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EVALUATION OF THYROID PROFILE IN PATIENTS WITH GALLSTONE DISEASE.

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ABSTRACT

Earlier various studies have been done to study the correlation of thyroid disorder with gallstone disease. Hypothyroidism have been shown to cause gallbladder disease by delayed emptying of biliary tract and by inhibited pro-relaxing effect of thyroxine on sphincter of oddi contractibility.

AIM: To evaluate thyroid profile in gallstone disease patients

PATIENT AND METHOD: A cross-sectional study was done in the Deptt. Of Sugery in PGIMS Rohtak comprising of 200 cases and 50 controls. Cases included the population with gallstone disease in the age group of 15-60 years and control included the healthy family members of the cases without gallstone disease in the age group of 15-60 years. A detailed history, clinical examination and laboratory blood test for T_3, T_4 and TSH were done.

RESULTS: Out 200 cases 161 (80.5%) were females and 39 (19.5%) were males, with 41% were in the age group of 50-60 years. there were 14% hypothyroid, 84.5% euthyroid and 1.5% hyperthyroid in cases compared to 4% hypothyroid and 96% euthyroid in controls. The peak age group of cases with hypothyroidism was in the age group of 15-60 years.

CONCLUSION: It was observed that there was more prevalence of hypothyroidism in female patients with gallstone disease in age group of 15-60 years.

KEYWORDS : Cholelithiasis, Hypothyroid, Thyroxine.

INTRODUCTION

Cholelithiasis is a prevalent abdominal disorder resulting in hospital admission in northern India. In western countries 10-12% of adults develop gallstones.[1-2] The prevalence of common bile duct stones in patients with gallstones varies from 8 to16%.[3]

There are three major types of gallstones: cholesterol, black pigment and brown pigment stones-based on composition and pathogenesis. Cholesterol stone constitute 80% in western countries and pigment stone constitute 80% in Asian countries.

Cholesterol stones-Pure cholesterol are uncommon and accounts for less than 10% of all stones. They usually occur as single large stones with smooth surface. Most other cholesterol stones contain variable amount of bile pigments and calcium, but are always more than 70% cholesterol by weight. These stones are usually multiple, of variable size, and may be hard and faceted or irregular, mulberry shape and soft. Color ranges from whitish yellow and green to black. Most cholesterol stones are radiolucent; less than 10%are radiopaque. Whether pure or of mix nature, the common primary event in the formation of cholesterol stone is super saturation of bile with cholesterol. Super saturation almost always is caused by cholesterol hyper secretion rather than reduced secretion of phospholipids or bile salts.[4]

Pigment stones contain less than 20% cholesterol and are dark because of presence of calcium bilirubinate. Black pigment stones are usually small, brittle, black and sometimes speculated. They are formed by super saturation of calcium bilrubinate, carbonate and phosphate and most often secondary to hemolytic disorder such as hereditary spherocytosis and sickle cell anemia. Like cholesterol stones they are almost always found in gall bladder.[4]

Brown pigment stones are usually less than 1 cm in diameter, brownish-yellow, and soft often mushy. They may form either in gallbladder or in bile ducts, usually secondary to bacterial infection caused by bile stasis. Precipitated calcium bilirubinate and bacterial cell bodies compose the major part of the stone. Brown stones are typically found in biliary tree of Asian populations and are associated with stasis secondary to parasitic infection. In western populations, brown stones occur as primary biliary duct stones in patients with biliary stricture. Subclinical hypothyroidism is a prevalent condition among adult population; however it is frequently overlooked. The previous studies about the prevalence of subclinical hypothyroidism among healthy subjects are few in number. In a recent study from United Kingdom, the prevalence of subclinical hypothyroidism among healthy subject was 2.6%.[5] The prevalence of hypothyroidism (clinical plus subclinical) among women older than 60 yrs may be as high as 20%.[6]

For decades, there has been a discussion, whether thyroid disorders could cause gall stone disease. Thyroid hormones are known to have a number of effects on cholesterol metabolism.[7] When serum cholesterol values rise in hypothyroidism, bile may get supersaturated with cholesterol, leading to gallbladder hypo motility, decreased contractibility and impaired filling, giving rise to prolonged residence of bile in the gallbladder.[8-10] This may contribute to the retention of cholesterol crystals, thereby allowing sufficient time for nucleation and continual growth into mature gallstones.[8] In addition the rate of bile secretion may be decreased,[11] physically impairing clearance of precipitates from the bile ducts and gallbladder. Furthermore, the sphincter of oddi has thyroid hormone receptors and thyroxin has a direct prorelaxing effect on the sphincter. Both low bile flow and sphincter of oddi dysfunction are regarded as important functional mechanism that may promote gall stone formation.[12] A crucial factor in forming of bile duct stones is biliary stasis, which may be caused by sphincter of oddi stenosis, dyskinesia, or bile duct strictures.

