Association of cholelithiasis with hypothyroidism

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Abstract
Hypothyroidism causes dyslipidemia and stasis of bile and sphincter of oddi dysfunction causing cholelithiasis and choledocholithiasis. Therefore patients with hypothyroidism should be screened for gall stones which can be managed prior to development of complications. A case control study was done comparing 110 cases and 110 controls were sampled. A significant portion of cases were diagnosed with subclinical hypothyroidism. With an odds ratio of 14.3. Female sex, age greater than 50 years, obesity, dyslipidemia, non-vegetarian diet were also significant risk factors for cholelithiasis. The bile leak and need for drain placement was found to be higher in hypothyroid patients as compared to euthyroid patients undergoing laparoscopic cholecystectomy.

Keywords: hypothyroidism, cholelithiasis, pathophysiology, laparoscopic cholecystectomy, case control study

Introduction
The highest incidence rates of cholelithiasis in the world are 21.5/100 000 in females in Delhi [1]. The disease frequently occurs in young to middle aged, otherwise healthy people with a prevalence of 11-36 % on autopsy report. The prevalence of hypothyroidism in India is 10.95%. [2]

Despite a significant percentage of cases being asymptomatic, gallstone disease adds substantially to health care costs and manpower, and its complications are sometimes life threatening.

According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases [3]. The prevalence differs not only between countries but also between ethnic groups. Age and gender also influence the prevalence of gallstone disease.

The aim of this study to evaluate the association of hypothyroidism and cholelithiasis and complications associated with laparoscopic cholecystectomy

Materials and Methods
A case control study was done in JSS hospital Mysuru. It included analysis of 110 cases and 110 controls

Inclusion criteria
Patients between age 18-72 years of age admitted to the department of general surgery

Exclusion criteria
Pregnancy
Known cases of haematological disorders
Patient on drugs causing hypothyroidism: Amiodarone, Lithium, antidepressants, Phenytoin, Interferon, Imatinib
Patient on drugs causing gallstones: Estrogen, Fenofibrate, Gemfibrozil.
Patients who do not give consent to participate in the study

Primary objective
To determine the association between hypothyroidism and cholelithiasis.
Secondary objectives
- Demographic study
- Anthropometric data
- Post-operative complications of laparoscopic cholecystectomy

Case group included 110 patients ultrasound proven cholelithiasis undergoing laparoscopic cholecystectomy, clinically euthyroid / undiagnosed hypothyroidism
Control group -110 Patients with no ultrasonographic evidence of cholelithiasis, clinically euthyroid/undiagnosed hypothyroidism

Measurement of exposure
Hypothyroidism was defined as >10, subclinical hypothyroidism defined as TSH 5-10, euthyroidism TSH <5.

Study of sex distribution in study
Total number of females in case group was 68 (61.8%) and males was 42 (38.2%).
Total number of females in control group was 39 (35.5%) and males was 42 (38.2%).

Study of BMI Affecting Cholelithiasis
Among the cases, 52 % of the hypothyroid cases were obese and 50 % of euthyroid cases were obese with BMI 25-30
66.7 % of the controls had normal BMI
Among the controls, 8.4 % of hypothyroid cases were and 8.4 % of the euthyroid controls were obese.

Study of sex distribution in study
Total number of females in case group was 68 (61.8%) and males was 42 (38.2%).
Total number of females in control group was 39 (35.5%) and males was 42 (38.2%).Males were statistically higher in the control group P=0.005

Table 1: Descriptive statistics age as a riskfactor for cholelithiasis and hypothyroidism

| Age group in yr | Case Count | Case Column N % | Control Count | Control Column N % |
|-----------------|------------|-----------------|---------------|-------------------|
| <30             | 14         | 12.7%           | 18            | 16.4%             |
| 31-40           | 20         | 18.2%           | 15            | 13.6%             |
| 41-50           | 23         | 20.9%           | 18            | 16.4%             |
| 51-60           | 34         | 30.9%           | 17            | 15.5%             |
| 61-70           | 13         | 11.8%           | 24            | 21.8%             |
| >71             | 6          | 5.5%            | 18            | 16.4%             |
| Total           | 110        | 100.0%          | 110           | 100.0%            |

Study duration: 18 months

Results
This case control study compared 110 patients with cholelithiasis and 110 controls without cholelithiasis.
Details were recorded in performas after obtaining due consent and analysis was performed. P value of less than 0.05 was considered significant

Descriptive statistics

Age distribution of the study
- Mean age in the case group was 48 years and mean age in control group was 51 years with standard deviation of 13 and 18 respectively
- Maximum age distribution was found to be in 51-60 year age group for cases and 61-70 years age group for controls.

