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Correlation between thyroid function tests and fibroscan measurements in patients with hypothyroidism-induced NAFLD

Amira A Barakat[1], Mohamed Elbasiony[2], Mohamed M Aboelnaga[1], Azza A El-Baiomy[3], Mervat M El-Eshmawy[1]*

[1]*Internal Medicine Department, Mansoura Specialized Medical Hospital, Faculty of Medicine, Mansoura University, Egypt*

[2]*Internal Medicine Department, Mansoura Specialized Medical Hospital, Faculty of Medicine, Mansoura University, Egyptian liver research institute, Sherben, Egypt.*

[3]*Clinical Pathology Department, Faculty of Medicine, Mansoura University, Egypt*

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common disorders of the liver worldwide. Recently, a correlation between thyroid dysfunction and NAFLD has been discussed with a more focus on the hypothyroidism-induced NAFLD. This study was conducted to explore the possible correlation of TSH, FT4 and FT3 with NAFLD indices and fibroscan measurements in hypothyroid patients with NAFLD.This study comprised 2 groups: 30 hypothyroid patients with NAFLD and 30 hypothyroid patients without NAFLD. Diagnosis of NAFLD was based on both fibroscan and hepatic steatosis index (HSI) with a cutoff value of 36. Anthropometric measurements, controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) using the technique of vibration-controlled transient elastography (VCTE), the NAFLD fibrosis score (NFS), the Fibrosis-4 (FIB-4) index, lipids profile and thyroid function tests including TSH, FT4 and FT3 were assessed. TSH was significantly higher in NAFLD group than in non-NAFLD group. CAP, HSI and NFS were significantly higher in NAFLD group than in non-NAFLD group whereas, there was no significant difference between both groups with regard to liver stiffness and FIB-4 score. TSH levels were significantly and positively correlated with HIS and CAP. Free T3 was significantly and positively correlated with FIB-4 score. TSH level is significantly correlated with HSI and CAP whereas, FT3 is significantly correlated with FIB-4 score in hypothyroid patients with NAFLD.

Keywords: Thyroid function tests, Fibroscan measurements, Hypothyroidism-induced NAFLD.

Full length article **Corresponding Author*, e-mail: amirakarma4@mans.edu.eg

1. Introduction

The disruptions of cellular thyroid hormone signaling have been identified to be a trigger of chronic hepatic disease such as nonalcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease [1]. Therefore, a more attention has been recently brought to the hypothyroidism-induced NAFLD. In a meta-analysis study, high thyroid stimulating hormone (TSH) have been found in patients with NAFLD/NASH. Indeed, TSH levels are increased with the progression of NAFLD [2]. TSH promotes liver de novo lipogenesis through stimulation of the PPARα pathway which promotes hepatic lipogenesis [3-4].

Obesity, dyslipidemia, insulin resistance, inflammation and increased oxidative stress are also reported as potential underlying factors supporting the link between hypothyroidism and NAFLD [5-9]. Fibroscan is an ultrasound-based, accurate and non-invasive method for the diagnosis of NAFLD. It has been widely evaluated for the detection of advanced fibrosis and cirrhosis [10-11]. However, it fails to produce a usable result in up to 15% of measurements, particularly in the obese population [12]. The Fibroscan device is simultaneously estimated the controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) using the technique of vibration-controlled transient elastography (VCTE).

Measurement of CAP and LSM enables assessment of hepatic steatosis and fibrosis, respectively [13]. This study was conducted to explore the possible correlation of TSH, FT4 and FT3 with NAFLD indices and fibroscan measurements including CAP and LSM in hypothyroid patients with NAFLD.

