THYROID DYSFUNCTION IN OBESE ADULT IN RELATION TO NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract:

Background: Hormones of the thyroid gland play an important role in the regulation of various metabolic processes. Disturbances in thyroid hormone concentrations may lead to hyperlipidemia and obesity, thus contributing to NAFLD. **Aim:** To evaluate thyroid dysfunction and determine its possible relationship to nonalcoholic fatty liver disease (NAFLD) in obese adults. **Methods**: our cross-sectional study recruited 100 obese patients, patients were subjected to a full medical history, physical examination, abdominal ultrasonography as well as routine laboratory tests in addition to liver function and thyroid function testing. NAFLD was recognized on the basis of ultrasonographic findings, and in the absence of other causes of liver disease. **Results:** Patients was divided in two groups, Group 1 (65 patients) with NAFLD and Group 2 (35 patients) without NAFLD. Out of 100 patients recruited in the study; the most common thyroid dysfunction was overt hypothyroidism (22%) followed by (9%) had subclinical hypothyroidism. 26 patients with NAFLD (40%) were found to have thyroid dysfunction, of them 8 NAFLD patients (12.3%) had subclinical hypothyroidism and 18 NAFLD patients (27.7%) had overt hypothyroidism. Although Prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) was 22 % and 9 % respectively among patients with obesity, there was non-significant positive correlation between BMI and TSH (r= 0.051 and P=0.612). Multivariate regression analysis revealed that; fatty liver , obesity index and dyslipedemia were predictors of thyroid dysfunction in obese patients. **Conclusion**:Thyroid hypofunction is common in obese patients with NAFLD, which has implications for screening for hypothyroidism in patients with NAFLD and for the administration of appropriate therapy for hypothyroidism.

Keywords: Non-alcoholic fatty liver disease, Hypothyroidism, Obesity.

Introduction:

NAFLD is an important health problem, It considered one of the most common causes of chronic liver disease (1) . NAFLD includes a wide range of pathology from simple steatosis to nonalcohol steatohepatitis (NASH), fibrosis, cirrhosis and is identified by excessive free fatty acids and triglycerides accumulation in the liver. Although Type 2 diabetes mellitus and obesity contribute as risk factors for NAFLD; other endocrine disorders such as thyroid dysfunction, adrenal insufficiency, growth hormone deficiency, and polycystic ovary syndrome also play role in occurrence of NAFLD (2).

The thyroid gland is significantly involved in regulation of energy expenditure, Adipogenesis, carbohydrate and lipid metabolism; thereby play an important role in the development of metabolic abnormalities (3, 4). Thyroid hormones affecting hepatic fat accumulation through multiple pathways, including stimulation delivery of free fatty acid to the liver for reesterification to triglycerides, and increasing β- oxidation fatty acid.

Several studies have revealed association between thyroid dysfunction and NAFLD but have demonstrated inconsistent results. Therefore, to better characterize this association, we conducted our study to evaluate thyroid dysfunction and determine its possible relationship to NAFLD in obese adults.

Patients and Methods:

This cross sectional study recruited 100 obese patients (BMI more than or equal to 30 kg/m^2) followed at obesity outpatient clinic of Internal Medicine Department at Assiut University Hospitals during the period between May 2017 and May 2018.

Exclusion criteria:

Patients with any liver diseases such as viral-induced hepatitis or liver cirrhosis , Liver malignancy, diabetic patients, patients with history of thyroid disease or other endocrinal disorders.

All participants in the study were subjected to:

(1)Full history taking and clinical examination, BMI was calculated as weight divided by squared height (kg/m^2),Waist circumference, and Waist-to-hip ratio (WHR) was calculated as the ratio of the circumference of the waist to that of the hips.

(2)Ultrasonographic examination of the liver: Liver ultrasound was performed by an experienced consultant by using conventional B-mode with a convex 2.5-5 MHz probe [logiq p5 GE Ultrasound]. NAFLD defined according to four ultrasonographic criteria for fatty liver : hepatorenal echo contrast, liver brightness, deep attenuation, and

vascular blurring (5), in absence of other causes of liver disease ,alcohol consumption or seropositivity to antibody to hepatitis C virus or hepatitis B surface antigen.

