ORIGINAL RESEARCH

Association between subclinical hypothyroidism and gallstone disease

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ABSTRACT

Introduction: Gallstone disease, also known as cholelithiasis is the most common biliary pathology worldwide. An increase in the prevalence of hypothyroidism, possibly associated with gallstones, might affect the diagnostic and therapeutic procedures in patients with gallstones.

Aim: To investigate the association between subclinical hypothyroidism and gallstone disease.

Methods: This observational study was conducted which included patients with gallstones.Patients were examined for serum thyroid-stimulating hormone levels to screen for thyroid dysfunction, and those with elevated levels were diagnosed with subclinical hypothyroidism.

Results: Total 250 patients were enrolled, of which 11 patients with clinical hypothyroidism were excluded from the study. Of the remaining 239 patients, 93 (38.91%) patients had subclinical hypothyroidism.The Majority of patients with subclinical hypothyroidism (58.1%) belonged to the age group of 33-46 years. Most of the patients with subclinical hypothyroidism were female (74.2%). Patients with subclinical thyroid status were more likely to have positive family history, multiple calculi and larger stone size than patients with normal thyroid status. A positive family history of hypothyroidism (OR=4.530, P=0.009), having multiple calculi (OR=3.420, P<0.001) and having a stone size larger than 10 m(OR=4.020, P=0.002)were all found to be independent risk factors for subclinical hypothyroidism.

Conclusion: Subclinical hypothyroidism may be a significant risk factor for the development of gallstone disease highlighting the importance of routine thyroid function screening in patients with cholelithiasis.

Keywords: cholelithiasis, gallstones, subclinical hypothyroidism, thyroid-stimulating hormone.

INTRODUCTION

Gallstone disease, also known as cholelithiasis, is the most common biliary pathology worldwide, with substantial geographical variation in the incidence rates.[1] It is estimated to affect approximately 4% of the population in India, whereas it affects about 10% to 15% of the population in the US.[2,3] Gallstones can be pigmented, cholesterol, or mixed depending on their composition 4.The most common cause of gall stone development is a bile chemical imbalance, resulting from the precipitation of one or more bile ingredients in the gallbladder [1].Gallstone formation is complex and multifactorial, and one of the contributing factors is believed to be a hypothyroid state.[4]. Subclinical hypothyroidism is characterized by elevated serum thyroid-stimulating hormone (TSH) levelsdespite normal levels of serum free thyroxine (T4).It is more prevalent among women and tends to increase with age. Subclinical hypothyroidism is highly likely to progress to clinical hypothyroidism, which is the most important implication[4]. Hypothyroidism may delay biliary tract emptying due to decreased pro-relaxing tendency of the sphincter of Oddi, which expresses the thyroid hormone receptors β1 and β2. This can result in bile stasis, making patients more prone to developing gallstones[5]. The rising prevalence of hypothyroidism,which may be associated with gallstones, can have an impact on the

diagnostic and therapeutic procedures in patients with gallstones. Therefore, the present study aimed to investigate the association between subclinical hypothyroidism and gallstone disease.

MATERIALS AND METHODS

Study design and setting: This observational study was conducted at the Department of Surgery, Himalayan Institute of Medical Sciences (HIMS), Dehradun. The study received approval from the Hospital Ethics Committee and written informed consent was obtained from each patient prior to their recruitment into the study.

Inclusion and exclusion criteria: Patients (18 to 65 years of age) presented at the outpatient department, diagnosed with gallstones by ultrasonography were included in the study. Patients who were diagnosed with hypothyroidism and currently taking medication, as well as those with a previous history of thyroid surgery or radioactive thyroid ablation were excluded from the study.

Study investigations: Patients were examined for subclinical hypothyroidism by testing fasting blood samples for serum thyroid-stimulating hormone (TSH). Patients were diagnosed with subclinical hypothyroidism on the basis of serum TSH value >4.25 μIU /mL (Normal range of TSH: 0.30-4.25 μIU/mL).

Sample size calculation: In this study, the prevalence of subclinical hypothyroidism in gallstone disease was based on a previous study by Manjusha et al. 6. According to this reference study, the prevalence of subclinical hypothyroidism in gallstone disease was 26%. This prevalence was used to calculate the required minimum sample size using the formula $N= Z^2_{\alpha/2} PQ / d^2$, whereZ is the standard normal deviate at 0.1 level of significance (1.64), P is the prevalence of subclinical hypothyroidism in gall bladder stone disease (26%), Q is the complement of P (74%), and d is the relative precision or error (20%). Based on these parameters, the minimum sample size required was 203. However, the sample size for this study was increased to 250 to increase the power of the study and account for potential dropouts or incomplete data.

