

Content available at: <https://www.ipinnovative.com/open-access-journals>

International Journal of Clinical Biochemistry and Research

Journal homepage: <https://www.ijcbr.in/>

## Original Research Article

## The role of routine thyroid assay in the management of gallstones

Sadaf Idris<sup>1</sup>, Manjula K S<sup>1,\*</sup><sup>1</sup>Dept. of Biochemistry, Rajarajeswari Medical College and Hospital, Bangalore, Karnataka, India

## ARTICLE INFO

## Article history:

Received 23-10-2020

Accepted 28-10-2020

Available online 21-01-2021

## Keywords:

Case-control

Hypothyroidism

Gallstones

Prevalence

Routine

Workup

## ABSTRACT

**Background:** Cholelithiasis is a type of biliary stone disease, with a high prevalence. Along with classic risk factors like obesity, weight loss, female sex hormones, age, an association with thyroid dysfunction has been established.

**Objectives:** To evaluate the importance of thyroid profile as a diagnostic/therapeutic workup of gallstones. **Materials and Methods:** The study included 200 subjects, above 18 years. 100 subjects (50 males+50 females) had cholelithiasis confirmed by ultrasonography and remaining as 100 subjects(50males+50females) control group without gallstones. After a detailed history and clinical examination, blood samples were analyzed for TSH, T3 and T4, using Chemiluminescence-Immunoassay. Subjects with history of thyroid dysfunction or on thyroid replacement therapy, diabetes mellitus, pregnancy, drugs affecting thyroid hormone levels were excluded.

**Statistical analysis:** Computing descriptive statistics was used. Any significant difference were tested using the unpaired sample student t-test.

**Result:** The case group had a mean age of  $45.70 \pm 13.76$  and the controls, a mean age of  $38.78 \pm 15.63$ . There was a significant increase in the prevalence of gallstones after the age of 40years, especially in females. 20% of cases were hypothyroid and 12% were hyperthyroid when compared to the controls which were 10% hypothyroid and 6% hyperthyroid. The higher prevalence of hypothyroid among cases was statistically significant. Among the hypothyroid cases, 80% had subclinical hypothyroidism.

**Conclusion:** Our study concludes by saying that thyroid assay could be made a part of the diagnostic work up of gallstone management thus providing early detection for thyroid dysfunction and thus reducing the surgical/anesthetic complications.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## 1. Introduction

Cholelithiasis or gallstone disease is a common type of biliary stone disease, with a prevalence of about 2 – 29% in the Indian subcontinent<sup>1</sup> and approximately 10-15% of the western adult population.<sup>2,3</sup> A large number of cases result in hospitalization and surgery for patients visiting the outpatient department.<sup>3,4</sup>

The pathogenesis of gallstones is a composite of factors affecting the content and flow of bile. The classic risk factors include demographic/genetics, obesity, weight loss, female sex hormones, age, gallbladder hypomotility,

pregnancy, ileal disease, chronic hemolysis, and cirrhosis.<sup>5</sup> But recently, an association between gall stones and thyroid dysfunction has been established.<sup>6–8</sup>

Thyroid hormones are known to alter lipid metabolism; there is a decline in the rate of lipid metabolism in hypothyroidism and vice versa. This change in the rate may alter the composition of bile and affect the gall bladder motility, thus playing a key role in the formation of gallstones.<sup>9</sup>

Animal model studies showed that thyroid dysfunction, either hypothyroidism or hyperthyroidism promotes the formation of cholesterol gallstones by different mechanisms.<sup>10,11</sup> But human studies showed that the gall

\* Corresponding author.

E-mail address: [drmanjulamurthy@gmail.com](mailto:drmanjulamurthy@gmail.com) (Manjula K S).

stone formation was mainly attributed to the hypothyroid state. Hypothyroidism leads to super-saturation of the bile with cholesterol, gallbladder hypo-mobility, decreased contractility and impaired filling; this, in turn, allows enough time for nucleation, micelle formation and continuous growth into mature gallstones. Furthermore, the sphincter of Oddi has thyroid receptors and thyroxine has a direct pro-relaxing effect on the sphincter.<sup>12–20</sup>

The identification of thyroid dysfunction in patients diagnosed with gallstones remains suboptimal and often missed,<sup>21</sup> thus delaying its management. Gall stone disorder has its surgical related morbidity and mortality<sup>22</sup> which can be avoided with a euthyroid state. Hence, we would like to investigate the overall association between thyroid status and gallstone disease. Thus, helping in early detection and treatment of thyroid disorders in patients with gallstone and this is possible by making TFT a routine laboratory investigation in gallstone management.

