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• *BRIEF REPORTS* •

Association between thyroid function and gallstone disease

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Abstract

AIM: To investigate those associations using data of the population-based Study of Health in Pomerania.

METHODS: A study population of 3 749 residents aged 20-79 years without previously diagnosed thyroid disease was available for analyses. Serum TSH was used to assess thyroid function. Cholelithiasis was defined by either a prior history of cholecystectomy or the presence of gallstones on ultrasound. Logistic regression was performed to analyze independent associations between thyroid function and cholelithiasis.

RESULTS: There were 385 persons (10.3%) with low (<0.3 mIU/L), 3 321 persons (88.6%) with normal and 43 persons (1.2%) with high serum TSH levels (>3 mIU/L). The proportion of cholelithiasis among males and females was 14.4% and 25.3%, respectively. Among males, there was an independent relation between high serum TSH and cholelithiasis (OR 3.77; 95%-CI 1.06-13.41; $P<0.05$). Also among males, there was a tendency towards an elevated risk of cholelithiasis in persons with low serum TSH (OR 1.40; 95%-CI 0.96-2.02; $P = 0.07$). In the female population, no such relation was identified.

CONCLUSION: There is an association between thyroid and gallstone disease with a gender-specific relation between hypothyroidism and cholelithiasis.

Key words: Thyroid function; Gallstones; Cholelithiasis; SHIP

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INTRODUCTION

For decades, there has been a discussion, whether thyroid disorders could cause gallstone disease. Particularly, there are several explanations for a possible relation between hypothyroidism and gallstone disease. These explanations include the known link between thyroid failure and disturbances of lipid metabolism[1] that may consecutively lead to a change of the composition of the bile. Recent studies[2] also demonstrated low bile flow in hypothyroid subjects. Furthermore, the sphincter of Oddi expresses thyroid hormone receptors and thyroxine has a direct prorelaxing effect on the sphincter[3]. Both low bile flow and sphincter of Oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation[4].

In a series of 668 female patients who had undergone cholecystectomy for gallstone disease, the proportion of treated hypothyroidism was 2.4% compared to 0.8% in the 782 controls[5]. Other studies[6] found a proportion of previously diagnosed hypothyroidism of 8% and 6% in patients having common bile duct and gallbladder stones, respectively, compared to a proportion of only 1% in the controls. The usage of thyroxine was even suspected to dissolve gallstones[7]. However, a spontaneous passage of the stone to the duodenum could not be excluded in this case report[7]. In an animal model of rabbits in whom a fatty diet induced gallstone formation, administering thyroxine was associated with a low gallstone weight, but did not dissolve the gallstones[8].

Previous studies[5,6] that investigated the association between thyroid function and gallstone disease in human beings, were conducted in a series of patients with potential for selection bias that may have produced false positive results. Furthermore, the statistical analyses were only controlled for age, but not for further confounders in both studies[5,6]. To our knowledge, there is only one large case-control study[9] that was appropriately adjusted for other risk factors of gallstone disease. In this study[9], no independent relation between thyroid disorders and gallstone formation was found. Unfortunately, the exposure was only defined as previous history of thyroid disease, and assessments of the current thyroid function status were not included. Moreover, there are currently no investigations that also include ultrasound to evaluate asymptomatic gallstones in this context.

Therefore, the aim of our study is to analyze the association between thyroid function and the risk of cholelithiasis using the data on the population-based Study of Health in Pomerania (SHIP).

MATERIALS AND METHODS

The Study of Health in Pomerania (SHIP) is a cross-sectional

examination in West Pomerania, the north-eastern part of Germany[10]. The study region is a formerly iodine deficient area with a high prevalence of iodine deficiency-related disorders such as goiter, thyroid nodules and decreased serum TSH levels[11]. A stable and adequate iodine supply has been achieved in the study area for the past decade. A random sample from the population aged 20-79 years was drawn. The sample was selected using population registries. Only individuals with German citizenship and main residency in the study area were included. There were 7 008 subjects sampled, with 292 persons of each gender in each of the 12 five-year age strata. The net sample (without migrated or deceased persons) comprised 6 267 eligible subjects. Selected persons received a maximum of three written invitations. In case of no response, letters were followed by a phone call or by home visits, if contact by phone was not possible. The final SHIP sample comprised 4 310 participants (final response proportion 68.8%). All participants gave informed written consent. The study protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

All 423 persons with known thyroid disorders or current thyroid medication according to the anatomic, therapeutic and chemical (ATC) code H03 (iodine, thyroid hormone replacement, suppression therapy or thyrostatics), 44 more persons without data on serum TSH levels and 94 more persons with no liver ultrasound or uncertainty with regard to cholelithiasis were excluded. This resulted in a study population of 3 749 subjects who were available for the present analysis.