Statistical analysis: Data were analyzed using statistical package for social sciences (SPSS) software Version 22. Descriptive statistics was used to describe categorical variables (frequency and percentages). Normally distributed data were analyzed using parametric test and not-normally distributed data were analyzed using non-parametric test. Qualitative and quantitative data were analyzed using Chi-squared and independent t-test or ANOVA, respectively. Multivariate analysis was used for assessing the risk factors of subclinical hypothyroidism in patients with gallstones. A P value <0.05 was considered statistically significant.

RESULTS

A total of 250 patients were enrolled, of which 11 patients with clinical hypothyroidism were excluded from the study. Of the remaining 239 patients, 146 (61.08%) patients had normal thyroid levels and 93 (38.91%) patients had subclinical hypothyroidism. Table1 depicts the association of different parameters with thyroid status in patients with gallstones. The majority of patients with subclinical hypothyroidism (58.1%) belonged to the age group of 33-46 years. Most of the patients with subclinical hypothyroidism were female (74.2%). However, there was no significant association between age group and gender of the patients with gallst one sand subclinically pothyroidism(P >0.05). The family history of hypothyroidism was significantly associated with subclinical hypothyroidism compared to normal thyroid levels (43.0 vs. 25.3%; P=0.007).Majority of patients with subclinical hypothyroidism had multiple calculi (59.1%). Of the 239 patients included in the study, 131 (54.8%) had a single calculus and 108 (45.2%) had a multiple calculi. The distribution of number of calculi varied significantly by thyroid status. Patients with subclinical thyroid status were more likely to have multiple calculi than patients with normal thyroid status (P=0.001). A total of 138 patients had stones smaller than 10 mm, while 101 patients had stone larger than 10 mm. The distribution of stone size also varied significantly by thyroid status (P= 0.001). Patients with stones larger than 10 mm were more likely to have subclinical hypothyroidism (54.8%) than those with stones smaller than 10 mm (34.2%). The multivariate analysis showedthat the risk of subclinical hypothyroidism increased with increasing age. The odds ratio of female patients was 1.26 times (95% CI: 0.651 - 2.45) higher than that of male patients, although this difference was not statistically significant. A positive family history of hypothyroidism (OR=4.530, 95% CI 2.5-8.2, P=0.009), having multiple calculi (OR=3.420, 95% CI 1.94-6.04, P<0.001) and having a stone size larger than 10 mm(OR=4.020, 95% CI 2.28-7.07, P=0.002)were all found to be independent risk factors for subclinical hypothyroidism[Table2]. thyroid levels (43.0 vs. 25.3%; P=0.007).Majority of patients with subclinical hypothyroidism had multiple calculi (59.1%). Of the 239 patients included in the study, 131 (54.8%) had a single calculus and 108 (45.2%) had a multiple higher than that of male patients, although this difference was not statistically significant. A positive family history of hypothyroidism (OR=4.530, 95% CI hypothyroidism increased with increasing age. The odds ratio of female patients was 1.26 times (95% CI: 0.651 - 2.45) higher than that of male patients, although this difference was not statistically significant. A positive

family history of hypothyroidism (OR=4.530, 95% CI 2.5-8.2, P=0.009), having multiple calculi (OR=3.420,

Table1: Association of different parameters with thyroid status among patients with gallstones

Parameters	Thyroid status		Total (N=239)	P value
	Normal (N=146)	Subclinical hypothyroidism (N=93)		
Age group (years)				
18 – 32	23 (15.8)	10 (10.8)	33 (13.8)	0.650
33 – 46	74 (50.7)	54 (58.1)	128 (53.6)	
>46	49 (33.6)	29 (31.2)	78 (32.6)	
Gender				
Male	32 (21.9)	24 (25.8)	56 (23.4)	0.532
Female	114 (78.1)	69 (74.2)	183 (76.6)	
Family history of hypothyroidism				
Yes	37 (25.3)	40 (43.0)	77 (32.2)	0.007
No	109 (74.7)	53 (57.0)	162 (67.8)	
Number of calculi				
Single	93 (63.7)	38 (40.9)	131 (54.8)	0.001
Multiple	53 (36.3)	55 (59.1)	108 (45.2)	
Size of stone (mm)				
<10mm	96 (65.8)	42 (45.2)	138 (57.7)	0.002
>10mm	50 (34.2)	51 (54.8)	101 (42.3)	
Data presented as n (%).				

