ABSTRACT Introduction: Hypothyroidism is said to cause biliary stasis and impaired cholesterol metabolism, thereby leading to the formation of gallstones. The incidence of thyroid dysfunction in patients with cholelithiasis has been studied in the past, but with inconclusive results. Hence, in this study, we have tried to assess if there is an association between thyroid profile and cholelithiasis concerning age, gender, BMI and Lipid profile. Settings and Design: This study was a prospective observational study conducted at Mahatma Gandhi Medical College & Research Institute, Pondicherry. Methods and Material: Thyroid profile and Fasting Lipid Profile (FLP) was done for all patients, once diagnosed to have Cholelithiasis by USG Abdomen, attending the General Surgery OPD, above the age of 18. Final results were tabulated, and a correlation of the incidence of thyroid dysfunction with that of cholelithiasis was determined. Results: Out of the 60 patients, 63.3% were females, and 36.7% were males. 63.3% of the patients were found to be euthyroid, 31.7% were found to be hypothyroid, and only 5% were found to be hyperthyroid. Among the hypothyroid patients, 53.7% had subclinical hypothyroidism. Increasing age was significantly negatively associated (p=0.017) with the risk of developing hypothyroidism (reduced risk of 7%). Compared to males, females had 19% reduced risk of developing hypothyroidism, but this was not statistically significant. Conclusions: This study concludes that there was no significant association between thyroid dysfunction and cholelithiasis, but there was a reduced risk of developing hypothyroidism in cholelithiasis patients with increasing age and of the female gender. However, further large group studies will be required to conclude the same.

KEYWORDS Cholelithiasis, Hypothyroidism, Thyroid Profile

Introduction

Cholelithiasis is one of the most frequently encountered diseases in developed Western countries. However, the incidence is gradually increasing in the Asian territory as well. For example, approximately 10-12% of the adult population in India is affected by Gallstone disease [1].

Gallstones are broadly classified into cholesterol stones, pigment stones and mixed stones, according to the components, which are cholesterol, bile pigments and calcium. While cholesterol gallstones are more prevalent in the USA and Europe, pigment stones are more common in Asian countries [2].

Role of thyroid disorders in gallstone disease has been a topic of debate over the past decade. While some studies have proven increased incidence of hypothyroidism in cholelithiasis, some have had contradicting results. Therefore, whether or not thyroid dysfunction leads to the development of gallstones is still questionable.

Thyroid hormones undergo enterohepatic circulation and closely affect cholesterol metabolism in different ways. In hypothyroidism, there is increased cholesterol synthesis and vice
versa in hyperthyroidism [3]. Recent studies have shown a decrease in the bile flow of patients having hypothyroidism. The Sphincter of Oddi also expresses thyroxine receptors, which is considered to relax the sphincter and therefore, its deficiency will lead to increased contraction of the Sphincter of Oddi [4]. Thus, comprehensively both biliary stasis and sphincter of Oddi dysfunction, which is enhanced in hypothyroidism, are important factors leading to the formation of gallstones.

Few studies have shown, on the contrary, that hyperthyroidism can also tend to induce cholesterol gallstones by causing overexpression of hepatic nuclear receptor genes, which are the key factors of cholesterol metabolism.[5]

In this study, we aimed to find out if there is an association between thyroid function and cholelithiasis by assessing levels of T3, T4 and TSH (Thyroid Stimulating Hormone) in patients with cholelithiasis and determined if there is an association between thyroid dysfunction and cholelithiasis concerning age, gender, BMI (Body Mass Index) and lipid profiles. We also assessed the risk of developing hypothyroidism in cholelithiasis patients concerning the above-mentioned variables.

**Subjects and Methods**

This cross-sectional observational study included all consecutive patients diagnosed with Cholelithiasis by USG Abdomen, attending the General Surgery OPD, above the age of 18 years, either symptomatic or asymptomatic, irrespective of undergoing Cholecystectomy or not, between the period of February 2019- July 2020. Those who were not willing to participate in the study, patients who had undergone thyroid surgery and thyroid supplementation, and pregnant women were excluded from the study. A consecutive sampling method was carried out, and the sample size was calculated based on the incidence of cholelithiasis recorded from previous population-based studies. Estimating proportion was done, with an alpha error of 0.05. A minimum of 43 cases were required, and 60 cases were recruited.