Sociodemographic characteristics and medical histories were assessed by computer-assisted personal interviews. Education was categorized into three levels [low (<10 years), medium (10 years), high (>10 years), categories based on the East German three-level school system]. Individuals who participated in physical training during summer or winter for at least 1 h a week were classified as being physically active. According to the smoking habits participants were categorized into current, former and non-smokers. Diabetes was defined as a self-reported physician's diagnosis of diabetes, or serum hemoglobin A1c >7%. Body height and weight were measured for the calculation of the body mass index (BMI = weight [kg]/ height^2 [m^2]). Blood samples were taken, and laboratory parameters were analyzed in a central laboratory. Serum low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were precipitated and measured photometrically (Boehringer GmbH, Mannheim, Germany). Serum thyrotropin (TSH) was analyzed by immunochemiluminescent procedures (LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). All TSH measurements were performed in one central laboratory. The functional sensitivity of the TSH assay was 0.03 mIU/L. The reference range was 0.3-3 mIU/L.

The liver was examined using a 5 MHz transducer and a high-resolution instrument (Vingmed VST Gateway, Santa Clara, USA). The sonographers were unaware of the participant's clinical and laboratory characteristics. Gallstones were present if the gallbladder contained echoes that moved with gravity except when the stones were large, a septum existed in the gallbladder or there was an enclosed infundibulum[12]. Cholelithiasis was defined as previous history of cholecystectomy or current, sonographically diagnosed gallstones.

Statistical analyses

Data on quantitative characteristics are expressed as mean±SD. Data on qualitative characteristics are expressed as percentage values or absolute numbers as indicated. The study population was divided according to the TSH reference values that were provided by the manufacturer. The three groups consisted of persons with low (<0.3 mIU/L), normal (0.3-3 mIU/L) and high (>3 mIU/L) serum TSH levels. Comparisons between groups were made using χ^2-test (nominal data) and analysis of variance (ANOVA, continuous data). Sex-stratified logistic regression was performed in order to evaluate independent relationships between thyroid function and cholelithiasis. All analyses were adjusted for age and further potential confounders. Since missing values were present in some variables, data of 30 males (1.54%) and 21 females (1.17%) were lost for multivariable analyses. Serum lipids as mediators were not considered. The odds ratio (OR) was calculated, values being given as lower and upper 95%-confidence interval (CI). A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software, version 11.0.5 (SPSS GmbH Software, Munich, Germany).

RESULTS

There were 385 persons (10.3%) with low, 3 321 persons (88.6%) with normal and 43 persons (1.1%) with high serum TSH levels. The three groups were compared with respect to baseline demographic and clinical characteristics (Table 1). Persons with low serum TSH levels were older, less educated, less physically active and had lower serum HDL cholesterol levels than persons with serum TSH levels within the reference range (Table 1). Compared to the latter persons, individuals with high serum TSH levels were more often of female gender and had higher serum total cholesterol concentrations (Table 1).

The proportion of persons with cholelithiasis among the total sample was 19.7% (Table 2). Women were affected nearly twice as often as men (OR females *vs* males 2.01; 95%CI 1.71-2.37). While gallstones were only slightly more often detected by ultrasound in women than in men (OR 1.54; 95%CI 1.24-1.92), females reported particularly more often a previous history of cholecystectomy compared to males (OR 2.63; 95%CI 2.09-3.30; Table 2). Given these gender-related differences, all multivariable analyses were performed separately among males and females. These analyses revealed an advanced age, high BMI and low serum HDL cholesterol levels as independent risk factors for cholelithiasis in males as well as in females (Table 3).

The prevalence proportions of cholelithiasis among males with low, normal and high serum TSH levels were 22.5%, 13.3% and 30.8%, respectively. Bivariate analyses revealed an increased proportion of cholelithiasis in male persons with low serum TSH levels. This association bordered statistical significance after adjustment for potential

Table 1 Baseline clinical characteristics of study participants with low (< 0.3 mIU/L), normal (0.3–3 mIU/L) and high (> 3 mIU/L) serum TSH levels

