

Thyroid Dysfunction and Choleduocholithiasis

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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 common bile duct (CBD) stones.

METHODS

This case-control study recruited 151 patients with preliminary diagnoses of CBD stone who underwent ERCP (cases). The control group comprised healthy people who met the study criteria in the same hospital. The control group underwent ultrasonography to exclude any asymptomatic bile duct lithiasis. A questionnaire that included demographic and anthropometrics data were completed by an assigned physician. Morning blood samples that followed 12 hours of fasting were taken from all participants for measurements of serum total thyroxin (T4), serum thyroid stimulating hormone (TSH), fasting blood sugar (FBS), triglycerides (TG), total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL).

RESULTS

The mean TSH in patients (2.59 ± 4.86 mg/dl) was higher than the control group (2.53 ± 4.13 9mg/dl). In subclinical hypothyroidism, serum TSH levels higher than 5 MU/L were found in 30.6% of cases compared with 22.5% of controls [OR: 1.53; 95 % confidence interval (95% CI): 0.968-2.438]. Hypothyroidism was detected in 10.8% of the control group and in 11.3% of cases (OR: 1.87; 95% CI: 0.578-2.043). The mean total cholesterol levels in cases was higher than the control group ($p=0.61$). The levels of TG ($p=0.05$), HDL (73.35 vs. 46.41; $p<0.01$) and LDL (64.81.88 vs. 111.04; $p<0.01$) was statistically significant between both groups.

CONCLUSION

There is an association between thyroid disorders and the presence of bile duct stones. Thyroid testing in patients with gallstone and bile duct stones is recommended because hypothyroidism may be a predisposing factor for stone passage from the gallbladder.

KEYWORDS

Choledocholithiasis; Thyroid hormones; Obesity

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INTRODUCTION

Cholelithiasis is a prevalent abdominal disorder resulting in hospital admissions in Western countries. The prevalence of cholelithiasis has

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been reported as approximately 5%-26% in different countries.¹ The prevalence of cholelithiasis in Iran is approximately 5%, however one survey on the prevalence of cholelithiasis in Iranian cadavers has been reported it at 6.3%.² The pathogenesis of cholelithiasis is not unique, but appears to be multifactorial.^{1,3} It has been shown that disturbances in lipid metabolism that occur during hypothyroidism, particularly cholesterol pathway, changes the rate of bile excretion and lead to the formation of gall stones. Recently, the pro-relaxing effect of serum total thyroxin (T4) on both human and pig sphincter of Oddi (SO) has been proven.^{4,5} 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. Some researchers have reported a higher prevalence of both hypothyroidism and subclinical hypothyroidism in common bile duct (CBD) stones which supports a possible relation between low T4 levels and CBD stones.^{5,6}

To our knowledge there are only few published articles that have discussed the prevalence of undiagnosed subclinical hypothyroidism among CBD patients. The current study investigates the prevalence of clinical and subclinical hypothyroidism in patients with CBD stones.

MATERIALS AND METHODS

This case-control study conducted from January 2008 to February 2012 enrolled 151 eligible patients with preliminary diagnoses of CBD stones who underwent ERCP at Firoozgar Hospital, Tehran, Iran.

Excluded were patients with a history of previously diagnosed or treated thyroid function abnormalities, history of thyroidectomy, pregnancy, serious underlying diseases, sepsis or cholanlangitis and those prescribed medications known to affect the thyroid function test such as phenytoin, carbamazepin, metoclopramide, amiodarone, and lithium.

The control group consisted of healthy individuals with no history of liver diseases such as elevations in liver enzymes. They were clinically euthyroid and matched by sex and age. In order to ensure

that the control group did not have asymptomatic bile duct stones, all participants underwent abdominal ultrasonography that was performed with a high resolution instrument (5 MHz transducer, Mylab50, The Netherlands). Excluded were subjects who had a history of cholecystectomy. Other exclusion criteria were as the same as for the case group.

A physician directly interviewed each individual and a questionnaire that included demographic and anthropometric data, past and present medical histories, drug history, and hypothyroidism symptoms was completed for each subject. A written informed consent was also signed. Morning blood samples were taken after 12 hours of fasting to measure serum total thyroxin (T4), serum thyroid stimulating hormone (TSH), fasting blood sugar (FBS), triglyceride (TG), total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) levels. Blood samples were taken at a central laboratory in Firoozgar Hospital. Serum T4 and TSH were measured by an immunofluorometric method. The normal range for serum T4 was 6-12 Mu/l; for TSH, it was 0.25-5 Mu/ml. The colorimetry method (Biosystem, Spain) was used for the remainder of laboratory analyses. Body weight (kg) and height (m) were precisely measured and the body mass index (BMI) was calculated by dividing a participant's weight to the square of their height. All laboratory results were analyzed by an expert endocrinologist who was blinded to the study groups.

