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Medical Sciences

HYPOTHYROIDISM-A RISK FACTOR FOR THE NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT:
INTRODUCTION. THYROID DYSFUNCTION IS A COMMON CONDITION THAT AFFECTS LIFELONG HEALTH. BECAUSE THETHYROID HORMONES PLAY A FUNDAMENTAL ROLE IN LIPID METABOLISM, HYPOTHYROIDISM MAY CAUSE HYPERCHOLESTEROLEMIA AND PLAY AN ESSENTIAL ROLE IN THE PATHOGENESIS OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD). MATERIAL, METHOD. THE AIM OF THIS STUDY WAS TO CHARACTERIZE THE RELATIONSHIP BETWEEN THE BROAD SPECTRUM OF HYPOTHYROIDISM AND THE NON -ALCOHOLIC FATTY LIVER DISEASE. THE STUDY GROUP CONSISTED OF 124 PATIENTS WITH THYROID DYSFUNCTION-SUBCLINICAL OR MANIFEST HYPOTHYROIDISM. CONTROLS WITH NORMAL-RANGE TSH LEVELS AND FT4 LEVELS WERE RANDOMLY MATCHED TO THE CASES BY AGE AND SEX. THE MEAN AGE OF THE SUBJECTS WAS 41.5 (SD 11.5) YEARS, RANGING FROM 18 TO 72 YEARS OLD. RESULTS, DISCUSSION. THE PREVALENCE OF NAFLD IN THE STUDY GROUP WAS 35.4%, WITH A POSITIVE DIAGNOSIS OF 40.9% AND 59.09% IN MEN AND WOMEN, RESPECTIVELY. NAFLD AND METABOLIC SYNDROME WERE STATISTICALLY SIGNIFICANTLY ASSOCIATED WITH HYPOTHYROIDISM (18.5% VS. 35.4% AND 17.74% VS. 31.4%, P<0.001, RESPECTIVELY). THE PREVALENCE OF NAFLD WITH ELEVATED ALT WAS SIGNIFICANTLY HIGHER IN THE SUBJECTS WITH HYPOTHYROIDISM (11.29% VS. 7.25%, P<0.01). CONCLUSIONS. THE HYPOTHYROIDISM IS ASSOCIATED WITH NAFLD AND MAY BE CONSIDERED A RISK FACTOR FOR THIS DISORDER. THERE IS A RELEVANT CLINICAL RELATIONSHIP BETWEEN THESE TWO DISEASES.

KEYWORDS: HYPOTHYROIDISM, NON-ALCOHOLIC FATTY LIVER DISEASE, METABOLIC SYNDROME

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INTRODUCTION

Thyroid dysfunction is a common condition that affects lifelong health[9]. Subclinical hypothyroidism, which refers to an elevated thyroid-stimulating hormone (TSH) level and a normal free thyroxine (T4) level, has been associated with metabolic syndrome, cardiovascular diseases and mortality[10]. Because the thyroid hormones play a fundamental role in lipid metabolism, hypothyroidism may cause hypercholesterolemia and play an essential role in the pathogenesis of Non-alcoholic fatty liver disease (NAFLD)[11].

NAFLD has been recognized as the most common liver disease and includes a spectrum of hepatic dysfunctions ranging from simple steatosis to non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma[12]. Because the mechanism underlying the development of NAFLD has been linked to insulin resistance and metabolic syndrome, NAFLD is considered to be the hepatic manifestation of metabolic syndrome[13] and the associations with many predictors of cardiovascular disease have been reported[14].

Previous studies have reported that thyroid dysfunction is associated with liver diseases, including chronic hepatitis C[15], hepatocellular carcinoma[16], primary biliary cirrhosis and primary sclerosing cholangitis[17] .Furthermore, a recent study showed that the prevalence of NAFLD is negatively correlated with free T4 levels, and decreased free T4 levels contribute to the risk of NAFLD[18].

While the exact etiology of NAFLD and NASH is unclear, insulin resistance appears to be central to the pathogenesis of NASH by allowing inappropriate levels of lipolysis from the adipose tissue and impairing peripheral glucose disposal. Besides insulin resistance, NAFLD is also closely associated with other characteristics of the metabolic syndrome including central obesity, hypertension and hyperlipidemia. The obesity epidemic and

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increasing prevalence of the metabolic syndrome is predicted to be paralleled by an increasing prevalence of NAFLD in the future[19].

PATIENTS, METHODS

We analyzed 350 patients examined in 2015 the Endocrinology Department for polymorph complaints. Eighty of them were excluded from the research because they were administered thyroid hormones or antithyroid drugs. Other 75 have admitted an alcohol intake of more than 20g/day, 35 had hepatitis B or C history and 36 were using hepatotoxic drugs.

The study group consisted of 124 patients with thyroid dysfunction-subclinical or manifest hypothyroidism. All these have signed an informed consent before the study enrolment and personal data processing.

Controls with normal-range TSH levels and FT4 levels were randomly matched to the cases by age and sex.