After obtaining ethical clearance (IHEC Reg. No. ECR/451/Inst/PO/2013/RR-16), Reference number: 02/2019/39, Approval Date: 26.02.2019, Thyroid profile (T3, T4, TSH) and FLP was done for all patients, once diagnosed to have Cholelithiasis by USG Abdomen. The reference range of TSH is 0.4-4.2 micro IU/ml, FT3 is 2.0-4.4pg/ml and FT4 is 0.93-1.7 ng/dL. FLP would include levels of total cholesterol, Triglycerides, HDL, LDL cholesterol. Patients were divided into 3 groups based on T3, T4, TSH:

a. A euthyroid group where TFT findings were normal.

b. Subclinical hypothyroidism included patients with TSH concentration above the upper limit of the normal range (more than 4.2 mIU/L), and T4 and/or T3 were within normal limits. Clinical Hypothyroidism in which TSH was more than 4.2mIU/L and T4 or T3 was decreased below normal limit.

c. Clinical Hyperthyroidism in which TSH was less than 0.4mIU/L.

Final results were tabulated, and correlation of incidence of thyroid dysfunction with that of cholelithiasis was determined. Statistical analysis was carried out using SPSS version 19.0 (IBM SPSS, US) software with Regression Modules installed. Age, BMI, and Lipid Profile values of study subjects were evaluated using mean, standard deviation and 95% Confidence Interval.

**Results**

The following results were obtained following statistical analysis of the variables. The age and gender distribution of the subjects were assessed. Out of the 60 patients recruited, 37% were below the age of 40 years, 28% of them were between the age group of 41-50 years, 16.7% were between 51-60 years, 10% were between 61-70 years, and 8% were above 70 years of age. This is shown in the figure (Fig:1). The mean age was 47.1. The standard deviation was 15.17, and the 95% confidence interval ranged from 43.3 to 50.9. Concerning the gender distribution, 36.7% were males, and 63.3% were females, as shown in the figure (Fig:2).

On assessing the BMI distribution, based on the WHO-Asian BMI Classification [6], out of the 60 patients recruited, 12 of them (20.0%) had normal BMI, 6 of them (10.0%) were overweight, and 42 of them (70%) were obese. None of the patients was found to be underweight. This is depicted in the figure below (Fig:3). The mean BMI was 25.99, which falls in the obese category. The

Figure 1: Distribution of age.

Figure 2: Gender distribution.
standard deviation was 3.56, and the 95% Confidence Interval ranged from 25.09 to 26.89.

The thyroid status of the study subjects was evaluated. Among the 60 patients recruited in this study, 38 of them (63.3%) were found to be Euthyroid based on TSH reference range (0.4-4.2uIU/ml), 19 of them (31.7%) were found to be Hypothyroid (TSH> 4.2uIU/ml), and only 3 of them (5%) were found to be Hyperthyroid (TSH < 0.4uIU/ml). This is shown in the figure (Fig:4) and table (Table:3). The mean TSH was 4.84uIU/ml, the Standard Deviation was 7.90, and the 95% Confidence Interval ranged from 2.81 to 6.89.

Among the 19 patients who were hypothyroid, only 4 patients (21.0%) had a low fT3 value (<2pg/ml) and 5 patients (26.3%) had a low fT4 value (<0.92ng/dl). However, 10 out of the 19 hypothyroid patients had normal fT3 and fT4 levels, indicating that 53.7% had subclinical hypothyroidism. The mean fT3 value was 2.64, the Standard Deviation was 0.85, and the Confidence Interval ranged from 2.42 to 2.86. The mean fT4 value was 1.50, the Standard Deviation was 1.28, and the Confidence Interval ranged from 1.17 to 1.83. Both these values fall within the normal range.