2. Materials and Methods

This study comprised 2 groups: 30 hypothyroid patients with NAFLD and 30 hypothyroid patients without NAFLD. The study participants were consecutively recruited from the Endocrinology Clinic at Mansoura Specialized Medical Hospital, Mansoura University, Mansoura, Egypt. All subjects signed an informed consent, and the study was approved by the local ethics committee. All participants were provided a thorough medical history and complete clinical examination. Anthropometric measurements including weight, height, body mass index (BMI), waist circumference (WC) and blood pressure were obtained according to the standardized techniques. Diagnosis of NAFLD was based on both of the measurements of steatosis using fibroscan and hepatic steatosis index (HSI) with a cutoff value of 36 [14-15]. After fasting for at least 3 h, participants were subjected to VCTE/CAP examination in accordance with the guidelines for validated fibroscan measurements. The criteria for exclusion were diabetes mellitus, liver or renal failure, chronic hepatitis B or C infection, and other chronic liver diseases, infection, connective tissue disorders, malignancy, pregnancy, women taking birth control pills or hormone replacement therapy and smoking. Patients taking drugs such as metformin, thiazolidinediones, steroids, steatosis-inducing drugs and alcohol consumption were also excluded.

2.1. The studied indices of NAFLD

2.1.1. The hepatic steatosis index (HSI)

HSI comprises alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio, BMI, gender and presence of T2D. Although HSI was previously reported to has a moderate accuracy to detect NAFLD, this marker was recently validated against magnetic resonance showing a sensitivity of 86% and specificity of 66% [16]. Formula:

$$8 \times (ALT / AST) + BMI + 2 \text{ (if T2D)} + 2 \text{ (if female)}.$$

2.1.2. The Fibrosis-4 (FIB-4) index

It comprises age, AST, ALT and platelet count. It has a moderate accuracy in diagnosing NAFLD whereas, it is comparable to the NAFLD fibrosis score. Formula:

$$\text{Age} \times \text{AST (IU/l)}/\text{platelet count } (\times 109\ /l) \times \sqrt{\text{ALT (IU/l)}}$$

with a lower cut off 1.3 and upper cutoff 2.67 [17].

2.1.3. The NAFLD fibrosis score (NFS)

NAFLD fibrosis score comprises age, BMI, presence of impaired fasting glucose or T2D, AST/ALT ratio, platelet count and serum albumin levels. It has been more extensively validated than the other scores [18]. Formula:

$$-1.675+0.037\times\text{age (years)}+0.094\times\text{BMI (kg/m}^2\text{)} +1.13\times$$

impaired fasting glycemia (IFG) or diabetes (yes=1, no=0) + 0.99×AST/ALT ratio −0.013×platelet (×109 /l) −0.66×albumin (g/dl) −1.455 0.676.

2.1.4. Laboratory Assay

ALT, AST, total cholesterol (TC), triglycerides (TGs), and HDL were assayed by automated chemistry analyzer (cobas c311) using its commercial kits supplied by Roche Diagnostic Germany. LDL was calculated according to Friedewald et al. [19]. CBC including Platelet count was done using Ruby automated cell count (USA). FT4, FT3 and TSH were measured by electro-chemiluminecent immunoassay, using Elecsys 2010 (Roche Diagnostic, Germany).

2.2. Statistical analysis

Data entry and analysis were performed using IBM-SPSS statistical package version 27, 2020. The data were expressed as number, percent and M±SD. Chi-square was used to compare 2 groups of qualitative variables. The correlations of TSH, FT4 and FT3 with NAFLD indices and fibroscan measurements were analyzed by the Spearman correlation analysis.

3. Results and discussion

Patients with hypothyroidism and NAFLD had significantly higher age than those without NAFLD. Female sex was significantly prevalent in patients with NAFLD compared with those without NAFLD. BMI, WC, TGs were significantly higher in the NAFLD group than in non-NAFLD group. TSH was significantly higher in NAFLD group than in non-NAFLD group. There was no significant difference between both groups with regard to SBP, DBP, AST/ALT ratio, TC, LDL, HDL, FT4 and FT3 (Table 1). CAP, HSI and NFS were significantly higher in NAFLD group than in non-NAFLD group whereas, there was no significant difference between both groups with regard to liver stiffness and FIB-4 score (Table 2). TSH levels were significantly and positively correlated with HIS and CAP. Free T3 was significantly and positively correlated with FIB-4 score (Table 3, Figures 1, 2 & 3). Over the past decade, a study done by Liangpunsakul et al., have brought attention for the association between thyroid dysfunction and NAFLD [20]. After some controversial reports numerous studies have confirmed an association between thyroid function and NAFLD [21-25]. Hypothyroidism is also promoting progression of NASH and liver fibrosis [26-29]. In the current study, TSH was significantly higher in hypothyroid patients with NAFLD than in those without NAFLD. Moreover, TSH was significantly and positively correlated with HIS and CAP in hypothyroid patients with NAFLD. In accordance, a meta-analysis comprised 13 studies from 11 countries speculated that there is epidemiological evidence for the association between hypothyroidism and NAFLD independent of other known NAFLD risk factors [2]. He et al. noticed an independent relationship between hypothyroidism either clinical or subclinical with NAFLD [30]. Of interest, we found a significant correlation between TSH and steatosis whereas, no significant correlation between free T4 and free T3 and steatosis was found. This is may reflect the impact of TSH on liver steatosis independent of thyroid hormones.