## 2. Materials and Methods

### 2.1. Ethics

Approval was taken from the institutional ethics committee and informed consent was taken from the research participants

### 2.2. Study design

With the approval of the institutional ethics committee, a single-center based, Observational study was conducted in 200 subjects, aged above 18years, visiting the department of surgery, out of which 100 subjects (50males + 50females) were admitted with clinical features suggestive of cholelithiasis. This was confirmed by ultrasonography (USG). The control group (50males + 50females) comprised of subjects who underwent USG/laparotomy for other purposes. All the participants were explained the purpose of the study and written informed consent was taken. The study was conducted for a period of 1year (January 2019 – January 2020).

### 2.3. Inclusion and exclusion criteria

A detailed history of presenting illness, history, family history, and personal history was taken, and clinical examination of the patient was done. Detailed interrogation of the patient with signs and symptoms suggestive of biliary lithiasis and thyroid dysfunction was done and the biochemical was done. Subjects with previous history of thyroid dysfunction or on thyroid replacement therapy, diabetes mellitus, pregnant women, Drugs affecting thyroid hormone levels - ocp's, estrogen therapy, fenofibrate were excluded.

### 2.4. Biochemical investigations

Venous blood samples were collected with strict aseptic precautions and serum was separated and analyzed for TSH, T3, and T4, using Chemiluminescence Immunoassay

Base on history and TFT values, patients were categorized as –

1. Euthyroid - clinically normal with normal TFT (S-TSH – 0.38 – 5.33miu/ml, S-TT3 – 87–178ng/dl and S-TT4 – 6.09- 12.23 mg/dl).
2. Subclinical Hypothyroid – patients without symptoms and with TSH concentrations above 5.33miu/ml.
3. Clinical Hypothyroid - symptoms of hypothyroidism with TSH more than 5.33 mIU /ml and S-TT3/ S-TT4 below the normal limit.
4. Hyperthyroid - symptoms of hyperthyroidism with TSH less than 0.38 mIU/ml.

### 2.5. Statistical analysis

The data collected was analyzed statistically by computing descriptive statistics, namely mean, standard deviation, range and any significant difference between the mean values of the study group and the control group were tested using the unpaired sample student t-test. If the p-value <0.05, the null hypothesis (there is no significant difference in the mean value between the two groups) was rejected.

## 3. Results

A total of 200 subjects were enrolled in this study. Case and control groups had equal number of males and females, i.e. 100 cases = 50 males + 50 females and 100 controls = (50 males + 50 females).

The case group had patients with age ranging from 23 - 73 years with a mean age of  $45.70 \pm 13.76$  and the control group had patients with age ranging from 19 – 70 years with a mean age of  $38.78 \pm 15.63$ .

Table 1 shows the age-wise distribution for gallstones (cases). Among the cases, there was a significant difference in the prevalence of gallstones after the age of 40years, where the prevalence was higher in females.

**Table 1:** Age wise distribution for gallstones (cases)

Gender Age	Male N (%)	Female N (%)	P value
Age <40years	22 44%	18 36%	0.4166
Age > 40years	28 56%	32 64%	0.0053
Total	50	50	

Table 2 shows the prevalence of thyroid status in cases and controls. Of the cases, 68% were euthyroid, 20% were hypothyroid and 12% were hyperthyroid. Of the controls,

84% were euthyroid, 10% were hypothyroid and 6% were hyperthyroid. This showed that thyroid dysfunction was higher in cases than the controls. There was a statistically significant difference in the prevalence of hypothyroidism among the cases.

**Table 2:** Thyroid status in cases and controls (study group)

	Case n (%)	Control n (%)	P value
Hypothyroid	20 (20%)	10 (10%)	0.048
Euthyroid	68 (68%)	84 (84%)	0.008
Hyperthyroid	12 (12%)	6 (6%)	0.1
Total	100	100	

Table 3 shows the prevalence of clinical and subclinical Hypothyroidism in cases. Out of the 20 cases with hypothyroidism, 80% had subclinical hypothyroidism and 20% had clinical.

