Prevalence of previously undiagnosed hypothyroidism in patients with cholelithiasis in a tertiary care center, North-East India

Debabrata Singha1*, Naresh Manohar Pawar1, Prabhu B. J.2, Nitesh Kumar1, Sankamithra Gopalarathnam1

1Department of General Surgery, 2Department of Radio-diagnosis, Silchar Medical College and Hospital, Silchar, Assam, India

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*Correspondence:
Dr. Debabrata Singha,
E-mail: drsinghadebabrata@gmail.com

ABSTRACT

Background: Earlier, the studies had an increased prevalence of previously diagnosed hypothyroidism in gallstone patient and recent studies also demonstrated low bile flow in hypothyroid subjects or the sphincter of oddi expresses thyroid hormone receptors and thyroxin has a direct prorelaxing effect on the sphincter. Iceberg of hypothyroidism was present in cholelithiasis patients. The objective of this study was to find out the prevalence of previously undiagnosed hypothyroidism in cholelithiasis patients.

Methods: A prospective study was conducted in the 500 consecutive patients with cholelithiasis between 1st October 2014 and 31st March 2016 to find relation between gallstone and hypothyroidism. Patients already diagnosed as hypothyroidism were excluded. In each patients, detailed history and clinical examination was done and sent for ultrasound of neck for goitre detection and laboratory Thyroid hormone assay (S-FT3, S-FT4 and S-TSH).

Results: A total of 2.2%, 5.0% and 6.6% (total 13.8%, 69 of 500) of the cholelithiasis patients were diagnosed to have clinical, subclinical and borderline subclinical hypothyroidism. In women older than 50 year, the prevalence of clinical and subclinical plus borderline-hypothyroidism was 6.8% and 25.6% (11.7%±13.9%) and clinical plus subclinical plus borderline-subclinical hypothyroidism was 32.4% in cholelithiasis patients.

Conclusions: Although a low prevalence of hypothyroidism was found in this study, but it is evident that subclinical and borderline subclinical hypothyroidism were significantly more common, compared with the clinical hypothyroidism and with increasing age there was increase in its prevalence, so we recommend that S-TSH level should be measured for every patient with cholelithiasis older than 50 years.

Keywords: Cholelithiasis, Goitre, Hypothyroidism, Thyroid hormone assay

INTRODUCTION

Gallstones are the most common biliary pathology, which can be divided into three main types: cholesterol, pigment (black, brown) or mixed stones. In the USA and Europe, 80% are cholesterol or mixed stones, where as in Asia, 80% are pigment stones. Cholesterol or mixed stones contain 51 - 99 % cholesterol plus admixture of calcium salts, bile acids, bile pigments and phospholipids.1,2 Gallstones may be single or multiple, large or small. Those containing calcium salts are radio opaque. Single stones are uncommon but usually consist mainly of cholesterol and arise due to a disorder of the physico-chemical equilibrium which normally maintains cholesterol in micelle form in the bile, small amount of cholesterol and traces of iron where detected.2,3 Many studies were done to identify risk factor for biliary lithiasis. In the West, studies have focused on hypersaturation of cholesterol in bile in nucleation process as a critical step in the genesis of bile stone.4 For
decades, there has been a discussion, whether thyroid disorders can cause gallstone disease.

Particularly, there are several explanations for a possible relation between gallstone disease and hypothyroidism; these explanations include the known link between thyroid failure and disturbances of lipid metabolism that may consecutively lead to change of composition of the bile.5 Recent studies also demonstrated low bile flow in hypothyroid subjects. Furthermore, the sphincter of Oddi expresses thyroid hormone receptors and thyroxin has a direct pro-relaxing effect on the sphincter.5,6

Both low bile flow and sphincter of Oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation.6 The usage of thyroxin was even suspected to dissolve gallstones, however, a spontaneous passage of the stone to the duodenum could be excluded in this case report.7 In western countries 10-12% of adults develop gallstones,8,9 The pathogenesis of gallstones is complex process involving factors affecting bile content and bile flow. A crucial factor in the forming of bile duct stones is biliary stasis, which may be caused by sphincter of Oddi stenosis, dyskinesia, or bile duct strictures.10,11