(3) Laboratory investigations: blood samples were obtained from each participant after overnight fasting. Laboratory studies included fasting blood sugar in mg/dl, urea, and creatinine; Lipid profile, liver function test; and hepatitis B virus surface antigen, hepatitis B surface antibody and antihepatitis C antibody. thyroid function tests [free T3, free T4, and thyroid stimulating hormone (TSH)], were assessed by enzyme-linked immunosorbent assay (ELISA) technique.

The study was approved by Assiut University ethical committee and review board. All the patients who participated in the study provided written informed consents.

Statistical Analysis

Data were collected and analyzed by computer program SPSS" ver. 24" Chicago. USA. Continuous variables were expressed as mean ± Standard deviation (SD); categorical variables were expressed as number and percentage. Student t-test and one-way ANOVA were used to compare continuous variables. Chi^2 test was used to compare categorical variables. Correlations between parameters measured were calculated using Spearman's correlation coefficient. Multivariate regression analysis was used to determine the predictors of thyroid dysfunction in obese adult patients. *P* value was significant if < 0.05.

Results

This cross-sectional study involving 100 obese patients, 55 males (55%) and 45 females (45%), mean age (30 ±4) years. 65 patients (65%) has NAFLD versus 35 patients (35%) with normal liver ultrasound. As regard to thyroid dysfunction in study group; 22 patients (22%) has overt hypothyroidism, 9 patients (9%) patients had subclinical hypothyroidism and 69 patients (69%) had normal thyroid function test;

comparison between different grades of thyroid dysfunction showed significant difference in obesity index, total cholesterol, TG, LDL (P value=0.02, 0.01,0.04,0.03) respectively; Table (1), Figure (1).

According to obesity index WHO classification in 2014 (6); patients divided in to 3 groups; 31 patients (31%) were obese class 1 (with BMI ranging from 30 to less than 35); 23 patients (23%) were obese class 2 (with BMI ranging from 35 to less than 40) and 46 patients (46%) were obese class 3 (with BMI equal to or more than 40). Prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) was 22 % and 9 % respectively among patients with obesity. There was non-significant positive correlation between BMI and TSH (r= 0.051 and P = 0.612) (Figure 2)

The comparison between patients with and without NAFLD described in (Table 2), with higher significant difference in the mean levels of each of BMI, ALT, AST, Ft3(P value = 0.001, <0.001, <0.001,0.008) respectively in patients with NAFLD than in those with normal liver ultrasound findings. Prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) among patients with and without NAFLD presented in Table (3). The current study showed that obesity index, dyslipidemia and fatty liver were independent factors for thyroid dysfunction in obese adult patients (Table 4).

Table (1). Comparison of clinical and laboratory findings between different grades of thyroid dysfunction.

Parameter		Normal (n=69)	Subclinical Hypothyroidism (n= 9)	Overt Hypothyroidism (n=22)	P value
Age (years)		30±4	32± 5	29±3	0.21
Gender (males)		39 (56%)	6 (67%)	10 (48%)	0.63
Body weight(kg)		98±8	103± 10	98±8	0.21
Height (m^2)		1.6±0.06	1.6± 0.07	1.5±0.6	0.44
BMI (kg/m^2)		38±3	40±4	39±3	0.23
WC (cm)		92±13	104 ±21	95±15	0.08
WHR		0.8±0.01	0.8±0.02	0.8±0.02	0.60
Systemic hypertension		18 (26%)	5 (55%)	5 (24%)	0.12
Obesity index	Obese class1	26 (38%)	5 (56%)	0 (0%)	**0.02**
	Obese class2	21 (30%)	1 (11%)	1 (5%)	
	Obese class3	22 (32)	3 (33%)	21 (95%)	
ALT(IU/L)		41±16	53±32	42±12	0.20
AST(IU/L)		20±7	25±9	21±8	0.16
Albumin (g/dl)		1.9±0.06	1.8±0.07	1.8±0.06	0.90
Total cholesterol(mg/dl)		147±46	205±40	202±30	**0.01**
Triglyceride(mg/dl)		120±44	148±66	146±42	**0.04**
HDL (mg/dl)		63±17	61±28	54±17	0.23
LDL (mg/dl)		62±23	108±41	86±35	**0.03**

BMI, body mass index; WC, waist circumference; WHR, waist hip ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase, TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone.