Some studies have laid the foundation for the direct impact of TSH level on liver. They stated that TSH can directly increase hepatic gluconeogenesis, repress hepatic bile acid synthesis, and cause hypercholesterolemia by decreasing HMG-CoA reductase phosphorylation, which further leads to the development of NAFLD [31-33]. In addition, TSH may promote liver de novo lipogenesis through stimulation of the peroxisome PPARα pathway leading to activation of sterol regulatory element-binding transcription factor 1 (SREBP-1c), which promotes hepatic lipogenesis 3-4]. Obesity, insulin resistance, inflammation and increased oxidative stress [5-9]. are also reported as potential underlying factors supporting the link between hypothyroidism and NAFLD. Insulin resistance induces hepatic de novo lipogenesis and increased adipose tissue lipolysis leading to fatty acids accumulation in the liver which stimulates tumor necrosis factor alpha-mediated liver damage [34-35]. Ectopic TGs accumulation in the liver is occurred due to increased esterification of fatty acids to TGs together with decreased fatty acids oxidation [36]. Free T3 was significantly and positively correlated with FIB-4 score in hypothyroid patients with NAFLD. In contrast, Manka et al., found that low free T3 levels but not TSH and free T4 were associated with higher liver stiffness and higher NFS [29]. It worth mentioning that in our study FT3, within the hypothyroid range, was positively correlated with FIB-4 score but not TSH and FT4.

The expression of thyroid hormone receptor beta (THRβ) mRNA was negatively associated with NAFLD severity, suggesting a lower hepatic response to thyroid hormones during disease progression [37]. Even in euthyroidism, central and peripheral sensitivity indices to thyroid hormones were associated with advanced hepatic fibrosis and NAFLD [38-40]. A decrease in deiodinase 1 enzyme and increase in Dio3 mRNA during the process of hepatic inflammation was observed [41]. Moreover, deiodinase 1 knockdown combined with a western diet with fructose leads to increased TGs in hepatic steatosis [42]. Therefore, the association between hypothyroidism and NAFLD may be a bi-directionally related. THRβ agonists were recently suggested to be effective for the prevention and treatment of hepatic steatosis [43]. BMI and WC were significantly higher in hypothyroid patients with NAFLD than those without NAFLD. This is in agreement with Xing et al. and Grander et al. [44-45]. A meta-analysis of 21 cohort studies showed that obese individuals have a 3.5-fold increased risk of developing NAFLD, and there is an obvious dose-dependent relationship between BMI and NAFLD risk [46]. From the previous discussion, it seems that TSH is positively correlated with hepatic steatosis whereas, FT3 is significantly correlated with hepatic fibrosis in hypothyroid patients with NAFLD. However, the exact underlying mechanism needs further study.

