (8%)

P value = <0.001(significant)

Graph 2



In majority of cases of choledocholithiasis, the Serum alkaline phosphatase was markedly raised as compared to controls.

Table 4

Serum ALP	Cases	Controls
< =150	3 (6%)	38 (76%)
> 150	47 (94%)	12 (24%)

P value = <0.001(significant)

AST was marginally raised in cases as compared to controls and the results were statistically significant.

Table 5

AST LEVELS	CASES	CONTROLS
< 45	14 (28%)	37 (74%)
>45	36 (72%)	13 (26%)

P value = <0.001(significant)

ALT levels were marginally raised in cases as compared to controls which was statistically significant.

Table 6

ALT LEVELS	CASES	CONTROLS
< 45	22 (44%)	37 (74%)
>45	28 (56%)	13 (26%)

P value = <0.001(significant)

DISCUSSION

This was a hospital based study conducted on a total of 100 patients who presented to the outpatient departments of the

Postgraduate Department of Surgery, Government Medical College, Srinagar. The patients were grouped into two groups, cases being diagnosed cases of choledocholithiasis (n=50) and controls being diagnosed cases of cholelithiasis (n=50). In our study there was a prevalence of 16% of hypothyroidism in study group as compared to 8% in the controls, showing an increased prevalence of 100% in cases as compared to control group. This was statistically significant difference.

Laukarrien J22 in their study found a prevalence of hypothyroidism in 10.2% in the CBD stone group as compared to a total of 2.8% in the control group. The prevalence of hypothyroidism was 3 to 4 times higher in the control group. There was a statistical significant difference between the prevalence of hypothyroidism in the case and control group.

Laukarrien J23 in another study concluded that hypothyroidism is common in bile duct stone patients.

Inkinen J21 concluded in their study that there is an association between CBD stone patients and treated hypothyroidism. The results of the study revealed that prevalence of primary hypothyroidism was 8% in the study group as compared to 1% in control group with a P value <0.01.

The increased prevalence in both the groups may be assigned to the fact that Kashmir is an endemic region for hypothyroidism but a 100% increase in prevalence of hypothyroidism in the cases group suggests that hypothyroidism has a role in the CBD stone formation.

The majority of our patients who were diagnosed as having choledocholithiasis with hypothyroidism were having subclinical hypothyroidism with 75% of patients (6/8) having subclinical hypothyroidism and only 25% (2/8) having clinical hypothyroidism. There was a female gender predisposition with 87% (7/8) of patients being females in the choledocholithiasis with hypothyroidism group.

There was a prevalence of 20% of hypothyroidism in females diagnosed as choledocholithiasis. Further, on evaluation it was found that around 17% of females with choledocholithiasis had subclinical hypothyroidism.

Laukkari J22 in his study concluded that there was clearly increased prevalence of subclinical hypothyroidism in the CBD stone group with a prevalence of nearly 20%

All patients who were diagnosed as having hypothyroidism were in the age group of 41-70 yrs with the majority being in the age group of 51-60 yrs. Among 8 patients diagnosed as hypothyroid in the study group, 5 were in the age group of 51-60 yrs revealing an increasing prevalence of hypothyroidism with age. These results were in statement to the results of previous studies.

Laukkari J22 in his study found that with increasing age there was increased prevalence of hypothyroidism with maximum no. of patients being in the age group of around 60 yrs with females being predominant.

In our study we found that among cases there was hyperbilirubemia with a Sr. bilirubin > 1.5 mg/dl in about 43 (86%) with a mean bilirubin of 4.49 mg/dl as compared to control group who had a mean bilirubin of 0.97 mg/dl with hyperbilirubemia present in 4 (8%) of patients. This was statistically highly significant with a P value of <0.0001.

Notash AY5 in his study found that Sr. bilirubin was elevated in 56.7% of patients in cases as compared to 6.7% in control group. This was statistically significant with a P value of <0.0001.

Laukkari J22 in his study found that Sr. bilirubin values were significantly higher in the CBD stone patients, compared with control patients with a significant P <0.001.

Barkun3 in his study found that Sr. bilirubin > 1.5 mg/dl was present in about 33% of patients who received a preoperative diagnosis of CBD stones and 56% of patients who were diagnosed as choledocholithiasis with a sensitivity of 74%, specificity of 48%, PPV = 57%, NPV = 66%.

Yang MH4 in his study found that total bilirubin has the highest sensitivity (87.5%), highest probability ratio (3.5), highest accuracy (84.1%) and highest PPV (27.4%) among the predictors of CBD stones. Sgourakis G24 found that d Bil was found in 42.3% of patients with PPV of 48% and NPV of 97% in their study.