Table (2). Clinical and laboratory data in patients with NAFLD versus patients without NAFLD

	Patients with NAFLD (n=65) (mean±SD)	**Patients without NAFLD (n=35) (mean±SD)**	P value
Age (years)	30.18±4.49	29.94±3.51	0.817
BMI (kg/m^2)	39.38±3.47	37.31±3.17	**0.001**
WC (cm)	92.69±14.05	94.73±15.72	0.896
ALT (IU/l)	47.91±13.66	32.75±19.95	**<0.001**
AST (IU/l)	22.67±6.23	16.27±7.52	**<0.001**
Albumin (g/dl)	1.87±0.06	1.87±0.06	0.561
Total cholesterol (mg/dl)	165.29±50.27	161.77±48.92	0.508
TGs (mg/dl)	124.90±41.04	134.11±57.23	0.859
LDL (mg/dl)	72.66±34.62	68.36±25.72	0.851
HDL (mg/dl)	59.48±16.01	64.33±22.04	0.299
FT3 (pg/dl)	3.36±1.04	3.9257±.83	**0.008**
FT4 (ng/dl)	3.44±3.44	4.69±4.42	0.190
TSH (μIU/ml)	9.07±3.09	3.69±2.88	0.114

Table (3): prevalence of thyroid dysfunction in patients with and without NAFLD

Parameter	Patients with NAFLD (n=65)	Patients without NAFLD (n=35)	*P* value
Subclinical hypothyroidism	8(12.3%)	1(2.8%)	**0.028**
Overt hypothyroidism	18(27.6%)	4(11.4%)	
Euthyroid state	39(60%)	30(85.7%)	

Table (4): Multivariate regression analysis for prediction of thyroid dysfunction in obese patients.

Variables	Odd's ratio	95%Confidence interval	P value
Obesity index	3.45	2.56- 5.68	**0.03**
Dyslipidemia	1.94	1.87- 3.33	**0.04**
Fatty liver	2.67	2.04- 6.09	**0.01**

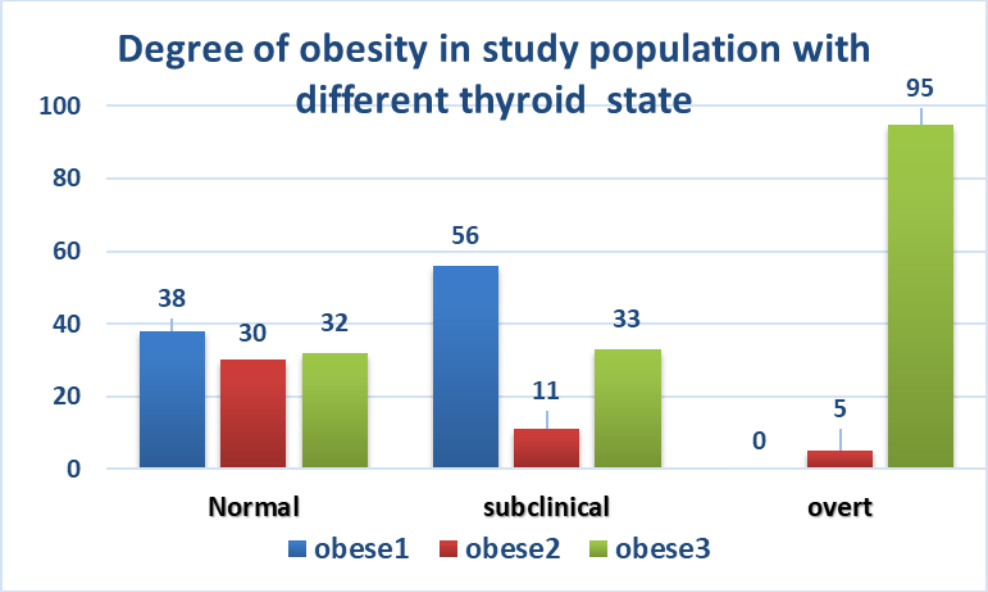

Figure (1) Shows degree of obesity in study group with different thyroid state.

