Hypoteriosis as a risk factor for development cholelithiasis

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Abstract: The article give information about hypoteriosis as a risk factor for development cholelithiasis.

Keywords: cholelithiasis, sphincter mechanism, hypothyroidism, biliary emptying, cholesterol metabolism

Introduction. Gallstone disease (GSD) is mentioned as a common pathology of the biliary tract, and gallstones can be pigmented, cholesterol, or mixed [1]. The literature shows that 2.4% of female patients treated for hypothyroidism underwent cholecystectomy [1; 2]. Impaired cholesterol metabolism, insufficient bile secretion and disruption of the sphincter mechanism of Oddi and sphincter relaxation are believed to contribute to the development of cholelithiasis and the formation of gallstones in the gall bladder and bile duct among patients with hypothyroidism [3-5]. Volzke et al. studied and presented results on the association between high levels of thyroid-stimulating hormone (TSH) and gallstones [6]. In 2003, Laukkarrinen et al. explained the long time of biliary emptying in cases of hypothyroidism [7], which is consistent with the findings of Bauer M et al. that there is a relationship between cholelithiasis and increased serum TSH levels [8]. In their studies, they proved that the prevalence of hypothyroidism (subclinical or clinical) in patients with cholelithiasis is about 8.8% [5; 9]. It is believed that cholelithiasis is the most common pathology of the biliary tract. To our knowledge, there are only a few published articles that discuss the prevalence of undiagnosed subclinical hypothyroidism among patients with cholelithiasis [10].

Target: determine the prevalence and correlation between hypothyroidism and gallstone disease.

MATERIAL AND METHODS. In a prospective non-randomized study, the results of 152 patients with a preliminary diagnosis of stones in the gallbladder and ducts were analyzed, who underwent ultrasound and ERCP in the SF RSNPTS and control studies of healthy participants in the number of 287 people. Patients were excluded with a history of previously diagnosed or treated thyroid dysfunction, a history of thyroidectomy, pregnancy, serious concomitant diseases, cholangitis, as

well as those prescribed drugs that are known to affect thyroid function, for example, phenytoin, carbamazepine, metoclopramide, amiodarone. The control group consisted of healthy people with no history of stone disease or elevated liver enzyme levels. Clinically, they were euthyroid and matched by gender and age. To ensure that the control group did not have asymptomatic stones in the bile ducts, all participants were examined using an HDI-3000 5 MHz ultrasound scanning complex. Patients with a history of cholecystectomy were excluded. The interview was administered directly to each patient with a questionnaire that included demographic and anthropometric data, past and present medical history, medication history, and symptoms of hypothyroidism. Written informed consent was signed. Morning blood samples were taken after 12 hours of fasting to measure total thyroxine (T4), thyroid-stimulating hormone (TSH), fasting blood sugar (FB), triglycerides (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Serum T4 and TSH were determined by immunofluorometry. The normal range for serum T4 was 6-12 IU/L; for TSH 0.25-5 IU/ml. For other laboratory analyses, the colorimetric method (Biosystem, Spain) was used. Subclinical hypothyroidism is defined as thyroid hormone levels that are within the normal range in the presence of a slightly elevated serum TSH (5 to 10 IU/ml). Hypothyroidism is characterized by elevated TSH levels greater than 10 IU/ml [7]. In case of borderline TSH levels, serum T4 and clinic were used to determine thyroid function. Patients with DM greater than 126 mg/dL (7 mmol/L) confirmed by repeated measurement were considered to have diabetes [8]. Dyslipidemia was defined as LDL levels greater than 130 mg/dL in diabetics and greater than 100 mg/dL in nondiabetics, HDL levels less than 50 mg/dL in women and less than 40 mg/dL in men, and TG greater than 150 mg/dL. Statistical analyzes were performed using SPSS version 16.0. Quantitative data were expressed as mean ± standard deviation (SD). P values <0.05 were considered significant. We used Mann-Whitney u tests and independent t tests for comparisons between groups. Cross-tabulations and chi-square tests were performed on qualitative variables.The association between the presence of gallstones and risk factors was assessed using multilevel logistic regression. The significance level for multivariate analyzes was 0.05. The risk of developing gallstones was estimated using odds ratios and 95% confidence intervals (CI).

