Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

The Prevalence of Hypothyroidism in Patients with Biliary Sludge and Gallstones

Raheleh Jabini(PhD)[1], Seyyed Mousa Alreza Hoseini (MD)[2], Maryam Shirdeli (MD)[3], Ali Alabaf Yousefi (MD)[3], Mohammad Reza Farzaneh Far (MD)[2].

[1]*Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2]*Department of Internal Medicine (Gastroenterology and Hepatology), Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3]*Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*

ARTICLE INFO

Article type
Original article

Article history
Received: 12 Sep 2019
Revised: 26 Mar 2020
Accepted: 14 Jun 2020

Keywords
Gallbladder Diseases
Gallstone
Hypothyroidism

ABSTRACT

Introduction: Gallbladder stone and sludge are common diseases worldwide. The causes of gallbladder stone and sludge are numerous. Since some studies have reported the effects of thyroid hormones on the function of the sphincter of Oddi and biliary discharge, the present study aimed to evaluate hypothyroidism as a risk factor for gallbladder stone formation.

Methods: This case-control study was conducted on patients whose sonography indicated gallbladder sludge or stone and those referring to our clinic with pain in the right upper quadrant of the abdomen. All the patients were initially examined by a sonologist to confirm gallbladder stone and sludge. Afterwards, thyroid function tests (TSH, T4, and T3RU via radioimmunoassay) were requested for the patients, and the results were analyzed and compared with the control group.

Results: Among 318 patients, 171 (53.77%) were male. In the case group, six females (8.4%) and 10 males (11.2%) had hypothyroidism. Overall, 9.9% of the patients (n=16) had hypothyroidism. In the control group, the prevalence of hypothyroidism was 2.5% (n=4) (OR: 2.082; 95% CI: 1.022-11.046; P=0.017). In the case group, 4.3% (n=7) had subclinical hypothyroidism, and 5.6% (n=9) had clinical hypothyroidism, while in the control group, only 1.9% of the patients (n=3) showed signs of subclinical hypothyroidism, and 0.6% (n=1) showed signs of clinical hypothyroidism. In the patients with gallbladder sludge and stone, the prevalence of clinical hypothyroidism was higher than subclinical hypothyroidism.

Conclusion: According to the results, hypothyroidism was prevalent in the patients with gallbladder stone and sludge. Therefore, it is recommended that the thyroid function of patients with gallbladder stone and sludge be examined even if the patients do not harbor any other risk factors for the disease.

Please cite this paper as:
Jabini R, Hoseini SMA, Shirdeli M, Alabaf Yousefi A, Farzaneh Far MR. The Prevalence of Hypothyroidism in Patients with Biliary Sludge and Gallstones. Rev Clin Med. 2020;7(1):5-9.

Introduction

There are numerous discussions involving hypothyroidism and its possible association with gallstone formation (1, 2). Some studies have revealed that altered bile composition, low bile flow rate, the sphincter of Oddi disorders, and gallstone formation may be the consequences of hypothyroidism and altered lipid metabolism (3).

In a study involving the comparison of 668 female patients undergoing cholecystectomy for gallstone disease with 782 controls, 2.4% and 0.8% of the subjects received treatment for hypothyroidism in the patient and control groups, respectively (1). In another research, only 1% of the control subjects were diagnosed with hypothyroidism, while 8% of the patients had common bile duct stones, and 6% of those with gallbladder

***Corresponding author:** Mohammad Reza Farzaneh Far.
Department of Internal Medicine (Gastroenterology and Hepatology), Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: Farzanehfm@mums.ac.ir
Tel: +989155083486*

stones were diagnosed with hypothyroidism (2).

According to the literature, the use of thyroxine could contribute to the dissolution of gallstones (1). However, the possibility of the spontaneous passage of the gallstone into the duodenum should also be considered in this case report (1). In a study conducted on rabbits, which received a high-fat diet to promote the formation of gallstones, thyroxine use was correlated with lower gallstone weight without the complete dissolution of the stones (2).