Table 2: Sex distribution in the study

| Gender | Case Count | Case Column N % | Control Count | Control Column N % |
|--------|------------|-----------------|---------------|-------------------|
| Female | 68         | 61.8%           | 39            | 35.5%             |
| Male   | 42         | 38.2%           | 71            | 64.5%             |

Table 3: Association of BMI with of cholelithiasis, hypothyroidism

| BMI kg/m2          | Case Thyroid abnormality | Control Thyroid abnormality |
|--------------------|--------------------------|-----------------------------|
|                    | Normal | Hypothyroidism | Normal | Hypothyroidism |
| Underweight (<18.5 kg/m2) | 0 | .0% | 0 | .0% |
| Normal (18.6-23kg/m2) | 7 | 11.7% | 2 | 4.0% |
| overweight (23.1-25 kg.m2) | 7 | 11.7% | 6 | 12.0% |
| Obese(25.1-30 kg/m2) | 30 | 50.0% | 26 | 52.0% |
| Morbid obese (>30 kg/m2) | 16 | 26.7% | 16 | 32.0% |

| p                  | 0.5  | 0.5 |

The collected data will be analyzed by the following statistical methods
- Summary statistics - by mean, standard deviation and proportion.
- Inferential statistics - by Chi square test, Independent T test, Odds Radio with 95% confidence interval.
- Software used: SPSS 21.0
- Study setting and method of collection of data

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Primary Objective: Association of Cholelithiasis and Hypothyroidism

- Mean T3, T4, TSH were 82.12, 6.85, 10.45 among cases and 38.98, 7.89 and 1.31 among controls suggesting significant association of cholelithiasis and hypothyroidism
- Among cases, 54.5 % were euthyroid, 21.8 % were subclinical hypothyroidism and 23.4 % were hypothyroid
- Among controls, 97.3 % were euthyroid, 2.7 % had subclinical hypothyroidism and 0 % had clinical hypothyroidism
- Thus with a p value of < 0.0001 there was significant proportion of cases with hypothyroidism compared to controls

Table 4: Distribution of thyroid disease among cases and controls

| Group                      | Case        | Control     | OR          | p     |
|----------------------------|-------------|-------------|-------------|-------|
|                            | Count       | N %         | Count       | N %   |       |
| Thyroid Normal             | 60          | 54.5%       | 107         | 97.3% | <0.0001 |
| Subclinical hypothyroidism | 24          | 21.8%       | 3           | 2.7%  | 14.3(4.1-49.3) |
| Clinical Hypothyroidism    | 26          | 23.6%       | 0           | 0.0%  |         |
| Thyroid abnormality Hypothyroidism | 60 | 54.5% | 107 | 97.3% | 29.7(8.9-99.4) | <0.0001 |

Fig 1: Distribution of Hypothyroidism

Fig 2: Study of TSH among cases and controls
Study of USG findings in the study
- Among cases 4.5% cases had acute calculous cholecystitis, 64.5% had cholelithiasis, 22.7% had chronic calculous cholecystitis, 5% cases had cholelithiasis with choledocholithiasis, 0.9% cases had choledocholithiasis with chronic calculous cholecystitis, 0.9% cases had mucocele.