We analyzed the following parameters:

- anthropometric data-height, weight, abdominal circumference, body mass index (BMI). The BMI was calculated according to the H/W^2 formula. Waist circumference (WC) was measured to the nearest millimeter at the midpoint between the lower costal margin and the anterior superior iliac crest, with the patient standing with the abdomen relaxed, arms at the sides of the body and feet side by side, using a tape
- for biochemical evaluation a blood sample was obtained by veinpuncture, after a 12-hour fast and including the following markers of liver function: albumin, total bilirubin, aspartate aminotranspherase (AST), alanine aminotranspherase (ALT), gamma-glutamyltranspeptidase (GGT) and the baseline thyroid function TSH and free T4 levels. The latter were determined by electrochemiluminescence (ECLIA).

Subclinical hypothyroidism was defined as a serum TSH level over 4.2mUI/mL, with a normal free T4 concentration.

We also evaluated the lipid profile, blood glucose and basal insulin levels and we determined the HOMA-IR index.

The blood pressure was measured in all the studied patients.

The NAFLD diagnosis was established by ultrasonographic examination of the liver and imaging assessment.

Statistical calculations were carried out using SPSS system. The p values of <0.05 were considered statistically significant.

The diagnosis of metabolic syndrome was performed in the presence of at least three of the following five components: WC (as defined by the Regional Office for the Western Pacific Region of the World Health Organization) $\leq$90cm in men and $\leq$80cm in women, HDL-c $\leq$40mg/dL in men and $\leq$50mg/dL in women, triglycerides $\geq$150mg/dL, fasting glucose $\geq$100mg/dL or treatment for diabetes and blood pressure $\geq$130/85mm Hg or treatment for arterial hypertension.

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RESULTS

The study group consisted of 124 subjects, of which 91were females (73.3%) and 33 (26.6%) males. The mean age of the subjects was 41.5 (SD 11.5) years, ranging from 18 to 72 years old.

The prevalence of NAFLD in the study group was 35.4%, with a positive diagnosis of 40.9% and 59.09% in men and women, respectively.

NAFLD and metabolic syndrome were statistically significantly associated with hypothyroidism (18.5% vs. 35.4% and 17.74% vs. 31.4%, p<0.001, respectively (table 1).

Variable	Euthyroidism n=124	Hypothyroidism n=124
Age (years)	41.5 ± 11.8	41.5± 11.8
Gender, female	91 (73.3%)	91 (73.3%)
WC (cm)	83.7 ± 8.2	86.4 ± 8.3
BMI (kg/m^2)	23.1 ± 5.1	23.9 ± 5.4
ALT (IU/mL)	19 ± 5.52	21 ± 16.4
AST (IU/mL)	29 ± 12.1	23 ± 18.3
Total cholesterol (mg/dL)	190.4 ± 35	196.8 ± 34.1
HDL-cholesterol (mg/dL)	56.4 ± 13.2	56.4± 13.7
Fasting glucose (mg/dL)	94.8 ± 16.1	97.1± 16.2
Triglycerides (mg/dL)	102.3 ± 71.63	135.2± 76.34
Hypertension-n (%)	15 (12.09%)	18 (14.05%)
TSH (mIU/mL)	1.5	5.4
FT4 pmol/L	17.1	14.9
NAFLD-n (%)	23 (18.5%)	44 (35.4%)
Metabolic syndrome-n (%)	22 (17.74%)	39 (31.45%)
Obesity (BMI ≥ 25)-n (%)	27 (21.7%)	32 (25.8%)
HOMA-IR	2.1 ± 1.91	3.9 ± 2.55

Table 1. Comparison between the means (SD) of the anthropometric and biochemical variables between the subjects with euthyroidism and hypothyroidism

The waist circumference, BMI, serum glucose, ALT, AST, triglycerides, blood pressure showed differences between the euthyroid and hypothyroid subjects.

NAFLD is a constituting element of MS, associated with visceral adiposity and IR. This study observed a significant association between IR, as indicated by the HOMA-IR, and the presence of NAFLD

Among the subjects with hypothyroidism, the prevalence of NAFLD increased withincreasing hypothyroidism grade (subclinical hypothyroidism 30.17% and overt hypothyroidism 37.5%), p<0.001 (table 2).

Variable	Hypothyroidism n=124	
	Subclinical-n=116 (93.5%)	Overt-n=8 (6.45%)
Age (years)	41.5 ± 11.8	54.8 (40-72)
Gender, female	84 (72.4%)	7(87.5%)
WC (cm)	86.4 ± 8.3	87.75 (81-96)
BMI (kg/m^2)	23.5 ± 5.5	24(20-28)
ALT (IU/mL)	21 ± 16.4	21(15-31)
AST (IU/mL)	23 ± 18.3	26(18-29)
Total cholesterol (mg/dL)	197.1 ± 34.1	202.1 (184-240)
HDL-cholesterol (mg/dL)	57.1 ± 13.5	52.3 (>40)
Fasting glucose (mg/dL)	97.1 ± 16.2	97.6 (89-108)