The present study aimed to determine the prevalence of hypothyroidism in patients with gallbladder stones and sludge and compare them with the controls without gallstones.

Methods

This case-control study was conducted at Ghaem Hospital in Mashhad, Iran during 2014-2017. All the patients were informed of the research objectives and provided written consent. The study protocol was approved by the Ethics Committee of the School of Medicine at Mashhad University of Medical Sciences. The patients visiting our clinic with abdominal pain in the right upper quadrant underwent sonography to investigate the presence of gallbladder stones or sludge.

The patients with gallbladder stones or sludge, as well as those whose gallbladder stone or sludge was incidentally found, were enrolled in the study as group I (n=161; median age: 42 years; age range: 18-79 years). The control patients (group II; n=157; median age: 41 years; age range: 21-80 years) were selected from the individuals who met the inclusion criteria.

The inclusion criteria of the study were no gallstones in ultrasonography/medical history, no history of cholecystectomy, and no history of diagnosis/treatment for thyroid function abnormalities. The patients receiving phenytoin or carbamazepine therapy, pregnant women, patients with a history of infertility, diabetes mellitus, voluntary weight loss or gallstone/cholecystectomy in the first-degree relatives were excluded from the study. The sonographers were blinded to the clinical conditions and laboratory results of the subjects, and the US examinations were carried out following a standard protocol.

Serum free thyroxine (S-FT4; radioimmunoassay; normal range: 0.8-2.7 ng/dl), thyroid stimulating hormone (S-TSH; radioimmunoassay; normal range: 0. 5-4.7 mU/l), and T3RU (S-T3RU; radioimmunoassay; normal range: 0.83-1.17 mole ratio) were measured in the blood samples that were obtained in the morning at the laboratory of Ghaem Hospital, and the results were compared between the case and control groups. The symptom-free patients with higher S-TSH concentrations than the upper limit of the normal range (5.0 mU/l) were recorded as the cases of subclinical hypothyroidism, and those with S-TSH levels close to the upper limit (10 mU/l) were considered to have clinically hypothyroidism.

Statistical Analyses

Data analysis was performed in SPSS version 13. To compare the values between the case and control groups, χ^2 was used for the nominal data, and the analysis of variance (ANOVA) was applied for the continuous data. The quantitative data were expressed as mean and standard deviation, and the P-value of less than 0.05 was considered statistically significant.

Results

The age and gender of the patients had similar distributions in groups I (gallbladder [GB] stone) and II (control). The GB group included 89 male (55%) and 72 female patients (45%), and the control group included 82 men (52%) and 75 women (48%). The differences in this regard were considered significant between the groups.

According to the findings, the S-TSH level was above the upper normal range (5.0 mU/l; subclinical hypothyroidism) in seven patients with GB stone (4.3%) compared to the three subjects in the control group (1.9%; OR: 0.256; 95% CI: 0.088-0.750; P=0.029). In addition, nine patients with GB stone (5.6%) had S-TSH levels close to the upper limit (10 mU/l; clinical hypothyroidism) compared to one control patient (0.6%; OR: 4.221; 95% CI: 1.379-12.922; P=0.007). In total, 4.3% and 5.6% (total: 9.9%, 16 out of 161 patients) of the patients with GB stone had subclinical or clinical hypothyroidism, respectively compared to 1.9% with subclinical hypothyroidism and 0.6% with clinical hypothyroidism in the control group (total: 2.5%, four out of 157 controls; OR: 2.082; 95% CI: 1.022-11.046; P=0.017).

