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Relationship of Non Alcoholic Fatty Liver Disease (NAFLD) and Serum Level of Thyroid Stimulating Hormone (TSH) in Normal Reference Range

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) can increase the incidence of cardiovascular disease and hepatocellular carcinoma. Thyroid hormones also play important roles in hepatic lipid metabolism and hepatic insulin resistance. Hypothyroidism is associated with reduced lipolysis and decreased liver uptake of free fatty acids derived from triglycerides. In recent years, the correlation between overt or subclinical hypothyroidism and NAFLD has been discussed. The relationship between NAFLD and thyroid function parameters remains unclear.
Aim: We aimed to evaluate the relationship between serum level of Thyroid Stimulating Hormone (TSH) within normal reference range and Non Alcoholic fatty liver Disease (NAFLD).
Subjects and Methods: This is a cross sectional case control study on 40 patients with NAFLD and a control group of 20 healthy individuals, who were attendants of Outpatient Clinic of Internal Medicine Department of Tanta University Hospitals and EL-Menshawy General Hospital from February 2018 to the end of January 2019.

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Results: In the present study, univariate regression analysis showed that serum levels of AST, FT3, FT4 and Anti-TPO were independent risk factors of NAFLD, while in multivariate analysis the only independent risk factor of NAFLD was Anti-TPO serum level.
Conclusion: Serum levels of AST, FT3, FT4 and Anti-TPO were independent risk factors of NAFLD in univariate regression analysis, while in multivariate analysis the only independent risk factor of NAFLD was Anti-TPO serum level. Despite the positive correlation between serum TSH level and grade of NAFLD, the study didn't show serum TSH level as independent risk factor of NAFLD.

Keywords: Non alcoholic fatty liver disease; thyroid stimulating hormone.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases [1].

NAFLD includes a broad range of conditions, such as simple steatosis and non-alcoholic steatohepatitis (NASH), which could progress to cirrhosis and hepatocellular carcinoma. In addition, NAFLD can increase the incidence of cardiovascular disease. Therefore, it is very important to identify the risk factors of NAFLD for the development of new preventive or therapeutic strategies [2].

NAFLD is considered the hepatic manifestation of metabolic syndrome (MS), which is associated with insulin resistance [3].

Metabolic disorders, such as hypertension, hyperlipidemia, diabetes, and central obesity, are known risk factors of NAFLD. Thyroid hormones regulate various metabolic processes involving carbohydrates, lipids, and proteins. Thyroid hormones also play important roles in hepatic lipid metabolism and hepatic insulin resistance. Hypothyroidism is associated with reduced lipolysis and decreased liver uptake of free fatty acids derived from triglycerides [4].

In recent years, the correlation between overt or subclinical hypothyroidism and NAFLD has been discussed and is considered controversial [5,6].

In the current study, we aimed to evaluate the relationship between serum level of Thyroid Stimulating Hormone (TSH) within normal reference range and Non Alcoholic fatty liver Disease (NAFLD).

2. SUBJECTS AND METHODS

The study was performed on sixty individual attending at Outpatient Clinic of Internal Medicine Department of Tanta University Hospital and EL-Menshawy General Hospital. The study was carried out during the period from February 2018 to the end of January 2019.

Individuals were divided to 2 groups:-

- Group I→ Twenty healthy individuals with No NAFLD.
- Group II→ Forty patients with NAFLD.
- Group II was subdivided into:
- Group II-a → patients with NAFLD who have serum level of TSH (≥0.3 &<2.5 mU/L).
- Group II-b →patients with NAFLD who have serum level of TSH (≥2.5 &≤4.1 mU/L).

2.1 Inclusion Criteria

- Subjects with and without NAFLD were included.

2.2 Exclusion Criteria

- Other liver pathology on history bases.
- Diabetes mellitus.
- Pregnant ladies.
- History of abnormal thyroid function.
- Drugs which could cause fatty liver disease.

2.3 All Subjects Were Subjected To

- Full history taking.
- Full clinical examination including blood pressure, pulse, temperature, head and neck, upper and lower limbs, chest, heart, abdomen, body mass index (BMI) and waist circumference (wc).