| Diagnosis                                      | Group | Case | Count | Column N % | Control | Count | Column N % |
|-----------------------------------------------|-------|------|-------|------------|---------|-------|------------|
| ascites                                       |       |      |       |            |         |       |            |
| Acute calculous cholecystitis                 |       | 7    |       | 4.5%       |         | 0     | .0%        |
| Fatty liver                                   |       | 0    |       | .0%        |         | 4     | 3.6%       |
| Blunt trauma abdomen                           |       | 0    |       | .0%        |         | 1     | .9%        |
| Cholelithiasi                                 |       | 71   |       | 64.5%      |         | 0     | .0%        |
| Cholelithiasi choledocholithias                |       | 5    |       | 4.5%       |         | 0     | .0%        |
| Chronic calculous cholecystitis               |       | 25   |       | 22.7%      |         | 0     | .0%        |
| Chronic calculous cholecystitis with choledocholithias | | 1   |       | .9%       |         | 0     | .0%        |
| Subacute intestinal obstruction               |       | 0    |       | .0%        |         | 1     | .9%        |
| Medical renal disease                         |       | 0    |       | .0%        |         | 1     | .9%        |
| Polycystic ovarian disease                    |       | 0    |       | .0%        |         | 2     | 1.8%       |
| Cystitis                                      |       | 0    |       | .0%        |         | 1     | .9%        |
| Empyema gb                                    |       | 1    |       | .9%        |         | 0     | .0%        |
| Hepatomegaly                                  |       | 0    |       | .0%        |         | 9     | 8.2%       |
| Hernia                                       |       | 0    |       | .0%        |         | 2     | 1.8%       |
| Splenomegaly                                  |       | 0    |       | .0%        |         | 1     | .9%        |
| Mucocele + calculous cholecystitis            |       | 1    |       | .9%        |         | 0     | .0%        |
| Normal study                                  |       | 0    |       | .0%        |         | 69    | 62.7%      |
| hepatosplenomegaly                            |       | 0    |       | .0%        |         | 1     | .9%        |
| Polycystic kidney disease                     |       | 0    |       | .0%        |         | 3     | 2.7%       |
| Uterine fibroid                               |       | 0    |       | .0%        |         | 1     | .9%        |
| Renal cyst                                    |       | 0    |       | .0%        |         | 1     | .9%        |

Study of hospital stay among cases
- 61.8% cases undergoing laparoscopic cholecystectomy had a mean hospital stay of less than 7 days.
- 38.2% cases had a mean hospital day of > 7 days.

| Hospital stay | Count | Column N % |
|---------------|-------|------------|
| <7 days       | 68    | 61.8%      |
| >7 days       | 42    | 38.2%      |
| Total         | 110   | 100.0%     |

Study of drain placement among cases
- 50.9% patients had a tube drain placed in the gall bladder bed.
- 49.1% patients did not require drain placement.
- Bile leak intraoperatively was documented in 53.6% cases.
- There was no bile leak in 46.4% cases.
- Mucocele was observed intraoperatively in 0.9% cases.

- Placement of drain in gall bladder bed was required in 62.5% of hypothyroid patients undergoing laparoscopic cholecystectomy as compared to 37.5% of euthyroid cases.
- The incidence of bile leak was 37.3% in euthyroid cases as compared to 62.7% cases undergoing laparoscopic cholecystectomy.
- The mean hospital stay was not found to differ significantly between cases with hypothyroidism and euthyroidism p value 0.9%

| Drain | Count | Column N % |
|-------|-------|------------|
| No    | 54    | 49.1%      |
| Yes   | 56    | 50.9%      |

| Leak  | Count | Column N % |
|-------|-------|------------|
| No    | 59    | 53.6%      |
| Yes   | 51    | 46.4%      |

| Mucocele | Count | Column N % |
|----------|-------|------------|
| No       | 109   | 99.1%      |
| Yes      | 1     | .9%        |
Study of drain placement among cases

Study of intraoperative bile leak

Table 14: Analysis of drain placement, intraoperative bile leak, number of calculi, hospital in hypothyroid and euthyroid cases undergoing laparoscopic cholecystectomy

| Thyroid   | Normal | Subclinical hypothyroidism | Clinical Hypothyroidism | p   |
|-----------|--------|---------------------------|-------------------------|-----|
|           | Count  | Row N %                   | Count                   | Row N % |     |
| DRAIN     | No     | 39 72.2%                  | 6 11.1%                 | 9 16.7%  | 0.001 |
|           | Yes    | 21 37.5%                  | 18 32.1%                | 17 30.4% | 0.002 |
| Leak      | No     | 41 69.5%                  | 7 11.9%                 | 11 18.6% | 0.3  |
|           | Yes    | 19 37.3%                  | 17 33.3%                | 15 29.4% | 0.3  |
| No calculi| MULTIPLE | 47 52.2%               | 19 21.1%                | 24 26.7% | 0.3  |
|           | SINGLE | 13 65.0%                  | 5 25.0%                 | 2 10.0%  | 0.3  |
| Hospital stay | <7 days | 37 54.4%               | 15 22.1%                | 16 23.5% | 0.9  |
|           | >7 days | 23 54.8%                  | 9 21.4%                 | 10 23.8% | 0.9  |

