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Association between Serum Thyroid Hormones and Fatty Liver Disease

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Abstract

Background: *Non-alcoholic fatty liver disease is one of the most common chronic liver diseases. Given the lack of definitive documentation for the effect of thyroid gland disorders on fatty liver, this study was conducted to determine the relationship between serum thyroid hormones levels and fatty liver in patients referring to Imam Hossain Hospital in Shahroud, in 2016.*

Methods: *This case-control study was performed on 150 patients. The case group consisted of fatty liver patients whose disease was diagnosed based on laboratory and ultrasound findings, and a control group of patients with any other diseases without fatty liver. After liver ultrasonography, blood samples were taken from all patients and thyroid hormones levels were measured.*

Results: *Of the 150 patients examined, the mean BMI of the patients was 24.79±6.9 kg / m2, which was significantly higher in the case group (P<0.012). The mean FBS level, was 131.5±83.5 mg / dl, which was significantly higher (P<0.001) in the case group. Similarly, the mean of TG was 245.5±128.5 mg / dl, which was significantly higher in the case group (P<0.047). On the other hand, the mean LDL of patients was 145.5±30.5 mg / dl, which was significantly higher (P<0.012) in patients with fatty liver. Further, the mean TSH of patients was significantly higher in the case group (P<0.014). Finally, there were no significant differences between the two groups regarding other variables.*

Conclusions: *The results of this study suggested that thyroid gland disorders, especially hypothyroidism, were significantly higher in patients with fatty liver than in other patients. Nevertheless, they could not be influential in the incidence, exacerbation and persistence of fatty liver as a favorable factor.*

Keywords: Non-Alcoholic fatty liver, T3, T4, TSH.
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Introduction

Fatty liver disease (FLD) refers to a spectrum of clinical and pathological conditions which is due to the deposition of fat droplets in the liver of patients who have no history of alcohol consumption. This condition ranges from simple steatos to liver disease such as non-alcoholic steatohepatitis, fibrosis, cirrhosis, and eventually hepatocellular cancers.[1-2] The natural liver contains 5 grams of fat per 100 grams of its weight, but if the fat content exceeds 5 to 10% of the liver's weight, the person has a FLD.[3] Fatty liver is one of the most common liver diseases in the world whose prevalence varies from region to region. The prevalence of this disease is estimated to be between 7% and 40% in Asian regions. The outbreak of FLD in western developed countries has been reported to be 2 to 3 times more than that of hepatitis B and C and alcohol-related liver disease; it is the most common cause of liver tests disorders.[1-3] The symptoms are non-specific and include fatigue, lethargy, and pain in the upper right abdomen; the patients may not be aware of their illness or it may be accidentally discovered in abdominal ultrasound or other examinations.[4] Risk factors associated with this disease include: increased age, high weight, abdominal obesity, abnormal blood lipids profiles, high blood pressure, high blood sugar, insulin resistance and metabolic syndrome, cigarette, and non-standard diet.[5] Also, taking medications such as corticosteroids, aspirin, methotrexate, tamoxifen, tetracycline, valproic acid, amiodarone, a well as viruses can also lead to this complication, but the main risk factor is diabetes and resistance to insulin.[6-7] Hormonal disorders are one of the risk factors that can affect the development and exacerbation of fatty liver. Thyroid gland disorders are one of the most common disorders.[7] Different studies worldwide have reported different rates of thyroid dysfunction. The range of these figures has been different from 1% to more than 20% in the hypothyroidism and hyperthyroidism.[8] Hypothyroidism is an endocrine disorder which gradually decreases thyroid function by inducing self-immune processes.[8-9] Hypothyroidism is one of the risk factors for ischemic cardiovascular disease. In hypothyroidism, atherogenic lipid disorders may be observed causing coronary artery obstruction.[10] On the other hand, in hyperthyroidism, with increased appetite and higher levels of food intake, there is a risk of lipid profile disorders.[11] Thyroid hormones play an important role in energy homeostasis and body weight. As hyperthyroidism triggers appetite and hypothyroidism with weight gain, the details and mechanism of association between thyroid hormone and lipid metabolism has been are important to be scrutinized.[11-12]

Given the complications of thyroid dysfunction, especially hypothyroidism, such as overweight, obesity, impaired glucose and fat metabolism, and lack of mobility known as the risk factors for fatty liver, it is therefore conceivable that thyroid hormones and especially TSH levels may affect the incidence of fatty liver.[13-14] The best diagnostic test for non-alcoholic

liver fatty liver is biopsy,[9-10] but ethical and medical considerations have limited its usage in patients. Increased liver enzymes are commonly found in these patients, but the characteristics of these tests are low. Therefore, clinical evaluation of non-alcoholic fatty liver was performed based on a combination of ultrasound findings and laboratory tests. Because of sparse studies in Iran regarding the effect of thyroid hormone function on the development of fatty liver and the association of this disorder with other risk factors, it is necessary to study it in patients with fatty liver. Accordingly, this study was conducted to determine the relationship between serum levels of T3, T4 and TSH and fatty liver in patients referring to Imam Hossain Hospital of Shahroud in 2016.