Subclinical hypothyroidism is defined as peripheral thyroid hormone levels that are within the normal range in the presence of mildly elevated serum TSH (between 5 to 10 Mu/ml). Hypothyroidism is characterized by an elevated TSH of over 10 Mu/ml.⁷ In case of borderline TSH levels, serum T4 and patients' symptoms were used to determine thyroid function. Subjects with FBS greater than 126 mg/dl, confirmed by repeated measurement, were considered as diabetic.⁸ Dyslipidemia was defined as LDL levels greater than 130 mg/dl in diabetics and greater than 100 mg/dl in non-diabetics, HDL levels less than 50 mg/dl in females and less than 40 mg/dl in males, and TG more than 150 mg/dl. Initially we included all patients who had preliminary diagnoses

of CBD stones; subsequently we excluded those whose ERCP findings were compatible with diseases other than CBD stones.

Statistical analyses were done by SPSS version 16.0. Quantitative data were expressed as mean \pm standard deviation (SD). P-values less than 0.05 were considered to be significant. We used the Mann-Whitney u and independent t-tests for comparison between groups. For qualitative variables, cross-tables and the chi-square test were performed. The association between the presence of gallstones and risk factors was evaluated by multilevel logistic regression. The significance level for multivariate analyses was 0.05. The risk of developing CBD stone was estimated by using odds ratios and the 95% confidence interval (CI).

This study was approved by the Ethical Committee of the Gastrointestinal and Liver Disease Research Center at Firoozgar hospital and the Ethical Committee of Tehran University of Medical Sciences.

RESULTS

A total of 151 patients with mean age of 59.49 ± 18.66 years comprised the case (CBD stone) group and 347 healthy individuals with a mean age of 59.53 ± 17 years were in the control group. There were 58.6% females in the case group and 52.1.0% in the control group (Figure 1). Mean BMI of cases was 29.97 ± 4.90 kg/m² and mean BMI for control subjects was 26.68 ± 4.75 kg/m².

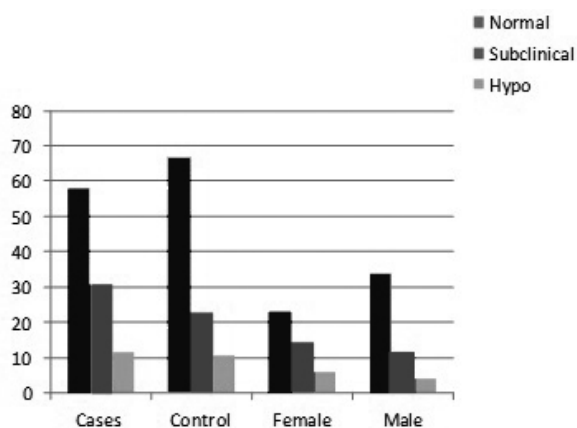


Fig. 1: Distribution of thyroid stimulating hormone (TSH) levels in case and control groups in relation to gender.

The mean serum TSH levels among cases (2.79 ± 4.86) was higher than controls (2.03 ± 4.13 ; $p=0.01$). Subclinical hypothyroidism was noted in 30.6% of cases and 22.5% of controls, whereas hypothyroidism was detected in 34 (10.8%) controls and 17 (11.3%) cases (Table 1). If those with serum TSH levels between 2.5 and 5.0 were considered at risk for subclinical hypothyroidism, then a difference between case and control groups ($p<0.05$) was observed. The mean serum T4 levels between the case (9.69 ± 5.19) and control (7.9 ± 6.6) groups was statistically significant ($p<0.01$). Subclinical hypothyroidism was found to be more prevalent in females in both groups (61.8% for cases and 51.3% for controls).

Table 1: Means of variables between case and control groups.

Group Variables	Case group	Control group	p-value
Sex (M/F)	63/88	166/181	<0.05
Age	59.49 ± 18	59.53 ± 17	0.91
BMI	29.97 ± 4.9	26.68 ± 4.7	0.007
TSH	2.79 ± 4.86	2.03 ± 4.13	0.01
T4	9.69 ± 5.19	7.9 ± 6.6	0.02
FBS	109.8 ± 47.5	110.2 ± 37.8	0.94
Cholesterol	189.75 ± 61.10	188.2 ± 43.10	0.61
TG	169.83 ± 133.0	143.07 ± 101.02	0.05
HDL	73.35 ± 43.08	46.41 ± 13.63	<0.05
LDL	64.81 ± 39.47	111.04 ± 39.73	<0.05
AST	83.09 ± 86.29	21.66 ± 9.01	<0.05
ALT	100.12 ± 109.30	19.23 ± 8.42	<0.05