Study of number of gall bladder calculi on USG
- 81.8 % cases had multiple gall bladder calculi
- 18.2 % cases had solitary calculi on USG
Study of comorbidities among cases and control
- 17.3 % Cases had hypertension, 15.5 % cases were diabetic and 0.9 % cases had ischemic heart disease.
- Among controls 21.8 % had hypertension, 15.5 % had type II diabetes mellitus and 2.7 % had ischaemic heart disease.

Table 9: Study of largest size of gall bladder calculi

| Thyroid abnormality   | Count | Mean   | SD    | p   |
|-----------------------|-------|--------|-------|-----|
| Normal                | 60    | 8.72   | 3.11  | 0.2 |
| Hypothyroidism        | 50    | 7.86   | 2.56  |     |
| Subclinical hypothyroidism | 24   | 7.58   | 2.69  | 0.24|
| Clinical hypothyroidism | 26   | 8.12   | 2.45  |     |

One way ANOVA, independent t test

Study of diet among cases and controls
- 79.1 % cases were non vegetarian and 20.9 % cases were vegetarian.
- 60.4 % controls were non vegetarian and 40 % were vegetarian.

Table 10: Study of comorbidities in cases and controls

| Group | Case | Control | p   |
|-------|------|---------|-----|
| IHD   |      |         |     |
| NO    | 109  | 99.1%   | 107 | 97.3% | 0.3 |
| YES   | 1    | 9%      | 3   | 2.7%  |     |
| HTN   |      |         |     |
| NO    | 91   | 82.7%   | 86  | 78.2% | 0.4 |
| YES   | 19   | 17.3%   | 24  | 21.8% |     |
| DM    |      |         |     |
| NO    | 93   | 84.5%   | 93  | 84.5% | NA  |
| YES   | 17   | 15.5%   | 17  | 15.5% |     |

Study of symptoms of cholelithiasis and hypothyroidism in cases
- The most common symptom of cholelithiasis was biliary colic which was present in 97.3 % cases.
- Vomiting was present in 35.5 % of cases, jaundice was present in 3.6 % cases, fever present in 3.6 % cases.
- 2.7 % patients had symptoms of hypothyroidism and 1.8 % cases had a goitre at presentation.

Table 11: Study of diet

| Diet | Case | Control |       |       |
|------|------|---------|-------|-------|
| NON  | 87   | 79.1%   | 66   | 60.0% |
| VEG  | 23   | 20.9%   | 44   | 40.0% |

Study of prior ERCP/pancreatitis prior to laparoscopic cholecystectomy
- 5.5 % cases underwent ERCP prior to laparoscopic cholecystectomy.
- 8.2 % cases had an episode of acute biliary pancreatitis prior to interval laparoscopic cholecystectomy.

Study of symptoms of cholelithiasis and hypothyroidism in cases
- The most common symptom of cholelithiasis was biliary colic which was present in 97.3 % cases.
- Vomiting was present in 35.5 % of cases, jaundice was present in 3.6 % cases, fever present in 3.6 % cases.
- 2.7 % patients had symptoms of hypothyroidism and 1.8 % cases had a goitre at presentation.

Table 12: Study of presenting symptoms amongst cases

|      | Case | Control |
|------|------|---------|
| Pain abdomen | 107  | 97.3%   |
| Vomiting    | 39   | 35.5%   |
| Fever       | 4    | 3.6%    |
| Jaundice    | 4    | 3.6%    |
| Hypothyroid | 3    | 2.7%    |
| Goitre      | 2    | 1.8%    |

Table 13: ERCP/pancreatitis prior to laparoscopic cholecystectomy

|      | Case | Control |
|------|------|---------|
| ERCP | No   | 104     |
| Yes  | 6    | 5.5%    |
| Pancreatitis | No | 101 |
|       | Yes | 91.8%   |

Discussion
This study tests the association of hypothyroidism with cholelithiasis by analysis of cases and controls. In the case group, female gender was a significant risk factor for gall stones. The age group 51-60 years was the most common age of presentation of gall stones. Obesity (BMI 25-30) was a significant risk factor for gall stones in this study.