Table2: Multivariate analysis for assessing the risk factor of subclinical hypothyroidism among patients with gallstones

Associated Variable		OR	95% CIfor OR		Pvalue
			Lower	Upper	
Age	18 – 32 years	1			
	33 – 46 years	.85	.245	2.29	0.540
	>46 years	1.123	.499	3.07	0.220
Sex	Male	1			0.489
	Female	1.264	.651	2.455	
Family history of hypothyroidism	No	1			0.009
	Yes	4.530	2.5	8.2	
Number of calculi	Single	1			<0.001
	Multiple	3.420	1.94	6.04	
Size of Stone	<10 mm	1			0.002
	>10 mm	4.020	2.28	7.07	
CI, confidence interval; OR, odds ratio.					

DISCUSSION

Gallstone disease is one of the most prevalent gastroenterological diseases and a common cause of hospitalization in gastroenterology. Predisposing factors for gallstone development include advanced age, female sex, hypercaloric diet, obesity and genetic factors[7].One well-known factor for the development of gallstones is the stasis of biliary products resulting from hypothyroidism.There are several reasons why hypothyroidism and gallstone disease may be linked. These include disruptions in lipid metabolism that can alter bile composition[8]. Studies have shown that hypothyroid subjects have reduced bile flow[9], and thyroxine has a direct relaxing effect on the sphincter[10]. Both low bile flow and sphincter dysfunction are thought to contribute to the development of gallstones[11]. In this study, 93 (38.91%) out of 239 patients with gallstones were diagnosed with subclinical hypothyroidism. Dhoka G et al. observed that 24.4% of patients diagnosed with cholelithiasis had subclinical hypothyroidism. Ina study conducted byAhmed N et al., the prevalence of subclinical hypothyroidism was 17.5%, whereas, Lai CC et al. reported an overall 2.0% prevalence of subclinical hypothyroidism[12, 13]. Gallstones are more likely in patients aged 40 years and above due to a decline in the activity of cholesterol 7 α -hydroxylase, an enzyme limiting the bile acid synthesis. This results in increasing cholesterol saturation and decreasing mobility of gallbladder emptying in aging individuals[3]. The present study showed that about 58.1% patients with subclinical hypothyroidism belonged to the age group of 33-46 years.This is comparable to the study in which all patients with

subclinical hypothyroidism were in the age group of 38–53 years [14]. Gender is a prominent risk factor for gallstone disease. A previous study hasreported that women are generally at higher risk of gallstone disease than men because of women's naturally higher estrogen levels, maternity, or ingestion of estrogen-based oral contraceptives[3].On similar lines, in this study,there was a female predominance of74.2%.Similarly, Ahmed N et al, reported 78.57% female predominance in the subclinical hypothyroid group; Ghadhban BR et al. reported 75% females with subclinical hypothyroidism [12, 14]. In this study, a positive family history was recorded in 43% of subclinical hypothyroidism patients. This prevalence wascomparatively lower than the study done by Ghadhban BR et al., where among subclinical hypothyroidism, 75% patients had positive family historyand 25% patients had negative family history[14]. This study showed that majority of patients (59.1%)with subclinical hypothyroidism had multiple calculi. However, Ahmed N et al. reported that 57.14% patients with subclinical hypothyroidism presented with single stones[12].Another study also showed that the patients with subclinical hypothyroidism had more prevalence of single gallstone (62.5%) than multiple stones (37.5%)[14].In present study, 54.8% patients with subclinicalhypothyroidism had stone size >10 mm. These results were comparable to the study whereall stones in patients with subclinical hypothyroidism were >1cm[12]. The major risk factors for cholesterol gallstones have been associated with aging, female gender, ethnicity, obesity, and the westernized diet[12]. Some of these risk factors hold true for this study where the multivariate analysis showed that patients with gallstones who have a positive family history of hypothyroidism, multiple calculi, or larger stones may benefit from routine thyroid function screening to detect subclinical hypothyroidism.

CONCLUSION

This study highlighted the importance of considering thyroid function in patients with cholelithiasis, particularly in females, those with family history, multiple calculi, and larger gallstone size.Overall, findings results suggest that various factors, including family history, stone size, and number of calculi, may be important in predicting the risk of subclinical hypothyroidism among patients with gallstones. Routine screening for thyroid dysfunction in these patients may help identify those with subclinical hypothyroidism and potentially reduce the risk of developing gallstone disease.

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