In the GB stone group, the prevalence of subclinical hypothyroidism (S-TSH≥5.0 mU/l) and clinical hypothyroidism (S-TSH≥10 mU/l) in women was 2.8% and 5.6%, respectively (total 8.4%). The rate was estimated at 5.6% and 5.6% (total: 11.2%) in the male patients of the GB stone group. Moreover, the prevalence of hypothyroidism (subclinical and clinical) was higher in men compared to women, while clinical hypothyroidism had a higher prevalence compared to subclinical hypothyroidism (Table 1).

Discussion

The present study aimed to evaluate the association between hypothyroidism and GB stones.

Table 1. Frequency of Healthy Participants and Patients with Subclinical/Clinical Hypothyroidism Based on S-TSH Levels in Group I (GB stone) and Group II (control) Overall and Based on Age Group

Age (year)	Total		Hypothyroidism (Total)			Men (Hypothyroidism)			Women (Hypothyroidism)		
Group I	N	%	Healthy	Sub-clinical	Clinical	Healthy	Sub-clinIcal	Clinical	Healthy	Sub-clinical	Clinical
10-20	1	0.62	1	0	0	0	0	0	1	0	0
20-30	29	18.01	27	1	1	13	1	0	14	0	1
30-40	60	37.26	54	3	3	30	2	1	24	1	2
40-50	37	22.98	32	2	3	20	1	2	12	1	1
50-60	25	15.52	23	1	1	13	1	1	10	0	0
60-70	5	3.1	5	0	0	2	0	0	3	0	0
70-80	4	2.48	3	0	1	1	0	1	2	0	0
Total	161	100	145 (90.1%)	7 (4.3%) α	9 (5.6%) β	79 (88.8%)	5 (5.6%)	5 (5.6%)	66 (91.7%)	2 (2.8%)	4 (5.6%)
Group II											
10-20	0	0	0	0	0	0	0	0	0	0	0
20-30	22	14.01	22	0	0	12	0	0	10	0	0
30-40	60	38.21	58	1	1	27	0	1	31	1	0
40-50	38	24.20	37	1	0	17	0	0	20	1	0
50-60	27	17.19	27	0	0	16	0	0	11	0	0
60-70	7	4.45	6	1	0	4	0	0	2	1	0
70-80	3	1.91	3	0	0	2	0	0	1	0	0
Total	157	100	153 (97.5%)	3 (1.9%) α	1 (0.6%) β	78 (98.73%)	0 (0%)	1 (1.27%)	75 (96.15%)	3 (3.85%)	0 (0%)

α: (P=0.029; subclinical hypothyroidism between groups I and II)

β: (P=0.007; clinical hypothyroidism between groups I and II)

α+β: (P=0.017; clinical and subclinical hypothyroidism between groups I and II)

Previously findings have suggested a possible correlation between common bile duct (CBD) stones and hypothyroidism, and the lack of the prorelaxing effect of T4 on the contractility of the sphincter of Oddi has been reported as the main cause of this observation (1-4).In the current research, the prevalence of hypothyroidism and GB stone was also investigated. According to the obtained results, the prevalence of subclinical and clinical hypothyroidism was significantly higher in the GB stone group compared to the controls (P=0.017). In addition, hypothyroidism was more common among men (11.2%) compared to women (8.4%). However, no significant differences were observed in age and gender between the control and GB stone groups. In the present study, the control subjects had no history of GB stones and gallstones as indicated in the ultrasonography. According to a study in this regard, approximately 95% of GB stones could be detected via ultrasonography (5). Since the control patients in the present study were not suspected of GB stones, only ultrasonography was used for the detection of GB stones, and other methods (e.g., magnetic resonance cholangiopancreatography) were not applied to further investigate the presence of stones.

Increased S-TSH concentration is considered to be the most prominent indicator of primary hypothyroidism, and the tests used for the measurement of S-TSH levels are most sensitive for the detection of early thyroid failure. In the present study, the patients with lower S-FT4 concentrations were considered clinically hypothyroid (6), while the patients with the subclinical form of the condition showed no symptoms with the elevated levels of S-TSH and normal S-FT4 concentrations (7).

