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Original Research Article

Is hypothyroidism a risk for gall stone disease? a study to assess the association

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ABSTRACT

Background: Gall stones are one of the most common problems affecting the digestive tract requiring hospitalization. The disease frequently occurs in young, otherwise healthy people with a prevalence of 11-36 % on autopsy report. Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. In the present study, we have tried to determine an association between gall stone disease, and previously diagnosed and undiagnosed hypothyroidism in patients presenting to our hospital for treatment. The aim of this study was to determine association between gallstones and hypothyroidism and to study the prevalence of previously undiagnosed hypothyroidism in all patients of gallstones.
Methods: The study was a hospital based cross sectional, observational study conducted on 200 patients with upper abdominal pain attending the Surgery OPD and Emergency over a period of 1 years. Patients were divided into 2 groups: Case group (100 patients) with gall stones on ultrasound and Control group (100 patients) without gall stones on ultrasound. Thyroid profile along with other biochemical investigations was done and both the groups were compared for the parameters.
Results: Both groups were comparable for age and sex of the patients. On considering the thyroid profile of the patients in both the groups we observed that 14% of patients were hypothyroid in case group and 8% of the patients in control group. On comparing the two groups, there was no statistically significant difference in the prevalence of hypothyroidism (p value 0.175) between the two groups. There was a significant difference when serum cholesterol and bilirubin levels were compared between the two groups. 7 patients out of 100 cholelithiasis had Choledocolithiasis too, these patients had significantly raised cholesterol and deranged liver function tests.
Conclusions: No significant relation between gallstones and hypothyroidism was found in this study (p value=0.175) and need further evaluation. Among the hypothyroid patients the incidence of gall stones was highest among 51-60 years of age so we recommend that TSH level should be measured for every patient with gallstone disease in this age range.

Keywords: Choledocolithiasis, Gall stone disease, Hypothyroidism

INTRODUCTION

Gall stones are one of the most common problems affecting the digestive tract requiring hospitalization. The disease frequently occurs in young, otherwise healthy people with a prevalence of 11-36 % on autopsy report.[1]

Most are asymptomatic, but still gallstone disease contributes substantially to health care, costs, and its complications are sometimes life threatening. The prevalence differs not only between countries but also between ethnic groups. Age and gender also influence the prevalence of gallstone disease. The reported prevalence

of gallstones in northern India is 6.12%.[2] A gallstones survey suggested that gallbladder stones occurred 7 times more commonly in north Indians than in south Indians.[3]

Bile stasis, bactibilia, chemical imbalances, pH imbalances, change of bile composition and formation of sludge are among the principle factors thought to lead to formation of gallstones. Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. India too is no exception. 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. In the present study, we have tried to determine an association between gall stone disease, and previously diagnosed and undiagnosed hypothyroidism in patients presenting to our hospital for treatment.

The aim of this study was to determine association between gallstones and hypothyroidism and to study the prevalence of previously undiagnosed hypothyroidism in all patients of gallstones.

METHODS

The study was a hospital based cross sectional, observational study conducted on the patients attending the Surgery OPD and Emergency at a hospital in north India over a period of 1 years. Total of 200 patients with upper abdominal pain were included in the study.

Exclusion criteria

- Pregnancy
- Previous history of thyroid surgery
- Known cases of haematological disorders
- 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
- Kidney function tests
- Liver function tests
- Thyroid function tests (FT3, FT4, TSH)
- Serum cholesterol
- Serum amylase (if needed)
- Coagulation profile
- Routine urine examination
- Transabdominal ultrasonography
- Chest radiograph.
- Electrocardiography (ECG).

Transabdominal ultrasound (TAU) was used for diagnosis of cholelithiasis. Grayscale ultrasound shows a high reflective echogenic focus within gallbladder lumen, normally with prominent posterior acoustic shadow. Gravity dependent movement on change of patient position ("rolling stone" sign). Power Doppler demonstrates the twinkle artefact and is particularly useful for identification of small stones.

On the basis of ultrasound findings patients were grouped into 2 groups.

Cases: Included patients with gallstone disease and

Controls: Included patients without gallstone disease.

Each group consisted of 100 patients. Subsequent evaluation of patients was done with emphasis on thyroid profile.

Measurement of thyroid hormone profile

About 3-5 ml of venous blood was collected and centrifuged to separate serum from the cells as soon as the clot was formed. Serum aliquots were stored at 4^0C to be run in batches. The samples were allowed to thaw prior to assay, mixed thoroughly. Hemolyzed and lipemic samples were rejected. Bilevel i.e. high and low control was run with each batch after standardizing. Thyroid function test (TFT) FT3, FT4, TSH were estimated by electro-chemiluminescence Immunoassay method using fully analyzer ECLIA 2010 (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.

