

FREQUENCY OF HYPOTHYROIDISM IN PATIENTS WITH CHOLELITHIASIS: EXPERIENCE AT A TEACHING HOSPITAL

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ABSTRACT

Background: Cholelithiasis is one of the most prevalent digestive system disorder requiring hospitalization while thyroid diseases are among the most frequent endocrine disorders worldwide.

Objective: To evaluate thyroid profile in patients with gallstone disease and to study the frequency of hypo and subclinical hypothyroidism in all the cases with gallstone disease.

Methodology: It was a hospital based study carried out in the Department of Surgery and Chemical Pathology department from January 2017 to December 2018. It was a cross sectional study conducted on 200 patients presented with upper abdominal pain in surgical OPD. They were divided into cases (n=100) with gall stones diagnosed on ultrasound and controls (n=100) without gall stones on ultrasonography. Thyroid profile was carried out along with other biochemical tests in both groups and parameters were compared.

Results: Out of 200 patients, 91 (46%) were male while 109 (54%) were females. Among them 33% were 20-35 years of age, 43% were between age group 36-55 while 24% were more than 55 years of age. There were 15% hypothyroid, 76% euthyroid, 9% subclinical hypothyroid in cases compared to 95% euthyroid, no hypothyroid and 5% subclinical hypothyroid in controls. The peak age group of cases with hypothyroid was 36-55 years while >55 years were having subclinical hypothyroid disorder.

Conclusion: Hypothyroidism was more common in adult females with gall stone disease in the age more than 36-60 years.

Keyword: Cholelithiasis, Hypothyroidism, Subclinical Hypothyroidism

INTRODUCTION

Gallstone disease is one of the most prevalent abdominal disorders all over the world requiring hospitalization.¹ Burden of this disease is reported to be 5%-26% among different countries,² 10-15% prevalence is observed in European adults while 3-5% of Asian and Africans populations are suffering from this disorder.³ Ten year cumulative incidence of new gallstones in Pakistan is found to be 4.6%⁴ and in the southern region of Sindh has reported the overall surgical incidence for gallstone as 9.03% affecting 14% of females and 4% male.⁵

Role of thyroid disorders in the causation of gall stones formation is a matter of debate for many years. The effect of thyroid hormones on lipid metabolism is well known.⁶ Hypothyroidism results in elevation of cholesterol levels resulting in super saturation of bile causing the slow motility of gall bladder affecting its contraction and impairing its filling resulting in prolonged stasis of bile in the gallbladder.⁷ Retention of

cholesterol crystal results in availability of sufficient time for nucleation and formation of gallstones.² The decreased rate of bile secretion directly affects the clearance of precipitates from gall bladder and bile ducts. In addition to this, presence of thyroid receptors over the sphincter of Oddi (SOD) causes pro relaxing effect on the sphincter through thyroxine.⁸ Collectively dysfunction of the sphincter and prolonged bile stasis both are considered an important causative mechanical factors in promoting stones formation in gallbladder.⁹

Hypercholesterolemia is associated with hypothyroidism resulting in elevation of total and low density lipoprotein (LDL-C) while on the other hand HDL-C, LDL-C and total cholesterol are observed to be low in patients with hyperthyroidism which promotes the pathway affecting reverse cholesterol transport.¹⁰ Association between cholesterol gallstone diseases in humans and hypothyroidism has been studied documenting dysfunction of sphincter of oddi, reduced bile flow rate, decreased number of hepatic LDL receptors and

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reduced fractional clearance of LDL.^{10,11,12,13} This study was conducted to determine the association of thyroid disorder with gallstone diseases in patients attending tertiary care hospital for treatment.

METHODOLOGY

It was a cross sectional study, conducted from January 2017 to 31st December 2018 in the Department of Surgery and Chemical Pathology at Sheikh Zayed Hospital, Rahim yar khan. A total number of 200 patients with upper abdominal pain, age > 20 years were selected by non probability purposive sampling technique. The study was conducted after the approval of the Institutional Review Board of Sheikh Zayed Medical College, Rahim Yar Khan.