Anthropometric measures (waist circumference, height, weight, BMI) were taken as following:

- Body weight was measured with light clothing and without shoes in kilograms (kg) and rounded to tenth.
- Height was measured without shoes and caps in meters (m) and rounded to tenth.
- Both body weight and height were measured using Detecto scale while the patient was standing and looking toward the wall the scale was touching. While, BMI was calculated as weight in kilograms divided by height squared in meters; i.e., BMI = weight (kg)/height2 (m2).
- Waist circumference (WC) was measured in centimeters (cm) using the measuring tape in a horizontal plane midway between the iliac crest and the costal margin at the end of expiration; normally (WC) in male<94cm, in female<80.

- Laboratory investigations including:

  - Thyroid function: Includes serum level of TSH, free T4, freeT3 and Anti-Thyroid peroxidase by automated system (TOSOH-AIA 1600).
  - Liver function: includes serum level of ALT, AST, total bilirubin and albumin by automated system (KONELAB Thermoscientific), serum INR level by stago analyzer.
  - Serum triglyceride and HDL-ch level by photometric assay.
  - Fasting plasma glucose level by photometric assay.

- Ultrasonographic diagnosis of NAFL:

  - The machine used was Sonoscape 7 with B-mode using curved probe 3.5-5 m hertez in two planes axial and sagital.
  - Subjects were fasting at least 6-8 hours before examination, both lobes were examined which appear hyperechoic compared to muscles.

  - Grades of NAFLD:

1. Slight diffuse increase in bright homogenous echos in liver parenchyma with normal visualization of diaphragm, portal, hepatic veins borders and normal hepatorenal echogencty contrast.
2. Diffuse increase in bright echos in liver parenchyma with slight impaired visualization of portal and hepatic veins borders.
3. Marked increase in bright echos at shallow depth with deep attenuation impaired visualization of diaphragm and marked vascular blurring.

2.4 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

3. RESULTS

There was significant difference between the groups as regard U/S grading of NAFLD (P value <0.001). But this difference was not significant comparing subgroups of group II.

Table 1. Comparison between the three studied groups according to U/S

	Group I (n= 20)		Group II-a (n= 20)		Group II-b (n= 20)		X^2	p
	No.	%	No.	%	No.	%		
Grades of NAFLD								
Grade 0	20	100.0	0	0.0	0	0.0	60.606*	<0.001*
Grade 1	0	0.0	12	60.0	10	50.0		
Grade 2	0	0.0	8	40.0	10	50.0		
Sig. bet. Grps	$^{MC}p_1$<0.001*, p_2<0.001*, p_3=0.525							

*NAFLD: non alcoholic fatty liver disease; χ^2: Chi square test MC: Monte Carlo; p: p value for comparing between the different studied groups; p_1: p value for comparing between group I and Group II-a; p_2: p value for comparing between group I and Group II-b; p_3: p value for comparing between Group II-a and Group II-b; *: Statistically significant at p ≤ 0.05*

Table 2. Comparison between the three studied groups according to laboratory investigations

	Group I (n= 20)	Group IIA (n= 20)	Group IIB (n= 20)	F	p
AST (U/L)	22.55 ± 2.14	26.20 ± 5.02	26.20 ± 4.96	4.899*	0.011*
Sig.bet.Grps	p_1=0.024*, p_2=0.024*, p_3=1.000				
ALT(U/L)	22.65 ± 2.25	24.30 ± 4.18	24.20 ± 4.03	1.322	0.275
Serum FT3(pg/ml)	2.90 ± 0.30	2.41 ± 0.50	2.36 ± 0.49	9.185*	<0.001*
Sig.bet.Grps	p_1=0.002*, p_2=0.001*, p_3=0.994				
Serum FT4(ng/dl)	1.53± 0.21	1.35± 0.32	1.26 ± 0.29	5.861*	0.005*
Sig.bet.Grps	p_1=0.002*, p_2=0.001*, p_3=0.994				
TSH level (mIU/L)	1.73± 0.20	1.96 ± 0.53	3.63 ± 0.49	115.243*	<0.001*
Sig.bet.Grps	p_1=0.222, p_2<0.001*, p_3<0.001*				
Triglyceride (mg/dL)	112.35 ± 27.96	128.45 ± 46.45	124.95 ± 44.53	0.874	0.423
HDL(mg/dl)	64.05 ± 7.71	48.60 ± 7.54	47.85 ± 7.41	29.310*	<0.001*
Sig.bet.Grps	p_1<0.001*, p_2<0.001*, p_3=0.947				
Bilirubin (mg/dL)	0.48 ± 0.12	0.90 ± 0.14	0.90 ±.13	72.170*	<0.001*
Sig.bet.Grps	p_1<0.001*, p_2<0.001*, p_3=1.000				
INR	1.04 ± 0.10	1.02 ± 0.11	1.03 ± 0.11	0.114	0.892
Albumin (g/dl)	4.10 ± 0.48	3.96 ± 0.47	3.89 ± 0.46	1.075	0.348
Fastingblood glucose (mg/d)	88.55 ± 7.74	87.60 ± 10.0	87.95 ± 8.47	0.060	0.942
Anti-TPO (IU/ml)	20.60 ± 1.64	27.20 ± 3.81	30.75 ± 3.84	49.930*	<0.001*
Sig.bet.Grps	p_1<0.001*, p_2<0.001*, p_3=0.003*				