	Low serum TSH n = 385	Normal serum TSH n = 3321	High serum TSH n = 43
Age (yr)	57.2±15.2[a]	48.4±16.3	51.1±12.7
Sex (male)	218 (56.6%)	1 723 (51.9%)	13 (30.2%)[a]
Education			
<10 yr	209 (54.6%)[a]	1 206 (36.6%)	14 (32.6%)
10 yr (Ref.)	132 (34.5%)	1 556 (47.2%)	19 (44.2%)
>10 yr	42 (11.0%)	535 (16.2%)	10 (23.3%)
Physical activity	130 (33.9%)[a]	1 445 (43.7%)	19 (44.2%)
Current cigarette smoking			
Never (Ref.)	125 (32.6%)	1 138 (34.4%)	15 (34.9%)
Former	151 (39.4%)	1 109 (33.5%)	17 (39.5%)
Current	107 (27.9%)	1 061 (32.1%)	11 (25.6%)
Diabetes mellitus	38 (10.0%)	269 (8.2%)	0
Body mass index; kg/m^2	27.4±4.5	27.1±4.7	27.9±4.6
Total cholesterol; mg/dL	221±44	223±49	240±53[a]
mmol/L	5.71±1.14	5.76±1.26	6.20±1.38[a]
LDL-Cholesterol; mg/dL	138±41	138±45	152±50
mmol/L	3.56±1.05	3.56±1.18	3.92±1.30
HDL-Cholesterol; mg/dL	54±17[a]	56±17	60±17
mmol/L	1.41±0.44[a]	1.45±0.44	1.56±0.43

χ^2-test (nominal data) or ANOVA (interval data) for inter-group comparisons; [a]P<0.05 *vs* reference group: normal serum TSH. LDL denotes low density lipoprotein, HDL; high density lipoprotein.

Table 2 Prevalence of previous history of cholecystectomy and sonographically detected gallstones among males and females

	History of cholecystectomy (%)	Ultrasound diagnosis of gallstones (%)	Total (%)
Males	122 (6.8)	160 (8.7)	282 (14.4)
Females	257 (16.1)	198 (12.9)	455 (25.3)
All	379 (11.2)	358 (10.6)	737 (19.7)

Table 3 Sex-specific independent risk factors for cholelithiasis

	Males OR (95%CI)	Females (95%CI)
Age; yr (Ref. <30)		
30–<40	4.15 (1.17–14.69)	1.97 (1.04–3.75)
40–<50	8.32 (2.47–28.03)	4.67 (2.55–8.52)
50–<60	16.68 (5.04–55.22)	7.16 (3.85–13.30)
60–<70	28.02 (8.44–93.05)	13.01 (6.81–24.88)
⩾70	40.09 (12.02–133.76)	19.60 (9.92–38.72)
Education; yr (Ref. 10)		
<10	0.88 (0.62–1.26)	0.93 (0.67–1.30)
>10	0.72 (0.44–1.16)	0.68 (0.44–1.05)
Physical activity	0.96 (0.71–1.29)	0.78 (0.60–1.02)
Smoking (Ref. non)		
Ex-smoker	1.15 (0.79–1.68)	0.73 (0.53–1.01)
Current smoker	1.03 (0.66–1.61)	0.78 (0.56–1.10)
Diabetes mellitus	1.37 (0.94–2.01)	1.10 (0.72–1.71)
Body mass index; per kg/m^2	1.04 (1.01–1.08)	1.08 (1.06–1.11)
LDL cholesterol; per 10 mg/dL	0.97 (0.94–1.02)	0.97 (0.94–1.01)
HDL cholesterol; per 10 mg/dL	0.87 (0.78–0.97)	0.87 (0.78–0.97)

Logistic regression analysis, OR denotes odds ratio; 95%CI, confidence interval; LDL, low density lipoprotein; HDL, high density lipoprotein.

confounding variables (Table 4). The full model in the male study population further revealed an independent association between high serum TSH levels and cholelithiasis (Table 4). The prevalence proportions of cholelithiasis among females with low, normal and high serum TSH levels were 31.7%, 24.7% and 26.7%, respectively. The relation between low serum TSH levels and cholelithiasis that was found in bivariate analyses was not stable after appropriate adjustment for relevant confounders. Likewise, there was no independent association between high serum TSH levels and cholelithiasis in women (Table 4).

Further analyses were performed using ultrasound diagnosis of gallstones as the dependent variable. In the male population, multivariable analyses did not attain statistical significance for the association between low serum TSH levels and the endpoint (OR 1.25, 95%CI 0.78-2.02; P = 0.36). High serum TSH levels, however, were again detected as an independent risk factor for sonographically detected gallstones (OR 4.85, 95%CI 1.19-19.74; P<0.05). In the female population, no such association was present. Additional multivariable analyses that were run with previous history of cholecystectomy as the dependent variable also did not find an association between serum TSH levels and this endpoint in women. However, in the male population, the relation between low serum TSH levels and previous history of cholecystectomy bordered statistical significance (OR 1.55, 95%CI 0.94-2.56; P = 0.07), whereas no association between high serum TSH levels and this endpoint was observed (OR 1.91, 95%CI 0.22-16.59; P = 0.56).