According to the findings of the current research, 4.3% of the patients with GB stones had higher S-TSH levels than the upper limit of the normal range (i.e., subclinical hypothyroidism) as opposed to 1.9% of the control patients (OR: 0.256; 95% CI: 0.088-0.750; P=0.029). Furthermore, nine patients (5.6%) in the GB stone group had higher S-TSH levels than the normal range (i.e., clinical hypothyroidism) as opposed to only one patient (0.6%) in the control group (OR: 4.221; 95% CI: 1.379-12.922; P=0.007). Therefore, it could be concluded that the subclinical and clinical forms of hypothyroidism were significantly more common in the patients diagnosed with GB stones compared to the control patients (OR: 2.082; 95% CI: 1.022-11.046; P 0.017).

In the present study, the determination of serum thyroid hormones was performed only once for each individual. As such, the obtained results are not based on the recorded persistent abnormalities. However, the thyroid hormone levels were evaluated equally in both groups. Presumably, repeated evaluations would not have significantly altered the prevalence of subclinical and borderline subclinical hypothyroidism between the study groups, while in clinical practice, the recording of a constant abnormality is preferred.

According to the current research, the prevalence of hypothyroidism was higher in men, while no such associations were identified in the female subjects. In the male population, the high serum TSH level was considered as an independent risk factor for cholelithiasis, which is consistent with the previous findings in this regard (1, 6). The absence of such an association among the female subjects could be justifies in two ways. Firstly, the study population only encompassed the individuals who were diagnosed with thyroid disorders until the time of the study, and more women were excluded from the study due to known thyroid disorders. Therefore, it could be inferred that hypothyroidism could be detected and treated earlier in women. Similarly, more women were observed to have cholelithiasis, which reflected the higher prevalence of cholecystectomy in this population. Gallstone symptoms may appear at earlier stages in women and lead to further medical interventions for hypothyroidism treatment. The association between high serum TSH levels and cholelithiasis is mainly observed in men and reinforces this assumption. Secondly, the male and female genders differ in terms of the type of gallstones. In a study in this regard (7), cholesterol stones were reported to be less common in men. It might be assumed that if gallstone disease is partly caused by hypothyroidism, stones with other compositions than cholesterol should form in men. The same study (9) failed to find an association between thyroid function and type of stones. The influential factors in bile content and flow contribute to the pathogenesis of GB stones. Biliary stasis, which could lead to decomposition by anaerobic bacteria and biliary lipid precipitation, could cause brown pigment stones (11, 12). A plugged biliary tract contributing to biliary stasis could also be caused due to bile duct strictures, sphincter of Oddi (SO) stenosis, and SO dyskinesia (8-10). Brown-pigment stones may also surround the nidus of black, cholesterol stones or foreign material, similarly plugging the CBD. Consequently, it is difficult to disrupt or reverse the pathogenic mechanism of stasis and bacterial overgrowth after they begin. As an individual ages, brown stones become more common, which is possibly due to the degradation of the SO function (8).

Thyroid hormones affect cholesterol metabolism variably (13-15). In hypothyroidism, the increased serum concentrations of cholesterol could super-saturate the bile with cholesterol, which in turn leads to GB hypomotility (11), lowered contractility (12), and hampered filling (13), extending the time that the bile remains in the GB. Bile accumulation causes the cholesterol crystals to have sufficient time for nucleation and development into mature GB stones (11). Furthermore, the lower rate of bile secretion (19) hinders the process of precipitate clearing in the bile ducts and GB.

In the current research, the levels of thyroid hormones were measured in the patients with GB stones. If T4 or its absence only affected the cholesterol metabolism and hepatic bile secretion, the patients with GB and CBD stones would presumably show the equally increased prevalence of diagnosed or subclinical hypothyroidism. In another research in this regard, hypothyroidism was reported to be twice as commonly diagnosed in patients with CBD stones compared to those with GB stones (1), which could be due to the formerly shown reduction in the prorelaxing effect of T4 on the SO in hypothyroidism (2, 14), ultimately leading to the postponed emptying of the bile duct into the duodenum (3, 4) and causing a suitable environment for the configuration or retention of

CBD stones.