*AST: aspartate amine transferase; ALT: alanine amine transferase; FT3: free tri iodothironine; FT4: free tetra iodothironine; TSH: thyroid stimulating hormone; HDL: high density lipoprotein; INR: international normalized ratio; Anti-TPO: anti thyroid peroxidase; F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey); p: p value for comparing between the different studied groups; p_1: p value for comparing between group I and Group IIA; p_2: p value for comparing between group I and Group II b; p_3: p value for comparing between Group IIA and Group II b; *: Statistically significant at p ≤ 0.05*

Table 3. Correlation between TSH level (mIU/L) and different parameters in each group

	TSH level (mIU/L)							
	Group I (n= 20)		Group II (n= 40)		Group IIA (n= 20)		Group IIB (n= 20)	
	r	p	R	p	r	p	r	P
Age (years)	0.225	0.339	0.101	0.535	0.309	0.185	0.266	0.256
Waist circumference	-0.080	0.736	0.063	0.700	0.293	0.210	-0.061	0.800
BMI (Kg/m2)	0.207	0.381	-0.130	0.425	-0.391	0.088	-0.249	0.291
AST (U/L)	-0.294	0.209	-0.176	0.277	-0.517	0.020*	-0.231	0.326
ALT(U/L)	0.090	0.707	0.042	0.798	0.023	0.923	0.215	0.362
Serum FT3(pg/ml)	-0.265	0.259	-0.090	0.581	-0.155	0.514	-0.051	0.832
Serum FT4(ng/dl)	-0.212	0.369	-0.285	0.075	-0.051	0.830	-0.103	0.665
Triglyceride(mg/dL)	0.404	0.077	0.031	0.849	0.114	0.633	0.175	0.460
HDL (mg/dl)	-0.272	0.247	-0.149	0.357	-0.307	0.187	-0.134	0.575
Bilirubin (mg/dL)	-0.110	0.644	-0.018	0.913	-0.049	0.839	-0.027	0.910
INR	-0.385	0.094	-0.053	0.746	-0.264	0.261	-0.078	0.744
Albumin (g/dL)	-0.008	0.974	0.032	0.843	0.243	0.302	0.187	0.431
Fasting blood glucose (mg/d)	0.212	0.369	-0.003	0.986	-0.008	0.973	-0.088	0.712
Anti-TPO (IU/ml)	-0.384	0.095	0.406	0.009*	0.208	0.378	-0.100	0.674
Grades of NAFLD	-	-	0.411	0.008*	0.747	<0.001*	0.648	0.002*

*r: Pearson coefficient; *: Statistically significant at p ≤ 0.05*

Table 4. Univariate and multivariate analysis for the parameters predicting NAFLD

	Univariate		#Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
AST (U/L)	0.006*	1.266 (1.069 – 1.499)	0.140	1.472 (0.881 – 2.461)
Serum FT3(pg/ml)	0.001*	0.061 (0.012 – 0.311)	0.742	0.532 (0.012 – 22.681)
Serum FT4(ng/dl)	0.014*	13.789 (1.711 – 111.097)	0.327	27.277 (0.036 – 20400.837)
Anti-TPO (IU/ml	0.001*	2.740 (1.536 – 4.889)	0.017*	2.985 (1.218 – 7.315)
TSH (≤1.66)	0.336	2.250 (0.431 – 11.758)	–	–

*OR: Odd`s ratio, C.I: Confidence interval; #: All variables with p<0.05 was included in the multivariate; *: Statistically significant at p ≤ 0.05*

Serum Anti –TPO level was significantly lower in group I in comparison to subgroups II-a and II-b (p value< 0.001), also, it was lower in subgroup II-a than II-b (p=0, 003). But the difference between groups was non-significant regarding serum levels of, ALT (p value=0.275), triglycerides (p value=0.423), INR (p value=0.892), albumin (p value=0.348), and fasting plasma glucose (p value=0.942).