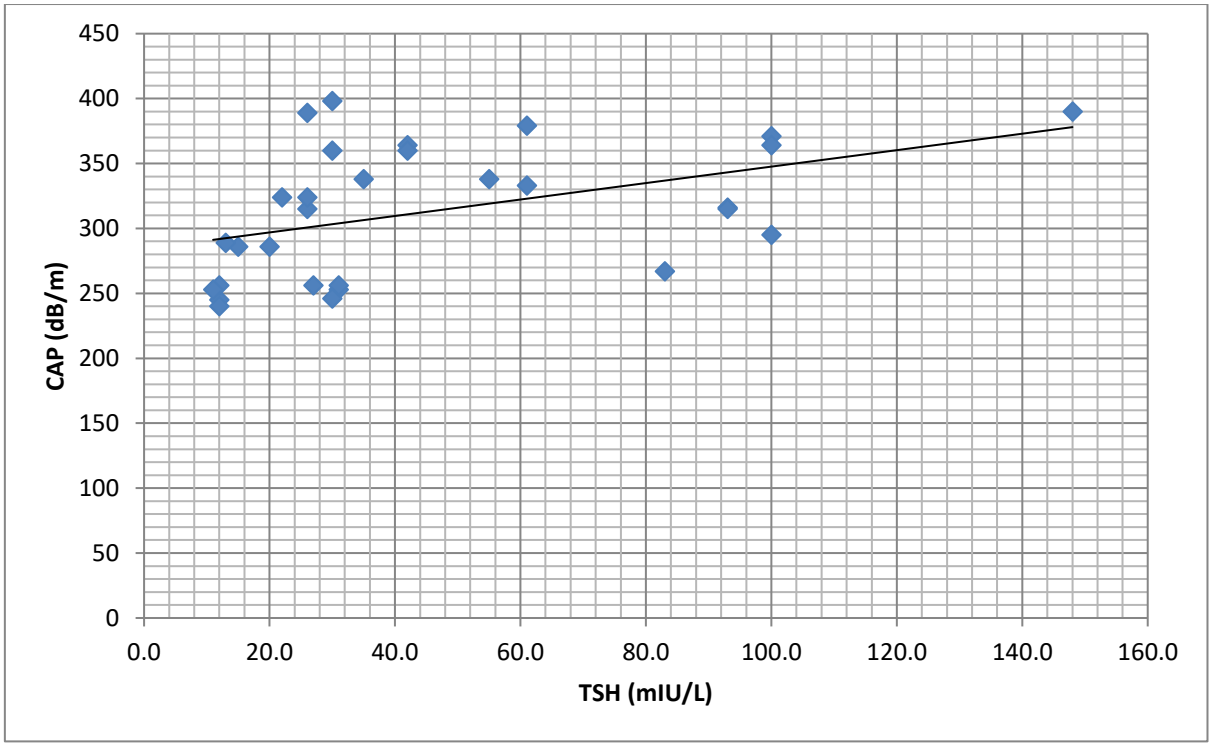

Figure 1: Scatter plot showing the correlation between TSH and CAP in hypothyroid patients with NAFLD.