Thyroid hormones are circulated enterohepatically (17, 18). Therefore, it is theoretically possible for lowered bile acid secretion to interfere with T4 circulation, which in turn increases the clearance of thyroid hormones and triggers hypothyroidism if the thyroid reserves of the individual are exhausted due to autoimmune thyroiditis for instance. This series of changes could explain the close correlation of hypothyroidism with GB stones (1), presumably as a corollary of T4 without a prorelaxing effect on the SO (29, 30). It could be further hypothesized that a direct effect is exerted on the SO contractivity as a consequence of reduced biliary T4 concentration. The prorelaxing effect of T4 on the SO has been reported in the experiments in-vitro (2, 16). However, it remains uncertain whether lower biliary T4 levels could have the same effects as lowered serum T4 levels with similar relaxation-impairing effects on the SO.

Conclusion

Traditional healers are considered to be a major public health concern as many people prefer these methods to conventional medicine for various reasons. Therefore, it is critical for healthcare authorities to raise the awareness of the community regarding this issue through implementing systematic planning in order to prevent future complications. This issue could be tackled by identifying the workplaces of the “Bandis” who practice illegally and stopping their activities, especially in the case of pediatric medicine.

Acknowledgements

Hereby, we extend our gratitude to the Research Deputy of Mashhad University of Medical Sciences for the financial support of this research project.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Inkinen J, Sand J, Nordback I. Association between common bile duct stones and treated hypothyroidism. Hepatogastroenterology. 2000;47:919-921.
2. Laukkarinen J, Sand J, Aittomäki S, et al. Mechanism of the prorelaxing effect of thyroxine on the sphincter of Oddi. Scand J Gastroenterol. 2002;37:667-673.
3. Laukkarinen J, Kööbi P, Kalliovalkama J, et al. Bile flow to the duodenum is reduced in hypothyreosis and enhanced in hyperthyreosis. Neurogastroenterol Motil. 2002;14:183-188..
4. Laukkarinen J, Sand J, Saaristo R, et al. Is bile flow reduced in patients with hypothyroidism? Surgery. 2003;133:288-293.
5. Laukkarinen J. The Effect of Thyroxine on Biliary Motility: Tampere University Press; 2002.
6. Honore L. A significant association between symptomatic cholesterol cholelithiasis and treated hypothyroidism in women. J Med. 1981;12:199-203..
7. Trotman BW, Soloway RD. Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. Am J Dig Dis. 1975;20:735-740..
8. Thistle JL. Pathophysiology of bile duct stones. World J Surg. 1998;22:1114-1118.
9. Osnes M, Løotveit T, Larsen S, Aune S. Duodenal diverticula and their relationship to age, sex, and biliary calculi. Scand J Gastroenterol. 1981;16:103-107..
10. Sandstad O, Osnes T, Skar V, et al. Common bile duct stones are mainly brown and associated with duodenal diverticula. Gut. 1994;35:1464-1467.
11. Donovan JM. Physical and metabolic factors in gallstone pathogenesis. Gastroenterol Clin North Am. 1999;28:75-97.
12. Biancani P. Gallbladder contraction in patients with pigment and cholesterol stones. Gastroenterology. 1989;97:1479-1484.
13. Jazrawi RP, Pazzi P, Petroni ML, et al. Postprandial gallbladder motor function: refilling and turnover of bile in health and in cholelithiasis. Gastroenterology. 1995;109:582-591.
14. Inkinen J, Sand J, Arvola P, Pet al. Direct effect of thyroxine on pig sphincter of Oddi contractility. Dig Dis Sci. 2001;46:182-186.