Serum ALP levels (>150 IU/L) were present in majority of cases who had sonological or radiological evidence of choledocholithiasis. In the cases 47 patients (94%) of patients had Sr. ALP >150 IU/L while in controls it was significantly elevated in only 12 patients (24%). There was a highly significant statistical association with a P value of <0.0001. These findings were in corroboration with following studies. Notash AY5 in his study found that the Sr. ALP level was more than 100 IU/L in nearly about 98.3%

of patients who were diagnosed as having CBD stones. This was a statistically significant association. Videhult P25 drew a conclusion from his study that Sr. ALP & Sr.bilirubin were the best predictors for CBD stones though not with a significant NPV.

Yang MH4 conducted a study results of which revealed that only GGT, Sr. ALP and total bilirubin were independent predictors of CBD stones. Prat F26 concluded in a study that simple screening of patients at risk for CBD stones can be achieved with three predictive criteria, dilated CBD, Sr. ALP and GGT. In this study, 44.4% of patients had elevated Sr.AL.P as compared with only 17.5% having a normal ALP with a significant association ($P=0.001$) depicting Sr.AL.P as a predictor of CBD stones.

Grand M27 in his study found that among 19 predictive variables for CBD stones, only four were statistically significant and independent among which Sr.AL.P was one important predictive factor. The predictive model sensitivity and Specificity were 92.9% and 99.2% respectively. Barkun S3 revealed in his study that Sr. ALP was raised ($>110\text{IU/L}$) in about 75% of patients preoperatively and about 62% of patients post operatively who had diagnosed CBD stones. On univariate study, the sensitivity of Sr.AL.P was 79%, specificity 35%, PPV=53%, NPV=65%.

Sgourakis G24 in the study concluded that selection criterion such as equal or greater than twice normal of sr.Bilirubin, Sr.AL.P, SGOT and CBD diameter $>10\text{mm}$ on USG can be objectively applied to predict CBD stones with Sr.AL.P $>2\text{N}$ in 51.2% with a PPV =42% and a NPV =95% on univariate analysis.

The presence of elevated Sr.AL.P in statistically significant proportion of cases implies that Sr. ALP can effectively be used as a predictor of choledocholithiasis and hence patients with elevated Sr.AL.P should be properly evaluated to rule out CBD stones.

We found in our study that there was an evidence of increased AST in 36 (72%) of patients when analysed in LFT of CBD stone group as compared to 13(26%) of patients in control group with a significant statistical association ($P < 0.001$). These results are in similarity to following studies. Notash AY5 found that AST level is raised above baseline in 72% of patients of CBD stone group with a P value < 0.00001 which is statistically highly significant. Nathwani RA28 found elevation of serum transaminases as an atypical presentation of

choledocholithiasis, nearly mimicking viral hepatitis.

Elevation of Sr.AST in significant no. of patients can be used as a biochemical predictor of CBD stones. In our study, we found that there was elevation of ALT in 23(56%) of patients among study group in comparison to 13(26%) of patients of control group. This was statistically significant with a P value < 0.001 . Our results were similar to results of previously conducted studies.

Notash AY5 found that AST level is raised above baseline in 56% of patients of CBD stone group with a P value < 0.00001 which is statistically highly significant. Nathwani RA28 found elevation of serum transaminases as an atypical presentation of choledocholithiasis, nearly mimicking viral hepatitis.

CONCLUSION

A prevalence of 16% of hypothyroidism among choledocholithiasis patients over the age of 60 years of age with female predominance was inferred from the study, thereby indicating that patients diagnosed as choledocholithiasis in this age group should be screened for current thyroid dysfunction. Nearly 20% prevalence of subclinical in females in age group of 60yrs in cases suggest that at least this subset of patients should be screened for thyroid dysfunction.

The elevation of Sr.bilirubin, ALP,AST,ALT in choledocholithiasis patients clearly suggests that these biochemical markers can be effectively used as predictors of choledocholithiasis.

To conclude, subclinical hypothyroidism is more common in the choledocholithiasis patients as compared to cholelithiasis group which supports the hypothesis that hypothyroidism might play a role in the formation of CBD stones. In addition, Sr.bilirubin, ALP,AST,ALT can be effectively used as predictors of choledocholithiasis.

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Author Information

Mir Mujtaba Ahmad, MBBS, MS

Senior Resident, Department of General Surgery, GMC
Srinagar, J&K, India
drmirujtaba1@gmail.com

Hanief Mohamed Dar, MBBS, MS

Senior Resident, Department of General Surgery, GMC
Srinagar, J&K, India

Hilal A Wani, MBBS, MS

Senior Resident, Department of General Surgery, GMC
Srinagar, J&K, India

Sheikh Imran Gul, MBBS, MS, FMAS

Consultant surgeon, Department of Health
Srinagar, J&K, India

Irfan Nazir Mir, MBBS

PG Scholar, Department of General Surgery, GMC
Srinagar, J&K, India

Wani Hamza, MBBS, MS

Senior Resident, Department of General Surgery, GMC
Srinagar, J&K, India