The usage of thyroxin was even suspected to dissolve gallstones.[13] In a animal model of rabbits in whom a fatty diet induced gallstone formation, administering thyroxin was associated with a low gallstone weight, but did not dissolve the gallstones.

The prevalence of previously undiagnosed thyroid function abnormality has never been studied in gallstone patients before in Haryana. If an increased prevalence of thyroid disorders will be found, it might have an effect on the diagnostic and therapeutic workup of patients with gallstone. Hence this study intends to evaluate thyroid function test in patients with gallstone disease.

AIMS AND OBJECTIVE

1. To evaluate thyroid profile in patients with gall stone disease.
2. To show the prevalence of previously undiagnosed hypothyroidism in patients with gallstone disease.

MATERIALS AND METHODS

The present study was a prospective study conducted in the

Department of Surgery and Biochemistry, Pt. B. D. Sharma PGIMS, Rohtak. In the study, a detailed history was taken in all the patients suffering from gall stone disease and without gallstone disease. The history included loss of appetite, gaining weight, tiredness, constipation, cold intolerance, menstrual disturbances, bradycardia and presence or absence of goiter. Investigations including T_3, T_4, TSH, lipid profile, LFT, ultrasound of abdomen and neck were done. Blood samples of 3 ml were taken in red cap vacutainers and sent to thyroid lab for evaluation of thyroid profile by chemi-luminisence. The reference range of TSH is 0.45-4.12 m IU/L, FT3 is 2.3-4.2 pg/ml and FT4 is 0.89-1.76 ng/dL. A detailed patients' performas were filled.

The study populations were divided into two groups:

1. Case group with 200 patients with gallstone disease admitted in surgery ward fulfilling the inclusion criteria. Case group patients were divided according to history, clinical examination, sonography of neck and laboratory test (T_3, T_4 and TSH) into following groups:

a. Euthyroid group where clinical and laboratory findings were normal.
b. Subclinical Hypothyroidism included the symptom free patients with TSH concentrations above the upper limit of normal range (more 4.12 m IU/L) and T_4 and / or T_3 decrease below normal limit.
c. Clinical hypothyroidism in which there were symptoms of hypothyroidism with TSH more than 10 m IU /L and with TSH more than 10 m IU/L and T_4 and / or T_3 decrease below normal limit.[16]
d. Clinical hyperthyroidism in which there were symptoms of hyperthyroidism with TSH less than 0.45 m IU/L.
2. Control group consisted of 50 family members of case group with age group of 15-60 years.

INCLUSION CRITERIA

For control group:
Family members of case group in age group of 15 – 60 years. For case group:

1. All patients with Cholelithiasis (presence of gallstones on USG) with age group of 15 - 60 years.
2. All patients of control group in whom ultrasonography showed gallstone disease were added in case group.

EXCLUSION CRITERIA

1. Previous history of thyroid surgery.
2. Patients taking Eltroxin for hypothyroidism
3. Previous case of biliary tract surgery.

ASSESSMENT TOOLS

All patients in the sample were followed by following investigation:
1. USG Abdomen.
2. T3, T4 &TSH.