Materials and Methods

This research is a case-control study conducted among patients referring to Imam Hossain Hospital of Shahroud (Northeastern of Iran) between January and December 2017. The case group was selected from patients with non-alcoholic liver disease diagnosed based on liver tests and sonography of their disease and categorized further.

Mild fatty liver: a brief increase in liver echogenicity where the diaphragm and vascular wall are well visible in ultrasound (grade 1).

Medium fatty liver: moderate increase in liver echogenicity where the diaphragmatic view and the intra-liver vessel wall are slightly disturbed in ultrasound (grade 2).

Sever fatty liver: increased liver echogenicity where the posterior lobe of the liver disappears in ultrasound while the diaphragm and the wall of the intra-liver vessel is barely visible or even unobservable (grade 3).[9]

The control group chosen had no symptoms in ultrasound and liver tests in favor of the fatty liver and referred to the ultrasound section for other reasons.

None of the patients and controls did not have liver disease, malignancy, chemotherapy, diabetes, thyroid hormonal disorders, pregnancy, and had no history of taking corticosteroids and alcohol over the past year.

Exposure and main predictor variables were age, sex, BMI, fasting blood glucose, triglyceride, total cholesterol, HDL-LDL, liver enzymes, T3, T4, and TSH.

Descriptive statistics including mean and standard deviation, as well as relative frequency were used to describe the data. To examine the relationships and comparisons between the two groups, the chi-square test was used for qualitative variables and t test for quantitative variables. Further, multiple logistic regression was employed to evaluate the odds of each of the variables. All analyses were performed using SPSS software version 16 with significance level considered $P<0.05$. The sample size using Epi info 7.2 at a significance level of 5% and a power of 80%, equaled 75 subjects in each group totally amounting to 150.

This study received an ethics code number (IR.SHMU.REC. 1395.95) from research deputy of Shahroud University of Medical Sciences. The essential information and the objectives of the study were explained to the patients, and written consent was obtained for participation in the study.

Results

In this study, 51 (34.0%) of the participants were male. The mean age of the all patients was 57.63±28.03 years, where there was no significant difference between the two groups. The mean BMI of the case group was 25.19±6.52 kg/m2 and that of the control group was 24.21±6.83 kg/m2, which was significantly higher in the case group (P=0.012). The mean TSH level in the case group was 4.8±2.1 ng/dl and in the control group 1.9±0.8 ng/dl, which was significantly higher in the case group (P=0.014). The results of biochemical and liver tests of patients in the two groups are reported in table 1. In this study, the relationship between predictor variables and FLD was investigated using a multiple regression model. As provided in table 2, the fatty liver outcome was significantly associated with LDL ($P<0.001$), triglyceride ($P<0.043$), and FBS ($P<0.001$) while there was no significant relationship with other variables. The results of the multivariate logistic regression model are presented in table 2.

Table 1. Results of biochemical and liver tests in two groups

Lab Test	Case group Mean±SD	Control group Mean±SD	Total Mean±SD	P.V
Fasting blood sugar (mg/dl)	137.5±53.5	124.5±62.5	128.5±59.5	0.001
Triglyceride (mg/dl)	223.5±130.5	218.5±125.5	220.5±128.5	0.047
Total cholesterol (mg/dl)	318.3±155.5	265.5±144.5	284.5±151.5	0.051
LDL cholesterol (mg/dl)	175.3±65.5	125.5±42.5	155.5±53.5	0.012
HDL cholesterol (mg/dl)	39.5±6.8	44.5±5.5	42.8±5.3	0.109
TSH (ng/ml)	4.8±2.1	1.9±0.8	3.1±1.3	0.014
AST (IU/L)	95.3±32.5	29.5±6.5	63.5±15.8	0.001
ALT (IU/L)	108.5±28.5	37.5±7.4	75.4±20.8	0.001
ALK-P (IU/L)	380.5±75.5	295.5±45.5	345.4±58.2	0.003

Table 2. Relationship between independent variables with fatty liver in multiple logistic regression model