Triglycerides (mg/dL)	135.2 ± 76.34	154.3 (<150)
Hypertension-n (%)	20 (17.24%)	2(25%)
TSH (mIU/mL)	5.3 (4.3-7.2)	15(10-45)
FT4 pmol/L	15 (12-22)	0.9(0.05-0.1)
NAFLD-n(%)	35 (30.17%)	3(37.5%)
Metabolic syndrome-n (%)	22 (17.74%)	39(31.45%)
Obesity (BMI ≥ 25)-n (%)	30 (25.8%)	3(37.5%)
HOMA-IR	3.8	4.1

Table 2. Comparison between the means (SD) of the anthropometric and biochemical Variables between the subjects with subclinical hypothyroidism and overt hypothyroidism

In the hypothyroidism study group 39 of the 124 patients had metabolic syndrome and 79.4% of those with NAFLD also had thediagnosis of MS, showing a significant association between MS and NAFLD (table 3).

Variables	**Presence of MS**		**p value**
	n	**%**	
Presence of NAFLD	31	79.4	0.01
Absence of NAFLD	8	20.6	

Table 3. The association between the presence of NAFLD and the diagnosis of MS

The prevalence of NAFLD with elevated ALT was significantly higher in the subjects with hypothyroidism. (11.29% vs. 7.25%, p<0.01)

In the hypothyroidism patients the prevalence of abnormal liver enzymes levels (ALT>40UI/L) was significantly higher than in the subjects with normal thyroid function (9.6% vs. 6.4%, p<0.001) (table 4).

Variable	**Hypothyroidism n=124**	**Euthyroidism n=124**	**p value**
NAFLD-n(%)	44 (35.4%)	23(18.5%)	< 0.001
ALT (IU/mL)	12 (9.6%)	8(6.4%)	< 0.001
AST (IU/mL)	25 (20.16%)	20(16.1%)	< 0.001
NAFLD with elevated ALT-n (%)	14 (11.29%)	9 (7.25%)	< 0.001

Table 4. The association between the presence of NAFLD, abnormal ALT levels and thyroid function

DISCUSSION

This study found out that there was a strong association of hypothyroidism and NAFLD. The prevalence of both NAFLD and liver enzyme levels was significantly greater in the patient with hypothyroidism than in the subjects with normal thyroid function.

Similar results have been reported by other studies. In 2012, in a much larger study group, Chung showed that the hypothyroidism is closely associated with NAFLD independently of known metabolic risk factors, confirming a relevant clinical relationship between these two diseases[20].

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Liangpunsakel and Chalasani showed that hypothyroidism was associated with non-alcoholic steatohepatitis, but this study did not include laboratory data regarding thyroid function[21].

Silveira et al. suggested that thyroid dysfunction is common in NAFLD, but they compared subjects with different liver diseases[22] .

Xu et al.[23] included only elderly euthyroid patients and concluded that thyroid dysfunction, even within the normal range, is associated with NAFLD.

Subclinical hypothyroidism, as defined by the TSH levels, is known to be associated with cardiovascular mortality and events[24]. In this study, the NAFLD prevalence and the abnormal liver enzymes levels increased with increasing TSH levels. One explanation for this association is that hypothyroidism is associated with metabolic syndrome, obesity and hyperlipidemia. Hypertriglyceridemia increases the import of triglycerides into the liver and is therefore associated with the development of NAFLD.

Resistance to insulin exists in patients with subclinical and overt hypothyroidism[25] . This is probably due to the accumulation of abdominal fat, since such metabolic abnormalities are very common in these individuals. IR has been strongly associated with NAFLD, both in the liver and the adipose tissue.

Individuals with NAFLD have inhibition of fatty acid oxidation, which occurs as a decrease in the intake of glucose and use as fuel. This suggests the possibility that IR may be an intrinsic disease defect, and that the lipolysis is triggered by the lower response to insulin in adipocytes. This therefore leads to the gradual accumulation of lipids in hepatocytes by increasing the release of free fatty acids in the liver. Lipid storage can reach toxic levels and intensify reactive oxygen species production in the liver, stimulating macrophages and TNF-a proliferation, which also interfere with insulin sensitivity. Hence, an irregular lipid peroxidation leads to direct damage to the liver, with inflammation and even fibrosis.

Many studies have shown that the accumulation of body fat in the abdominal region, notwithstanding the total body fat content of the organism, is an independent predictive factor for the accumulation of fat in hepatocytes, and therefore crucial for NAFLD's pathogenesis.

Visceral fat is drained directly into the portal vein system, exposing the liver to large amounts of free fatty acids, which increases the hepatic synthesis of triglycerides and may also decrease its ability to secrete them, resulting in accumulation in hepatocytes[26].

In a previous study[27], Handisurya showed that T4 replacement therapy improved the insulin sensitivity in subjects with overt hypothyroidism.

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CONCLUSIONS

The hypothyroidism is associated with NAFLD, be it subclinical or overt, and may be considered a risk factor for this disorder. There is a relevant clinical relationship between these two diseases. Hence, the need and importance of monitoring the hypothyroidism in the NAFLD screening.

Author Contributions

All authors have an equal contribution in preparing this manuscript and thus share first authorship.

There is no conflict of interests for any of the authors.

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