The prevalence of previously undiagnosed thyroid function abnormalities has never been studied in gallstone patients before. If an increased prevalence of thyroid disorders will be found, it might have an effect on the diagnostic and therapeutic work up of patient with gallstone.12 Hypothyroidism is the most common cause of secondary hypercholesterolemia. Patients with hypothyroidism have serum level of cholesterol approximately 50% higher than level in Euthyroid patients and 90% of all hypothyroid patients have elevated cholesterol level.13

METHODS

A prospective study was done in the 500 consecutive cholelithiasis patients between 1st October 2014 and 31st March 2016, detailed history and clinical examination including name, age, sex etc. and symptoms and signs of hypothyroidism including presence or absence of goitre will be taken. Investigations to be done in study include, neck ultrasound and level of S-FT3, S-FT4, and S-TSH.

Patients were divided according to history, clinical examination, ultrasound of the neck and thyroid hormones assay (S-FT3, S-FT4, S-TSH) into 4 groups;

- The symptom-free patients with S-TSH concentrations above the upper limit of the normal range (>6.0 mU/L) and S-FT4 / S-FT3 level below the normal limit (<9.0 pm/L / <2.6 pm/L) were considered as clinically hypothyroid.
- Euthyroid group with clinical and thyroid hormones assay normal (S-TSH (0.2-4.5mU/L), S-FT4 (9–21pmol/L) and S-FT3 (2.6-6.2pmol/L)).

All these groups may present with or without goitre.

Statistical tool used were mean, median, mode, fisher’s exact probability, x² text etc.

RESULTS

In this prospective study, 500 patients with cholelithiasis were randomly selected. 425 (85%) were females and 75 (15%) were males with median age was 43 years (range 24 - 68 years) and 38 years (30 - 63 years) respectively, as shown in Table 1.

Peak age of the patients in this study was between 40 - 50 years followed by 51 - 60 years and 31 - 40 years age groups, as shown in Figure 1.

Thyroid disorder in the form of hypothyroidism was found in 69 (13.8%) patients, all were females. Among them, 25 (5%) were diagnosed as subclinical hypothyroidism, 33 (6.6%) as subclinical borderline and 11 (2.2%) as clinical hypothyroidism. In women older than 50 year prevalence of clinical, subclinical and borderline-subclinical hypothyroidism was 6.8%, 11.7% and 13.9% respectively as shown in Table 2.

![Figure 1: Number of cases of cholelithiasis in relation to age and thyroid function.](image)

Among 69 hypothyroidism patients, in laboratory investigation we found that, 36 patients recorded with high S-TSH and low S-FT3, S-FT4, 24 patients with high S-TSH and low S-FT4 and 9 patients with high S-TSH and low S-FT3 as shown in Table 3.
DISCUSSION

In past decades, the studies have been shown that, there is an association between diagnosed hypothyroidism and delayed emptying of the biliary tract in experimental and clinical hypothyroidism, explained at least partly by the lack of prorelaxing effect of T4 on the sphincter of Oddi contractility. We further investigated to find out the prevalence of previously undiagnosed hypothyroid abnormalities in cholelithiasis patients.

The laboratory hallmark of primary hypothyroidism and the most sensitive test for detecting early thyroid failure is an increased TSH concentration. We found an independent relation of high serum TSH levels with gallstones among females. Similar finding was found by Honore LH probably due to higher number of female patients in the study. But Völzke H et al said there is an independent relation of high serum TSH levels with gallstones among males, predominantly among those who had sonographically detected gallstones.

The majority of patients were in 40-50 years age group in our study, while in study done by Johanna L et al it was in women older than 60 years while in other study by Honore LH, and Inkinen J it was noted that high

From 500 cholelithiasis patients, 14 (2.8%) were found with goitre, 2 (0.4%) (according to the thyroid hormone assay) were euthyroid and 12 (2.4%) had hypothyroidism. Among 486 (97.2%) non-goiter patients 429 (85.8%) were euthyroid and 57 (11.4%) had hypothyroidism as shown in Table 4. From total number of hypothyroidism none was males and 69 were females F/M ratio found is 69:0.

