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Review Article

Thyroid function and gallstone disease: is there an association?

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ABSTRACT

Gallstone disease, amounts to a significant amount of disease burden to the medical society, more commonly encountered in the West. Various predisposing factors are associated with the development of cholelithiasis, namely age, gender, dietary food habits and haemolytic conditions, but whether or not thyroid dysfunction is a causative factor, till date, is a subject of dispute. Gallstones can be classified into cholesterol stones and pigment stones which are black or brown (with cholesterol) in colour. Thyroid hormones are said to have a direct effect on the sphincter of oddi, thereby aiding in biliary emptying. They also alter the lipid metabolism which is said to cause supersaturation of cholesterol in bile, and hence result in the formation of cholesterol stones. Several studies have tried to establish this hypothesis and have concluded with diversified results. This review article throws light into the concept of the association between thyroid dysfunction and formation of gallstones by evaluating several articles through a systematic approach in order to arrive at a better consensus.

Keywords: Cholelithiasis, Hypothyroidism, Cholesterol, Sphincter of oddi

INTRODUCTION

The disorders associated with biliary tract stones dates way back to the 21st Egyptian dynasty and not just in the modern era. Around 2000 years ago, young Egyptian women had gallstones, during the period of The Roman Empire, as suggested by archaeological evidence.[1] The core process involved in this chronic hepatobiliary disease, Cholelithiasis, is impaired cholesterol, bilirubin and bile acid metabolism, resulting in the formation of gallstones in the hepatic duct, common bile duct or gallbladder. In the western population, majority of the Gallstones are cholesterol stones. Around 6.12% of the adult Indian population is affected by Cholelithiasis.[2] The incidence has increased these days, partly because to the wide use of ultrasonography in the last two decades and also due to the changing socio-economic conditions and other epidemiological factors including diet.[3]

Some of the non-modifiable risk factors for cholesterol gallstone formation are ethnicity, increasing age of the patient, female gender and a family history of gallstones. On the contrary, the modifiable risk factors for the formation of cholesterol stones include sedentary lifestyle, obesity and rapid loss of weight. Diseases like cirrhosis, chronic haemolysis and Crohn's disease have been identified as risk factors for the formation of black pigment stones. Gallstone disease in children is rare and has been found to have an association with risk factors which are similar to those in adults, particularly obesity.[4]

There are several possible hypotheses explaining the correlation between hypothyroidism and gallstone disease. These being, the relationship between thyroid dysfunction and disturbance of lipid metabolism which then results in changes in the composition of bile. Also, there is a β1 and β2 Thyroxine receptor mediated relaxing

action on Sphincter of Oddi at physiological levels of serum T4. So, the decreased levels of serum thyroxine, affects the normal function of sphincter of Oddi, thereby resulting in its contraction. Reduced relaxing effect on the Sphincter of Oddi, in addition to the biliary stasis and increased cholesterol load, altogether results in a shift in the balance, leading to formation of gall stones.[5]

This topic, however has been widely studied by several investigators and contradicting results have been reported.

METHODOLOGY

The aim of this review was to identify if there is any correlation between thyroid function and gallstone disease by analyzing existing articles using databases like pubmed, google scholar, medline, pubmed central with the help of keywords like cholelithiasis, thyroid profile and hypothyroidism. All articles were in English and the oldest article dated to 1981. The articles were prospective, case control and cross-sectional studies. A total of 50 articles were analyzed and 35 were excluded since they did not meet the criteria of the subject of discussion.

DISCUSSION

Pathophysiology of thyroid dysfunction causing gallstone disease

Thyroid dysfunction affects cholesterol metabolism, bile content and bile acid synthesis at multiple levels. In thyroid disease, both composition and transport of lipoproteins tends to get affected. In hypothyroidism, there is increase in the levels of cholesterol, thereby causing increased concentrations of LDL. Conversely, in hyperthyroidism, there is reduction in the levels of total cholesterol and LDL.[6] Hypothyroidism causes hypercholesterolemia resulting in supersaturation of bile with cholesterol, thereby causing reduced motility, contractility and filling of gall bladder, which in turn leads to prolonged stagnation bile. This results in the retention of cholesterol crystals and adequate time for them to nucleate and grow into mature gall stones.[7]

The association between thyroid function and cholelithiasis has been a reason of debate over more than a decade. A case report published back in 1981, by Vasilakkis et al, about disappearance of gallstones during treatment of toxic goitre with carbimazole and thyroxine within 6 months, aroused suspicion regarding this relationship between thyroid abnormalities and gallstones via alteration of cholesterol metabolism.[8]

Choledocholithiasis or Cholelithiasis?