**Table 3:** Prevalence of clinical and subclinical Hypothyroidism in cases

Subclinical	16 (80%)
Clinical	4 (20%)
Total	20

Table 4 shows the TFT values in cases with hypothyroidism. The mean value of S-TSH was higher in cases than the controls and this was statistically significant. The mean values S-T3 and S-T4 were lower in the cases than the controls but the p-value was not statistically significant.

**Table 4:** TFT values in cases with hypothyroidism

	Cases	Controls	P value
TSH(mIU/ml)	3.50±2.45	2.50±1.39	0.002
T4 (mg/dl)	7.9±6.6	9.89 ± 4.50	0.059
T3 (ng/dl)	106.8±29.7	117.3 ± 36.3	0.061

#### 4. Discussion

Along with the classical etiological factors causing gallstone,<sup>5</sup> several studies have shown a positive association between symptomatic thyroid dysfunction and biliary stone disease.<sup>14,23,24</sup>

The various hypotheses that explain the connection between thyroid failure and gallstone formation are as follows.<sup>15,19,25</sup>

1. Thyroid abnormality causes disturbance of lipid metabolism and change in bile composition, thus decreases bile flow into the duodenum.
2. Decreased cholesterol secretion → super-saturation of bile with cholesterol → sludge formation and gallstone formation.

3. A decreased pro-relaxing action of thyroxine on the sphincter of oddi.
4. Dysmotility of the digestive tract in hypothyroidism.

Many a time the thyroid dysfunction, commonly hypothyroidism, is undiagnosed or one can say, subclinical, in people presenting with Cholelithiasis.<sup>17,26</sup> Hence this study was conducted to delve into the prevalence of thyroid dysfunction in patients with gallstones who did not show any symptoms of thyroid abnormality.

Gallstones are considered as a disease of fat forty, fertile females.<sup>1,5</sup> It is known that the prevalence of gallstone disease is higher in female gender.<sup>1,5,27,28</sup> Hence in this study, we have taken an equal number of males and females in both case and control groups. Among the cases, a higher prevalence of gallstone disease was seen after the age of 40 years in both the genders. This was in concordance with studies by Subramani et al<sup>15</sup> who showed 60% of the patients presented with gallstones after 41 years. The study by Vivek et al.<sup>17</sup> showed that gallstone occurred in the age group of 50-60 years. AK Singh et al<sup>9</sup> showed that 75% of all his cases were more than 41 years of age and 60% of these were above 50 years of age. Thus, showing that increasing age is a risk factor for gallstone disease.

Comparing the men and women in the case group, a higher number of women had gallstone disease after 40 years. This gender distribution was statistically significant which was in par with the studies by Sing BR et al.,<sup>1</sup> Volzke et al,<sup>18</sup> Laukkanen J et al,<sup>23</sup> Priya et al,<sup>22</sup> Vivek et al.<sup>17</sup>

Studies by Yousif et al,<sup>20</sup> Maru et al,<sup>3</sup> Ahmad et al,<sup>25</sup> Laukkanen J<sup>12,23</sup> showed a high prevalence of previously diagnosed hypothyroidism in patients who presented with gallstones. Ahmed MM et al<sup>25</sup> showed statistical significance in the presence of hypothyroidism in not just Cholelithiasis but also in cases with choledocholithiasis. In this study, 68% of the gallstone cases were euthyroid, 20% were hypothyroid and 12% were hyperthyroid but these were previously undiagnosed cases of thyroid dysfunction. The occurrence of hypothyroidism was significantly higher when compared to the controls.

Also, 80% of these previously undiagnosed hypothyroid cases were subclinical, i.e. they did not show any symptoms and had normal thyroid hormone levels. This was in correlation with studies by various studies<sup>1,13-18,22,24</sup> showed an association between undiagnosed/subclinical hypothyroidism with gallstones. Singh BR<sup>1</sup> concluded that subclinical hypothyroidism was common in female patients belonging to the age group of 40-50 years. Stephen et al<sup>13</sup> showed the prevalence of subclinical hypothyroidism was 13% and therefore patients with gallstones, especially females, should be checked for S-TSH and thyroid hormones. Vivek<sup>17</sup> showed a 10.5% prevalence of subclinical hypothyroidism in comparison to just 4% in non-gallstone subjects. A study by Priya et al<sup>22</sup> showed an 11% prevalence of subclinical hypothyroidism in gallstone

cases. Inkinen et al<sup>24</sup> showed a prevalence of 8% of hypothyroidism in CBD patients in comparison to 1% in the control group.