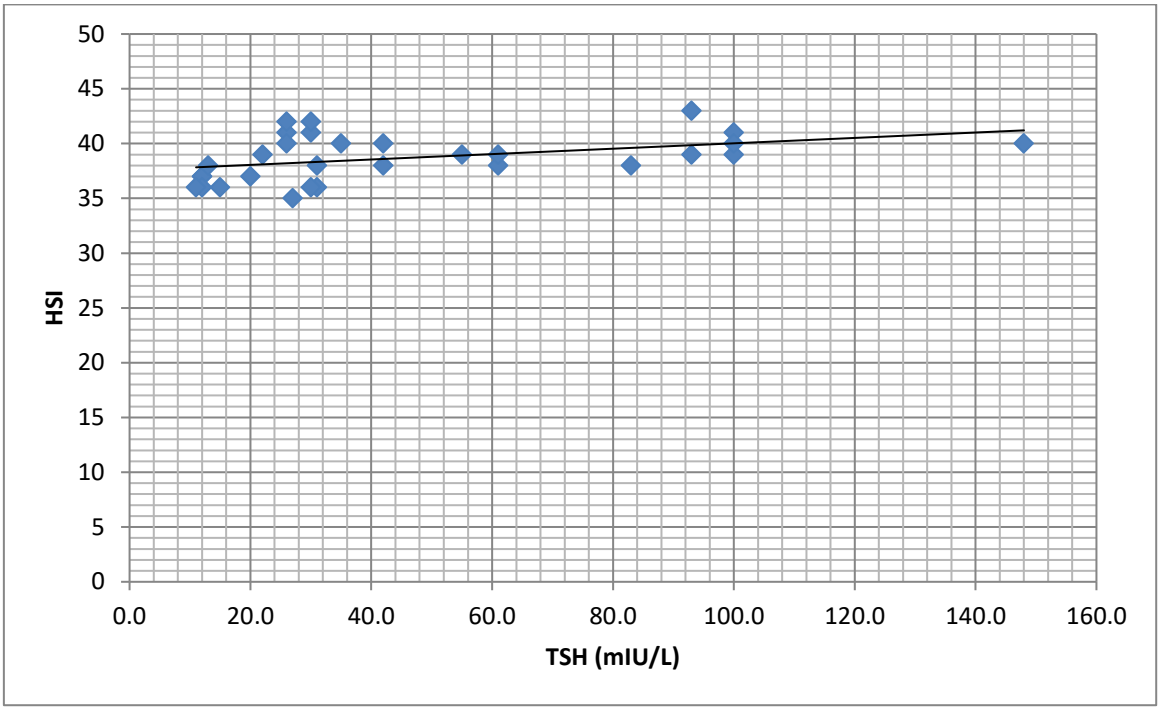

Figure 2: Scatter plot showing the correlation between TSH and TSI in hypothyroid patients with NAFLD.

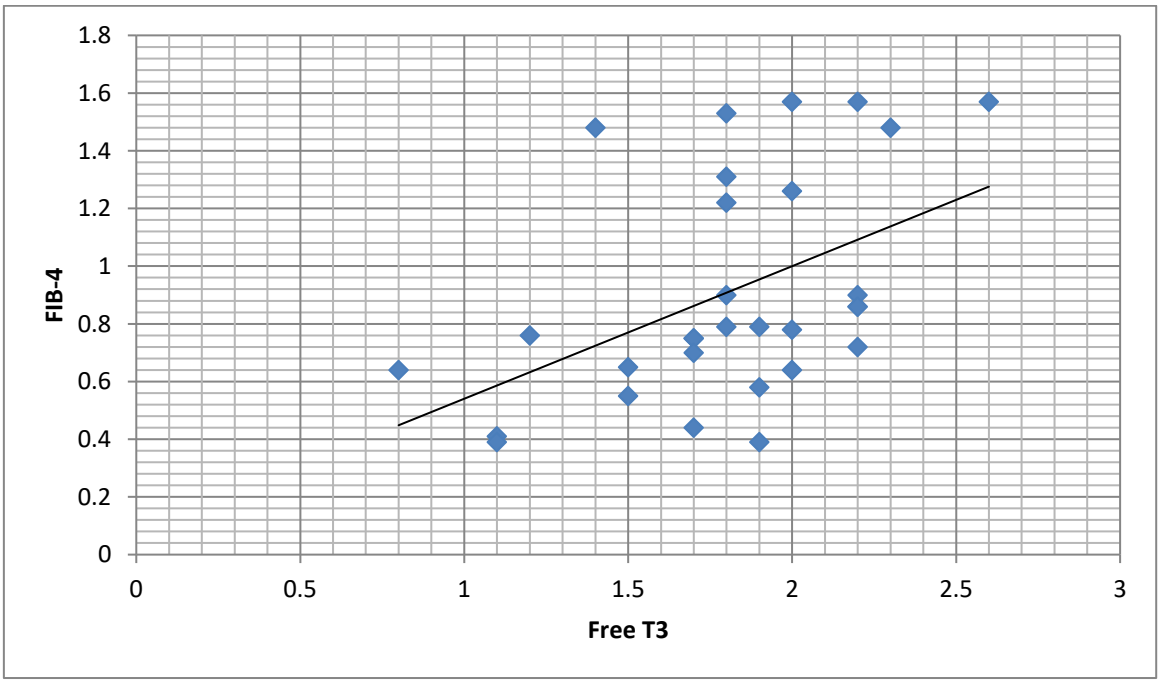

Figure 3: Scatter plot showing the correlation between Free T3 and FIB4 in hypothyroid patients with NAFLD.