Total Cholesterol and Triglyceride levels were considered to assess the distribution of Fasting Lipid Profile (FLP) in the study population. Out of the 60 participants of this study, 46 (76.7%) had normal total cholesterol values. In contrast, 14 of them (23.3%) had hypercholesterolemia (Total cholesterol: >200mg/dl), and 80% of them had normal triglyceride values, while 20% of them had Hypertriglyceridemia (>150mg/dl).

On assessing the distribution of thyroid function concerning age, it was observed that among the 22 patients below 40 years of age, 13 of them (59%) had normal thyroid function, 8 of them (36.4%) were hypothyroid, and 1 patient (4.6%) was hyperthyroid. In 41-50 years, 70.6% were euthyroid, 17.6% were hypothyroid, and 11.8% were hyperthyroid. The remaining 8 out of 19 hypothyroid patients were equally distributed (4 each) between 51-60 and 61-70. There were no hyperthyroid patients beyond the age of 50. All 5 patients above the age of 70 years were euthyroid. This has been depicted in the figure (Fig:5). On identifying the correlation, p-value was 0.893 (> 0.05) and hence not statistically significant.

Out of the 38 females, 13 were hypothyroid (34.2%), 23 were euthyroid (60.5%), and 2 were hyperthyroid (5.3%). Among the 22 males, 68.2% were euthyroid, 27.3% were hypothyroid, and only 1 male patient was hyperthyroid (4.5%).

On correlating the association between thyroid function and BMI, it was observed that 10.5% of each of the euthyroid patients and the hypothyroid patients were overweight. 73.7% of the hypothyroid patients and 68.4% of the euthyroid patients were obese. In the hyperthyroid group, 66.7% were obese, and 33.3% had normal BMI, as shown in the figure (Fig:6). P-value was 0.935, >0.005 and hence not statistically significant.

81.6% of the euthyroid patients had normal cholesterol levels, while 68.4% of the hypothyroid patients and 66.7% of the hyperthyroid patients had normal cholesterol levels. On the other hand, among the 38 euthyroid patients, only 18.4% had hypertriglyceridemia, while 15.8% of hypothyroid patients and 66.7% of hyperthyroid patients had hypertriglyceridemia. Again, this was not statistically significant as the P-value was 0.496 (>0.005) and hence not statistically significant.
Discussion

Around 5-30% of the global population is considered to be affected with Cholelithiasis, the most commonly come across surgical disease [7]. There have been various theories and hypotheses about the role of thyroid function in the manifestation of Cholelithiasis, as mentioned earlier. In this study, we have tried to assess the same, and our findings did not show any significant association between thyroid function and cholelithiasis.

Out of the 60 patients with diagnosed Cholelithiasis recruited in this study, the majority of them were below the age of 50 years. Our results are consistent with studies conducted by Parambil et al. in Kerala in the year 2016, which showed that the age group most commonly being affected with gallstone disease was between 31-50 years [8] and Bansal et al. in Uttar Pradesh, who concluded that the mean age of occurrence of Gallstones is 43.5 years [9].

Studies conducted by Sun et al. in China, Figueredo et al. in California, Sharma et al. in India all suggested that cholelithiasis is more in the female gender than in males, which correlates with this study where patients were predominantly females [10-12].

In this study, 53.7% were having Subclinical Hypothyroidism among the hypothyroid patients. This correlates with the study conducted by Laukkarinen et al. wherein the prevalence of subclinical hypothyroidism in cholelithiasis patients was significantly high [13].

Jagjit Singh et al. conducted a study to identify the incidence of hypothyroidism in cholelithiasis and concluded that there is no specific correlation between hypothyroidism in gallstone disease since out of 100 patients that he recruited, only 27 of them had hypothyroidism [14].

Watali et al., in his study, stated that there is no association between thyroid dysfunction, especially hypothyroidism and cholelithiasis, since only 14% of his patients were Hypothyroid in the case group and 8% were Hypothyroid in the control group, the p value was 0.175, which was not significant [15]. These findings are consistent with this study, wherein only 31.7% of the patients were hypothyroid.

According to Avvai et al., most euthyroid patients belonged to the age group of 51-60 years, while subclinical hypothyroidism was equally distributed among all the age groups [16]. However, in our study wherein the euthyroid patients were more seen in the age group of 40-60 years, and hypothyroidism was more in patients <40 years of age.