In the current study we found that a significant positive correlation between serum TSH level and Anti-TPO level and grade of NAFLD in group II. Also, the correlation between serum TSH level and grade of NAFLD was positively significant in group II-a and group II-b. Group II-a, showed significant correlation between serum TSH level and AST level.

In the current study, univariate regression analysis showed that serum levels of AST, FT3, FT4 and Anti-TPO were independent risk factors of NAFLD, while in multivariate analysis the only independent risk factor of NAFLD was Anti-TPO serum level.

4. DISCUSSION

This study revealed that there was significant difference between studied groups regarding AST(was higher in NAFLD patients), FT4(lower in NAFLD patients), FT3, TSH, HDL, bilirubin and Anti –TPO, but the difference between groups was non significant regarding ALT, triglyceride, INR, albumin, and fasting plasma glucose.

Also, Xu et al., [7] showed that The NAFLD group had higher ALT, AST, triglyceride (TG), levels and a lower HDL-C level [7].

Another study by Pagadala et al., showed some contradictory result to our study with some degree of agreement, they showed that the mean levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphtase and thyroid stimulating harmone (TSH) were higher in NAFLD compared to controls [8].

Moreover, Chen et al., [9] data agrees with the present study as level of AST, was higher in participants with NAFLD for both genders, other results support the findings in the present work, ALT and hyperlipidemia were higher in participants with NAFLD for both genders [9].

On the other hand Gheibi et al., [10] showed that an increase of 10 U/L in ALT, AST and ALK increased the odds of NAFLD 101%, 127% and 2%, respectively. An increase of 10 mg/dL in TG was associated with an 8% increase and also 10 µlu/mL of TSH with a 55% increase in the odds of NAFLD [10].

Similarly Bano et al. [5] showed that there was a positive linear association between TSH levels and NAFLD risk (OR, 1.09; CI, 1.01–1.19 per 1 log-TSH) [5].

Also, Xu et al., [7] agrees with our result as showed that thyroid function is significantly associated with NAFLD in euthyroid elderly Chinese [7].

In addition to Guo et al., showed that NAFLD patients had significantly higher TSH levels than healthy controls regardless of adults or children and adolescents. Such a difference remained significant in subjects with normal TSH levels. TSH levels were further increased with the progression of NAFLD [11].

In contrast to our results, Ittermann et al., conducted a population-based study in Germany including 3, 600 healthy individuals that found only a significant association between NAFLD and FT_4, but not FT_3, TSH [12].

Chen et al. [9] agreed with the current study. They found that, the prevalence of TPO/TgAb (+)

was higher in NAFLD group than in control group (statistical significance was seen in women and marginal association was shown in men), while TPO/TgAb (+) and US (+) was significantly higher in NAFLD group for both genders (all p <0.01) [9].

Zhang, et al., [13] conducted a population-based study involving more than 1300 Chinese subjects and showed similar findings to the present study, as they found that TSH is not an independent risk factor for NAFLD [13], also Carulli et al., reported that an increased serum TSH level is an independent risk factor for NASH compared to patients with NAFLD [14].

Liu et al., [15] performed another health survey study in China including almost 2600 participants and showed that FT_3 was independently associated with NAFLD, but FT_4 was only significantly associated with NAFLD in a subgroup of postmenopausal women. However, there have also been a few large trials that found no association [15].

5. CONCLUSION

Serum levels of AST, FT3, FT4 and Anti-TPO were independent risk factors of NAFLD in univariate regression analysis, while in multivariate analysis the only independent risk factor of NAFLD was Anti-TPO serum level. Despite the positive correlation between serum TSH level and grade of NAFLD, the study didn't show serum TSH level as independent risk factor of NAFLD

6. RECOMMENDATIONS

We recommend to carry out this study on a wide scale including large number of patients for better evaluation of the relationship between TSH level with normal reference range and NAFLD.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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