Analysis of comorbidities revealed 17.3 % Cases had hypertension, 15.5 % cases were diabetic and 0.9 % cases had ischemic heart disease. Among controls 21.8 % had hypertension, 15.5 % had type II diabetes mellitus and 2.7 % had ischaemic heart disease. Thus comorbidities were not found to affect the formation of gallstones.

87 cases consumed a mixed diet while 23 cases consumed a vegetarian diet. In the control arm 66 patients consumed a mixed diet while 44 cases consumed a vegetarian diet. This observation was statistically significant as consumption of a non vegetarian diet leads to higher lipid content in blood and early onset of fatty liver thus causing supersaturation of bile with lipids which would lead to gall bladder sludge and cholelithiasis.

Mean value of T3, T4, TSH were 82.12, 6.85, 10.45 among cases and 38.98, 7.89 and 1.31 among controls suggesting significant association of cholelithiasis and hypothyroidism.

Among cases, 54.5 % were euthyroid, 21.8 % were subclinical hypothyroidism and 23.4 % were hypothyroid. Among controls, 97.3 % were euthyroid, 2.7 % had subclinical hypothyroidism and 0 % had clinical hypothyroidism. Thus with a p value of < 0.0001 there was significant proportion of cases with hypothyroidism compared to controls. The odds ratio for hypothyroidism 29.7. To conclude, patients with hypothyroidism were 30 times more likely to develop cholelithiasis as compared to the euthyroid population.

Results of a cross sectional study done in Bhagad [4] in 2015 examined 103 cases of cholelithiasis stated 8 out of 103 that is 7.8% had subclinical hypothyroidism.

Analysis of ultrasonographic findings suggested there was no correlation between thyroid profile and number or size of stones. The most common symptom of cholelithiasis was biliary colic which was present in 97.3 % cases. Vomiting was present in 35.5 % of cases, jaundice was present in 3.6 % cases, fever present in 3.6 % cases. 2.7 % patients had symptoms of hypothyroidism and 1.8 % cases had a goitre at presentation.

50.9 % patients had a tube drain placed in the gall bladder bed. 49.1 % patients did not require drain placement. Bile leak intraoperatively was documented in 53.6 % cases. There was no bile leak in 46.4 % cases. Mucocele was observed intraoperatively in 0.9 % cases. Placement of drain in gall bladder bed was required in 62.5% of cases.
hypothyroid patients undergoing laparoscopic cholecystectomy as compared to 37.5% of euthyroid cases. The incidence of bile leak was 37.3% in euthyroid cases as compared to 62.7% cases undergoing laparoscopic cholecystectomy. The mean hospital stay was not found to differ significantly between cases with hypothyroidism and euthyroidism p value 0.9%.

This study concludes that hypothyroidism impacts cholelithiasis with an odds ratio of 29, followed by age, female sex, obesity. The theories that suggest the role of hypothyroidism causing bile stasis and cholelithiasis have been proven. Intraoperative bile leak and need for drain placement was also higher in the hypothyroid group as compared to euthyroid. Thus early detection and treatment of hypothyroidism could prevent cholelithiasis.

Conclusion
The study was aimed at determination of the association between hypothyroidism and cholelithiasis. Results state that subclinical hypothyroid/hypothyroid patient were 29 times more likely to develop cholelithiasis as compared to euthyroid population. Upon comparison with previous studies, this study reaffirms that hypothyroidism is a significant risk factor for cholelithiasis. Other risk factors determined by the study included female gender, age 51-60, non-vegetarian diet, BMI (25-30).

Further prospective studies to determine the role of thyroxine supplementation in subclinical hypothyroid patients and long term follow up to determine formation of gall stones are necessary. Recommendations from this study in the management of hypothyroidism and cholelithiasis include:
- TSH screening for patients admitted with gall stones.
- Thyroxine supplementation for subclinical hypothyroidism to prevent gall stones.
- Obese, female, hypothyroid/subclinical hypothyroid patients, consuming non-vegetarian diets should undergo a routine ultrasonogram to rule out cholelithiasis and plan early laparoscopic cholecystectomy.

3.12 References
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