Inkinen et al, in his study, has shown a significant association between common bile duct stones and hypothyroidism compared to gallbladder stones and hypothyroidism, and also suggested that merely cholesterol metabolism alteration is not the sole mechanism for the development of gallstones.[9]

A case control study conducted by BJ et al to establish an association between hypothyroidism and gallstone disease showed that patients with undiagnosed or subclinical hypothyroidism were 12 times more likely to develop choledocholithiasis when in comparison to the normal population.[10]

Avvai et al, in her cross sectional study, concluded that hypothyroidism was seen more commonly in patients having gallbladder stones than those with stones in the common bile duct (7 out of 60 patients had cholelithiasis and only one patient had CBD stones).[11]

Animal studies

Inkinen et al studied the effects of thyroxine on pig Sphincter of Oddi contractility. Because of the pro-relaxing action on the sphincter of Oddi due to thyroxine, the lack of this hormone can cause an increased tension of the Sphincter, leading to bile stasis and a conducive medium for gallstone formation.[12]

Laukkarinen et al conducted an interventional study in rats, to assess the bile flow to the duodenum in the presence of thyroid dysfunction. He concluded that the flow was reduced by 44% in the hypothyroid group compared to the hyperthyroid rats.[13]

Wang et al, in his in vivo study using animal models, found that both hyper and hypothyroidism was associated with the formation of cholesterol gallstones in gallstone susceptible mice, suggesting that clinicians must be aware of significant thyroid dysfunction in patients with cholelithiasis.[14]

Gender-wise association

In a German case control study conducted by Völzke et al, patients with thyroid disease were more often associated with cholelithiasis than those without any thyroid dysfunction. But, there was no independent relationship between thyroid and gallstone disease in males as well as females.[15]

According to Arun et al., who also conducted a study on the prevalence of hypothyroidism in diagnosed cholelithiasis patients in Trissur Medical College, Kerala, male hypothyroids were of larger number when compared with females in gallstone disease. He concluded that gallstone patients should be checked for serum TSH because of high incidence of hypothyroidism in these patients.[16]

The above-mentioned studies have shown varying results with respect to incidence of the thyroid dysfunction and cholelithiasis in accordance to gender.

Prevalence of hypothyroidism in Gallstone disease

Issa et al reported significant increase in the presence of hypothyroidism in cholelithiasis patients (p=0.0001).[17] Similarly, Sanniyasi et al also in his study concluded that 28.5% of the patients were hypothyroid and in comparison with epidemiological studies in eight other cities of India, it was found to be statistically significant (p=0.0000).[18]

Jabini et al, in his case control study, stated that subclinical hypothyroidism was more commonly encountered in cholelithiasis patients (case group), p-value =0.029.[19] Gafoor et al also conducted a case control study in which 15% of those in the case group were hypothyroid and 9% of this group had subclinical hypothyroidism. None of the control group patients had hypothyroidism (p-value=0.005).[20]

Ghimire et al conducted a prospective cross sectional study in West Nepal, which showed that 43 out of 160 (26.7%) patients with gallstone disease had hypothyroidism, out of which 21.1% had subclinical hypothyroidism and remaining 5.6% had clinical hypothyroidism.[21]

All the above studies are in favour of the hypothesis that hypothyroidism is a risk factor for the development of gallstones since they reported significant prevalence of hypothyroidism in the recruited cholelithiasis patients.

Studies which reported no association between thyroid dysfunction and Cholelithiasis

As opposed to the above-mentioned hypothesis, there have been a number of studies who have reported contradicting results which has been discussed below.

A prospective study conducted by Singh et al., on the prevalence of thyroid disorders in patients with gallstone disease in Uttar Pradesh, suggested that gallstone disease occurred more in the age group of 51-60 years. However, no definite relation was observed between thyroid hormones disorders and so he concluded that thyroid dysfunction was not linked to cholelithiasis.[22]

A study conducted by Zaini and Zwain et al., in Iraq, showed that there is no significant relationship between hypothyroidism and gallstones in both genders (p=0.12). However, gallstone patients between the age group of 51-60 years should be checked for serum TSH, T3 and T4, because there was a relatively high incidence of hypothyroidism observed in this age group.[23]

A prospective study conducted by Sundareshwari et al, showed that only a total of 12% of the patients with cholelithiasis were found to be hypothyroid and it was not statistically significant (p>0.05). However, majority of them had subclinical hypothyroidism.[24]

A case control study by Watali et al, showed that there was no statistically significant association between hypothyroidism and the prevalence of gallstone disease, on comparing the 2 groups - with and without cholelithiasis. (p=0.175). However, among those with hypothyroidism, the majority of them were between the age group of 51-60 years.[25]

A cross sectional study by Wali et al, showed that 38 out of 200 patients with cholelithiasis, had high TSH values, which was not statistically significant (p=0.849).[26]

Stone analysis

Rahman et al conducted a case control study in Srinagar which showed that 38.7% of the patients in the case group were hypothyroid compared to 22% of the patients in the control group. This study also emphasized on stone analysis and concluded that 93.1% of the hypothyroid patietns had cholesterol stones and only 6.9% had mixed stones in comparison to the euthyroid group where 69.6% only had cholesterol stones. The results were statistically significant (p value <0.005).[27]

A prospective analysis by Hassan et al in Iraq showed that most of the patients recruited (95 out of 150) had cholesterol gall stones and it was statistically significant (p=0.0001). However 8 out of 12 hypothyroid patients had cholesterol stones and this was not statistically significant (p=0.178).[28]

CONCLUSION

Thus, studies conducted in the last two decades, have found a relative association between thyroid dysfunction and cholelithiasis, especially in terms of gender. There have also been speculations about higher incidence of subclinical hypothyroidism in cholelithiasis and also varying results with respect to thyroid dysfunction being more prevalent in patients with choledocholithiasis. Most of these studies have analyzed a relatively small sample size and are predominantly of the retrospective type. However, further research is required in the future to conclude if thyroid abnormality has a role in the development of gallstones or not.

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