Exclusion criteria included: Pregnancy Previous history of thyroid surgery. Patient on drugs causing hypothyroidism: Amiodarone, Lithium, antidepressants, Phenytoin, Interferon, Imatinib Patient on drugs causing gallstones: Estrogen, Fenofibrate, Gemfibrozil.

All the patients were worked up and assessed according to the following protocol:

detailed history, complete clinical examination, complete blood count, thyroid function tests (FT₃, FT₄, and TSH), Liver function tests Serum lipid profile, Serum amylase (if needed), Transabdominal ultrasonography (TAU) Transabdominal ultrasound was used for the identification and diagnosis of cholelithiasis. Sonographic findings of reflective echogenic foci within the lumen of gall bladder with prominent posterior acoustic shadow and rolling stone sign on patient changing position were noted. Small stones were identified with the help of power Doppler showing twinkle like artifact was used.

The study population was divided into two groups: 1. Case group with 100 patients with gallstone disease admitted in surgery ward fulfilling the inclusion criteria. Case group patients were divided according to history, clinical examination, abdominal ultrasonography and laboratory test (FT₃, FT₄ and TSH) into following sub-groups:

- Euthyroid group: where clinical and laboratory findings were normal.
- Subclinical Hypothyroidism: included the symptom free patients with TSH concentrations above the upper limit of normal range (more 4.12 mIU/L) and T₄ and/or T₃ within normal limits.
- Clinical hypothyroidism: in which there were

symptoms of hypothyroidism with TSH more than 10 m IU /L and FT₄ and / or FT₃ decrease below normal limit.¹⁰

About 3-5 ml of venous blood was collected and centrifuged (within 30 minutes of collection) to separate serum from the cells as soon as the clot was formed. Serum aliquots were stored at 4°C to be run in batches. The samples were allowed to thaw prior to assay, mixed thoroughly. Hemolyzed and lipemic samples were rejected. Two levels (high and low) of controls were run with each batch after successful calibration. Thyroid function test (TFT) FT₃, FT₄, TSH were estimated by electro-chemiluminescence Immunoassay method using analyzer ECLIA e 411 (Roche Diagnostic Germany). Patients with a serum level TSH of 0.5 - 4.9 m IU/L was considered as normal. Serum level TSH of 5 - 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. Data was analyzed by using SPSS 20. Prevalence of undiagnosed hypothyroidism in cases of gallstone disease was assessed and association of gall stones with hypothyroidism and subclinical hypothyroidism was noted.

RESULTS

The study included 200 subjects which were divided into two groups. Cases (n=100) included ultrasonographically diagnosed patients with gall stone disease and this group was compared with age and gender matched patients without any gallstone disease on ultrasound but with complaint of upper abdominal pain. Overall there were 54% females and 46% male in both groups. Among cases 38% were between the age group 20-35 years, 41% were within 36-55 years of age and 21% were more than 55 years of age. Mean age of cases from 18-72 years was 45.73±13.86. Age group of patients in control group was 20-70 years with a mean of 44.78±13.63. In controls, 37% were between 20-35 years of age, 40% were of age 36 to 55 years and 23% were more than 55 years of age.

Thyroid profile of patients in both groups revealed that in cases, 76% were euthyroid, 15% were hypothyroid, 9% were having subclinical hypothyroid while in control group, 95% were euthyroid, no hypothyroid and 5% were with subclinical hypothyroidism, *p* value(<0.005) found to be significant between two groups. TSH, FT₄ and FT₃ values are shown in Table I, whereas, sex distribution is shown in table II

Table I: Comparing variables between cases and control group.

Variables	Cases with cholelithiasis (n=100)	Controls without cholelithiasis (n=100)	P value
Age	45.73±13.86	44.78±13.63	NS
Sex (F/M)	58/42	51/49	NS
TSH(μIU/ml)	7.49±2.51	3.33±1.67	0.05
FT4(ng/dl)	1.09±0.42	1.35±0.22	0.05
FT3(pg/ml)	1.6±0.86	3.80±0.77	0.05
Blood glucose fasting(mg/dl)	98.09±18.60	95.29±22.56	0.94
S/Cholesterol(mg/dl)	183.30±40.10	188.2±43.10	0.60
S/Triglyceride(mg/dl)	169.83±38.01	123.07±44.02	<0.01
LDL-C(mg/dl)	120.44±34.49	113.9±53.73	0.300
HDL-C	36.70±6.69	56.41 ± 3.63	<0.05

Table II: Thyroid status of male and female patients.