OBSERVATIONS

This was a prospective study done in the Department of Surgery PGIMS Rohtak from December 2014 to September 2016. The study populations were divided into two groups. Group A consisted of 200 patients with gallstone disease admitted in surgery ward fulfilling the inclusion criteria. Group B consisted of 50 family members of case group in the age group of 15-60 years. In our study there were more females in cases than controls (80.5% vs 52%: p value <0.05). This is because earlier symptomatology of gallstone disease in women as well as higher incidence of thyroid disease in women. Patients who had gallstones 14% were in the age group of 20-29, and 22.5% in the age group of 30-39, and 23% in the age group of 40-49, and 41% in the age group 50-60. The mean of age in case group was 43.773±12.08 and in control group was 40.02±12.95. In our study 10.5% case group were subclinical hypothyroid comparing 4% in control group. Clinical hypothyroid were 3.5% cases against 0% controls. Hyperthyroid were 1.5% cases against 0% controls. P value is >0.05 which is not significant. The mean value of TSH in case group was 3.408±2.83 and in control group was 2.853±1.454. The prevalence of subclinical hypothyroid in the age group of 40-49 years, 30-39 years and 20-29 years were 19%, 24% and 14% respectively in the case group. The p value of the observation is less than 0.05 which is significant. It was seen that the prevalence of subclinical hypothyroid was more in the age group of 50-60 years. In our study, 4 out of 7 clinical hypothyroid cases were in the age group of 50-60 years and one each in 20-29 years, 30-39 years and 40-49 years. There were no subjects as control. This suggested that clinical hypothyroid is more prevalent in gallstone patients in the age group of 50-60 years. There was low prevalence of gallstone in young age group (14-19 years). It was observed that (10.5%) cases were subclinical hypothyroid, out of this 3(1.5%) were males and 18(9%) were females. Male to female ratio of subclinical hypothyroid was 1:6. Moreover 8(44%) out of 18 females were in the age group of 50-60 years. Clinical hypothyroid population was 7(3.5%); out of this (6)3% were female and (1)0.5% male. Moreover 57% of clinical hypothyroid population was in the age group 50-60 years. Total population of hypothyroid was 28(14%), out of this 4(2%) were male and 24(12%) were female; and 46% population were in the age group 50-60 years. It was seen that hypothyroid status increase with age and females were mostly affected. In our study the number of case with low FT_3 are 25 against no controls. All controls have normal FT_3 hormone level. P value <0.05 is significant. The mean of FT_3 in case group was 3.123±1.361 and in control group was 3.158±0.54. The number of cases with low FT_4 was 27 against no controls. All controls have normal FT_4 levels. P value of the observation is .014103 which is significant. This suggested that low FT_4 is involved in the pathogenesis of gallstones. The mean value of FT_4 of case group was 1.274±0.65 and control group was 1.227±0.21.

TABLE-1 THYROID PROFILE IN OUR STUDY

	CASE GROUP (n=200)	CONTROL GROUP (n=50)
Subclinical hypothyroid	21(10.5%)	2(4%)
Clinical hypothyroid	7(3.5%)	0(0%)
Euthyroid	169(84.5%)	48(96%)
Hyperthyroid	3(1.5%)	0(0%)

DISCUSSION

Earlier, an association between gallstone and diagnosed hypothyroidism and delayed emptying of the biliary tract in experimental and clinical hypothyroidism has been shown, explained at least partly by the lack of prorelaxing effect of T_4 on the sphincter of oddi contractility. In this study, we have evaluated the thyroid function test in patients with gall stones diseases and studied the prevalence of undiagnosed hypothyroidism in patients with gallstone disease.

In our study, female prevalence was higher (80.5%) against male (19.5%) population (p value <.05). This is because of early symptomatology of gallstones in females and higher incidence of thyroid disease in women. In a study conducted by Hassan H Yousif in 2008 in AL-Najaf on 150 cases with cholecystectomy, there was a remarkable gender difference with predominance of female gender as it constituted 132(88%) versus 18(12%) males.[14] These results are very similar to our study. In another study conducted by Nazim Hayat et al in 2012 at Faisalabad, out of 200 patients that were included in the study, 166(83%) were females and 34(17%) were male.[15] It has been documented in many studies that being female is the single most important, non modifiable cause of gallstones.