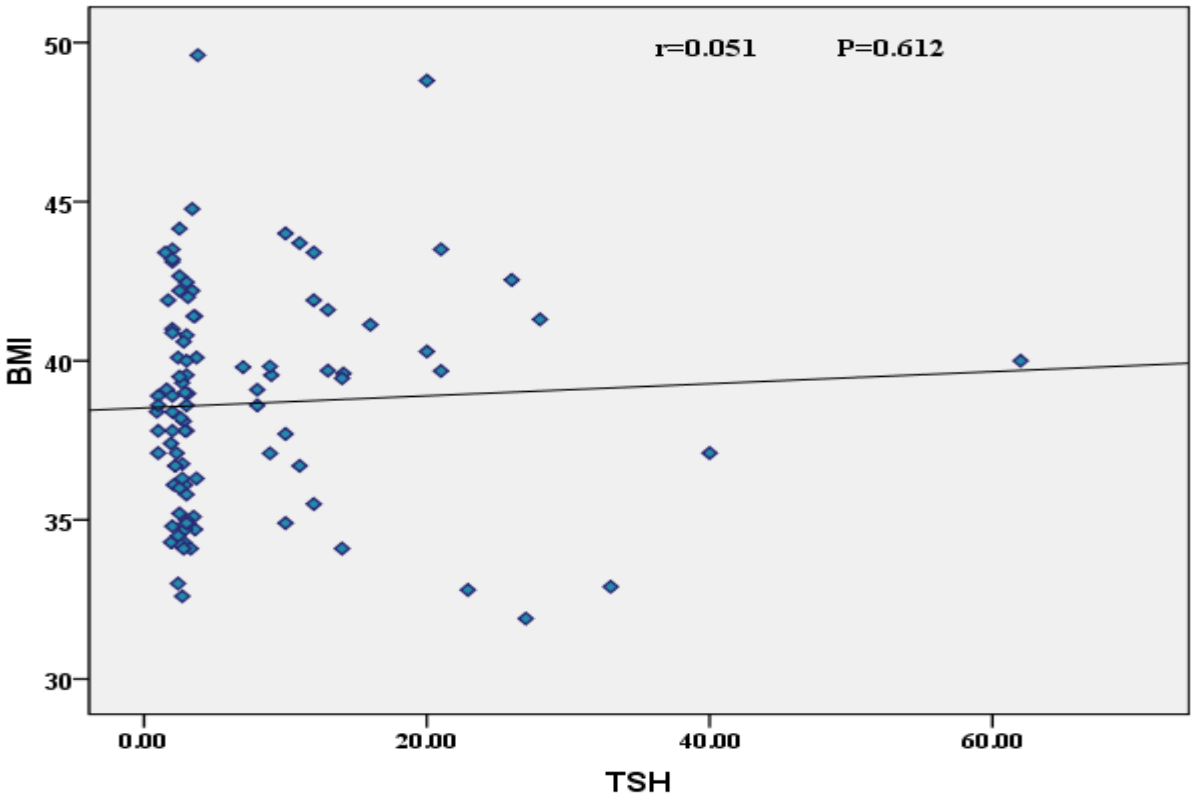

Figure (2) Shows correlation between TSH and BMI.

Discussion

In this study 100 obese patients were recruited with mean age (30 ±4) years, 55 males (55%), 45 females (45%). In this study mean body mass index was (39 ±3) with 3 grades of obesity and a statistically significant difference between the three groups in mean level of TSH ($p < 0.05$). The association between TSH and BMI was clarified by Chan et al.(7) to be under the impact of adipose tissue signals and leptin may have significant effects on thyroid function by central regulation of thyroid releasing hormone (TRH). Although 22 patients who were overt hypothyroidism 21(95%) of them were obese grade 3 with BMI equal or more than 40, There was non-significant positive correlation between BMI and TSH ($r = 0.051$ and $P = 0.612$).These findings came in contrast with Solanki et al who reported a significant positive association between participants BMI and their mean serum TSH levels (8). Moreover, Knudsen et al. (9) showed that serum TSH is positively correlated with BMI.