Hypothyroidism reduces the consumption of oxygen and affects the various organ functions due to decreased metabolism of the body. Hypothyroidism also affects drug metabolism, and this could have an adverse effect on anesthesia.<sup>4,29</sup> Hence it becomes necessary to screen the patients presenting with gallstone diseases, especially those above the age of 40 years and requiring surgical intervention. The surgeon/anesthesiologist should be aware of the thyroid status of the patient presenting with biliary stones so that early treatment for thyroid dysfunction could be given and thus reduce the surgical or anesthetic complications.

S-TSH is the most sensitive marker for detecting thyroid failure.<sup>15,16,22</sup> As subclinical hypothyroidism is more prevalent, measuring the S-TSH levels should be made a routine investigation test along with the standard preoperative workup that includes LFT (liver function test) and USG.

## 5. Conclusion

Our study concludes by saying that thyroid assay must be made a part of the diagnostic workup of gallstone management. Thus, leading to early diagnosis of undiagnosed hypothyroidism and lead to a complication-free outcome of gallstone surgery.

## 6. Source of Funding

None.

## 7. Conflict of Interest

The authors declare no conflict of interest.

## References

1. Raghuwanshi BS, Jain S, Damor M, Patbamniya NK. Prevalence of subclinical hypothyroidism in cases of cholelithiasis. *Int Surg J*. 2017;5(1):34–8. doi:10.18203/2349-2902.isj20175524.
2. Cao AM, Eslick GD. Epidemiology and Pathogenesis of Gallstones. In: Cox M, Eslick G, Padbury R, editors. *The Management of Gallstone Disease*. Cham: Springer; 2018.
3. Maru NP, Parmar A, Dawan ML, Mahesh MS. Study The Association Between Thyroid Disorder And Gall Stone Diseases (Cholelithiasis & Choledocholithiasis). *J Evol Med Dent Sci*. 2014;3(26):7286–9.
4. Sanniyasi S, Edwin RRS. Does Hypothyroidism Promote Gallstone Formation? *Int J Sci Stud*. 2018;5(11):1–3.
5. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Cholelithiasis, Cholecystitis, and Cholangitis. In: *Harrison's Principles of Internal Medicine*. New York: The mcgraw-Hill Companies; 2018.
6. Kala S, Verma S, Singh P, Saxena N, Singh A, Singh S. A Prospective Study Comparing the Clinicobiochemical Profile in Obese and Non-Obese Subjects with Gall Stone Disease. *Int J Recent Sci Res*. 2018;9(4):26330–4.
7. Ajdarkosh H, Khansari MR, Sohrabi MR, Hemasi GR, Shamspour N, Abdolahi N, et al. Thyroid Dysfunction And Choledocholithiasis. *Mid East J Dig Dis*. 2013;5(1):141–5.
8. SI I. The Impact of Thyroid Dysfunction and TSH on the Pathogenesis of Gallstone and Its Composition. *J Kufa Nurs Sci*. 2014;4(1):1–6.
9. Singh AK, Kaul RK, Singh NK, Sinha SP. Prevalence Of Thyroid Disorders In Patients Of Gall Bladder Stones: A Prospective Study. *Ann Int Med Den Res*. 2018;4(4):6–9.
10. Wang Y, Yu X, Zhao QZ. Thyroid dysfunction, either hyper or hypothyroidism, promotes gallstone formation by different mechanisms. *J Zhejiang Univ Sci B*. 2016;17:515–540.
11. Günay Y, Tütüncü T, Öcalan T, Bilgihan A, Korkmaz G, Kama NA. Assessment of Effects of Thyrotoxicosis on Gallstone Formation in Rabbits. *Med Bull Haseki*. 2019;57(1):91–7. doi:10.4274/haseki.galenos.2019.4752.