A study conducted in Germany by Völzke et al. showed a gender-wise relationship between thyroid function and gallstone disease. Males were found to have thyroid dysfunction as an independent risk factor for developing Cholelithiasis compared to females [17]. However, in our study, the proportion of hypothyroidism was more in females than in males, probably because the sample size recruited in our study was smaller compared to the above mentioned German study.

A study conducted by Milionis et al. showed that 70.9% of the hypothyroid patients were obese with a BMI of >25kg/m2 [18]. This correlates with our study, where most of the hypothyroid patients (73.7%) were obese.

A study conducted by Alamdari et al. to assess the incidence of dyslipidemia in hypothyroid patients showed that serum cholesterol was significantly higher in overt hypothyroidism patients. However, there was no difference in cholesterol levels in euthyroid and subclinical hypothyroid patients [19]. In our study, most of the hypothyroid (68.4%) had normal cholesterol levels, which contradicts the study mentioned above, probably because all hypothyroid patients were included in their study. In contrast, only patients with diagnosed cholelithiasis having hypothyroidism were assessed in our study.

Similarly, concerning the triglyceride levels, among the patients that we recruited, the majority of the hyperthyroid patients had elevated triglyceride levels. This was converse to the results of a study conducted by Lee et al. He concluded that there is a decreased risk of hypertriglyceridaemia in patients with hypothyroidism [20].

In addition to the factors mentioned above, few studies have also identified the gallstones associated with Hypothyroidism. Raghuvanshi et al. conducted a study to look for the prevalence of hypothyroidism in gallstone disease, which also assessed the type of gallstones. Most hypothyroid had cholesterol stones (58.3%), while the euthyroid patients predominantly had pigment stones [21].

There have also been descriptions about cholecdocholithiasis being associated with thyroid dysfunction, which Laukkarinen et al., in his study, showed that more than gallbladder stones, CBD stones were associated with increased prevalence of hypothyroidism which proves that not only does thyroid hormone increase cholesterol synthesis, but also has effects on the sphincter of Oddi relaxation [22]. Unfortunately, these factors were not evaluated in our study, which is one of the drawbacks. The other limitations of this study are that it was an observational study with small sample size. Also, previously diagnosed hypothyroid patients on treatment were included in the study, which could hinder the study results.

Conclusion

To conclude, this study did not show a significant association between thyroid dysfunction and cholelithiasis concerning the demographic variables, BMI and FLP. Furthermore, only one-third of the patients included in this study were hypothyroid, most of them being subclinically hypothyroid. There was, however, reduced risk of developing hypothyroidism in cholelithiasis patients, with increasing age and of the female gender. Nonetheless, further studies with greater sample size and case-control studies are required to consider thyroid function tests as a part of the routine therapeutic workup of patients with cholelithiasis.

Acknowledgement

I thank Prof. Dr. Ramanathan M for his guidance and inspiration, which were essential to the completion of this study. I also thank Dr. Vinoth S, Associate Professor, Department of General Surgery and Dr. Siddartha Gowthman, Assistant Professor, Department of General Surgery, for their guidance and support. I thank the patients who have voluntarily participated in my study. I am grateful to my fellow post-graduate residents, Dr.
Meenal Jain and Dr. Keerti Ramesh, for all the help and assistance I have received from them over last two years. I sincerely thank my family members for their support throughout.

**Ethical Committee Approval**

Obtained ethical clearance (IHEC Reg. No. ECR/451/Inst/PO/2013/RR-16). Reference number: 02/2019/39, Approval Date: 26.02.2019

**Funding**

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of interest**

There are no conflicts of interest to declare by any of the authors of this study.

**References**

1. Wali MI, AP K, Mukkapati K. Association of thyroid dysfunction in patients with biliary calculi: A study in tertiary care hospital. Int J Surg Sci. 2020; 4:624–7.

2. Singh G, Rajiv. Incidence of various types of gallstones in patients of cholelithiasis in North India. J Evol Med Dent Sci. 2015; 1:4.

3. Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol. 2018; 14:259–69.