Prevalence of undiagnosed hypothyroidism in cases of gallstone disease was assessed and association of gall stones with hypothyroidism was studied.

RESULTS

The study included 200 patients divided into two groups consisting of 100 patients each. Case group (100 patients) included patients with gall stone disease as compared to control group (100 patients) which included patients with upper abdomen pain without gall stones on ultrasonography. The case group had patients with age ranging from 18-72 years and a mean age of 45.73±13.86. Age group of patients in control group was 18-70 years with a mean of 44.78±13.63. Both the groups were comparable with a p value of 0.625. 59% of the patients were male in the case group as compared to 70% male patients in the control group. There was no significant difference in the two groups as far as sex distribution is concerned with a p value of 0.105. On considering the thyroid profile of the patients in both the groups we observed that 14 out of 100 patients in the case

group had hypothyroidism with TSH > 5m IU/L. Rest 86 patients in the case group were euthyroid with TSH within 0.5-4.9 m IU/L. In the control group 8 patients were hypothyroid and the rest 92 patients were euthyroid. On comparing the two groups, there was no statistically significant difference in the prevalence of hypothyroidism (p value 0.175) between the two groups (Table 1).

Table 1: Thyroid status of patients (case and control).

Thyroid status	Case	Control
Hypothyroid	14	8
Euthyroid	86	92
p-value	0.175 (not significant)	

Table 2: Thyroid status of male and female patients.

	Male		Female	
Thyroid status	**Case**	**Control**	**Case**	**Control**
Hypothyroid	9 (15.25 %)	6 (8.57%)	5 (12.20 %)	2 (6.67%)
Euthyroid	50 (84.75 %)	64 (91.43 %)	36 (87.80 %)	28 (93.33 %)
p-value	0.144 (not significant)		0.181 (not significant)	

Table 3: Comparing variables between cholelithiasis and Choledocolithiasis group.

	Cholelithiasis	Cholelithiasis with Choledocholithiasis	P value
Age	45.06±13.15	54.57±20.52	NS
Sex	57:36 (M:F)	2:5 (M:F)	<0.01
TSH (mu/l)	4.60±4.84	6.54±6.33	NS
FT4 (ng/dl)	2.95±0.66	2.96±0.98	NS
FT3 (ng/dl)	0.35±0.11	0.40±0.08	NS
Blood sugar fasting (mg/dl)	98.09±18.60	95.29±22.56	NS
Serum cholesterol (mg/dl)	150.22±21.17	166.43±31.34	<0.01
Serum bilirubin (mg/dl)	0.49±0.29	5.2±3.29	<0.01
SGOT (IU/L)	26.17±8.30	54.29±17.49	<0.01
SGPT(IU/L)	25.4±6.69	45.71±12.85	<0.01
ALP (IU/L)	139.87±47.79	159.29±23.29	<0.01
Haemoglobin (mg/dl)	11.47±0.99	10.74±1.08	NS

Prevalence of hypothyroidism in male patients of case group was 15.25% (9/59 patients) whereas in control group it was 8.57% (6/70 patients). Female patients of the case group had a prevalence of 12.20% (5/41 patients) for hypothyroidism as compared to 6.67% (2/30 patients) in control group. Neither of the sex in case group had a statistically significant difference when they were compared with their counterpart in the control group (Table 2).

Both the groups were evaluated for serum cholesterol levels. The mean level of serum cholesterol in cholelithiasis group was 151.01±22.64 mg/dl as compare to 144.95±16.99 mg/dl in control group. The difference was statistically significant (p-Value=0.0333). On observing the liver function test of both the groups, the mean level of serum bilirubin was 0.82±1.48 mg/dl in the case group as compared to 0.52±0.19mg/dl in control group which was statistically significant (p-Value <0.01%). The difference in the levels was liver enzymes was statistically in significant.

Out of the total 100 patients of cholelithiasis, 7 patients were diagnosed to have Choledocolithiasis along with cholelithiasis. On comparing the patients of Choledocolithiasis with cholelithiasis, there was a statistically significant difference in serum cholesterol, serum bilirubin and all three liver enzymes (SGOT, SGPT, ALP) (Table 3).