12. Laukkanen J, Sand J, Saaristo R, Salmi J, Turjanmaa V, Vehkalahti P. Is bile flow reduced in patients with hypothyroidism? *Surg*. 2003;133(3):288–93. doi:10.1067/msy.2003.77.
13. Stephen J. Prevalence Of Subclinical Hypothyroidism In Gall Stone Disease- A One-Year Study. *Int J Sci Res*. 2016;5(4):83–88.
14. Singha D, Pawar NM, Prabhu BJ, Kumar N, Gopalathnam S. Prevalence of previously undiagnosed hypothyroidism in patients with cholelithiasis in a tertiary care center, North-East India. *Int Surg J*. 2017;4(3):932–5. doi:10.18203/2349-2902.isj20170507.
15. Subramani B, Balasubramanian MVP, Madhavan L, Selvam G. A Study of Prevalence of Hypothyroidism in Cholelithiasis. *J Evid Based Med Healthc*. 2017;4(11):606–10. doi:10.18410/jebmh/2017/118.
16. Sundareswari P, Ravisankar J, Kumar SG, Premchand G. A Prospective Study of Hypothyroidism in Diagnosed Case of Gallstone Disease. *J Evid Based Med Healthc*. 2016;3(88):4819–23. doi:10.18410/jebmh/2016/1015.
17. Deswal V, Arora BK. Evaluation of Thyroid Profile In Patients With Gallstone Disease. *Glob J Res Anal*. 2017;6(2):723–6.
18. Völzke H, Robinson D, John U. The association between thyroid function and gallstone disease. *Exp Clin Endocrinol Diabetes*. 2005;113(S 1):5530–4. doi:10.1055/s-2005-862907.
19. 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. doi:10.18203/2349-2902.isj20173406.
20. Yousif HH. Relationship between Serum Levels of TSH and Cholesterol with Types of Gallstones. *Iraqi Postgrad Med J*. 2011;10(1):7–12.
21. Nagarkar R, Roy S. Incidence of Thyroid Disorders in India: An Institutional Retrospective Analysis. *Int J Dent Med Spec*. 2015;2(2):19–23.
22. Priya JV, Saravanakumar A. Correlation of Subclinical Hypothyroidism in Cholelithiasis in and around Coimbatore. *IOSR J Dent Med Sci*. 2016;15(08):01–06. doi:10.9790/0853-1508110106.
23. Laukkanen J, Sand J, Aittomäki S, Pörsti I, Kööbi P, Kalliovalkama J, et al. Mechanism of the Prorelaxing Effect of Thyroxine on the Sphincter of Oddi. *Scand J Gastroenterol*. 2002;37(6):667–73. doi:10.1080/00365520212492.
24. Inkinen J, Sand J, Nordback I. Association between common bile duct stones and treated hypothyroidism. *Hepatogastroenterol*. 2001;47:919–21.
25. Ahmad M, Nazir M, Dar H, Ali U, Mirza M, Kawoosa K. Evaluation of thyroid profile in biliary tract stones. *Int Surg J*. 2015;2(3):344–7. doi:10.18203/2349-2902.isj20150496.
26. Laukkanen J, Kiudelis G, Lempinen M, Rätty S, Pelli H, Sand J, et al. Increased Prevalence of Subclinical Hypothyroidism in Common Bile Duct Stone Patients. *J Clin Endocrinol Metab*. 2007;92(11):4260–4. doi:10.1210/jc.2007-1316.
27. Battacharya R. Cholecystectomy in west port. *Indian J Surg*. 1983;p. 450–455.
28. Sharma MP, Duphare HV, Nijhawan S, Dasarathy S. Gallstone disease in north India: clinical and ultrasound profile in a referral hospital. *J Clin Gastroenterol*. 1990;12(5):547–56.
29. Shubhakaran KP, Khichar RJ. Perioperative care and hypothyroidism. *Res Opin Anesth Intensive Care*. 2018;5(3):258. doi:10.4103/roaic.roaic\_80\_16.

## **Author biography**

**Sadaf Idris**, Assistant Professor

**Manjula K S**, Associate Professor

**Cite this article:** Idris S, Manjula K S. The role of routine thyroid assay in the management of gallstones. *Int J Clin Biochem Res* 2020;7(4):461–465.