Independent variables		Odds Ratio	95% Confidence Interval	P.V
Age category	Less than 30 years	1.00		
	30 to 50 years	1.08	0.06-1.34	0.065
	More than 50 years	1.09	0.07-1.45	0.055
Sex	Male	1.00		
	Female	0.79	0.61-1.01	0.069
History of diabetes mellitus	Negative	1.00		
	Positive	1.11	0.81-1.25	0.063
Body mass index (kg/m^2)	18-25	1.00		
	<18	0.72	0.56-0.99	0.059
	>25	1.37	0.91-1.73	0.023
Triglyceride (mg/dl)	<150	1.00		
	>150	1.15	0.87-1.32	0.043
Total cholesterol (mg/dl)	<180	1.00		
	>180	1.33	1.11-1.54	0.052
LDL cholesterol (mg/dl)	<130	1.00		
	>130	1.49	1.22-1.76	0.001
HDL cholesterol (mg/dl)	>40	1.00		
	<40	1.03	0.86-1.28	0.079
Fasting blood sugar (mg/dl)	<126	1.00		
	>126	1.55	1.26-1.85	0.001
TSH (ng/dl)	1.5-5	1.00		
	<1.5	1.08	0.85-1.22	0.068
	>5	1.43	1.16-1.73	0.051

Discussion

The results of this study revealed that predictor variable such as BMI, LDL, triglyceride, and fasting blood glucose had a significant relationship with fatty liver, while other predictor variables such as age, sex, triglyceride, HDL, chol, diabetes, TSH were not significantly correlated with the outcome in logistic regression model. According to logistic regression model findings, thyroid gland dysfunction (TSH level) did not increase the risk of fatty liver and there was no significant relationship between the changes in this hormone and fatty liver disease. This finding was in line with the results of Pearce' study who concluded that there is an association between hypothyroidism and fatty liver disease.[15]

In a study by Duntas et al., it was found that more than 50% of these patients had varying degrees of impairment in fat profile where hypercholesterolemia and hypertriglyceridemia levels were higher in them. However, no significant relationship was found between thyroid gland disorders and non-alcoholic fatty liver, which is in perfect agreement with the present study findings.[16]

The results of this study suggested that changes in thyroid hormones, especially hypothyroidism, can significantly increase the chance of developing fatty liver. This finding is consistent with the results of Kim et al. study.[17] They found that the reason may be due to decreased metabolism of the body and consequently diminished mobility, increased body mass index, and fat accumulation in different tissues and especially in the liver.

In a study by Ludwig et al., who researched the risk factors affecting fatty liver, variables such as age, waist circumference, BMI, FBS, triglyceride, and cholesterol showed a significant correlation with the incidence of fatty liver; the significance of all these variables was well consistent with the present study results.[18]

In the study of Shiva Kumar et al., which was performed on 350 patients with fatty liver, parameters such as weight gain and obesity, lipid profiles, glucose levels, and hormonal disorders, especially hypothyroidism, were studied. It was found that all of these factors can be associated with the development of a fatty liver as an independent factor, but there was no statistically significant difference between the groups. Again, this finding is consistent with the results of the present study.[19]

As observed, the present study revealed a strong relationship between obesity as well as overweight and the incidence of fatty liver disease. Fat tissue storage and release of energy in the form of triglycerides during excessive consumption of food and hunger can be one of the most important factors in this regard.[20] Further, fat tissue produces hormones such as leptin, adiponectin, and pro-inflammatory cytokines such as interleukin-6 and alpha-tumor necrosis factor. Increased levels of obesity and obesity lead to imbalance of hormones and cytokines. In response, the inflammatory mechanisms and insulin resistance increase, especially in the liver thereby raising the risk of hepatic steatosis and nonalcoholic fatty liver.[20-22]

Since the efficacy and safety of drug therapy in patients with non-alcoholic fatty liver is not definitively known, lifestyle changes, diet modifications, and weight loss are commonly used treatments for non-alcoholic liver fatty acids; 5-10% weight loss can dramatically improve the metabolic function of the liver.[23- 24]

The results of this study suggested that changes in TSH level were significantly higher in patients with fatty liver than

in other patients. However, this factor was not confirmed as a contributing factor in the incidence, exacerbation, and persistence of fatty liver. In order to fully confirm this, more research is required with a larger sample size. Therefore, all patients with fatty liver requiring attention to hormonal disorder and lifestyle changes, should be carefully evaluated for thyroid disorder and, if such findings are detected, be corrected as soon as possible.

The limitations of this research included the impossibility of a biopsy to confirm the ultimate fatty liver (due to ethical barriers) and self-declaration of patients about chronic diseases. By performing accurate and complete liver ultrasonography, along with relevant tests and completely explaining the research purposes for patients, attempts were made to offset this limitation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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