BMI: Body mass index; TSH: Thyroid stimulating hormone; T4: Serum total thyroxin; FBS: Fasting blood sugar; TG: Triglycerides; HDL: High density lipoprotein; LDL: Low density lipoprotein

This study evaluated a number of metabolic factors that included BMI, TG, HDL, LDL, and total cholesterol. There was a difference in BMI between cases (29.97 ± 4.90) and controls (26.68 ± 4.75 ; $p<0.01$). The mean total cholesterol levels in cases was slightly higher than in controls, but was not significant ($p=0.61$). There was a statistically significant difference in HDL and LDL levels between the two groups. According to bivariate analysis, cholesterol levels have an association with CBD

stones. The ratio of TG levels in the case and control groups was 1.18 ($p < 0.05$; Table 1).

According to multivariate analysis, there was no confirmed correlation between hypothyroidism (95% CI: 0.968-2.438) and subclinical hypothyroidism (95% CI: 0.578-2.043) with CBD stone. However the TSH levels were significantly different between both groups (OR: 3.07; 95% CI: 1.51-6.24), which could be a risk factor for the development of CBD stones. The potential risk for developing subclinical hypothyroidism showed no statistical association with CBD stone formation (OR: 1.34; 95% CI: 0.790-2.279), although it might be considered a risk factor. There was no association between LDL and TG.

DISCUSSION

During last two decades the etiologies of choledocholithiasis have been evaluated more seriously. In addition to classic risk factors such as age, gender, obesity and genetics, the associations between CBD stones and delayed emptying of the biliary tract in hypothyroidism have been shown. This is related to lack of the prorelaxing effect of the thyroid hormone on SO contractility.¹⁻³ In this study we have evaluated the prevalence of thyroid dysfunction in patients with CBD stones.

Serum TSH is a hallmark of thyroid dysfunction. The subclinical form of hypothyroidism is characterized by increased serum TSH levels along with normal serum FT4 levels and a lack of clinical symptoms. The mean TSH levels in the present study among the case group were higher than the control group. Although subclinical hypothyroidism was more common in patients with CBD stones (OR: 1.53; 95% CI: 0.968-2.433), this difference was not significant. There were more females with subclinical hypothyroidism in both groups in this study. This can possibly be attributed to the fact that females have usually been more considered to have thyroid dysfunction. A study by Laukkarinen has shown subclinical hypothyroidism to be a common problem among patients with CBD stones. He concluded that hypothyroidism played a role in the formation of CBD stones secondary of its effects

on SO relaxation; which in turn might be influence on emptying of the biliary system. The pro-relaxing effect of T4 on SO has been previously reported.^{4,6,9} In the present study, there was a close relation between T4 levels according to binary analysis with choledolithiasis ($p < 0.01$) which was similar to earlier studies, however this was not confirmed in multivariate analysis.^{5,9} Some studies have reported that thyroxin replacement therapy has a positive effect on cholesterol level, cardiovascular, neuromuscular and choledolithiasis.¹⁰⁻¹⁴ We did not evaluate the influence of thyroxin replacement therapy.

It is expected that increasing age increases subjects' exposure to risk factors of CBD stones or thyroid dysfunctions. In our study there was no association between age and thyroid disorders which might be related to the number of patients. This correlation has been reported in different studies. In one study on cadavers there was a positive relationship between age and prevalence of cholelithiasis.² According to different studies, among the elderly, the rate of hyperthyroidism was 2.1-6% and for hypothyroidism it was 2.0-2.9%. The prevalence of subclinical hypothyroidism in women older than 60 years of age was 11.4% in CBD-stone patients compared with 1.8 % in control patients.¹⁵⁻¹⁹

We have also evaluated metabolic factors in these two groups. Obesity is considered as a risk factor for gallstones. Supersaturated bile among obese subjects may be a mechanism for this phenomenon. In our study, there were more overweight cases compared to controls which supported results from previous studies.^{15,20}

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. In the present study, although the mean cholesterol levels in the case group was not comparable with the control group, differences were observed in mean HDL, LDL, and TG levels. These results were almost consistent with other studies.^{15,20} In regression multivariate analysis, we concluded that serum-TSH level was an independent factor that could be

considered a risk factor for the formation of CBD stones (OR: 3.07; 95% CI: 1.51-6.2). HDL levels, however, had a negative correlation.

In conclusion, thyroid dysfunction is more common among patients with CBD stones and it may be a risk factor for biliary stone formation. This may be attributed to the absence of the pro-relaxing effects of thyroid hormones.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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