### Table 1: Distribution of patients of cholelithiasis in relation to gender, age and hypothyroidism.

<table>
<thead>
<tr>
<th>Gender</th>
<th>No.</th>
<th>Percentage</th>
<th>Age Mean</th>
<th>Range</th>
<th>Clinical</th>
<th>SC</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>75</td>
<td>15</td>
<td>38 years</td>
<td>30-63 years</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Female</td>
<td>425</td>
<td>85</td>
<td>43 years</td>
<td>24-68 years</td>
<td>11</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>P&gt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fisher’s exact probability= 0.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. The prevalence of clinical, subclinical and subclinical borderline hypothyroidism and euthyroid in relation with cholelithiasis in different age groups and in total.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Clinical hypothyroid</th>
<th>SC hypothyroid</th>
<th>BSC hypothyroid</th>
<th>Total hypothyroid</th>
<th>Euthyroid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>31-40</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>41-50</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>11</td>
<td>184</td>
<td>195</td>
</tr>
<tr>
<td>51-60</td>
<td>16</td>
<td>7</td>
<td>4</td>
<td>33</td>
<td>84</td>
<td>117</td>
</tr>
<tr>
<td>&gt;60</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11 (2.2%)</td>
<td>25 (5.0%)</td>
<td>33 (6.6%)</td>
<td>69 (13.8%)</td>
<td>431 (86.2%)</td>
<td>500 (100%)</td>
</tr>
</tbody>
</table>

$X^2 = 50.6856; p= 0.0001$

### Table 3: The levels of S-FT3, S-FT4 and S-TSH in 69 hypothyroid patients with cholelithiasis.

<table>
<thead>
<tr>
<th>Cholelithiasis with low S-FT3 and S-FT4</th>
<th>No. of patients</th>
<th>High S-TSH</th>
<th>Low S-FT3</th>
<th>Low S-FT4</th>
<th>Low S-FT3 and S-FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis with low S-FT4</td>
<td>24</td>
<td>24</td>
<td>0</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Cholelithiasis with low S-FT3</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>69</td>
<td>69</td>
<td>9</td>
<td>24</td>
<td>36</td>
</tr>
</tbody>
</table>

### Table 4: Thyroid enlargement in relation to Hypothyroidism and euthyroid, in patients with cholelithiasis.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Goitre</th>
<th>Euthyroid (%)</th>
<th>Hypothyroid (%)</th>
<th>Non goitre</th>
<th>Euthyroid (%)</th>
<th>Hypothyroid (%)</th>
<th>Total cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2</td>
<td>12</td>
<td>354</td>
<td>57</td>
<td>425</td>
<td></td>
<td>425</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>75</td>
<td>0</td>
<td>75</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2 (0.4%)</td>
<td>12 (2.4%)</td>
<td>429 (85.8%)</td>
<td>57 (11.4%)</td>
<td>500 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value N.S.≥0.05 S≤0.05

S/N.S: significant / not significant
gallstones prevalence was found in women > 65 years of age. This probably contributed to the sex hormonal imbalance at this age.6,17,19

In study done by Johanna L, the prevalence of subclinical hypothyroidism was 11.4% in gallstones and none of the patients were clinically hypothyroid.18 But in this study the prevalence of previously undiagnosed thyroid disorder in the form of hypothyroidism was found in 13.2% patients. Subclinical hypothyroidism was 5.0%, borderline subclinical hypothyroidism was 6.6% and clinical hypothyroidism was 2.2% in females. There was no hypothyroidism found in males with no clinically significant association between hypothyroidism and gallstones (p-value >0.05).

Volzke H in his study found that, there were (10.3%) patients with high TSH, which is approximately the same as in our study (13.8%) and (88.6%) with normal TSH which is approximately the same as this study (86.2%).18

In present study it was found that in the cholelithiasis patients, subclinical and borderline subclinical hypothyroidism are significantly more common, compared with the clinical hypothyroidism (11.6 vs. 2.2%; P value 0.0001) and the prevalence in the subgroup of women older than 50 year is high.

CONCLUSION

Although a low prevalence of previously undiagnosed hypothyroidism was found in this study, but it was evident that subclinical and borderline subclinical hypothyroidism were significantly more common, compared with the clinical hypothyroidism and with increasing age there was increase in its prevalence, so we recommend that, S-TSH level should be measured for every patient with cholelithiasis older than 50 years.

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REFERENCES


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