RESEARCH RESULTS. A total of 152 patients with a mean age of 58.45±17.16 years formed the main cholelithiasis group, and 287 healthy people with a mean age of 59.29±17.51 years were in the control group. The main group included 58.6% were women, and in the control group - 52.1%. The average BMI of patients was: 29.28±3.52 kg/m2, and the average BMI in the control group was 27.93±3.99 kg/m2. The mean serum TSH level among patients (2.79±0.86) was higher than in controls (2.03±0.13; p=0.01). Subclinical hypothyroidism was noted in 32.2% of

cases and 19.5% of controls, while overt hypothyroidism was detected in 16.4% and 11.2% of cases, respectively. When patients with serum TSH levels between 2.5 and 5.0 mg/dL were considered at risk of subclinical hypothyroidism, there was a difference between the study and control groups ($p<0.05$). The mean serum T4 levels between the study (9.69±5.19) and control (7.9±6.6) groups were statistically significant ($p<0.01$). Subclinical hypothyroidism was found to be more common in women in both groups. The present study assessed a number of metabolic factors, which included: BMI, TG, HDL, LDL and total cholesterol. BMI indicators differed between patients of the main (29.97±4.90) and control groups (26.68±4.75; $p<0.01$). The difference in mean total cholesterol levels 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 are associated with cholelithiasis. The ratio of TG levels in the study 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 the formation of cholelithiasis. However, TSH levels differed significantly between both groups (OR: 3.07; 95% CI: 1.51-6.24), which could be related to the risk factor for the development of cholelithiasis. Potential risk of developing subclinical hypothyroidism did not show a statistical association with cholelithiasis (OR: 1.34; 95% CI: 0.790-2.279), although this could be considered a risk factor.There was no association between LDL and TG levels.

Table 1.

Mean values of variables between the main and control groups

Group variables	Main group	Control group	P-values
Age	59.49±18	59.53±17	0.97
BMI kg/m2	29.97±4.9	26.68±4.7	0.007
TSH IU/ml	2.79±0.86	2.03±0.13	0.01
T4 IU/l	9.69±5.19	7.9±6.6	0.02
SC mmol/l	5.9±0.05	6.7±0.07	0.94
Cholesterol, mmol/l	189.75±61.10	188.2±43.10	0.61
TG mg/dl	169.83±133.0	143.07±101.02	0.05
HDL ml/dl	73.35±43.08	46.41±13.63	<0.05
LDL	64.81±39.47	111.04±39.73	<0.05

DISCUSSION OF RESEARCH RESULTS. Over the past two decades, the etiology of cholelithiasis has been assessed more substantially. In addition to classical risk factors (age, gender, obesity and genetics), associations have been shown between cholelithiasis and delayed biliary emptying in hypothyroidism. This is due to the lack of a pro-relaxing effect of thyroid hormone on the contractility of the sphincter of Oddi [3; 10]. Serum TSH level is a hallmark of thyroid dysfunction. Subclinical hypothyroidism is characterized by elevated serum TSH levels along with normal serum FT4 levels and the absence of clinical symptoms. The mean TSH

levels in the present study were higher in the study group than in the control group. Although subclinical hypothyroidism was more common among patients with cholelithiasis (OR: 1.53; 95% CI: 0.968-2.433), this difference was not significant. In the present study, there were more women with subclinical hypothyroidism in both groups. This may be because women were generally more likely to be considered to have thyroid dysfunction. A study by Laukkarinen J, et al. showed that subclinical hypothyroidism is a common problem among patients with cholelithiasis. He concluded that hypothyroidism played a secondary role in the formation of cholelithiasis, compared with its effect on relaxation of the spicter of Oddi; which, in turn, can affect the emptying of the biliary system [7]. Increasing age is expected to increase patients' exposure to risk factors for stone formation and bile duct dysfunction. In our study, there was no association between age and thyroid dysfunction, which could be related to the number of patients. This relationship has been reported in various studies. According to various studies, among older people the incidence of hyperthyroidism was 2.1 - 6%, and for hypothyroidism - 2.0 - 2.9%. The prevalence of subclinical hypothyroidism in women over 60 years of age was 11.4% in patients with choledocholithiasis, compared with 1.8% in control patients. We also assessed metabolic factors in the two study groups. Obesity is considered a risk factor for the formation of gallstones. Oversaturated bile in obese individuals may be a mechanism for this phenomenon. Our study found more cases of overweight compared to the control group, which confirmed the results of previous studies. Patients with hypothyroidism are more likely to have elevated serum cholesterol levels. The mechanism of influence of thyroid hormones on cholesterol metabolism is multifactorial. Thyroid hormones influence the synthesis, absorption and use of cholesterol. In the present study, although mean cholesterol levels in the study group were not comparable to the control group, differences in mean HDL, LDL, and TG levels were observed.These results were almost consistent with data from other studies [1; 5]. In multivariate regression analysis, we concluded that serum TSH level was an independent factor that could be considered a risk factor for CBD stone formation (OR: 3.07; 95% CI: 1.51-6.2). HDL levels, however , had a negative correlation.

CONCLUSION. Hypothyroidism is more common in gallstone patients compared with controls and may be a risk factor for stone formation, supporting our hypothesis. At a minimum, women over 60 years of age with common bile duct stones should be screened for borderline or overt subclinical hypothyroidism.

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