In our study, the population with gallstones was highest in the age group of 50-60. It is expected that increasing age increase subjects to risk factors of gallstones or thyroid dysfunction. Our study had shown a prevalence of 41% for the age group of 50-60 years (p value <.05). In a prospective study conducted by Chen CY et al in July 1998 in 3647 Chinese patients, factors manifesting an increase in risk for the development of gallstone disease were age (p<.05).[16] In another study by Henry Volzke et al in 2005 to evaluate the

independent risk factors for gallstone formations in a region with high cholelithiasis prevalence. The study was conducted with data available of 4202 patients and found advancing age, increased BMI and low HDL levels as independent risk factors for the development of cholelithiasis.[17] In another study conducted by Mirella Fraquelli et al in October 2001 analyzed 330 patients. They observed that gallstones were significantly associated with age ($p<0.001$) being 13%, 36% and 51% in patients aged 44 years and younger, 45 to 59 years and 60 years and older, respectively.[18]

In our study, thyroid profile of cases and controls were done. TSH, FT_3 and FT_4 levels were estimated by taking early morning blood samples. Serum TSH is a hallmark of thyroid dysfunction. The subclinical form of hypothyroidism is characterized by increased serum TSH levels and a lack of clinical symptoms. The mean TSH levels in the present study among the case group were higher than the control group. There were more females with subclinical hypothyroidism with gall stone disease. This can possibly be attributed to the fact that females have usually been more considered to have thyroid dysfunction.

In our study in case group there were 10.5% subclinical hypothyroid, 3.5% hypothyroid, 1.5% hyperthyroid and 84.5% euthyroid; comparing it with control group in which there were 4% subclinical hypothyroid and 96% euthyroid population (p value is >0.05). There were 21(10.5%) cases of subclinical hypothyroid, out of this there were 3(1.5%) male and 18(9%) female, and male to female ratio of subclinical hypothyroid is 1:6. Out of 18 females 8 were in the age group of 50-60 years. It comprised 44% of the female subclinical hypothyroid population and 4% of total population. P value is significant (<0.05). Clinical hypothyroid population was 3.5%; female 3% and male 0.5% which is significant ($p<0.05$). In clinical hypothyroid population 57% were in the age group 50-60 years. Total hypothyroid population was 28(14%). Out of these, males were 4(2%) and females were 24(12%); 46% population was in the age group 50-60 years. This clearly illustrate that hypothyroid status increases with age and females are predominantly affected by it.

A cross sectional study was done in MCH Trivandrum in 2015 to know the prevalence of subclinical hypothyroidism in patients with symptomatic gall stone disease. During which period total of 93 patients with gall stone disease were studied to see the relation between hypothyroidism and gall stones. Out of 92 patients with gallstone 50 (54.3%) were females and 42 (45.7%) were males. Thyroid disorder in form of subclinical hypothyroidism was found in 12 (13%), from this 10 (83.3%) were females and males were 2 (16.7%). From 92 cases with gallstones diseases 7(7.6%) cases complaining from goiter. Peak age was less than 40 years. 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.[19]

A study was conducted by P Sundeshwari et al in 2014 at GRH Madurai on 200 gallstone patients. Among them, 18 patients had subclinical hypothyroidism and 6 patients had clinical hypothyroidism. A total of 12% of gallstone patients were diagnosed to have hypothyroidism showing that there is association of hypothyroidism with gallstone disease.[20]

In a study conducted in August 2016 Aishwin Saravanakumar in Coimbatore (Tamil Nadu), out of 50 patients 34% were male and 66% were female. In the study 66% were euthyroid, 14% were sub clinical hypothyroid, 10% hypothyroid and 10% hyperthyroid. Of the 14% subclinical hypothyroid, 4% were in the age group 30-45, 10% were in the age group of more than 45. Hypothyroidism was more in female patients (80%).[21]

In a study conducted by Mir Mujtaba Ahmad in 2015 at SMHS Srinagar over a period of 2 years on a total of 100 patients, 50 diagnosed as having cholelithiasis and 50 having choledocholithiasis. A complete history, detailed clinical examination followed by evaluation as per protocol was done. There was an increased prevalence of choledocholithiasis with increasing age (maximum patients 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 hypothyroidism in 8% of cholelithiasis group with subclinical hypothyroidism present in maximum number of patients (75%) and clinical in 25% of patients. Abnormal high levels of serum TSH and cholesterol were reported in 12 cases (8%) and in 15 cases (10%) respectively.[22]

