A PROSPECTIVE STUDY OF HYPOTHYROIDISM IN DIAGNOSED CASE OF GALLSTONE DISEASE

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ABSTRACT

BACKGROUND
Disturbances in lipid metabolism, which occur during hypothyroidism lead to the formation of gallstones. This study aims to evaluate the thyroid function pattern in patients with gallstones.

The aim of this study was to investigate the association between hypothyroidism and gallstone disease.

MATERIALS AND METHODS
200 patients admitted as inpatients for management of gallstone disease in Department of General Surgery, GRH, Madurai, between September 2014 to August 2015 were evaluated with details of cases, full history, clinical examination, symptoms and signs of hypothyroidism (loss of appetite, gaining weight, tiredness, constipation, cold intolerance, menstrual disturbances, bradycardia, presence or absence of goiter, etc.) and investigations (USG abdomen, USG neck, thyroid function test (T3, T4, TSH). Patients are divided according to history, clinical examination, USG neck and lab estimation of T3, T4 and TSH.

1. Subclinical Hypothyroidism: Symptom free patient with TSH concentration above upper limit of normal range and T3/T4 or both decrease below normal limit.
2. Clinical Hypothyroidism: In which, there are symptoms of hypothyroidism with TSH level above the upper limit and T3/T4 or both decrease below normal limit.
3. Euthyroid Group: Where clinical and lab tests are within normal range (all these groups may present with or without goiter).

RESULTS
This study included 200 gallstone patients who were studied prospectively over a period of 1 year from September 2014 to August 2015. Among them, 18 patients had subclinical hypothyroidism and 6 patients had clinical hypothyroidism. A total of 12% of gallstone patients were diagnosed to have hypothyroidism showing that there is association of hypothyroidism with gallstone disease.

CONCLUSION
Thyroid dysfunction is more common among patients with gallstones and it maybe a risk factor for biliary stone formation. This may be attributed to the absence of the pro-relaxing effects of thyroid hormones on SO and influence of thyroid hormones on synthesis, absorption and usage of cholesterol.

KEYWORDS
Hypothyroidism, Gallstone, Thyroid Function Test.


BACKGROUND
Cholelithiasis is a prevalent abdominal disorder resulting in hospital admissions. The pathogenesis of cholelithiasis is multifactorial. Disturbances in lipid metabolism that occur during hypothyroidism, particularly cholesterol pathway, changes the rate of bile excretion and lead to the formation of gallstones. Recently, the pro-relaxing effect of serum total thyroxin on both human and pig sphincter of Oddi has been proven.

 Possibly, the lack of T4 may contribute to SO contractility, which in turn not only disturbs the normal bile flow, but also prohibits the passage of stones formed in the gallbladder to the duodenum.

OBJECTIVES OF THE STUDY
To know the association between hypothyroidism and gallstone disease.
**Association between Hypothyroidism and Gallstones**

THs interaction with nuclear receptors.

By intracellular mechanism and nuclear transcription.

Various Thyroid Hormone Receptors
1. Specific thyroid hormone transports 8 (MCT 8).
2. Specific thyroid hormone transports 10 (MCT 10).
3. Anion transporting polypeptide IC1 (OPTPICI).

**Metabolism of Liver Cholesterol Decreased by Hypothyroidism**

![Diagram](image)

**Reduction in Hepatic Bile Secretion due to Hypothyroidism**

In a prospective study in humans, the dynamic Tc-99m HIDA scintigraphy performed in the acute hypothyroid stage after thyroidectomy showed that the hepatic maximal uptake and appearance of radioactivity in the large bile ducts at the hepatic hilum was similar to the euthyreotic stage in the same patients. This suggested that bile secretion by hepatocytes is not reduced in the early phase.

However, in rats, where bile secretion rate can be measured by bile duct cannulation proximal to the SO, it has been reported that bile secretion reduces in hypothyroidism, whereas no effect on hyperthyroidism.

**Bile Flow into the Duodenum Reduced by Hypothyroidism**

Hypothyroidism reduced and hyperthyroidism increased the bile flow into the duodenum where the effect of sphincter of Oddi is not excluded. In another prospective study in humans, hepatic clearance was significantly decreased when compared to the euthyreotic stage in the same patients. In hypothyroid stage, bile flow into the duodenum is reduced due to changes in bile composition and gallbladder motility and because of changes in the resistance to flow (in the SO motility).

**Impaired Relaxation of Sphincter of Oddi in Hypothyroidism**

In 2001, it was shown for the first time that thyroxine has a direct effect on SO contractility in physiological concentrations in pig experiments. Triiodothyronine had a similar effect on thyroxine, whereas cortisone, oestrogen and testosterone had no effect. Progesterone, which is thought to be involved in the smooth muscle relaxation seen in pregnancy, reduced not only the ACh and Hist-induced, but also KC1-induced SO contractions. Thus, its effect on SO relaxation differs from the more specific effect of thyroxine. Thyroxine reduced receptor-mediated acetylcholine and histamine-induced SO contraction, but had no effect on unspecific, KC1 induced SO contraction, which suggests a direct effect of thyroxine on the control mechanisms of SO motility. Since the effect of thyroxine on the precontracted SO is relaxing, the absence/insufficient concentration of thyroxine may result in increased tension of the SO in hypothyroidism. A similar relaxant effect of thyroxine was also shown in human SO specimens indicating that the findings may also be of clinical significance.