Moreover, persons with a previous history of thyroid disease were compared to the study population with respect to their risk of cholelithiasis. Among both the sexes, persons with thyroid disease had cholelithiasis more often than persons without known thyroid disease (23.0% *vs* 14.5% in males and 38.4% *vs* 25.6% in females; P<0.05). After adjustment for the full model, however, there was no independent relation between thyroid and gallstone disease in males as well as females.

DISCUSSION

The present study investigated possible associations between serum TSH levels and gallstone disease. There was an independent relation of high serum TSH levels with cholelithiasis among males, predominantly among those who had sonographically detected gallstones. In the female population, no such associations were identified.

At least in the male population, the finding of high serum TSH levels as an independent risk factor for cholelithiasis confirm previous research[5,6]. An absence of such an association among females might be explained by two points. Firstly, the study population only comprised persons with as yet undiagnosed thyroid disorders. Females were more often excluded due to a known thyroid disorder than males. Thus, there might be earlier diagnosis and treatment of hypothyroidism in women compared to men, reflected by a longer and more intense exposure in males. Likewise, the higher proportion of cholelithiasis in women compared to men was mainly due to the higher proportion of previous history of cholecystectomy in females. Thus, in women,

Table 4 The association between serum TSH levels and cholelithiasis according to sex

	Regression models	Low (<0.3 mIU/L) OR (95%CI)	Serum TSH normal (0.3–3.0 mIU/L) OR (95%CI)	High (> 0.3 mIU/L) OR (95%CI)
Males;	Crude	1.89 (1.34–2.67)[1]	1.0 (Reference)	2.90 (0.90–9.49)
OR	Adjusted for confounding variables[2]	1.40 (0.96–2.02)	1.0 (Reference)	3.77 (1.06–13.41)[1]
Females;	Crude	1.42 (1.01–2.01)[1]	1.0 (Reference)	1.11 (0.49–2.52)
OR	Adjusted for confounding variables[2]	0.89 (0.61–1.32)	1.0 (Reference)	0.91 (0.38–2.19)

[1]Logistic regression analysis, [2]Age (decades), education (three categories), physical activity (yr/*n*), smoking (three categories), diabetes (yr/*n*), body mass index (cont.). OR denotes odds ratio; 95%–CI, confidence interval.

gallstones may become symptomatic earlier than in men and the consecutive diagnostic procedures may further lead to an earlier detection and treatment of hypothyroidism. This assumption is supported by the fact that the association between high serum TSH levels and cholelithiasis was mainly found in males with sonographically detected gallstones. Secondly, there are also gender differences with respect to the type of gallstones. In one study[13], males had less often cholesterol stones than women. One may assume that, if hypothyroidism would indeed be a causal factor for gallstone disease, then this may lead to a specific type of stone other than cholesterol stones. In the same study[13], however, there was no association between thyroid function and the stone type.

In the male population, also an association between low serum TSH levels and cholelithiasis bordered statistical significance in the full model. This was not expected, because experimental evidence suggested a direct association between thyroid function and the bile flow to the duodenum. While the flow was reduced in hypothyroidism, it was enhanced in hyperthyroidism[14]. However, this study[14] was performed in rats without gall bladder. In hamsters, extremely high doses of thyroxine may induce the formation of gallbladder stones[15]. In the present study, particularly males with low serum TSH levels had a higher risk of previous cholecystectomy. Thus, a cholelithiasis may become symptomatic in an earlier state in hyperthyroid persons. In general, the role of hyperthyroidism with respect to gallstone formation in human beings is currently not well investigated and further research is needed.

The exclusion of patients with known thyroid disorders resulted in small numbers of individuals with hypothyroidism, limiting the power of the statistical analysis. We therefore repeated the analyses including these persons. The results confirmed an increased cholelithiasis prevalence in persons with previously diagnosed thyroid disease, however, there was no independent relation between these two parameters. In patients with known thyroid disease the thyroid function status may change dramatically over time mainly due to the effects of treatment. Further confounding variables in patients with known thyroid disease may include medical treatment, better health education and more frequent and intense contact with medical personnel.

Previous studies[16] that were conducted in a neighborhood region identified a high cholelithiasis prevalence proportion of greater than 30% and 55% in men and women who were ⩾65-years old, respectively. This high prevalence is in good agreement with the results of our study. Also in accordance with other studies[17], an advanced age, high BMI and serum lipids were identified as major independent risk factors for cholelithiasis. This argues for the good validity of the diagnostic method to define cholelithiasis used in the present study.

We conclude, that there is a gender-specific relation between hypothyroidism and cholelithiasis. Especially males with gallstones should be further examined for thyroid disorders. Further research is needed to explain the role of low serum TSH levels with respect to gallstone disease in men.

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