Thyroid status	Male		Female	
	Cases	Control	Cases	Control
Euthyroid	35	47	41	48
Hypothyroid	4	0	11	0
Subclinical hypothyroid	3	2	6	3
P-value	0.005			

DISCUSSION

Cholelithiasis is a major cause of morbidity around the globe, affecting 24% population of the developed countries but its prevalence is low in underdeveloped part of the world.¹¹⁻¹⁴ The present study investigated possible associations between serum TSH levels and gallstone disease. In our study, it was found to be more common among females as compare to male gender with ratio of 1.6:1. This finding is consistent with the findings reported by Central Department of Statistics in Saudi Arabia and also of Channa et al documenting 71% females affected with gallstone disease.^{4,12} For the evaluation of thyroid function, serum TSH is a hallmark. But subclinical hypothyroid is diagnosed on the basis of high serum TSH levels with normal FT4 levels in the absence of clinical signs and symptoms of hypothyroidism.¹⁵⁻¹⁸ As it showed in our study that the mean TSH level was high in cases as compare to control group but more subclinical cases were observed in female patients. This finding was also

studied by Laukkarinen et al showing more cases of subclinical hypothyroidism in females with CBD stones, concluding that thyroid dysfunction underlies in the development of CBD stones.¹⁹ The results of another study conducted in Faisalabad in 2012 by Nazim Hayat et al also concluded that 166 (33%) females were diagnosed with gallstones disease out of 200 patients and only 34 (17%) were male.¹³ It is well documented in different studies that being female is a non modifiable single most important factor in the development of gall stone disease. In this study there was no statistical difference between the age group of cases and controls. The study done by Volzke H et al, stated advanced age as independent risk factor for gallstone formation in both genders.¹⁴

In this study, there was no significant difference was observed in the mean cholesterol level and LDL-C b/w the two groups (p=0.60) but it was found to be significant in HDL-C and triglycerides. The patients with hypothyroidism sometimes develop secondary hyperlipidemia as the effect of thyroid hormone on lipid metabolism is multifactorial. These observations are consistent with other studies documenting the thyroid hormones influence over the synthesis, absorption and usage of lipoproteins.^{15,16}

The possible relationship between dyslipidemia and thyroid disorder may lead to the changes in the bile composition as stated by different studies.¹⁷ These studies include the possible role play of different factors including diminished activity of UDP glucuronyl transferase in hypothyroidism,¹⁸

supersaturation of bile with cholesterol producing sludge or gall stones formation,¹⁹ expression of receptors for thyroxine hormone on sphincter of oddi causing its prorelaxing effect directly²⁰ and derangements in lipid metabolism and thyroid failure which may cause changes in the bile composition.²¹ In our study there were 15 cases with low fT₄ and 11 with low fT₃ against none in controls. *P* value is significant (*p*<.05). This suggested that low fT₄ is involved in the pathogenesis of gallstones. The results of thyroid profile in our study were comparable to other studies.²² Moreover 9 subclinical hypothyroid cases were reported in present study. 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.²³

According to a study involving 668 female cases with gallstone disease that underwent cholecystectomy showed 2.4% proportion of treated hypothyroid cases as compared to 0.8% in 782 controls.²⁴ Results of other studies found a proportion of previously diagnosed hypothyroidism of 8% and 6% in patients having common bile duct and gallbladder stones, respectively, compared to a proportion of only 1% in the controls.^{25,26} In our study, 46.8% population of subclinical hypothyroid is in the age group 50-60 years. Moreover 52% of population in clinical hypothyroid group exists in this age group. From this study it is recommended 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.

CONCLUSION

From this study it is concluded that there is gender and age specific relation between cholelithiasis and hypothyroidism which must be further evaluated on larger scale research to explain the thyroid dysfunction with respect to gallstone disease.

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