DISCUSSION

It has been a matter of discussion for decades whether the thyroid disorders are responsible for the gall stone disease. Several studies have shown the possible relationship between hypothyroidism and gall stone disease. These studies include the link between thyroid failure and disturbances of lipid metabolism that may consecutively lead to a change of the composition of the bile.[4] There are several hypothesis for a possible relation between hypothyroidism and biliary tract stones, these hypothesis include:

- Link between thyroid failure and disturbances of lipid metabolism that may conservatively lead to a change of composition of bile.[5]
- Low bile flow to duodenum in the hypothyroid state.[6]
- Sphincter of oddi express thyroid hormone receptors and thyroxine has a direct pro relaxing effect on the sphincter of oddi.[7]
- Thyroxine usage in certain cases has been suspected to dissolve gall stones and common bile duct stones.[8]
- There is dysmotility of digestive tract in hypothyroidism.[9]
- Biliary secretion of cholesterol is reduced in hypothyroidism, bile may also become supersaturated with cholesterol causing sludge or gall stone disease.[10]
- In some studies, hypothyroidism has been associated with reduced bilirubin excretion due to decreased actively of UDP glucuronyl transferase.[11]

In a recent series of 668 female patients who had undergone cholecystectomy for gallstone disease, the proportion of treated hypothyroidism was 2.4% compared to 0.8% in the 782 controls.[12] 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. 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 this case report.[5] 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.

The present study was conducted to find the prevalence of hypothyroidism in patients diagnosed as cholelithiasis and was compared with patients without gall stone disease and was aimed to find the role of hypothyroidism in development of gallstones. In the present study, there was a prevalence of 14% of hypothyroidism in case group as compared to 8% in the controls, showing an increased prevalence of hypothyroidism in cases as compared to control group. However, there was no statistically significant difference in prevalence of gallstones with hypothyroidism (p-value = 0.175). In present study, the age group is similarly distributed in both case and control group. There was no statistically significant difference (p-value=0.625) in age group between two groups. Volzke H et al, in their study found that the advanced age was an independent risk factor for cholelithiasis in males as well as females.[6] Laukkarinen J had similar results in his study with median age of 68 years for cases as compared to 65 years.[7] Clearly with increasing age, prevalence of biliary tract stones increases, hence forth increasing age is a risk factor for stone formation. In the present study, in the study group there was a distribution of 59% males as against 41% females while as in control group there was a distribution of 70% males as against 30% females. This gender distribution was however statistically insignificant with a P value of 0.1050. This is in discordance with most of the studies which have shown female predominance to cholelithiasis. Volzke H et al, in a study carried out on 3749 residents aged 20-79 years found the proportion of cholelithiasis among males and females as 14.4% and 25.3%, respectively. This study showed that women were affected nearly twice as often as men.[6] In the present study the male predominance in cases as well as controls may be attributed to the fact that women in our part of the country tend to neglect minor symptoms and present to hospital only after a disease causes marked morbidity.

Results of the present study showed, in males the prevalence of hypothyroidism was 15.25% (n=9) and 8.57% (n=6) in cases and controls, respectively. It had a p-Value of 0.114 making it statistically not significant. In females with gallstones the prevalence of hypothyroidism was 12.20% (n=5) compared to 6.67% (n=2) in control group. This too was statistically not significant (p value=0.181). Volzke H et al, in their study observed that among males, there was an independent relation between high serum TSH and cholelithiasis. Also among males, there was a tendency towards an elevated risk of cholelithiasis in persons with low serum TSH. In the female population, no such relation was identified. They concluded that there was an association between thyroid and gallstone disease with a gender-specific relation between hypothyroidism and cholelithiasis.[6] Laukarrien J, 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 case group. There was a statistical significant difference between the prevalence of hypothyroidism in the case and control group.[7] In the present study there were 7 patients of cholelithiasis who also had CBD stones. TSH levels of patients with Choledocolithiasis and cholelithiasis in the present study were comparable with patients having Choledocolithiasis (p value > 0.05).

Limitations of this study were small sample size, assessment of composition of gall stones may have help to explain the hypothesis of disturbance in lipid metabolism in patients with hypothyroidism and assessment of motility of the biliary tract can be helpful.

CONCLUSION

No significant relation between gallstones and hypothyroidism was found in this study (p-Value=0.175) and need further evaluation with larger sample size in the future. The prevalence of hypothyroidism in this study was slightly more than other studies (14% versus 10.3%) in the world, the increased prevalence may be assigned to the fact that northern India is an endemic region for hypothyroidism. Among the hypothyroid patients the incidence was highest among 51-60 years of age so we recommend that TSH level should be measured for every patient with gallstone disease in this age range.

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