4. Singh D, Pawar NM, J PB, Kumar N, Gopalarathnam S. Prevalence of previously undiagnosed hypothyroidism in patients with cholelithiasis in a tertiary care center, North-East India. Int Surg J. 2017; 4:932–5.

5. Wang Y, Yu X, Zhao Q, Zheng S, Qiong W, Miao C, et al. Thyroid dysfunction, either hyper or hypothyroidism, promotes gallstone formation by different mechanisms. J Zhejiang Univ Sci B. 2016 Jul;17(7):515–25.

6. Girdhar S, Sharma S, Chaudhary A, Bansal P, Satija M. An epidemiological study of overweight and obesity among women in an Urban area of North India. Indian J Community Med 2015;41:154-7.

7. Rahnam DY, Hassan* DY, Hussain DA, Ahmad DMN, Awan DN, Zaieem DM. Association between cholelithiasis and thyroid profile – a tertiary hospital care-based study. World J Pharm Med Res;2018; 4(12).

8. Parambil SM, Matad S, C SK. Epidemiological, demographic and risk factor profile in patients harbouring various types of gallbladder calculi: a cross sectional study from a south Indian tertiary care hospital. Int Surg J. 2017 ;4(2):525–8.

9. Bansal A, Akhtar M, Bansal A. A clinical study: prevalence and management of cholelithiasis. Int Surg J. 2014; 1:134.

10. Sun H, Tang H, Jiang S, Zeng L, Chen E-Q, Zhou T-Y, et al. Gender and metabolic differences of gallstone diseases. World J Gastroenterol WJG. 2009; 15(15):1886–91.

11. Figueiredo JC, Haiman C, Porcel J, Buxbaum J, Stram D, Tambe N, et al. Sex and ethnic/racial-specific risk factors for gallbladder disease. BMC Gastroenterol. 2017; 17(1):155.

12. Sharma H, Gupta G, Sharma MK. Correlation of Gallstone Characteristics with the Clinical Parameters in Cases of Cholelithiasis. 2015; 4:5.

13. Laukkarinen J, Sand J, Nordback I. The Underlying Mechanisms: How Hypothyroidism Affects the Formation of Common Bile Duct Stones—A Review. Vol. 2012, HPB Surgery. Hindawi; 2012. p. e102825:

14. Singh P, Jagjit P. Cholelithiasis and Hypothyroidism. Int Surg J. 2016; 6:135.

15. Watali YZ, Jain R, Bali RS, Mittal A. Is hypothyroidism a risk for gall stone disease? a study to assess the association. Int Surg J. 2017; 4(8):2665–9.

16. Avvai T. The prevalence of undiagnosed thyroid dysfunction and diagnosed diseases of gallstones. IAIM 2019; 6(3):231-236.

17. Völzke H, Robinson DM, John U. Association between thyroid function and gallstone disease. World J Gastroenterol WJG. 2005; 11(35):5530–4.

18. Milionis A, Milionis C. Correlation between Body Mass Index and Thyroid Function in Euthyroid Individuals in Greece. Vol. 2013, ISRN Biomarkers. Hindawi; 2013. p. e651494.

19. Alamdari S, Amouzegar A, Tohidi M, Gharibzadeh S, Kheirkhah P, Kheirkhah P, et al. Hypothyroidism and Lipid Levels in a Community Based Study (TTS). Int J Endocrinol Metab. 2015; 14(1).

20. Lee J, Ha J, Jo K, Lim DJ, Lee JM, Chang SA, et al. High Normal Range of Free Thyroxine is Associated with Decreased Triglycerides and with Increased High-Density Lipoprotein Cholesterol Based on Population Representative Data. J Clin Med. 2019; 8(6).

21. Raghuvanshi BS, Jain S, Damor M, Pathamaniya NK. Prevalence of subclinical hypothyroidism in cases of cholelithiasis. Int Surg J. 2017; 5(1):34–8.

22. Laukkarinen J, Koobi P, Kalliovalkama J, Sand J, Mattila J, Turjanmaa V, et al. Bile flow to the duodenum is reduced in hypothyreosis and enhanced in hyperthyreosis. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2002;14(2):183–8.