**Mechanisms by which Thyroxine Mediates SO Relaxation**

Thyroxine acts via hormone-receptor complex by release of pro-relaxin that relaxes sphincter of Oddi. TH passes through cell membrane, cytoplasm and nuclear membrane, it also binds to a nuclear protein. These events occur relatively fast followed by transcriptional and translational process; this process is time consuming, so thyroxine mediate sphincter of Oddi relaxation does not occur immediately. Regulatory protein synthesis thyroxine-induced gene expression by that mediate thyroxine. Thus, the effect of thyroxine could be mediated by regulatory proteins partly synthesised as a result of thyroxine-induced gene expression. Thyroxine causes opening of ATP sensitive K+ channels in SO smooth muscle causes hyperpolarisation. Hyperpolarisation closes all the membrane Ca2+ channels that reduces Ca2+ influx and also reduces contraction of sphincter of Oddi.

**METHODOLOGY**

200 patients admitted as inpatients for management of gall disease in Department of General Surgery, GRH, Madurai, between September 2014 to August 2015 were evaluated with details of cases, full history, clinical examination, symptoms and signs of hypothyroidism (loss of appetite, gaining weight, tiredness, constipation, cold intolerance, menstrual disturbances, bradycardia, presence or absence...
of goiter, etc.) and investigations (USG abdomen, USG neck, thyroid function test (T3, T4, TSH)).

Patients are divided according to history, clinical examination, USG neck and lab estimation of T₃, T₄ and TSH.

1. Subclinical Hypothyroidism: Symptom free patient with TSH concentration above upper limit of normal range and T₃/T₄ or both decrease below normal limit.
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3. Euthyroid Group: Where clinical and lab tests are within normal range (all these groups may present with or without goiter).

### Inclusion Criteria
1. Patients more than 13 years of age groups in both sexes with cholelithiasis, prior history of cholecystectomy.
2. Patients consented for inclusion in the study according to designated proforma.

### Exclusion Criteria
1. Patients with previous history of hypothyroidism on treatment.
2. Patients not consented for inclusion in the study.

### RESULTS
This study included 200 gallstone patients who were studied prospectively over a period of 1 year from September 2014 to August 2015. Among them, 18 patients had subclinical hypothyroidism and 6 patients had clinical hypothyroidism. A total of 12% of gallstone patients were diagnosed to have hypothyroidism showing that there is association of hypothyroidism with gallstone disease.

![Figure 1. Incidence of Goiter](image1)

![Figure 2. Incidence of Hypercholesterolaemia](image2)
Figure 3. T3 Values in Clinical Hypothyroidism, Subclinical Hypothyroidism and Euthyroidism

Figure 4. T4 Values in Clinical Hypothyroidism, Subclinical Hypothyroidism and Euthyroidism

Figure 5. TSH Values in Clinical Hypothyroidism, Subclinical Hypothyroidism and Euthyroidism
DISCUSSION
In addition to classic risk factors such as age, gender, obesity and genetics, the associations between gallstone and delayed emptying of the biliary tract in hypothyroidism have been shown. This is related to lack of the pro-relaxing effect of the thyroid hormone on SO contractility. In this study, we have evaluated the association of thyroid dysfunction in patients with gallstones. Serum TSH is a hallmark of thyroid dysfunction. The subclinical form of hypothyroidism is characterised by increased serum TSH levels along with normal serum, T4 levels and lack of clinical symptoms. A study by Laukkarinen has shown hypothyroidism to be a common problem among patients with gallstones. He concluded that hypothyroidism played a role in the formation of gallstones secondary to its effects on SO relaxation, which in turn might influence on emptying of the biliary system. The pro-relaxing effect of T4 on SO has been previously reported. In the present study, there was a close relation between hypothyroidism and gallstones, which was similar to earlier studies. Some studies have reported that thyroxin replacement therapy has a positive effect on cholesterol level, cardiovascular system, neuromuscular system and gallstones. Patients with hypothyroidism are more prone to have high serum cholesterol levels. The mechanism of thyroid hormones on cholesterol metabolism is multifactorial. Thyroid hormones influence the synthesis, absorption and usage of cholesterol. Hence, it is concluded that serum TSH level is an independent factor that could be considered a risk factor for the formation of gallstones.

CONCLUSION
According to My Study
Thyroid dysfunction is more common among patients with gallstones and it maybe a risk factor for biliary stone formation. This may be attributed to the absence of the pro-relaxing effects of thyroid hormones and influence of thyroid hormones on synthesis, absorption and usage of cholesterol.

SUMMARY
In summary, association between hypothyroidism and gallstones has been reported in several studies. Not only changes in the cholesterol metabolism or bile excretion rate, but particularly changes in the function of the SO underline the association between gallstones and hypothyroidism, which suggest high prevalence of hypothyroidism in gallstone patients. It remains to be investigated whether compared to euthyroid individuals, hypothyroid individuals who have undergone cholecystectomy are at an increased risk to develop gallstones. The lack of thyroxine in hypothyroidism gives rise to decreased bile flow in many ways. In addition to the increased cholesterol load in bile and the reduced bile secretion rate, the deficiency of the pro-relaxant effect of thyroxine on the SO plays an important role in gallstone formation.

Thyroxine replacement therapy is not sufficient to maintain normal function of sphincter of Oddi leading to high risk for gallstone formation, whereas subclinical hypothyroid patients have demonstrated positive effect on the changes in the serum cholesterol level with early replacement treatment with thyroxine. It is assumed that patients at risk for gallstone formation due to subclinical hypothyroidism may benefit from early treatment. Hence, it is worth investigating thyroid function while treating patients with gallstones.

REFERENCES