This study showed that prevalence of NAFLD increases with higher obesity index ($p < 0.05$), as out of 46 patients' obese grade 3; 39(85%) were reported to had NAFLD which highlight the importance of weight reduction strategies for prevention and management of NAFLD. Also A. Katrina et al study showed a strong association between BMI and prospectively recorded diagnoses of NAFLD/NASH and (10)

Over the past decade, the relationship between thyroid dysfunction and NAFLD has become an important research topic. After controversial reports, many studies have confirmed an association between thyroid function and NAFLD (11).

The association between hypothyroidism and NAFLD may due to may underlying mechanisms. Hypothyroidism has been associated with insulin resistance (12), obesity (13) ; dyslipidemia (14)and all of which are significant components of the metabolic syndrome. Furthermore, hypothyroidism is also related to metabolic syndrome (15), which plays vital role in development of NAFLD (16).

In this study there was a significant (P=0.028) higher prevalence of thyroid dysfunction in the form of overt and subclinical hypothyroidism (27.6% and 12.3%) respectively among patients with NAFLD. From the 9 patients who diagnosed to be subclinical hypothyroid 8 were fatty liver with a percentage 89%, and from the 22 patients who were diagnosed to have overt hypothyroidism 18 patients were have fatty liver with a percentage 82%.Concordant with our result Chung et al, study which showed higher prevalence of NAFLD in patient with hypothyroidism (17). Bano et al, revealed that primary hypothyroidism was independently associated with an increased risk of NAFLD (18).Also He et al, in review involving 13 observational studies showed that primary subclinical and overt hypothyroidism were associated with an nearly 50% higher risk of NAFLD, even after adjustment for numerous metabolic confounders (19).Inversely, Lee et al, reported that both subclinical and overt hypothyroidism were not independently associated with an increased risk of a NAFLD (20).

Hypothyroidism may worsen preexisting lipid abnormalities in patients with NAFLD, leads to elevated cholesterol and low density lipoproteins, affects the synthesis, mobilization and degradation of all features of lipid metabolism (14). In our study there is significant increased in cholesterol, triglyceride and LDL levels in hypothyroid subjects than euthyroid patients which came in agreement with Canaris et al study that revealed patients with subclinical hypothyroidism had higher total cholesterol and LDL level in comparison to euthyroid population (21). Another study in Austria did not find those differences (22). A sample analysis of the National Health and Nutrition Survey (NHANES III) revealed higher both serum cholesterol and TG levels in patients with subclinical hypothyroidism compared to euthyroid participants. However, this difference disappeared after adjusting for variables such as sex, age and race (23). Also Erem established the occurrence of hypercholesterolemia and hypertriglyceridemia in overt hypothyroidism (24).

In conclusion, according to our study, hypothyroidism independently increases the risk of NAFLD, which has implications for screening for hypothyroidism in patients with NAFLDs. In the meantime, it may also be useful to identify hypothyroidism in patients with non-alcoholic fatty liver disease and to administer appropriate treatment for hypothyroidism. Therefore, the results of this study are of great importance for the preventive medicine of hypothyroidism and NAFLD.

One of the limitations of our study is that the diagnosis of NAFLD was manufactured on an ultrasound examination, while the liver biopsy is considered as the reference method for the detection of mild steatosis or hepatic fibrosis. However, liver biopsies are not routinely performed in the diagnosis of NAFLD because of their invasiveness and potential complications. In addition, abdominal ultrasound has a sensitivity of 80% to 90% for liver detection by other imaging modalities.

We recommend further research by using prospective studies to assess the prevalence of hypothyroidism in NAFLD. In addition, the efficacy of using thyroid-related drugs to prevent steatosis and the development of NASH must be explored in animal and cellular culture models.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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