Table 1: Baseline characteristics of the study subjects.

Variables	Hypothyroid patients with NAFLD	Hypothyroid patients without NAFLD	P-value
Age (years)	41.83 ± 9.39	37.10 ± 7.72	**0.037***
Sex Women/Men	21/9	11/19	**0.01***
BMI (kg/m^2)	37.53 ± 7.98	28.34 ± 3.18	**<0.001***
BMI categories Normal	1 (3.3%)	1 (3.3%)	**<0.001***
Overweight	7 (23.3%)	7 (23.3%)	
Grade I obesity	3 (10%)	3 (10%)	
Grade II obesity	6 (20%)	6 (20%)	
Grade III obesity	13 (43.3%)	13 (43.3%)	
WC (cm)	116.27 ± 13.04	100.83 ± 9.57	**<0.001***
SBP (mmHg)	121.33 ± 9.73	121.67 ± 9.13	0.892
DBP (mmHg)	77.67 ± 7.28	76.33 ± 6.69	0.463
AST/ALT ratio	1.14 ± 0.38	1.10 ± 0.44	0.716
TC (mg/dL)	224.83 ± 44.83	220.63 ± 37.16	0.694
TGs (mg/dL)	144.07 ± 59.34	107.80 ± 27.83	**0.004**
LDL (mg/dL)	133.77 ± 34.92	122.43 ± 33.94	0.208
HDL (mg/dL)	53.10 ± 5.29	49.13 ± 5.75	0.007
TSH (mIU/L)	46.23 ± 35.43	18.75 ± 9.13	**<0.001**
Free T4 (ng/dL)	0.60 ± 0.093	0.62 ± 0.07	0.221
Free T3 (pg/ml)	1.80 ± 0.40	1.76 ± 0.39	0.695

Data are expressed as means ± standard deviation, numbers or percentages, NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TC: total cholesterol, TGs: triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TSH: thyroid stimulating hormone, FT4: free thyroxine, FT3: triiodothyronine, *P is significant if ≤ 0.05.

Table 2: Fibroscan parameters and NAFLD scores.

Variables	Hypothyroid patients with NAFLD	Hypothyroid patients without NAFLD	P-value
CAP (dB/m)	313.53 ± 50.52	216.17 ± 13.42	**<0.001**
Liver stiffness (kPa)	5.06 ± 1.87	4.46 ± 0.67	0.109
HSI	38.70 ± 2.08	31.60 ± 2.44	**<0.001**
NFS	-1.70 ± 1.04	-2.75 ± 0.95	**<0.001**
FIB-4 score	0.90 ± 0.39	0.75 ± 0.43	0.139

Data are expressed as means ± standard deviation, NAFLD: nonalcoholic fatty liver disease, CAP: controlled attenuation parameter, HIS: hepatic steatosis index, NFS: nonalcoholic fatty liver disease fibrosis score, FIB4: Fibrosis Index Based on 4 Factors, *P is significant if ≤ 0.05.

Table 3: Correlation between TSH, FT4 and FT3 with NAFLD scores and fibroscan parameters in patients with hypothyroidism and NAFLD.

Variables	TSH		FT4		FT3	
	r	P-value	r	P-value	r	P-value
HSI	0.463	**0.01***	-0.158	0.405	-0.175	0.356
CAP	0.539	**0.002***	-0.057	0.766	-0.171	0.366
Liver stiffness	0.294	0.115	-0.031	0.870	-0.258	0.169
NFS	0.214	0.256	-0.061	0.747	0.117	0.537
FIB4 score	-0.256	0.172	0.169	0.372	0.527	**0.003***

NAFLD: nonalcoholic fatty liver disease, CAP: controlled attenuation parameter, HIS: hepatic steatosis index, NFS: nonalcoholic fatty liver disease fibrosis score, FIB4: Fibrosis Index Based on 4 Factors, *P is significant if ≤ 0.05.

4. Conclusions

TSH level is significantly correlated with HSI and CAP whereas, FT3 is significantly correlated with FIB-4 score in hypothyroid patients with NAFLD. This is may be clinically relevant for pharmacological treatment of NAFLD.

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