A cross sectional study was done in Al-Sader Teaching Hospital in Al-Najaf city between 15th of February 2008 and 1st of November 2009 of 225 cases were taken to show relation between gallstone and hypothyroidism. Out of 225 patients with gallstone 198 (88%) were females and 27 (12%) males. Thyroid disorder in form of hypothyroidism was found in 24 (10.6%), from this percentage 22 (9.7%) were females and from this 18 (8.0%) were subclinical and 4 (1.7%) were clinical hypothyroidism and males were 2 (0.9%) with subclinical cases. Out of 225 cases with gallstones, 22(9.7%) cases complaining from goiter with peak age between 51- 60 years.[23]

A study conducted by Suaad L Ibrahim in 2014 to measure level of TSH in serum blood of (100) patients with gallstones diagnosed by sonographically or current cholecystectomy with regarded to the differences between sex of patients and predominated of gallstone type with age .In this study, there were 10 (0.1%), 38(38%), and 52(52%) patients for low, normal and high levels of TSH respectively. It showed a high proportion of females (53%) compared to the males (47%). Females were demonstrated high prevalence of normal TSH (71.69%) , 13.20% and 15 for both high and low levels TSH respectively. while males demonstrated high prevalence (95.47%) of high levels of TSH and (4.53%) of low levels of TSH.[24]

A study conducted by Rana Ranjit Singh in 2016 demonstrated the percentage of males with gallstone disease diagnosed as hypothyroid, euthyroid and hyperthyroid is 24%, 64% and12% respectively. The percentage of females with gallstones diagnosed hypothyroid, euthyroid and hyperthyroid was 24.4%, 65.85 and 1% respectively.[25] In a study done by Johanna L, Gediminas K (2007), the prevalence of subclinical hypothyroidism was 11.4% in gallstones and none of the patients was clinically hypothyroid.[26]

The results of thyroid profile in our study were comparable to other studies. In our study the number of cases with low FT_4 were 27 against none in controls. All controls had normal FT_4 levels. P value of the observation is .014103 which is significant ($p<.05$). This suggested that low FT_4 is involved in the pathogenesis of gallstones. In our study, the number of case with low FT^3 were 25 against no controls. All controls had normal FT_3 hormone level. P value is 0.0194 which is significant. This indicated that low thyroid hormone level is involved in the pathogenesis of gallstone disease.

In a study Hassan H Zaini et al in 2008 on 225 patients, 24 were of hypothyroid. Out 0f these in laboratory investigation we found that 20 cases recorded with high TSH and low T3, T4 , 3 cases with high TSH and low T4 and 1 case with high TSH and low T3. These results are comparable to our study where out of 200 cases 27 have low FT_4 and 25 have low FT_3.[23]

SUMMARY AND CONCLUSION:

The study was concluded, data were analysed and following conclusions were drawn:-

1. Gallstones are more prevalent in female population than males in ratio of 6:1. In our study 80.5% females are affected with gallstone. Age group of 50-60 years is at risk of developing gallstone disease. 41% of the population in the age group of 50-60 years is affected with gallstones. Elderly females are mostly affected because hormonal imbalance and high prevalence of hypothyroidism in this age group.

2. In our study patients with subclinical hypothyroid group do not presented with typical symptoms of hypothyroidism. This group of patients has raised serum TSH levels with no symptoms of hypothyroidism. Further studies are needed to investigate whether early treatment of subclinical hypothyroidism or overt hypothyroidism could prevent the gallstones. At least a subgroup of gallstone patients older than 50 years should be screened for thyroid dysfunction and offered replacement therapy.

3. In our study 10.5% of gallstone patients are subclinical hypothyroid as against 4% of control. Population with clinical hypothyroid is 3.5% and hyperthyroid is 1.5%. Euthyroid population is 84.5%. Total hypothyroid population (subclinical plus clinical hypothyroid) is 14%. These results are comparable to results of other studies.

4. In our study 42.8% population of subclinical hypothyroid is in the age group 50-60 years. Moreover 57% of population in clinical hypothyroid group exists in this age group. So TSH should be checked in every cholelithiasis patient above 50 years and TSH may be seen as a marker for detecting subclinical hypothyroid and treat it before full blown hypothyroidism ensues.

5. Our recommendation is that every patient with gallstones above 50 years should be screened for thyroid status, serum TSH may be used as marker so that hypothyroid status could be diagnosed at early stage and progression to full blown hypothyroidism is halted. Further studies are needed to establish the role of thyroxine hormone in the treatment of cholelithiasis.

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